Genetic Eye Diseases - Facing The Challenges of the Future

21. Meeting
International Society for Genetic Eye Diseases and Retinoblastoma (ISGEDR)
a joint meeting with
Section DOG-Genetics

August 29 – 31, 2019

Medical Education Building of the Medical Faculty of the Justus-Liebig-University Giessen, Germany

Local Host: Prof. Dr. Birgit Lorenz President of ISGEDR, Speaker of Section DOG-Genetics
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The International Society for Genetic Eye Diseases

ISGEDR

Mission Statement
To bring together individuals interested in the field of genetic diseases of the eye and in retinoblastoma

To provide a forum for researchers in the field of genetic diseases of the eye to share information

To promote international collaborations in the study of genetic diseases of the eye and in Retinoblastoma

To disseminate scientific knowledge through international conferences and through its official publication, Ophthalmic Genetics

ISGEDR Executive Committee
Birgit Lorenz, Giessen, Germany, President
Elias I. Traboulsi, Cleveland, USA, Executive Vice President
David Mackey, Perth, Australia, Immediate Past President
Brenda Gallie, Toronto, Canada, Member-at-Large – Retinoblastoma
Bart Leroy, Ghent, Belgium, Member-at-Large – Genetics
Alex Levin, Philadelphia, USA, Member-at-Large – Genetics
Francis Munier, Lausanne, Switzerland, Member-at-Large – Retinoblastoma
Richard Weleber, Portland, USA, Member-at-Large – Genetics
Honorary Lectures

The Franceschetti Lecture & Medal honours the unique contributions of the Swiss ophthalmologist, Adolphe Franceschetti (1896 – 1968), one of the founders of the field of ophthalmic genetics.

François lecture honours the Belgian ophthalmologist Jules François (1907 - 1984) for his contributions in ophthalmic genetics as a specialty.


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<td>Ellsworth Lecturer: Annette C. Moll</td>
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<td><strong>2015 - Halifax, Nova Scotia, Canada</strong></td>
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<td>Franceschetti Lecturer: Elise Héon</td>
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<td>François Lecturer: Richard G Weleber</td>
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<td><strong>2013 - Ghent, Belgium</strong></td>
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<td>Franceschetti Lecturer: Edwin M. Stone</td>
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<td>François Lecturer: Elias I. Traboulsi</td>
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<tr>
<td>Ellsworth Lecturer: Francis Munier</td>
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<td><strong>2011 - Bangalore, India</strong></td>
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<td>Franceschetti Lecturer: Elias I. Traboulsi</td>
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<td>Ellsworth Lecturer: Guillermo L. Chantada</td>
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<td><strong>2008 - Strasbourg, France</strong></td>
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<td>Franceschetti Lecturer: Josseline Kaplan</td>
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<td>Ellsworth Lecturer: Brenda Gallie</td>
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<td><strong>2005 - Whistler, Canada</strong></td>
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<td>Franceschetti Lecturer: Richard A. Lewis</td>
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<td>Ellsworth Lecturer: A. Linn Murphree</td>
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<td><strong>2003 - Paris, France</strong></td>
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<td>Franceschetti Lecturer: Anthony Moore</td>
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<td>Ellsworth Lecturer: John Hungerford</td>
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<td><strong>2001 - Ft. Lauderdale, USA</strong></td>
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<td>Franceschetti Lecturer: Richard Weleber</td>
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<td>Ellsworth Lecturer: Daniel M. Albert</td>
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<td><strong>2019 - Geneva, Switzerland</strong></td>
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<td>Franceschetti Lecturer: David Abramson</td>
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<td>Ellsworth Lecturer: Anna Meadows</td>
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<td><strong>2016 - Hobart, Australia</strong></td>
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<td>Franceschetti Lecturer: Alan Bird</td>
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<td>Hereditary retinal dystrophies</td>
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<td><strong>2014 - Niagara Falls, Canada</strong></td>
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<td>Franceschetti Lecturer: Irene H. Maumenee</td>
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<td>The Marfan Syndrome</td>
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<td><strong>2012 - Siena, Italy</strong></td>
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<tr>
<td>Franceschetti Lecturer: John Opitz</td>
</tr>
<tr>
<td><strong>2010 - Calloway Gardens, USA</strong></td>
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<tr>
<td>Franceschetti Lecturers: Thaddeus Dryja &amp; Eliot Berson</td>
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<tr>
<td>Mutations in the rhodopsin gene in Retinitis pigmentosa</td>
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<td><strong>1988 - Lisbon, Portugal</strong></td>
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<td><strong>1986 - Amsterdam, The Netherlands</strong></td>
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<tr>
<td>Franceschetti Lecturer: A.F. Deutman</td>
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<td><strong>1984 - Ghent, Belgium</strong></td>
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<td>Franceschetti Lecturer: Robert Gorlin</td>
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<tr>
<td><strong>1982 - San Francisco, USA</strong></td>
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<tr>
<td>Franceschetti Lecturer: Mette Warburg</td>
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<tr>
<td><strong>1980 - Jerusalem, Israel</strong></td>
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<td>Franceschetti Lecturer: Mette Warburg</td>
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Scientific Committee of the 21st Meeting

- Birgit Lorenz, Giessen, D
- Elias Traboulsi Cleveland, USA
- Francis Munier Lausanne, CH
- Brenda Gallie Toronto, CN
- Knut Stieger, Giessen, D
- Markus Preising, Giessen, D
- Walter Lisch, Hanau, D
- Dietmar Lohmann, Essen, D

This Meeting is kindly support by major grants from

Deutsche Forschungsgemeinschaft
Kennedyallee 40
53175 Bonn
Germany
https://www.dfg.de/en/index.jsp

and

German Ophthalmological Society (DOG)
Platenstrasse 1
80336 Munich
Germany
https://www.dog.org/?cat=4&lang=en

Contributing commercial sponsors are listed separately at the end of this booklet.

Conflict of Interest Disclosure
The content of this meeting is independent of commercial interests.
Any conflict of interest by the scientific organizers or the presenters will be disclosed in the related presentations and with the abstracts.

Continuing Medical Education
Certification for 18 CME credits is granted by the State Medical Association of Hesse (LÄKH) and the European Accreditation Council for Continuing Medical Education (EACCME).
Certificates will be issued daily. Attendance must be confirmed by signature.
Meeting Office
The meeting office is available during the meeting at the venue. Any inquiries after the meeting shall be directed to:

PD Dr. Dipl.-Biol. Markus Preising
Department of Ophthalmology
Justus-Liebig-University Giessen
Friedrichstr. 18, 35392 Giessen, Germany
Tel: +49-641-985-43837
Email: markus.preising@uniklinikum-giessen.de

During the meeting you can reach the meeting office at +49-641-985-58919

Meeting Homepage
https://isgedr.com/2019-giessen/

Social Programm Locations

Gala Dinner 29.08.2019
Hotel & Restaurant Heyligenstaedt
Aulweg 41
35392 Gießen
Phone. +49 641 4609650
info@restaurant-heyligenstaedt.de

Gala Dinner 30.08.2019
Schloss Rauischholzhausen
Ferdinand-von-Stumm-Straße
35085 Ebsdorfergrund-Rauischholzhausen
Phone.: +49 6424-301-100
https://www.uni-giessen.de/about/rhh

Thanks to the helping hands in the back office

ISGEDR Office
Sandy Wong
Cleveland Clinic, Cleveland OH, USA

Abstract submission page, online registration page and fee cashing
Nicole Fennel, Sarah Janesz
Education Institute Cleveland Clinic, Cleveland OH, USA

Meeting homepage and AV recording
Geoff Cross, Harrogate, UK
Dear colleagues, dear friends, dear supporters,

For the second time since its inauguration in 2011, the section DOG-Genetics has joined with an international society to present you a multidisciplinary meeting on genetic eye disorders. I am delighted and curious by the opportunities emerging from the cooperation with the International Society for Genetic Eye Diseases and Retinoblastoma (ISGEDR) in organizing an international meeting. A large number of internationally highly renowned scientists have followed our invitation to give an overview on their most recent cutting edge research. In 34 invited lectures, the state of the art in the identification of genetic causes of inherited retinal degenerations (IRD), the development of biomarkers to characterize the progression of IRDs, and the current developments in retinoblastoma diagnostics and management will be presented. The discussion of treatment options for both types of eye disorders will summit in an expert panel on the first approved and commercially available gene therapy for one form of IRD.

The highlights of the program are three prestigious lectures established by ISGEDR.

The Franceschetti lecture is given by the outgoing director of the US National Eye Institute (NEI) newly appointed director of the Center for Ocular Regenerative Therapy at UC Davis, Prof. Paul Sieving on “Clinical features and molecular basis of X-linked retinoschisis: From mechanism to therapy”. Along with the lecture, Prof. Sieving will be honored with the Franceschetti medal for his extraordinary achievements in research on IRDs and the development of treatment options.

The Ellsworth lecture is dedicated to retinoblastoma research and will be presented this year by Dr. Laurence Desjardins, a director of the institute Curie in Paris and on the topic of “Retinoblastoma around the world in 2019”.

Finally, I am very delighted and extremely honored to have been selected to present this year’s François lecture. I will focus on “Biomarkers in IRDs: scientifically valid – clinically relevant” as an extremely important prerequisite for all treatment approaches.

The scientific program further encompasses 32 free paper presentations and 42 free poster presentations from basic and clinician scientists, bringing together researchers from 21 countries from all over the world to share their knowledge. The mixture of participants ensures a vital communication and spreading of knowledge throughout all countries involved in research for inherited eye disorders.
I am grateful to all contributors whose efforts helped in establishing the programme starting with the scientific committee (Elias Traboulsi, Francis Munier, Brenda Gallie, Knut Stieger, Markus Preising, Walter Lisch, and Dietmar Lohmann) and the local organizational team. In this respect, my very special thanks go to Markus Preising who has really accomplished most of the organizational work to make the meeting happen as it is.

Major contributions from the German Research Foundation (DFG) and the German Ophthalmological Society (DOG) helped us to gather together experts from all over the world and to honor six young scientists with travel grants. This year, we were able to double the number of travel grants (usually 3 issued by ISGEDR) through the support of the DOG.

Finally, without the generous support of our commercial partners we would not have been able to establish the local setting in the pleasant way as it is. Therefore, I recommend visiting the industrial exhibition at the ground floor and express my gratitude to all our sponsors.

I am extremely delighted by the large number of participants who followed our invitation and wish all of you a pleasant stay, exciting discussions, beneficial encounters for your scientific success and stimulating exchanges with old and new friends.

Birgit Lorenz
President of ISGEDR
Speaker of the DOG Section Genetics
Dear Prof. Lorenz,
Dear colleagues,
Dear conference organisers, distinguished guests and conference participants,

I warmly welcome you to the 21st Meeting of the International Society for Genetic Eye Diseases and Retinoblastoma (ISGEDR), a joint meeting in cooperation with the DOG-section of the German Ophthalmological Society, here at Justus-Liebig-University Gießen (JLU).

Founded in 1607, the JLU is one of Germany’s top research universities featuring an extraordinarily broad range of subjects. Our university has developed from a small-scale institution to a large, modern university with several areas of excellence and courses in law, economics, the humanities and the social sciences alongside a constellation of subjects in the natural and life sciences that is unparalleled in Germany. Around 28,000 students are presently enrolled at JLU’s eleven successful faculties. One of these faculties is the Medical Faculty which hosts this meeting under the president of the ISGEDR, Prof. Birgit Lorenz, who I want to thank for the programme’s organisation and for inviting extraordinary researchers.

Since 1975, the ISGEDR summons interested scientists in international symposia with worldwide venues on a biennial turn. I am pleased that, this year, the ISGEDR meeting is home at our university – for the first time ever in Germany. Under the main topic of “Advances in the treatment of inherited retinal diseases and retinoblastoma” the meeting’s programme provides benefits for all participants by addressing basic and application research. All participants are invited to present their data providing a useful input at all levels. Not only experts but also young scientists on several subspecialties of inherited eye disorders and treatment have gathered. Thirty-four internationally acknowledged scientists followed the faculty’s invitation to give an overview of their recent front-end research. I welcome each and every one of you. Among the meeting’s subspecialties are gene therapy research, research in cellular therapy, developments in genetic diagnostics of various eye disorders, the treatment of retinoblastoma and the influence of therapeutic approaches on extraocular tissues – to name only a few of them.

The highlights of the programme are three prestigious lectures established by the ISGEDR. The Franceschetti lecture is given by the outgoing director of the US National Eye Institute (NEI)
Prof. Paul Sieving on “Clinical features and molecular basis of X-linked retinoschisis: From mechanism to therapy”. Along with the lecture Prof. Sieving will be honoured with the Franceschetti medal for his achievements in research on IRDs and the development of treatment options.

The Ellsworth lecture is dedicated to retinoblastoma research and will be presented this year by the Dr. Laurence Desjardins, the director of the French Society of Ophthalmology, on the topic of “Retinoblastoma around the world in 2019”.

Finally, this year’s François lecture will be held by Prof. Lorenz. It will focus on “Biomarkers in IRDs: scientifically valid – clinically relevant” as a preliminary for all treatment approaches.

This scientific programme is completed with 32 free oral presentations and 41 free poster presentations by scientists and researching clinicians joining presenters from 21 countries and all continents of the world. The JLU is proud to host such an international committee. Within the last years, the JLU developed an internationalisation strategy which, amongst others, aims at helping the university to contribute to a global intercultural and scientific exchange. Today is an outstanding example for experts and young scientists on their way to expertise who gather here in Gießen in order to benefit from each other’s research and to make various interesting new observations.

I hope all of you will find this meeting to be profitable and enjoyable. I wish you insightful conversations and new impressions. Thank you for attending the annual meeting at the Justus-Liebig-University Gießen.

Yours sincerely

Prof. Dr. Joybrato Mukherjee
President of Justus-Liebig-University Gießen
Giessen Map

Venue
Medical Education Centre of the Medical Faculty of the Justus-Liebig-University Giessen
Klinikstrasse 29, 35392 Giessen, Germany

Floor Plans
1. Floor, Lecture Hall
Lower Floor, Poster, Coffee Breaks, Industrial Exhibition

From Central Station
By car: drive in by Garfikstrasse
100 m from Motorway

From Central Station
Car Park

UK Großen
Venue Klinikstrasse 29

Restaurant Hoytenstaedt
Aulweit 47, 35392 Giessen
Gala Dinner
20.08.2019
Scientific Content
# Scientific Program

## Thursday

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<td>8.00 h</td>
<td>Onsite registration opens</td>
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<tr>
<td>8.30 h – 09.00 h</td>
<td>Welcome</td>
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<tr>
<td></td>
<td>Prof. Dr. Birgit Lorenz</td>
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<td></td>
<td>President of ISGEDR</td>
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<td>Speaker of the Section Genetics of the German Ophthalmological Society (DOG)</td>
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<td>Head and Chairman of the Department of Ophthalmology, Justus-Liebig-University Giessen and University Medical Center Giessen and Marburg GmbH, Giessen Campus</td>
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<td>Prof. Dr. Joybrato Mukherjee</td>
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<td>President of the Justus-Liebig-University Giessen</td>
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<td>President elect of the Germany Academic Exchange Service (DAAD)</td>
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<td>Prof. Dr. Wolfgang Weidner</td>
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<td></td>
<td>Dean of the Medical Faculty, Justus Liebig-University, Giessen</td>
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<td>Prof. Dr. Andreas Bönning</td>
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<tr>
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<td>Chief Medical Officer, University Medical Center Giessen and Marburg GmbH, Giessen Campus</td>
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### 09.00 h – 10.50 h 1. Session

#### Performing And Communicating Molecular Diagnostics

*Chair: Hanno Bolz, David Mackey*

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<th>Time</th>
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<tr>
<td>09.00 h</td>
<td>Bolz, Hanno Jörn, Frankfurt, Germany</td>
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<td>T01: NGS: Diagnostic opportunities and challenges of gene panel, whole-exome and whole-genome sequencing</td>
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<td>09.20 h</td>
<td>Mackey, David, Subiaco, Australia</td>
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<td>T02: Predictive testing in glaucoma</td>
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<td>09.40 h</td>
<td>Capasso, Jenina, Philadelphia, USA</td>
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<td>T03: We need more genetic counselors!</td>
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<td>10.00 h</td>
<td>Arno, Gavin, London, United Kingdom</td>
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<td>O01: Interrogation of the 100,000 genomes project ophthalmic disease cohort reveals novel genes, new associations and previously undetectable mutations</td>
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<td>10.10 h</td>
<td>Debenedictis, Meghan, Cleveland, USA</td>
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<td></td>
<td>O02: The value of CNV analysis for inherited retinal diseases</td>
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<tr>
<td>10.20 h</td>
<td>Hufnagel, Robert, Bethesda, USA</td>
</tr>
<tr>
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<td>O03: Modeling gene constraint in disease populations for clinical molecular diagnostics</td>
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<tr>
<td>10.30 h</td>
<td>Kellner, Ulrich, Siegburg, Germany</td>
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<td>O04: DNA testing in a series of 944 patients with inherited retinal dystrophies from a single German reference center</td>
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<td>10.40 h</td>
<td>Wells, Kirsty, Helsinki, Finland</td>
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<td>O05: Enhancing diagnostic performance in inherited retinal diseases through advances in high resolution copy number detection and RPGR ORF15 sequencing</td>
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#### Associated Posters

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<td>Lei, Bo, Zhengzhou, Henan, China</td>
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<td>P01: Whole-exome sequencing identifies a novel homozygous missense variant in REEP6 in a retinitis pigmentosa patient complicated with macular hole</td>
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<tr>
<td>10.50 h</td>
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Majander, Anna, Helsinki, Finland

P11: Clinical characteristics of early onset retinal dystrophy in association with the TULP1 c.148delG mutation

Mauring, Laura, Strasbourg, France

P12: Alström syndrome with atypical retinal dystrophy and inheritance

Prasov, Lev, Flint, USA

P13: Clinical and genetic features of Jalili syndrome in a North American patient cohort

Starosta, Daniela Aneta, Giessen, Germany

P14: Phenotype in five related patients with isolated optic nerve atrophy associated with a heterozygous mutation in the spastic paraplegia gene 7.

Lunch Break

Poster Session

3. Session

Bachmann, Björn, Cologne, Germany

14.30 h

T06: Treatment options for limbal stem cell deficiency in inherited eye diseases

Karl, Mike, Dresden, Germany

14.50 h

T07: Towards modeling of neuronal and glial pathologies in retinal organoids

Banin, Eyal, Jerusalem, Israel

15.10 h

T08: Derivation of RPE cells from human embryonic stem cells (hESCs): The journey from basic research to clinical application

Battu, Rajani, Bangalore, India

15.30 h

O12: Differentiation and characterization of RPE from hiPSC and its subretinal transplantation in RCS rats

Galardi, Angela, Rome, Italy

15.40 h

O13: Proteomics profiling of retinoblastoma derived exosomes

Coffee Break

Poster Session

Franceschetti Medal & Lecture

Introduction to the Franceschetti Medal & Lecture

16.35 h

L1: Clinical features and molecular basis of X-linked retinoschisis: From mechanism to therapy.

4. Session

Aleman, Tomas, Philadelphia, USA

17.05 h

T09: AAV2-hCHM subretinal delivery to the macula in choroideremia: performance of outcome measures

Hoffmann, Michael, Magdeburg, Germany

17.25 h

T10: Plasticity and its limits - Cortical visual field representations in achromatopsia

Gocho, Kiyoko, Inzai, Japan

17.45 h

T11: High-resolution retinal imaging analysis in female carriers of choroideremia

Lima de Carvalho Jr, Jose Ronaldo, Recife, Brazil

O14: Multimodal imaging of patients with Best Vitelliform Macular Dystrophy (BVMD): a 4-year follow-up study.
18.15 h Sallum, Juliana, Sao Paulo, Brazil
O15: Characterization of the Brazilian ARSACS phenotype: clinical, ophthalmological, neuroimaging, and genetic features of fourteen cases

18.25 h Studer, Fouzia, Strasbourg, France
O16: Retinal implantation with Argus II artificial retina in 3 patients with Bardet-Biedl syndrome

Tanrikulu, Özgün, Giessen, Germany
Associated Posters
P15: Analysis of outer retinal layer alterations in patients with RPE65 deficiency using Optical Coherence Tomography A-scan-analysis

19.30 h Gala Dinner
Restaurant Heyligenstaedt, Aulweg 41, 35392 Gießen

Friday
30.08.2019

8.00 h Onsite Registration

8.30 h – 10.00 h 5. Session
Luxturna Therapy – Recent Developments
Chair: Stephen Russell, Paul Sieving
T12: Voretigene neparvovec for RPE65-related inherited retinal dystrophies: The Philadelphia Experience
T13a: How long does gene therapy last? 4 Year followup and adult versus pediatric outcomes of phase 3 voretigene neparvovec trial in RPE65-associated LCA/inherited retinal disease
T13b: Electrophysiology following subretinal treatment with voretigene neparvovec (Luxturna)
T14: Our experience with gene therapy approaches for RPE65 inherited retinal diseases
T15: Country specific problems to get started with EMA-approved gene therapy with Luxturna
T16: The post-authorization safety study of voretigene neparvovec-rzyl
Panel Discussion

10.00 h – 10.30 h
Coffee Break
Poster Session

10.30 h – 11.15 h
Ellsworth Lecture
Introduction to Ellsworth Lecture
L2: Retinoblastoma around the world in 2019

11.15 h – 13.25 h 6. Session
Precision Care for Children with Retinoblastoma
Chair: Brenda Gallie, Dietmar Lohmann
T17: Proteomics for biomarker identification in retinoblastoma liquid biopsy
<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker(s)</th>
<th>Title</th>
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<tbody>
<tr>
<td>11.35 h</td>
<td>Cole, Trevor, Birmingham, United Kingdom</td>
<td>T18: The current and future role of cell free DNA analysis in the management of retinoblastoma.</td>
</tr>
<tr>
<td>11.55 h</td>
<td>Gallie, Brenda, Toronto, Canada</td>
<td>T19: Disruptive innovations to reach precision retinoblastoma care</td>
</tr>
<tr>
<td>12.15 h</td>
<td>Soliman, Sameh, Toronto, Canada</td>
<td>T20: Optimizing focal laser photocoagulation therapy for retinoblastoma</td>
</tr>
<tr>
<td>12.35 h</td>
<td>Everett, Lesley, San Francisco, USA</td>
<td>O17: Retinoblastoma treatment in the age of intravitreal and intra-arterial chemotherapy: the UCSF experience</td>
</tr>
<tr>
<td>12.45 h</td>
<td>De Jong, Marcus, Amsterdam, Netherlands</td>
<td>O18: Screening for pineal trilateral retinoblastoma revisited: a meta-analysis</td>
</tr>
<tr>
<td>12.55 h</td>
<td>Menges, Julia, Essen, Germany</td>
<td>O19: A human organoid-based model for retinoblastoma</td>
</tr>
<tr>
<td>13.05 h</td>
<td>Tsygankov, Alexander, Moscow, Russian Federation</td>
<td>O20: New retinoblastoma cell culture establishment and drug resistance assessment</td>
</tr>
<tr>
<td>13.15 h</td>
<td>White, Jaclyn, Clayfield, Australia</td>
<td>O21: Delay in the diagnosis of retinoblastoma: the role of parents and practitioners</td>
</tr>
</tbody>
</table>

**Associated Posters**

P16: Bilateral retinoblastoma with 13q-syndrome in a patient carrying an X;13 balanced translocation without rearrangement of the RB1 gene

**13.25 h – 14.05h**

Lunch Break
Poster Session

**14.05 h – 14.45 h**

**7. Session**

**Clinical Studies in Gene Therapy II**

Chair: Birgit Lorenz, Bart Leroy

T21: Gene therapy for X-linked retinitis pigmentosa caused by mutations in RPGR

T22: Surgical challenges and outcomes with voretigene neparvovec (Luxturna)

**Treatment-associated Posters**

P17: Intravitreal ranibizumab (Lucentis®) in the treatment of non-leaking macular cysts in retinal dystrophy

P18: Laser photocoagulation for hemorrhagic retinopathy in a newborn with Norrie disease

P19: Enhancing glycolytic metabolism with gene therapy and a small molecule drug attenuates neurodegeneration

P20: Individual treatment of an infant with severe conjunctivitis lignosa (CL) and other systemic manifestations of plasminogen deficiency, caused by a compound mutation of the PLG gene

**15.00 h**

Excursion by bus
Marburg

**19.30 h**

Gala Dinner
Schloß Rauischholzhausen, Ebsdorfer Grund

Return to Giessen
### Saturday 31.08.2019

#### 8.00 h

**ISGEDR General assembly**

#### 9.00 h – 10.30 h 8. Session

<table>
<thead>
<tr>
<th>Time</th>
<th>Name</th>
<th>Location</th>
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<tbody>
<tr>
<td>09.00 h</td>
<td>Ketteler, Petra, Essen, Germany</td>
<td>Essen, Germany</td>
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<tr>
<td>09.20 h</td>
<td>Moll, Annette, Amsterdam, Netherlands</td>
<td>Amsterdam, Netherlands</td>
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<tr>
<td>09.40 h</td>
<td>Lohmann, Dietmar, Essen, Germany</td>
<td>Essen, Germany</td>
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<tr>
<td>09.50 h</td>
<td>Abdel-Rahman, Mohamed, Columbus, USA</td>
<td>Columbus, USA</td>
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<tr>
<td>10.00 h</td>
<td>Reddy, M. Ashwin, London, United Kingdom</td>
<td>London, United Kingdom</td>
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<tr>
<td>10.10 h</td>
<td>Shah, Parag, Coimbatore, India</td>
<td>Coimbatore, India</td>
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<tr>
<td>10.20 h</td>
<td>van Hoefen Wijsard, Milo, Amsterdam, Netherlands</td>
<td>Amsterdam, Netherlands</td>
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</tbody>
</table>

**Secondary Cancer and Survival in Retinoblastoma**

*Chair: Petra Ketteler, Ashwin Reddy*

- **T23**: The Impact of the Type Of Predisposing *RB1* Variants on the Incidence of Malignancies
- **T24**: Retinoblastoma and second primary malignancies: a Dutch overview and update
- **O22**: Understanding and predicting tumor risk in heritable retinoblastoma
- **O23**: Study of genetic predisposition to uveal melanoma
- **O24**: Prognostic information for mosaic and high penetrant carriers of *RB1* mutations
- **O25**: Outcomes of *RB1* gene testing from blood samples of 113 retinoblastoma survivors and their families (398 in total) collected on a single day at Aravind Eye Hospital, Coimbatore, India.

**Associated Posters**

- **P21**: Patient-reported outcome measures for retinoblastoma: A scoping review
- **P22**: Should postlaminar optic nerve tumor invasion into the outer layers be considered a risk-factor for leptomeningeal spread of retinoblastoma? A case report and review of the literature
- **P23**: Long-term follow-up after retinoblastoma: secondary malignancy.

#### 10.30 h – 11.00 h

**Coffee Break**

**Poster Session**

#### 11.00 h – 12.30 h 9. Session

<table>
<thead>
<tr>
<th>Time</th>
<th>Name</th>
<th>Location</th>
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<tr>
<td>11.00 h</td>
<td>Dollfus, Helene, Strasbourg, France</td>
<td>Strasbourg, France</td>
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<tr>
<td>11.15 h</td>
<td>Fujinami, Kaoru, Toyko, Japan</td>
<td>Tokyo, Japan</td>
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<tr>
<td>11.30 h</td>
<td>Dimaras, Helen, Toronto, Canada</td>
<td>Toronto, Canada</td>
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<tr>
<td>11.45 h</td>
<td>Gallie, Brenda, Toronto, Canada</td>
<td>Toronto, Canada</td>
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<td>11.55 h</td>
<td>Badura, Franz, Amberg, Germany</td>
<td>Amberg, Germany</td>
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<tr>
<td>12.05 h</td>
<td>Fasser, Christina, Zürich, Switzerland</td>
<td>Zürich, Switzerland</td>
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<td>12.15 h</td>
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**Patients in Focus**

*Chairs: Christina Fasser, Helene Dollfus*

- **T25**: What could be the EYE-EYE role in rare eye diseases care in Europe?
- **T26**: Clinical and genetic characteristics of East Asian patients with inherited retinal disorders
- **T27**: Achieving meaningful patient research partnership: development of the Canadian Retinoblastoma Research Advisory Board
- **T28**: DEPICT HEALTH "full view for life" for circle of care including families will empower research
- **T29**: The PRO RETINA patient registry
- **T30**: Leave no one behind –Patient’s perspective

**Panel Discussion**
### Scientific Program

**21st Meeting of ISGEDR in Association with Section DOG Genetics**

**Associated Posters**

<table>
<thead>
<tr>
<th>Poster</th>
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<tbody>
<tr>
<td>P24</td>
<td>The Swiss Registry of Rare Eye Diseases</td>
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<tr>
<td>P25</td>
<td>The Canadian Retinoblastoma Research Registry</td>
</tr>
<tr>
<td>P26</td>
<td>The top 10 retinoblastoma research priorities in Canada as determined by patients, clinicians and researchers</td>
</tr>
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**12.30 h – 13.15 h**

**Français-Lecture**

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>12.30 h</td>
<td>Bart Leroy</td>
<td>Ghent, Belgium</td>
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<tr>
<td>12.45 h</td>
<td>Lorenz Birgit, Giessen</td>
<td>Germany</td>
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**13.15 h – 14.00 h**

**Lunch Break**

**Poster Session**

**Microphthalmia – Anophthalmia – Coloboma – Developmental Failures**

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<thead>
<tr>
<th>Poster</th>
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<tbody>
<tr>
<td>P27</td>
<td>Novel mutations in MFRP and PRSS56 genes associated to posterior microphthalmos</td>
</tr>
<tr>
<td>P28</td>
<td>Mendeliome in patients with microphthalmia, anophthalmia and coloboma – results and challenges</td>
</tr>
<tr>
<td>P29</td>
<td>Early onset severe retinal dystrophy with irido-chorioretinal coloboma with optic disc dysplasia and macular hypoplasia in one eye due to a heterozygous GDF6-mutation</td>
</tr>
<tr>
<td>P30</td>
<td>Genotype phenotype correlation in a case series of nanophthalmos</td>
</tr>
<tr>
<td>P31</td>
<td>Novel phenotype-genotype correlation with PEX6 gene in Saudi patients with Heimler syndrome</td>
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<tr>
<td>P32</td>
<td>Microcephaly and chorioretinopathy associated with TUBGCP4 mutation</td>
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**14.00 h – 15.00 h**

**10. Session**

**Understanding Treatment Effects from Natural History Studies**

*Chair: Elias Traboulsi, Hendrik Scholl*

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<th>Time</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>14.00 h</td>
<td>Scholl Hendrik</td>
<td>Basel, Switzerland</td>
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<tr>
<td>14.20 h</td>
<td>Hahn Leo</td>
<td>Amsterdam, Netherlands</td>
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<tr>
<td>14.30 h</td>
<td>Nguyen Xuan-Thanh-An</td>
<td>Leiden, Netherlands</td>
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<tr>
<td>14.40 h</td>
<td>Senatore Alfonso</td>
<td>Durham, USA</td>
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<thead>
<tr>
<th>Poster</th>
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<tbody>
<tr>
<td>O27</td>
<td>Natural history of the progression of atrophy secondary to Stargardt disease (ProgStar) study</td>
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<tr>
<td>O28</td>
<td>Long-term follow-up, phenotypic and genetic spectrum of patients with juvenile X-linked retinoschisis in the Netherlands</td>
</tr>
<tr>
<td>O29</td>
<td>The disease course of rhodopsin (RHO)-associated retinitis pigmentosa (RP): a follow-up study</td>
</tr>
<tr>
<td>O30</td>
<td>“Further evaluation of a simple perimetric approach to the differential diagnosis between blue cone monochromacy (BCM) and achromatopsia (ACHM)”</td>
</tr>
</tbody>
</table>
### Scientific Program

**14.50 h**  
Testa, Francesco, Napoli, Italy  
O30: Longitudinal natural history study in patients with Retinitis Pigmentosa in preparation for gene therapy clinical trials

**15.00 h – 15.30 h**

| 15.00 h – 15.30 h | Coffee Break  
Poster Session  
**Glaucoma** |
<table>
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<tbody>
<tr>
<td>Hosono, Katsuhiro, Hamamatsu, Japan</td>
<td>P33: A case of childhood glaucoma with a combined partial monosomy 6p25 and partial trisomy 18p11 due to an unbalanced translocation</td>
</tr>
<tr>
<td>Lang, Elena, Zurich, Switzerland</td>
<td>P34: Genotypic and phenotypic characterization of childhood glaucoma</td>
</tr>
<tr>
<td>Naruse, Sho, Kitakyushu City, Japan</td>
<td>P35: Development of glaucoma after early cataract surgery in case of oculo-facio-cardio-dental syndrome</td>
</tr>
<tr>
<td>Pisuchpen, Phattrawan, Philadelphia, USA</td>
<td>P36: The Robison D. Harley, MD Childhood Glaucoma Research Network (CGRN) International Pediatric Glaucoma Registry</td>
</tr>
</tbody>
</table>

**Foveal Hypoplasia**

| 15.30 h – 16.50 h | 11. Session  
Gene and Cell based Therapies  
*Chair: Knut Stieger, Volker Busskamp* |
|---|---|
| 15.30 h | Ader, Marius, Dresden, Germany  
T32: Photoreceptor transplantation into the mammalian retina |
| 15.50 h | Stieger, Knut, Giessen, Germany  
T33: DNA repair mechanisms in photoreceptors |
| 16.00 h | Busskamp, Volker, Dresden, Germany  
T34: Forward programming of human stem cells to photoreceptors |
| 16.10 h | Müller, Brigitte, Giessen, Germany  
O31: DNA repair after ISce-I mediated DSB in photoreceptors and RPE cells following AAV mediated gene transfer in vivo |
| 16.30 h | Wimmer, Tobias, Giessen, Germany  
O32: A bioluminescence resonance energy transfer based sensor for the precise determination of non-homologous end joining DNA repair events |

**Associated Posters**

| 16.50 h | Weller, Maria, Giessen, Germany  
P42: First steps to a MMEJ genome editing approach correcting CLN3/Cln3deltaEx7/8 |

**16.50 h**  
Farewell  
**17.00 h**  
End of conference
2019 Travel Grant Recipients

ISGEDR Travel Grants

Takitani, Guilherme, MD
UNIFESP – EPM; São Paulo – Sp, Brazil
Poster presentation, Saturday, Glaucoma
P32: Microcephaly and Chorioretinopathy Associated with TUBGCP4 Mutation

Lesley Everett, MD
University of California, San Francisco, USA
Poster Presentation, Thursday, Phenotypes - Free Papers
P08: Ocular findings in two patients with vascular smooth muscle myopathy secondary to ACTA2 mutations
Paper presentation, Friday, 11.15 h – 13.25 h, Precision Care for Children with Retinoblastoma
O17: Retinoblastoma treatment in the age of intra-vitreal and intra-arterial chemotherapy: the UCSF experience

Jose Ronaldo Lima de Carvalho MD
Federal University Of Pernambuco, Recife, Brazil
Paper presentation, Thursday, 17.05 h – 18.35 h, Biomarkers for Substantiating Success in Treatment
O14: Multimodal imaging of patients with Best Vitelliform Macular Dystrophy (BVMD): a 4-year follow-up study

DOG-Genetics Travel Grants

Pia Chaudhuri MD,PhD
Lady Hardinge Medical College & Associated Hospitals, University Of Delhi, PGIMER, Dr RML Hospital, New Delhi, India
Paper presentation, Thursday,11.20 h - 12.00 h,Phenotypes - Free Papers
O11: Pedigree analysis of familial primary concomitant horizontal strabismus in a south Asian population
Poster presentation, Saturday, Foveal Hypoplasia
P37: Novel variant in SLC38A8 gene segregating with foveal hypoplasia in an autosomal recessive South Asian family

Pisuchpen, Phattrawan MD
Pediatric Ophthalmology And Ocular Genetics, Wills Eye Hospital, Philadelphia, USA
Poster presentation, Saturday, Glaucoma
P36: The Robison D Harley, MD Childhood Glaucoma Research Network (CGRN) International Pediatric Glaucoma Registry

Alfonso Senatore, MD
Duke Eye Center, Durham, NC, USA
Paper presentation, Saturday, 14.00 h – 15.00 h, Understanding treatment effects from natural history studies
O29: Further evaluation of a simple perimetric approach to the differential diagnosis between blue cone monochromacy (BCM) and achromatopsia (ACHM)
Session 1

Performing And Communicating Molecular Diagnostics
T01: NGS: Diagnostic opportunities and challenges of gene panel, whole-exome and whole-genome sequencing

Hanno Jörn Bolz
Senckenberg Centre for Human Genetics, Frankfurt, Germany

Purpose: Next-generation sequencing (NGS) has transformed research and diagnostics of hereditary disorders. This presentation will show that this is particularly true for eye diseases because many of them have a monogenic basis.

Methods: The opportunities and challenges of current diagnostic applications of NGS – gene panel, whole-exome (WES) and, occasionally, whole-genome sequencing (WGS) – are discussed based on examples from the literature and own experience, mostly from the genetically most heterogenic group, the retinal dystrophies.

Results: The diagnostic application of NGS results in a high diagnostic yield. While the causative mutation is easy to pinpoint in many patients, some cases are challenging regarding potential pitfalls and misleading “hits”. The discovery of new genotype-phenotype correlations and, depending on the NGS approach, of new disease genes is demonstrated. Some genes are candidates for therapeutic approaches that may not be restricted to classical gene therapy.

Conclusions/Significance: While generating a patient’s genetic data is no longer the analytical bottleneck, data interpretation requires profound knowledge of the genetic and phenotypic characteristics and close cooperation between geneticists and ophthalmologists in order to draw the correct conclusion from the challenging complexity of genetic data. The diagnostic application of even genome-wide NGS approaches such as whole-exome and whole-genome sequencing has now blurred the borders between diagnostics and research. This offers new opportunities, including the discovery of new disease genes. The information on the causative gene enables personalized medical follow-up that may, in case of syndromic entities, require the involvement of other clinicians than ophthalmologists. As the first gene therapies are being applied, the genetic analysis has gained a potential therapeutic dimension.

Conflict of interest disclosure: none
T02: Predictive testing in glaucoma

David Mackey
University Of Western Australia, Subiaco, Australia

**Purpose:** To present the current state of predictive DNA testing for glaucoma.

**Methods:** Data from the UK biobank UKBB and International Glaucoma Genetics Consortium IGGC suggest that multiple genetic risk alleles contribute to glaucoma. Over the last two decades we have been able to provide predictive DNA testing for a small number of families with Mendelian forms of glaucoma such as *MYOC*, *OPTN* and *MCCRP3*.

**Results:** SNPs near over 100 genes have now been associated with genetic risk for Primary Open Angle Glaucoma.

**Conclusions:** Although we could provide genetic risk scores in a similar way to glaucoma clinical risk scores, we need to test the predictive power of genetic risk scores in other populations, involving both people with a family history of glaucoma and the general population.

**Conflict of interest disclosure:** none
T03: We need more genetic counselors!
Jenina Capasso
Wills Eye Hospital, Philadelphia, PA, USA

As genetics integrates into nearly every subspecialty of medicine, it becomes increasingly important to have genetic counselors in clinical practice. Abacan et al., reported on the global state of the profession in 2018, with only a few countries meeting the work force recommendation of 6-12 counselors/million population. The number of genetic counselors in North America is estimated around 5,000 and those who work in ocular genetics or with some overlap is approximately 50. At Wills Eye Hospital, we have trained several fellows who return to practice in countries with little to no access to genetic counselors. This talk aims to describe the current under availability of genetic counselors in ocular genetics subspecialty and propose a model for training more counselors globally.


Conflict of interest disclosure: none
O01: Interrogation of the 100,000 genomes project ophthalmic disease cohort reveals novel genes, new associations and previously undetectable mutations

Gavin Arno¹
Ba-Abbad, Rola¹; Jurkute, Neringa¹; Mahroo, Omar¹,²; Moosajee, Mariya¹; Yu Wai Man, Patrick¹,³; Michaelides, Michel¹; Webster, Andrew R.¹
1. UCL Institute Of Ophthalmology And Moorfields Eye Hospital, London, UK
2. Department Of Ophthalmology, St. Thomas' Hosp, London, UK
3. Mitochondrial Biology Unit, MRC And Cambridge Centre For Brain Repair, London, UK

Purpose: To characterise pathogenic variants in whole genome sequencing (WGS) data from a cohort of patients with a broad spectrum of ophthalmic disorders.

Methods: Patients and families were recruited from the inherited eye disease clinics at Moorfields Eye Hospital, London as part of the UK 100,000 genomes study. A cohort of 420 probands with ophthalmic disease underwent clinical variant interpretation according to the American College of Medical Genetics guidelines and discussion at a multidisciplinary meeting following WGS and automated variant prioritisation in a curated virtual gene panel (https://panelapp.genomicsengland.co.uk). Unsolved cases were selected for research including non-coding/structural variant analysis in the gene panel, new gene/disease associations and novel gene investigation. Potential pathogenic structural and non-coding variants were selected for functional analysis by applying an integrated analysis pipeline incorporating deep phenotyping and variant filtering and interpretation tools in patients unsolved following coding variant analysis. Variant effects were confirmed where possible using molecular biology techniques.

Results: To date, our analysis pipeline has identified likely pathogenic genotypes in 253/420 (60%) probands. These include more than 30 patients harbouring variants in unexpected or novel genes or non-coding/structural variants across the virtual gene panel, including: 1. splice region and deep intronic single nucleotide variants that give rise to altered splicing. 2. upstream gene regulatory region variants that alter the level of gene transcription through changes in transcription factor binding sites. 3. deletion/duplication affecting at least one coding exon across the gene panel.

Conclusions: Implementation of WGS in a clinical genomic pipeline enables detection and interpretation of potential pathogenic variants across the entire genomic footprint of a diagnostic gene panel. Unsolved cases underwent expanded variant discovery analysis yielding a significant number of additional findings. We report newly identified variants otherwise missed by exon-focused diagnostic strategies that account for a significant proportion of missing heritability in IRD. In silico and functional investigation confirms the pathogenicity of these variants and should be integrated in future clinical diagnostic pipelines incorporating WGS screening.

Conflict of interest disclosure: none
O02: The value of CNV analysis for inherited retinal diseases
Meghan DeBenedictis
Traboulsi, Elias
Cole Eye, Cleveland Clinic, Cleveland, OH, USA

Multiple genetic testing labs offer large retinal dystrophy NGS panels and some include CNV analysis. Utilizing a panel approach that includes CNV analysis has shown to be valuable in identifying etiology of disease. The following cases highlight the importance of genetic testing, including CNV analysis, for patients with retinal dystrophies. The first case is an 8 year male with an onset of vision loss at age 4. He had no systemic health problems. The family history was negative for vision loss or genetic disease. He was diagnosed with Leber congenital amaurosis by an ophthalmologist. A 31 gene LCA NGS panel was negative. Subsequent testing via a 280 gene retinal dystrophy panel with CNV analysis identified him to have a heterozygous c.1056+3A>C pathogenic variant in the \textit{CLN3} gene. Additionally, CNV analysis identified him to have a 0.3 kb deletion in \textit{CLN3}. This test result is consistent with a diagnosis of Juvenile neuronal ceroid lipofuscinosis. He was referred to a Batten disease center of excellence for management. The second case is a 41 yr female who became symptomatic at age 31 with nyctalopia and decreased peripheral vision. Ophthalmic exam was consistent with RP. Medical history was unremarkable. She had undergone genetic testing for a panel of 13 recessive RP genes in 2012 which was negative. NGS of a larger 262 gene retinal dystrophy panel was performed in January, 2016, which identified a homozygous c.783G>A pathogenic variant in the \textit{CDHR1} gene, consistent with recessive RP. Two years later, results from prior participation in a research study (308 gene panel with CNV analysis) became available which identified her to be hemizygous for the \textit{CDHR1} variant. She also was found to have a 7.38 MB deletion on chromosome 10, which included the entire \textit{CDHR1} gene, in addition to the \textit{PTEN} gene, among 10 others. She had a maternal history of uterine cancer and thyroid problems. She and her mother were referred to \textit{PTEN} clinic for management. These are two of many cases where genetic testing profoundly impacts patient care and illustrate the medical necessity of pursuing a comprehensive test.

Conflict of interest disclosure: none
O03: Modeling gene constraint in disease populations for clinical molecular diagnostics

Robert Hufnagel
Bryan, John; Woo, Geena; Guan, Bin; Mcgaughey, David
National Eye Institute, Bethesda, MD, USA

Purpose: Clinical molecular genetic testing interpretation depends primarily on individual variant-level information and healthy population frequency data. Often, novel variants lacking additional information needed to assign likely pathogenic or benign status are designated as variants of uncertain significance. To address this need, we generated and applied gene-level and disease-population allele frequency data to current genetic testing interpretation criteria.

Methods: Whole exome and genome datasets from gnomAD and publicly available genetic variant datasets of patients with retinal degenerations (RD) were downloaded and processed to generate individual variant and gene-level allele frequencies for subsequent visualization and analysis. Statistical enrichment was determined by Fischer’s exact test of independence with Bonferroni correction.

Results: Gene models comparing RD-population to general-population (gnomAD) allele frequency data permitted statistical analysis of variants enriched in RD. Individual gene models for autosomal dominant (PRPH2), autosomal recessive (ABCA4), and X-linked recessive (RS1) retinopathies exhibited strong correlation with manually curated variant interpretation. Genome-wide models further demonstrated independent enrichment of known disease genes in a large RD cohort. Next, gene constraint analysis of the general-population dataset was used to calculate total rare variation frequencies for missense, truncating, and synonymous variation for every gene below population frequencies typically used for clinical variant interpretation. Notably, genes frequently detected with novel variants in next-generation sequencing data for RD were among those with the highest rare gene-level variation frequencies.

Conclusions/Significance: Gene-level variant information and RD-population frequency data add confidence to genetic testing interpretation of known and novel variation by providing information beyond general population allele frequencies. By comparing gene constraint models with expected single-gene contributions to disease prevalence, we can better estimate the likelihood of pathogenicity for novel variants detected in patients with RD.

Conflict of interest disclosure: none
O04: DNA testing in a series of 944 patients with inherited retinal dystrophies from a single German reference center

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Purpose: To report the findings of DNA testing in a series of 944 patients with inherited retinal dystrophies (IRD) from a single German reference center.

Methods: Following ophthalmological diagnosis of inherited diseases based on clinical findings, retinal imaging and/or electrophysiological examinations, patients underwent molecular genetic evaluation based on the clinical diagnosis with direct Sanger sequencing or custom designed gene panel analysis. The number of genes tested per patient ranged from one to 124.

Results: In 944 patients (813 unrelated families) disease-causing mutations (1 mutation in adIRD or xIRD and 2 mutations in arIRD) were identified in 422 subjects (44.7 %; 357 families (43.9 %). Disease causing mutations were identified in 58 different genes, most frequently in ABCA4 (24.9 % of families), BEST1 (11.8 %), PRPH2 (9.2 %), RS1 (9.0 %), RPGR (7.0 %), USH2A (5.6 %), RHO (4.8 %), CHM (2.8 %), EYS (1.7 %), and PRPF31 (1.4 %). Together, mutations in these 10 genes were associated with 76.8 % of all solved cases. In addition, 44 patients with macular dystrophy or cone-rod dystrophy (4.7 %) were found to be monoallelic carriers of a disease-causing ABCA4 mutation and a further 31 patients were monoallelic carriers of one disease-causing mutation in other recessive genes.

Conclusion: Comprehensive DNA testing reveals a high number of cases solved due to gene mutations in known retinal disease genes. Delineation of the impact of these mutations on the clinical course of the disease can only be achieved in a large cohort with clinical longtime follow-up as the one presented in this work.

Conflict of interest disclosure: none
**O05: Enhancing diagnostic performance in inherited retinal diseases through advances in high resolution copy number detection and RPGR ORF15 sequencing**

**Kirsty Wells**

Kämpjärvi, Kati; Guidugli, Lucia; Sistonen, Johanna; Känsäkoski, Johanna; Sarantaus, Laura; Västinsalo, Hanna; Mehine, Miika; Valori, Miko; Sankila, Eeva-Marja; Schleit, Jennifer; Saarinen, Inka; Muona, Mikko; Myllykangas, Samuel; Koskenvuo, Juha; Tuupanen, Sari; Alastalo, Tero-Pekka

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2. Helsinki University Eye Hospital, Helsinki, Finland

**Purpose:** Inherited retinal dystrophies (IRDs) are clinically and genetically diverse disorders. Therefore, a comprehensive genetic testing strategy is essential to maximise diagnostic yield and select targeted therapies. However, due to technical limitations, genetic tests for IRD commonly do not capture the full spectrum of causative genetic variation. We aimed to develop a comprehensive next generation sequencing-based (NGS) RD panel, able to detect not only coding sequence alterations, but also copy number variants (CNVs), known pathogenic deep intronic variants, and variants in the difficult to sequence RPGR ORF15 hotspot. We then aimed to assess diagnostic yield and mutational spectrum in large RD cohorts, with emphasis on the prevalence and characteristics of CNVs and diagnostic RPGR ORF15 variants.

**Methods:** Diagnostic yield and mutational spectrum of sequence variants were evaluated in a cohort of 1587 RD patients, and tested using an NGS panel covering 266 IRD-associated genes. The rates and characteristics of CNVs were evaluated in a cohort of 2754 patients. Sequencing was performed by targeted OS-Seq using the Illumina NextSeq500 platform, or the IDT xGEN Exome Research Panel using the Illumina NovaSeq platform. CNVs were detected by CNVkit and an in-house developed deletion caller.

**Results:** The 266-gene RD panel yielded a diagnosis in 58% of cases. Diagnoses were made in 111 genes in total, the most frequently implicated genes being ABCA4, USH2A and RPGR. A molecular diagnosis in RPGR was identified in 5.7% of patients; 31% of RPGR diagnoses involved variants in the difficult-to-sequence central region of ORF15. In 4.6% of patients, a CNV matching the phenotype was reported; the majority (88%) being deletions. Of these, 49% were partial gene deletions, 25% one exon deletions, 12.5% whole gene deletions and 1.6% partial exon deletions. CNVs were identified in 47 genes, and USH2A and PRPF31 were enriched in CNVs compared to other genes.

**Conclusions/Significance:** Genetic testing of a large cohort of patients with IRD has revealed an important diagnostic contribution by CNVs and RPGR ORF15 variants. The broad mutation spectrum in our cohort demonstrates the importance of a comprehensive genetic testing approach in RD diagnostics, to optimize diagnostic yield and clinical care.

**Conflict of interest disclosure:** The following conflict(s) of interest must be disclosed:

Kämpjärvi, Kati; Guidugli, Lucia; Sistonen, Johanna; Känsäkoski, Johanna; Sarantaus, Laura; Västinsalo, Hanna; Mehine, Miika; Valori, Miko; Schleit, Jennifer; Saarinen, Inka; Muona, Mikko; Myllykangas, Samuel; Koskenvuo, Juha; Tuupanen, Sari; Alastalo, Te are employees of Blueprint Genetics, Helsinki, Finland
Session 1:

Associated Posters
**P01: Whole-exome sequencing identifies a novel homozygous missense variant in *REEP6* in a retinitis pigmentosa patient complicated with macular hole**

Bo Lei  
Li, Ya; Zhang, Lujia; Xie, Kunpeng  
Henan Eye Institute, Zhengzhou, Henan, China

**Purpose:** The receptor expression enhancing protein 6 encoded by *REEP6* gene is involved in the transport of receptors from the endoplasmic reticulum (ER) to the cell surface. *REEP6* plays an essential role in maintaining cGMP homeostasis though facilitating the stability and trafficking of guanylate cyclase and maintaining ER and mitochondrial homeostasis. This study was to identify the underlying gene defect leading to retinitis pigmentosa in a Chinese patient.

**Methods:** The 55-year-old Asian male proband complained night blindness and decrease of vision for 20 years. Ophthalmic examinations including fundus photography, SD-OCT, AF, IR and full-field ERG were conducted. Blood samples from the proband, his non-consanguineous parents, son and wife were collected. Whole-exome sequencing (WES) followed by Sanger validation was performed.

**Results:** The vision of the proband was light perception in the right eye and 0.02 in the left eye. Fundus showed bone-spicule deposits and the ERG responses were non-recordable. Outer nuclear layer and ellipsoid zone loss outside the fovea was observed. Bilateral macular hole was evident. WES data analyses identified 2 presumably homozygous variants in *REEP6* (MIM: 609346) and *NPHP4* (MIM: 607215) respectively. Since the patient did not present kidney and mental disorders, the causative variant was most likely attributed to the novel missense mutation in exome 3 of *REEP6* (c.268G>C, p.V90L, Chr1: 5934602). With a frequency of 0.01158 (ExAC), this variation has not been reported previously. Bioinformatics analysis with Mutation Taster, SIFT and PolyPhen2 indicated the mutation was harmful. The parents and the son of the proband, who did not present any signs, were heterozygous of the variant, while the wife did not have such a variant.

**Conclusions:** A novel homozygous missense variant c.268G>C, p.V90L in *REEP6* in a retinitis pigmentosa 77 patient originating from a non-consanguineous Chinese couple may be disease-causing. Whether the bilateral macular hole was related with the variant remains unclear.

**Conflict of interest disclosure:** none
P02: Shaping ‘PreventionGenetics’ comprehensive inherited retinal disorder panel for the clinical setting and to improve diagnostic yield

Madhulatha Pantrangi¹
Reeves, Melissa²; Goetz, Kerry²; Schroeder, Jocelyn¹; Rath, Julie¹; Londre, Gina¹; Weber, James¹
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2. Eyegene, National Institute Of Health, National Eye Institute, Bethesda, MD, USA

Purpose: Our comprehensive inherited retinal disorders panel includes sequencing of over 300 genes, analysis of the mutational hotspot ORF15 in RPGR, and copy number variant (CNV) detection using NGS data to improve diagnostic yield.

Methods: NGS analysis was performed for targeted genes including RPGR, with specialized Sanger sequencing for the ORF15 region that cannot be analyzed by short-read NGS and regular Sanger chemistry. CNVs are detected from NGS data.

Results: To date, we have tested 531 individuals with IRDs. In 47% of cases, a positive diagnosis was made; 9% of those cases were due to CNVs, and 4% of the cases were due to variants in RPGR ORF15.

Conclusions: Comprehensive targeted gene panels with CNV detection are the best prospect to yield a genetic diagnosis for IRDs with overlapping clinical presentations, which is important to guide treatment in the era of developing novel therapies.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
Patrangi, Madhu; Schroeder, Jocelyn; Rath, Julie; Londre, Gina; Weber, James are employees of PreventioGenetics, USA.
P03: Genetic testing for macular dystrophies: The Singapore National Eye Centre experience

Choi Mun Chan
Singapore National Eye Centre, Singapore, Singapore

**Purpose:** Gene testing is not commonly done at the Singapore National Eye Centre for financial reasons, as patients have to bear the cost of testing. However, many patients and their families have expressed an interest in obtaining a confirmatory molecular diagnosis so as to be able to prognosticate, do family planning, and possibly participate in therapeutic trials in the future. We obtained some research funding to perform gene testing on a small group of patients with Stargardt's or molecular dystrophy to determine the robustness of gene testing in dystrophy patients in our setting.

**Setting/Venue:** 18 consecutive patients who presented to the retinal and macular dystrophy clinic at the Singapore National Eye Centre with clinical signs consistent with Stargardt's disease or macular dystrophy were recruited.

**Methods:** These 18 patients had a detailed history taken, family pedigree drawn up, physical examination and investigations including visual acuity, colour vision, colour fundus photographs, autofluorescence imaging, ocular coherence tomography scans of their macula, wide field imaging and electrophysiology. Whole exome sequencing was performed, and the results were analysed using guidelines from the American College of genomic medicine, with the help of a multidisciplinary team consisting of ophthalmologists, geneticists, genetic counsellors and bioinformatics analysts.

**Results:** Fourteen out of the 18 samples returned variants. Four had no causal variants found. Of the 14 variants, eight were variants in the *ABCA4* gene. The remaining variants found included *RP1L1*, *RP1*, *CYP4V2*, *PRPH2* and *COL9A3*.

**Conclusions:** We obtained a positive return rate of more than 75 percent. Where no causal variants were found, it is possible those areas were not well covered by next-generation sequencing. The next step would be to do Sanger backfill sequencing for known deep intronic regions and promoter regions to find a possible variant. Going forward, we plan to commence gene testing for the rest of our retinal dystrophy patients.

**Conflict of interest disclosure:** none
Session 2

Clinical Studies in Gene Therapy I
T04: Safety & efficacy of antisense oligonucleotide therapy (QR-110) in LCA10 patients with the c2991+1655A>G allele in CEP290

Bart P Leroy1

Cideciyan, Artur V2; Jacobson, Samuel G3; Ho, Alan C.3; Garafalo, Alexandra2; Roman, Alejandro J2; Schwartz, Mike4; Biasutto, Patricia4; De Wit, Wilma4; Cheetham, Michael E5; Adamson, Peter S4; Rodman, David4; De Zaeytijd, Julie1; Van Cauwenbergh, Caroline1; Drack, Arlene V.6; Russell, Stephen R.6

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5. Institute Of Ophthalmology, Univ College Of London, London, United Kingdom
6. Dept Of Ophthalmology, Iowa University Hospitals, Iowa City, IA, USA

Purpose: to assess safety and efficacy of the antisense oligonucleotide QR-110 in LCA10 patients with the c.2991+1655A>G allele in the CEP290 gene.

Methods: in a 3-center open-label clinical trial (NCT03140969) subjects received intravitreal injections of QR-110 in the worse seeing eye. Systemic and ocular safety were evaluated using standard methods. Efficacy was evaluated with best-corrected visual acuity (BCVA), oculomotor control and instability (OCI), two-colour full-field sensitivity testing (FST) as well as mobility testing.

Results: 10 patients received between 1 and 4 injections and were followed for up to 9 months. At 3 months after the first injection, treated eyes showed significant improvement compared to baseline by an average of 0.67 log (7 lines), 0.62 log in red FST and 0.81 log in blue FST. At 3 months after the second injection, BCVA and FST results remained improved. Adverse events included cataracts and macular oedema.

Conclusions: preliminary results suggest that QR-110 has an acceptable safety profile, and potential for improvement of BCVA and light sensitivity.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
The authors received research support grants and travel grants from ProQR Therapeutics
T05: Leber Hereditary Optic Neuropathy: Gene therapy for an ultra-orphan blinding disease
José-Alain Sahel

Purpose: Leber Hereditary Optic Neuropathy (LHON) is the quintessential orphan disease, with 1 per 30,000 - 50,000 new patients afflicted each year. It is a maternally inherited genetic disease causing mitochondrial dysfunction and leading to sequential bilateral vision loss in otherwise healthy young adults. As it is due to a single point mutation within mitochondrial DNA, LHON is the ideal candidate for interventional gene therapy. rAAV2/2-ND4 is a gene therapy that enables allotopic expression of \( \text{ND4} \)- the mitochondrial gene mutated in \( \text{ND4}-\text{LHON} \) - in retinal ganglion cells. The clinical efficacy of rAAV2/2 ND4 is currently being assessed in Phase III clinical trials.

Methods: REVERSE (NCT02652780) is a Phase III, randomized, multicenter, double masked, sham controlled trial in which 37 LHON subjects with the G11778A \( \text{ND4} \) mutation received a single unilateral intravitreal injection of rAAV2/2-ND4. Visual functions and associated psychophysical metrics of vision were monitored along with measurements of relevant retinal anatomy for 96 weeks following treatment administration.

Results: At Week 96, an improvement of +15 ETDRS letters equivalent was seen in treated eyes. Untreated eyes showed a similar improvement in visual acuity (+13 ETDRS letters equivalent), counter to expected natural history of the disease. Contrast sensitivity (Pelli-Robson) showed a bilateral improvement from baseline to Week 96, more robust in treated eyes comparing to untreated eyes. In parallel, anatomic retinal structures observed at Optical Coherence Tomography (OCT) and including ganglion cell layer (GCL) volume and retinal nerve fiber layer (RNFL) thickness, were relatively preserved in treated vs. sham eyes. The gene therapy showed a favorable safety profile throughout all clinical development phases.

Conclusions: Therapy with rAAV2/2-ND4 showed a meaningful improvement in visual function, and afforded relative preservation of RGC and RNFL, suggesting the biological targets of this gene therapy were successfully engaged. Gene therapies in orphan diseases can be developed with success, and afford a unique window into exploring new avenues within drug development.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
José-Alain Sahel received grants or research support from LabEx LIFESENSES (ANR-10-LABX-65), Foundation Fighting Blindness
José-Alain Sahel received honorary or consultation fees from Pixium Vision, GenSight Biologics, SparinVision
José-Alain Sahel is stock shareholder of Pixium Vision, GenSight Biologics, Phrophese, Chronolife
Free Papers

Phenotypes
O06: Homozygous frameshift mutations in FAT1 cause a syndrome characterized by colobomatous-microphthalmia, ptosis, nephropathy and syndactyly

Brian Brooks

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Purpose: To evaluate the role of the atypical cadherin, FAT1, in optic fissure closure and ocular malformation.

Methods: Exome sequencing of patients affected with coloboma, deep clinical phenotyping. Modeling in animal models (mouse, fish) and RPE cell culture.

Results: Five consanguineous families with four different homozygous presumed loss-of-function mutations in FAT1 were identified. Clinical findings include coloboma±microphthalmia; variable congenital blepharoptosis; skeletal abnormalities, including hypotrophy of digits and osseous syndactyly; and nephropathy. FAT1 is expressed in the developing optic cup and periocular mesenchyme of mouse. Knockout of Fat1/fat1a results in colobomatous microphthalmia in mouse and zebrafish embryos. FAT1 localized to the earliest cell-cell junctions in RPE, the initial cells to fuse during optic fissure closure, consistent with it having a role in the first stages of this developmental process.

Conclusions/Significance: Our findings establish FAT1 as a gene that, when mutated, results pleiotropic effects in human and in animal models. Our data suggest a role of FAT1 in forming the first contacts of presumptive RPE during optic fissure closure.

Conflict of interest disclosure: none
**O07: Molecular and cellular mechanisms in NR2E3-linked retinal degenerations**

Pascal Escher

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**Purpose:** Description and analysis of mouse models of Nr2e3-linked retinal degenerations, and functional analysis of potential underlying molecular mechanisms

**Methods:** We characterized retinal degeneration in newly generated ‘knock-in’ mice with targeted modifications in the DNA-binding domain (DBD) and the ligand-binding domain (LBD) of Nr2e3; in vivo, by fundus photography, optical coherence tomography (OCT) and spectral electrotoretinography (ERG); post mortem by histology and immunohistochemistry. Additional in vitro analyses included RNA expression profiling (RNAseq), quantitative PCR, Western blotting and bioluminescence resonance energy transfer (BRET) assays.

**Results:** Knock-in mice homozygous for a targeted missense mutation in the LBD show a phenotype similar to the Nr2e3<sup>rd7/rd7</sup> mice, an established mouse model of the recessively inherited retinal degeneration enhanced S-cone sensitivity syndrome (ESCS). Retinal spots and rosette-like structures first appear at postnatal day (P) 12 in the outer nuclear layer of the dorsal retina and reach maximal expansion at P21. At that age, the dorso-ventral M-cone gradient and the opposing ventro-dorsal S-cone gradient are present. Microglial cells and monocytes/macrophages are detected within ‘rosettes’. The highest density in rosettes is observed within a region located between 100 and 350 µM with respect to the optic nerve head where they persist the longest. Rosettes disappear by 9 to 12 months, and slow photoreceptor degeneration, at a rate of an approximately 3 % loss of outer nuclear layer thickness per month, is observed. The impact of mutations in the LBD on cofactor assembly was analyzed by BRET assays. Knock-in mice homozygous for a targeted missense mutation in the DBD exhibit a more severe phenotype. Remarkably, mice heterozygous for the DBD variant do not exhibit rosettes, but a thinning of the outer nuclear layer similar to the homozygous mice is observed. Finally, RNAseq analysis reveals distinct transcriptional regulation in the different mouse models.

**Conclusion:** The newly generated knock-in mouse models allow to delineate the contribution of the Nr2e3 DBD and the LBD to retinal degeneration.

**Conflict of interest disclosure:** The following conflict(s) of interest must be disclosed:

Pascal Escher received honorary or consultation fees from Novartis Pharma, Switzerland
**O08: ATOH7 loss-of-function mutations in a family with hypoplasia of the optic nerve**

David Grubich Atac¹

Koller, Samuel¹; Hanson, James²; Feil, Silke¹; Tiwari, Amit¹; Bahr, Angela¹; Baehr, Luzy¹; Magyar, Istvan¹; Kottke, Raimund³; Gerth-Kahlert, Christina²; Berger, Wolfgang¹

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2. Department Of Ophthalmology, University Hospital Zurich, Zurich, Switzerland
3. Department Of Diagnostic Imaging, University Children's Hospital Zurich, Zurich, Switzerland

**Purpose:** Bilateral optic nerve hypoplasia (ONH) is a congenital optic nerve abnormality due to underdevelopment of retinal ganglion cells (RGCs), often resulting in legal blindness. Mutations in several genes have been associated to this disease, however more than half of all cases remain without a clear molecular explanation. The early retinal transcription factor atonal basic helix-loop-helix (bHLH) transcription factor 7 (ATOH7) is expressed in retinal progenitors and has a key role in RGC differentiation. Consequently, ATOH7 is a potential candidate gene for ONH. Here we present two siblings with bilateral ONH and macular hypoplasia where exome sequencing identified compound heterozygous missense variants in ATOH7, one very rare and one novel, affecting a conserved residue within the HLH domain. The variants were predicted deleterious by several algorithms. In addition, we have functionally characterized the identified variants at the protein level.

**Methods:** Whole exome sequencing (TruSeq exome) of the index patient was performed with an Illumina NextSeq 550 platform and segregation analysis of putative pathogenic variants in additional family members by Sanger sequencing. Expression constructs with ATOH7 patient-derived variants were cloned into a plasmid vector for functional characterization by transgene expression in HEK293T cells. To stimulate heterodimerization, a putative dimerization partner (E47) was cloned and co-expressed. ATOH7 patient variants were characterized by Western blot and cycloheximide chase assays, ELISA based protein and DNA interaction assays as well as luciferase reporter assays.

**Results:** Protein amount as well as stability of ATOH7 variants were significantly reduced in the presence of a putative dimerization partner E47. Functional assessment showed significant reduction in heterodimerization as well as DNA-binding of the two ATOH7 variants. Finally, transcriptional activation of luciferase reporter expression was abolished.

**Conclusions:** Increased dimerization-dependent protein degradation as well as structural changes in dimerization and chromatin binding ultimately cause loss of function of the transcription factor ATOH7 with the two patient-derived variants. These findings strongly support pathogenicity of the two ATOH7 sequence variations. Additionally, this report highlights the impact of altered ATOH7 dimerization on protein amount and function. Genetic analysis of this gene should be performed in patients with ONH.

**Conflict of interest disclosure:** none
O09: Prevention of intravitreal melphalan-induced chorioretinopathy: identification of potential risk factors

Francis Munier
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**Purpose:** Retinal toxicity of melphalan is a potentially sight-threatening complication of intravitreal chemotherapy. Identification of risk factors for the complication remains as yet inconclusive.

**Methods:** Retrospective review of 90 consecutive eyes receiving their primary treatment for vitreous disease in Jules-Gonin Eye Hospital with intravitreal melphalan injections between 2008 and 2017 according to the safety-enhanced technique. Melphalan-induced retinopathy was assessed based on the previously described grading of the toxicity. For each case, timing and total injected dose until the apparition of the first clinical signs of the complication were noted. Mean total intravitreal concentration at time of the complication was evaluated without and with consideration of the intraocular tumor volume. Vitreous volume calculation was based on axial length estimated according to age or corrected age in case of prematurity. Tumor volume was estimated based on height, longitudinal and transverse radii of each tumor measured with ultrasonography (12 MHz).

**Results:** Overall 37 eyes (n=37/90, 41%) suffered a melphalan-induced chorioretinopathy, which was grade 1 in 15 (n=15/90, 17%), grade 2 in 19 (n=19/90, 21%) grade 3 in 3 eyes (3/90, 3%). There were no significant differences between the eyes presenting grade 1 or 2 versus grade 3 toxicity regarding the mean time to develop the complication, the total injected dose until the first clinical signs, or the injected concentration when the latter was evaluated taking into account the age-related vitreous volume only. On the contrary, when the intravitreal concentration was calculated subtracting the tumor volume from the age-related vitreous volume, the toxic retinopathy was significantly related to the intravitreal drug concentration when exceeding 10µg/ml (p=0.04).

**Conclusion:** Our findings imply that in addition to age-matched vitreous volume, intraocular tumor volume is an important factor to consider when choosing the melphalan dose to be injected into the vitreous. Recommended melphalan doses for intravitreal chemotherapy according to age and percentage of the vitreous volume occupied by the tumor(s) are presented.

**Conflict of interest disclosure:** none
O10: The genetic and clinical landscape of nanophthalmos in an Australian cohort

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Purpose: Refractive error is caused by a disparity between the axial length and focusing power of the eye. Microphthalmia is a rare ocular abnormality in which one or both eyes are abnormally small, typically causing hypermetropic refractive error. Nanophthalmos, is a rare subtype of microphthalmia associated with an increased risk of glaucoma. These findings detail the genetic architecture of nanophthalmos in a predominantly European cohort, their relative clinical phenotypes, and highlight the shared genetic architecture of rare and common disorders of refractive error.

Methods: Genetic analysis of cohort of 19 unrelated nanophthalmic probands from the Advanced Glaucoma registry. Correlated with clinical findings in the proband and affected family members.

Results: Nine probands (47.4%) were assigned a genetic diagnosis, with variants in PRSS56, MFRP, and previously reported variants in TMEM98 and MYRF. Four probands were explained by biallelic variants in PRSS56, encoding a secreted serine protease important for prenatal and postnatal ocular growth. Two of the four PRSS56 probands harboured the previously described c.1066dupC frameshift variant, yet their surrounding haplotypes were distinct from each other, and from a previously reported Tunisian c.1066dupC haplotype. Three probands had biallelic variants in MFRP. Mean axial length was shorter in the subset of individuals with a genetic diagnosis compared to those without, with PRSS56 variants associated with the shortest axial length.

Conclusions/Significance: A large proportion of nanophthalmos can be explained by the known and recently described genes. Clinically those with a gene result had shorter axial length, lower acuity, higher hypermetropia and earlier glaucoma.

Conflict of interest disclosure: none
O11: Pedigree analysis of familial primary concomitant horizontal strabismus in a south Asian population

Zia Chaudhuri¹, ²

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**Purpose:** Primary concomitant strabismus (PCS) comprising intermittent exotropia (IE) and accommodative esotropia (ET) are two most common forms of ocular misalignment. Familial forms of PCS have been observed across all populations. However, in most cases, neither a definitive mode of inheritance nor other genetic and epigenetic determinants are concretely established. Recently next generation sequencing (NGS) technology has emerged as a powerful tool in discovery genomics and a large number of novel disease-causing variants are being reported. As a first step, we recruited informative families for subsequent genetic analysis for disease-causing variant identification.

**Methods:** All consecutive families of south Asian origin living in different parts of India, with two or more affected members with PCS were prospectively recruited at the ophthalmic outpatients department (OPD) of Lady Hardinge Medical College and PGIMER, Dr RML Hospital, New Delhi, India from August 2014 to April 2019. Detailed phenotypic evaluation and pedigree documentation by Cyrillic 3.0.400 software was performed.

**Results:** Of the 62 recruited PCS families, 100% concordance was observed in 56, 24 with ET and 32 with XT. In 4 families, the affected members demonstrated both, ET and XT. 15/24 ET (62.5%), 26/32 XT (81.2%) and 3 of 4(75%) families with both ET and XT demonstrated the phenotype of PCS in at least two generations implying possible vertical transmission. In 2 families, one of the siblings each had XT and the other sibling demonstrated Duane retraction syndrome (DRS). Thus while these families were considered as having familial strabismus, there was coexistence of comitant XT in both cases along with DRS, esotropic in one and exotropic in the other. Consanguinity was observed in 2 families, both with ET. In two families with XT and autosomal recessive (AR) inheritance, nystagmus and low vision were additional phenotypes. In another two families with XT, the proband had autism in one and an associated mitochondrial myopathy in the other.

**Conclusions:** The pedigree analysis of this large and unique familial cohort in this geographical location of south Asia, recruited for future genetic analysis, opens up perspectives on the varied phenotypic heterogeneity of the condition in this population.

**Conflict of interest disclosure:** none
Session 2:

Associated Posters
P04: Assessment of the clinical phenotype of BAP1 germline whole gene and large deletions

Mohamed Abdel-Rahman
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**Purpose:** Germline pathogenic mutations in BAP1 are associated with a hereditary cancer predisposition syndrome with four main cancers uveal melanoma, cutaneous melanoma, mesothelioma and renal cell carcinoma. Most of the reported cases were for patients with single nucleotide polymorphisms or <3 base pair alterations. The aim of this study was to assess the clinical phenotype of germline whole gene and large deletions of the BAP1 gene.

**Methods:** Whole gene deletions were diagnosed in clinical laboratories or in our laboratory using multiplex ligation probe amplification (MLPA) or Sanger sequencing. Segregation in family members was carried out by quantitative PCR using at least 2 different probes or by sequencing.

**Results:** We identified three probands and one relative with germline whole gene deletions and one proband and a relative with multi-exon deletion of BAP1. Five of them were female and one male. Average age was 39 years (range 16-62 years). Two subjects presented with uveal melanoma (ages 16 and 30 years), one with a uveal nevus (age 29 years), two with BAP1-inactivated melanocytic nevus/melanocytoma (ages 39 and 42 years) and one with two primary cancers colon (54 years) and basal cell (60 years). None of the cases with whole gene deletion were identified by Sanger sequencing.

**Conclusion:** Whole gene deletion is important mechanism for germline alteration in BAP1. Assessment for large deletions should be included in clinical testing. The clinical phenotype of patients with germline large deletion in BAP1 similar to patients with pathogenic mutations but occasionally patients present with milder phenotype. Further assessment of the phenotype in additional subjects as well as study of environmental and genetic modifier of the phenotype is warranted.

**Conflict of interest disclosure:** none
P05: Suspicion for \textit{ABCA4}-related retinal dystrophy: Clues beyond the typical Stargardt phenotype

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\textbf{Purpose:} As wide panel-based testing for retinal dystrophies is implemented in ophthalmic care, novel genotype-phenotype correlations are being identified. Recognition of phenotypic characteristics associated with specific genes is necessary for appropriate counseling of patients, making of clinical recommendations, and ordering of genetic testing. In our clinical cohort, we sought to identify clinical characteristics of patients in which \textit{ABCA4} genetic variants were shown to be the cause of disease when this was not originally predicted to be the case.

\textbf{Methods:} A chart review was performed on patients with two pathogenic/likely pathogenic variants or one pathogenic/likely pathogenic variant and one variant of unknown significance (VUS) in the \textit{ABCA4} gene. From this cohort, patients were selected if, before genetic testing, the fundus appearance was not considered to be consistent with Stargardt disease. A chart review was conducted for visual acuity, Goldmann visual field, electroretinogram responses, dilated fundus exam, ophthalmic photography, and \textit{ABCA4} variants.

\textbf{Results:} One hundred ninety-nine patients met the genetic criteria specified above. Of these, 169 were diagnosed with Stargardt disease or a macular dystrophy prior to genetic testing. Thirty patients received a non-macular dystrophy diagnosis as their primary or differential diagnosis prior to genetic testing. Seven of these patients had a characteristic appearance on OCT, with lobular areas of atrophy extending throughout the entire retina. Of these 7 patients, five also demonstrated diffuse retinal atrophy, macular atrophy, choroidal loss, and pigment deposition in the periphery. The two patients (the youngest of the cohort, ages 27 and 38) did not have this characteristic fundus appearance but had a fundus appearance consistent with Retinitis Pigmentosa. Both scotopic and photopic ERGs were significantly impaired in these patients, with values non-recordable or 95% reduced in 5 of these patients.

\textbf{Conclusion:} Mutations in \textit{ABCA4} are most commonly associated with Stargardt disease, but are also known to cause several other phenotypes. The recognition of clinical characteristics associated with disease beyond the typical Stargardt phenotype in patients with \textit{ABCA4} mutations is important for the identification, management, and appropriate counseling of these patients.

\textbf{Conflict of interest disclosure:} none
P06: Misinterpretation of an OMD phenotype from a common sequence variation in *RP1L1* in a family with multiple sclerosis

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**Introduction:** Occult macular dystrophy (OMD) presents as progressive loss of visual acuity but with unremarkable fundoscopy, fundus autofluorescence (FAF), and full-field electroretinography (ffERG). Normal-tension glaucoma (NTG) and retrobulbar optic neuritis (RON) may complicate diagnosis. Increased latencies of visually evoked potentials (VEP) indicates an involvement of optic nerve transmission. Multifocal electroretinography (mfERG) detects reduced amplitudes even in asymptomatic carriers.

**Methods:** A female patient was followed between the age of 3 months and 45 years. The age-matched examinations included best corrected visual acuity (BCVA), refraction, kinetic (GVF) and fundus controlled visual fields (MP1), spectral-domain optical coherence tomography (SD-OCT), fundus photography, FAF, and electrophysiological recordings (ffERG, mfERG, VEP). MRI recordings were performed since the age of 34. The patient was tested for sequence variants underlying cone-rod-dystrophies (CRD) using a panel-based next-generation sequencing (NGS) approach.

**Results:** The patient was followed because of strabismus sursoadductorius and reduced BCVA since the age of 3 months. Her brother and maternal uncle were reported to have multiple sclerosis (EMD). No retinal disease was recognized in her family. At age 16 y she noticed recurrent headache and unilateral numbness in her left face, hand, and foot and at 21 y she received the diagnosis of EMD. At that time her BCVA fluctuated around 0.4 / 0.5 Snellen and she was unsuccessfully treated for suspected recurrent RON with corticosteroids at 27 y. Prolonged latencies in VEP were interpreted as EMD-related RON. BCVA kept fluctuating around 0.4 Snellen. GVF was stable peripherally but developed a central scotoma confirmed by reduced central sensitivity in MP1 and reduced amplitudes in the central hexagons of mfERG in her 30ies. Apart from a glial scar the MRI revealed no abnormalities. Retinal imaging by SD-OCT, fundus photography, and FAF detected outer retinal changes in the most recent examinations. Molecular genetic testing identified a common *RP1L1* mutation (p.R45W) linked to OMD.

**Discussion:** VEP abnormalities and reduced BCVA are common in occult macular dystrophy but may be misinterpreted as RON because of an unremarkable presentation of the retina in young patients. Within the presence of a family history of neurological disorders this warrants caution in interpretation.

**Conflict of interest disclosure:** none
P07: Double Struggle

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Purpose: To describe the co-existence of additional non-ocular genetic diseases in patients diagnosed with inherited retinal degenerations (IRD).

Methods: A retrospective chart review of patients diagnosed with IRD and additional rare systemic diseases. The chart review included the ophthalmic and the genetic aspects of each patient. Ophthalmic examination included best-corrected visual acuity, biomicroscopic examination, cycloplegic refraction, retinal imaging (fundus photos, optical coherence tomography, fundus autofluorescence) and electoretinography. Genetic testings include homozygosity mapping, whole exome sequencing and Sanger sequencing.

Results: Fifteen index cases diagnosed with IRD and one or more rare systemic diseases were identified. Six of the families were consanguineous. Of six patients with complete molecular diagnosis, four (66%) had pathogenic variants in two autosomal recessive (AR) disease genes, and of the total pathogenic variants identified, AR mutations were the most common (16/22, 72%). One patient was diagnosed with mutations in three different genes, underlying three distinct genetic conditions. Nine patients could have had a wrong clinical diagnosis based on clinical evaluation only (e.g. retinitis pigmentosa and hearing loss could have been diagnosed as Usher syndrome).

Conclusion: The common working paradigm for the ophthalmologist is combining the different symptoms observed in a patient to one unifying diagnosis. However, IRD is a strikingly heterogeneous condition, and may coincide with other genetic (and non-genetic) rare conditions. Establishing a correct diagnosis is important for both the patients and their family members, as it enables prediction of disease prognosis, it aids in tailoring correct follow-up and treatment, and it allows the patients to pursue prenatal counseling and reproductive planning

Conflict of interest disclosure: none
P08: Ocular findings in two patients with vascular smooth muscle myopathy secondary to ACTA2 mutations

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**Purpose:** Present two patients with Moyamoya disease, recurrent strokes, and smooth muscle myopathy secondary to ACTA2 mutations.

**Methods:** Clinical cases, retinal imaging, genetic analyses, and systemic comorbidities are presented.

**Results:** ACTA2 is a smooth muscle alpha-actin isoform specific to vascular smooth muscle cells (SMC). Heterozygous ACTA2 mutations cause coronary artery disease, strokes, Moyamoya, thoracic aortic disease, and gastrointestinal motility disorders. We present two pediatric patients with similar clinical courses, both with de-novo ACTA2 mutations. Patient-1 is a 9-year-old (c.536G>A, p.R179H) with history of recurrent strokes and diffuse cerebrovascular arteriopathy status-post bilateral revascularization procedures. She also has dilation of the ascending aorta and aortic root causing aortic regurgitation, a history of intestinal malrotation, and urinary retention. Patient-2 is a 10-year-old (c.535C>T, p.R179C) with a history of Moyamoya, multiple strokes, pulmonary hypertension, patent ductus arteriosis, gastrointestinal motility defect, and hydronephrosis with atonic bladder. Both patients have good visual acuity (20/25 OU for Patient-1, 20/30 OD and 20/40 OS for Patient-2) and prominent mydriasis with fixed, dilated pupils to 7.5-8.0 mm that do not react to light, accommodate, or constrict after pilocarpine administration. In both cases, there is no strabismus, nystagmus, or motility defect. Both patients have persistent bilateral pupillary membranes, but otherwise normal anterior segment exams. The optic nerves and maculae are normal in both patients, but they have tortuous retinal arterioles and normal veins. Both patients have a hyperopic astigmatic refractive error and require bifocals given their inability to accommodate. Their exams have remained stable over several years.

**Conclusions:** ACTA2 mutations result in multi-systemic vascular smooth muscle dysfunction, with arterial complications including aortic dilatation and aneurysms, strokes, and decreased SMC contractile function in the iris, bladder, and GI tract. Ocular findings include mydriasis and tortuous retinal arteries. Five patients have been reported with the R179H mutation (found in Patient-1) and two with an R179L substitution. Subsequently, a 3-year-old with the R179C mutation (same as Patient-2) was reported with previously undescribed abnormal lobulation of the frontal lobes who died during surgery due to vascular fragility and ductus arteriosus rupture.

**Conflict of interest disclosure:** none
P09: Stargardt Misdiagnosis: How Ocular Genetics Helps

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Purpose: Ocular Genetics at Wills Eye sees a wide range of rare disorders for accurate diagnosis. To demonstrate how focused consultation and DNA testing results in precise diagnoses, we investigated false diagnosis rates for patients referred for Stargardt disease.

Methods: Retrospective review of patients referred with Stargardt over three years. Results of diagnostic testing and DNA were compared to standard definition of Stargardt.

Results: Of 40 patients, 14 (35.0%) had been misdiagnosed. Five had non-Stargardt phenotype of which 3 had \textit{ABCA4} mutation, and 9 had another DNA confirmed diagnosis.

Conclusion: Our study highlights the essential role of the subspecialty field of ocular genetics in obtaining accurate diagnoses for the delivery of correct counseling and interventional trial eligibility assessment.

Conflict of interest disclosure: none
P10: A novel homozygous in-frame deletion of GNAT1 gene cause golden discolouration of the fundus and reduced dark-adapted ERG similar to that of Oguchi disease in a Japanese family

Shuhei Kameya¹
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Purpose: GNAT1, encoding the alpha-subunit of transducin in rod, is an important element of the phototransduction cascade. Defects in GNAT1 are very rare and have been identified in autosomal dominant and autosomal recessive congenital stationary night blindness (CSNB) and autosomal recessive rod-cone dystrophy with reduced rod ERG response in all patients reported. We performed observational clinical study to identify the phenotype-genotype relationship of a non-consanguineous Japanese family with GNAT1 mutation.

Methods: Detailed ophthalmic examinations including ISCEV standard ERG were performed on the patients and their family member. Whole exome sequencing (WES) was applied to the DNA obtained from the family member. Filtering with available genomic databases and in silico analyses were used to identify the disease causing variants. Sanger sequencing and co-segregation analysis of the family members were performed to identify the most likely pathogenic variant.

Results: Two female (13 and 11 years old) and a male (15 years old) patients from a family had night blindness from their childhood. Fundus appearance of these three patients showed a mild golden-yellow discoloration. Mizuo-Nakamura phenomenon had not been observed with three hours dark adaptation. Electrophysiological analysis revealed distinguished b-wave of rod responses and severely reduced a- and b-wave of mixed rod-cone responses with electronegative form in all patients. Cone responses are mildly reduced in two patients and severely reduced in a female patient. Dark adapted responses are similar to that of Oguchi disease in these patients. Using WES on the DNA sample of the family, we identified a homozygous 1 amino-acid in-frame deletion c.818_820delAGA, p.Lys273del in the GNAT1. Variants were verified by Sanger sequencing and were co-segregated with the disease in five members of the family. Parents were not consanguineous, however both parents harbor the same heterozygous mutation. According to ACMG standards and guideline, the variant was classified into pathogenic.

Conclusions/Significance: Our data indicate that the mutation of GNAT1 can cause CSNB with golden discolouration of the fundus and reduced dark-adapted ERG similar to that of Oguchi disease in Japanese patients.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
Shuhei Kameya’s spouse / partner Kyoko Gocho is supported by Imagine Eyes
P11: Clinical characteristics of early onset retinal dystrophy in association with the \textit{TULP1} c148delG mutation

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\textbf{Purpose:} To report clinical characteristics of the homozygous tubby-like protein 1 (\textit{TULP1}) gene variant, c.148del, enriched in the Finnish population with the allele frequency of 0.3\% according to the gnomAD database.

\textbf{Methods:} A retrospective observational study of twelve patients carrying the homozygous \textit{TULP1} c.148delG, p.Glu50AsnfsTer59, mutation and followed in the Departments of Ophthalmology of the Helsinki and Oulu University Hospitals, Finland, at the age between 4 months to 56 years old. Family history, ophthalmological features, disease onset and progression, were recorded.

\textbf{Results:} Nystagmus and head nodding were present from the age of 4 months and nyctalopia from the age of 2 years old. After initially normal retinal findings, progressive bull’s eye maculopathy, peripheral pigment epithelial atrophy, bone spicules and, in some patients, optic disc edema progressing to drusen were recorded at the age of 3 years old or later. Both rod and cone electroretinogram responses were severely impaired. Hypermetropia of +5 to +6 diopters was common in childhood, accompanied by esotropia in some cases. Posterior subcapsular cataract developed in early adulthood. Despite nystagmus, infants were able to fix and follow. Best corrected visual acuities up to 0.2 logMAR were recorded with significant variation and progressive deterioration to the level of light perception.

\textbf{Conclusion:} The phenotypic features of the founder \textit{TULP1} c.148delG mutation in the Finnish patients include better early visual performance than expected for sensory congenital nystagmus, onset of progressive macular and peripheral retinopathy in early childhood, onset of posterior subcapsular cataract in early adulthood, and, in some patients, optic disc edema and drusen.

\textbf{Conflict of interest disclosure:} none
Purpose: We present a case of Alström syndrome affecting only cone function.

Methods: The case is about a 14-year-old female patient who has a history of cardiomyopathy at 1 month of age. First visual symptoms started in pre-school with certain degree of photophobia and loss in visual acuity. The patient has no night-blindness. Loss of hearing started at the age of six. The diagnosis of Alström syndrome was evoked at the age of 9 because of retinal dystrophy and cardiomyopathy. Genetic analysis with family segregation was carried out to confirm the diagnosis.

Results: First electroretinogram was carried out at the age of 7 years that showed the cone dysfunction and preservation of rod function. Visual acuity is limited to logMAR 0.60 in both eyes. There is no nystagmus. The fundus shows irregularity of the retinal pigment epithelium in the foveal region. The electroretinogram that was done at the age of 13 confirmed only the cone dysfunction with no alterations in the rod function. As for genetic aspects, 2 clearly pathogenic variants in gene ALMS1 were identified (c.[286C>T;1211C>G], p.[Gln96*;Ser404*]) by next generation sequencing. Family segregation confirmed the paternal heritance of the second variant while the first one was de novo.

Conclusion/Significance: Alström syndrome is a multisystemic disorder that is characterized by cone-rod dystrophy, hearing loss, obesity, insulin resistance and hyperinsulinemia, type 2 diabetes mellitus, dilated cardiomyopathy and progressive hepatic and renal dysfunction. Alström syndrome is transmitted autosome-recessively. The cone-rod dystrophy is a characteristic feature of Alström syndrome and usually it starts very early in the infancy. We report a case of genetically confirmed Alström syndrome with a very unusual preservation of rod function until at least the age of 13. The molecular analysis confirmed 2 pathogenic compound heterozygous truncating mutations in ALMS1 gene. One of the variants was inherited form the father and the other was proved to be de novo. To our knowledge, de novo mutations in ALMS1 gene have never been reported in scientific literature.

Conflict of interest disclosure: none
P13: Clinical and genetic features of Jalilli syndrome in a North American patient cohort

Lev Prasov
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Purpose: Jalili syndrome is a rare multisystem disorder with most prominent features of cone-rod dystrophy and amelogenesis imperfecta. Few cases have been reported in the Americas.

Methods: We describe a retrospective case series of Jalili syndrome patients seen at the National Eye Institute Ophthalmic Genetics Clinic from 2016-2019. Three unrelated sporadic cases were systematically evaluated for ocular and systemic phenotype.

Results: All patients were determined to have cone-rod dystrophy, with bull’s eye maculopathy, photophobia and nystagmus, along with amelogenesis imperfecta. Two of these patients had Guatemalan ancestry and had the same novel homozygous \textit{CNNM4} variant (p.Arg236Trp c.706C>T) without evidence of consanguinity. This variant met likely pathogenic criteria by ACMG/AMP guidelines. An additional patient had a homozygous deleterious variant in \textit{CNNM4} c.279delC p.Phe93Leufs*31, which resulted from paternal uniparental isodisomy for chromosome 2p22-2q37. This individual had additional syndromic features including developmental delay and spastic diplegia, likely related to mutations at other loci.

Conclusions: Our work highlights the genotypic variability of Jalilli syndrome and expands the genotypic and phenotypic spectrum of this condition by describing the first series of patients seen in the United States.

Conflict of interest disclosure: none
P14: Phenotype in five related patients with isolated optic nerve atrophy associated with a heterozygous mutation in the spastic paraplegia gene 7
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Purpose/Background: Hereditary optic nerve neuropathy is a condition with autosomal dominant, autosomal recessive, X-linked or mitochondrial-DNA pattern of inheritance. Mutations in the paraplegin-encoding spastic paraplegia gene 7 (SPG7) cause hereditary spastic paraplegia (HSP) with pure phenotype or associated with optic neuropathy, ophthalmoplegia, cerebellar ataxia and cerebellar atrophy (complicated phenotype), with variable expression. The heterozygous mutation (Asp411Ala) in the SPG7 is an uncommon cause of isolated autosomal dominant optic atrophy (ADOA). The ocular signs of ADOA are progressive visual loss from the first decade of life, pale optic disc in funduscopic examination, retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) thinning in spectral domain optical coherence tomography (SD-OCT).

Methods: A clinical, genetic and psychophysical examination as well as multimodal imaging were performed in a family with five members with early onset of visual loss.

Results: We report on five family members of three consecutive generations, aged 3 to 67 years, with a genetically confirmed heterozygous mutation (Asp411Ala) in SPG7, who presented with bilateral, progressive visual loss from the first decade of life, pale optic discs, and RNFL and GCL thinning on SD-OCT. The two eldest patients (aged 67 and 45) showed not further differentiated peripheral neuropathy signs but with unremarkable cerebral MRI. The neurologic examination was to date unremarkable in other affected family members.

Conclusion: The SPG7 mutation (Asp411Ala) in the heterozygous state is a recently discovered rare cause of ADOA. It can present as an isolated optic neuropathy without further neurologic features typical for SPG7 mutations during decades, however with progressive visual loss.

Conflict of interest disclosure: none
Session 3

Stem Cells
T06: Treatment options for limbal stem cell deficiency in inherited eye diseases

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A wide range of diseases can lead to limbal stem cell deficiency (LSCD). Besides conservative treatment options for the first time in Europe there is an approved surgical therapy for the transplantation of autologous limbal stem cells available. However, autologous limbal stem cells are available in unilaterally affected patients only and genetic causes of LSCD typically affect both eyes. Transplantation of allogeneic stem cells often leads to graft failure within the first few years despite systemic immunosuppression. An alternative surgical approach is the implantation of a Boston type I keratoprosthesis (BKPro). Although the initial results after implantation of a BKPro are very exciting the patients are confronted with a wide range of complications during the postoperative course. Recent experimental approaches aim to transplant allogeneic epithelial stem cells with less immunogenic properties.

Conflict of interest disclosure: none
T07: Towards modeling of neuronal and glial pathologies in retinal organoids

Mike Karl
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Retinal organoids derived from pluripotent stem cell are an experimental model system that promises mechanistic access to retinal diseases and therapy development in a human setting. We sought to develop a human retinal organoid system providing robust baseline parameters to model major pathologies of retinal neurodegenerative diseases. We established that the organoid cell composition includes the major types of retinal neurons, rod and cone photoreceptors, and glia, the radial Müller glia, which become postmitotic by culture day 150. In control conditions, human photoreceptors and glia did not present hallmarks of cell death or reactive gliosis, even up to at least 260 days. On contrary, reactive gliosis is well-known to be strongly induced upon culture of primary animal and human retina. Therefore, we hypothesized that our human organoid system might facilitate modeling of pathologic processes. Through a screen of 16 different pathological challenges in mouse organoids (>2000 organoids), we discovered that combined application of two signaling factors previously associated with retinal diseases are sufficient to induce a severe retinal dystrophy in the human organoid system. The human model dynamically develops within 10 days (>300 organoids, >3 different hiPS cell lines) and involves simultaneous cone and rod photoreceptor dystrophy, reactive (proliferative) gliosis, remodeling, and scars in one complex histopathology – a hallmark of age-related macular degeneration (AMD). Of note, we discovered photoreceptor cell degeneration involves cell extrusion, which is reminiscent of reports in human AMD patients. In conclusion, several distinct and complex pathologic processes can be modeled in human retinal organoids, including some that have not yet been reproduced in animal models, which provide the opportunity to decipher the underlying pathomechanisms, to validate them in human patient samples and to apply them in preclinical translational therapy development and optimization.

Conflict of interest disclosure: none
T08: Derivation of RPE cells from human embryonic stem cells (hESCs): The journey from basic research to clinical application

Eyal Banin¹
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2. Cell Cure Neurosciences Ltd., Jerusalem, Israel
3. Bio Time Inc., Alameda, CA, USA

**Purpose:** In 2003 we set out to explore the possibility of using hESCs as a platform for the treatment of retinal disease. I will describe our journey from the development of a directed differentiation protocol that allows efficient derivation of RPE cells from hESCs "in the culture dish" to the application of this technology in an ongoing phase I/IIa trial in patients with advanced dry AMD (NCT02286089). Accumulated safety and imaging data from all subjects in the first 3 cohorts (n=12) and ongoing 4th cohort, which is treating patients with better vision (20/64-20/250), will be reported.

**Methods:** Transplantation is performed by subretinal injection of 50-200k hESC-derived RPE cells (OpRegen) in suspension to the worse vision eye following conventional 23G vitrectomy under local anesthesia. Systemic immunosuppression is administered prior to transplantation until 3 months after implantation. Systemic and ocular safety is closely monitored. Retinal function and structure are monitored using various imaging modalities including BCVA, color fundus, SD-OCT, and FAF imaging.

**Results:** Overall, treatment has been well tolerated and there have been no unexpected adverse events (AEs) or treatment-related systemic serious adverse events (SAEs) reported. The most common ocular AEs were the formation of predominately mild epiretinal membranes (ERM), though one severe ERM was successfully peeled 2 months following dosing. The patient’s visual acuity improved above baseline levels following the procedure. Additionally, one patient experienced a retinal detachment. Within the area of the RPE cell transplant, signs of changes in drusen as well as improvements of the ellipsoid zone and RPE layers at the border of GA were seen in some subjects. Persistent changes observed following treatment, including subretinal pigmentation and hyper-reflective areas in the outer retina on OCT, are findings that support the continued presence of the transplanted cells RPE cells based on previous animal work performed.

**Conclusions:** Subretinal transplantation of hESC-derived RPE cells in patients with advanced dry AMD and GA appears well tolerated to date. Imaging findings suggest presence of transplanted cells in the subretinal space. Potentially positive structural and clinical changes observed in some patients will require additional follow-up over time.

**Conflict of interest disclosure:** The following conflict(s) of interest must be disclosed:
Eyal Banin and Benjamin Reubinoff received honorary or consultation fees from and are consultants and IP holder of Cell Cure Neurosciences Ltd
O12: Differentiation and characterization of RPE from hiPSC and its subretinal transplantation in RCS rats

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**Purpose:** Retinal degenerative diseases like Age-related Macular Degeneration (AMD) and Retinitis Pigmentosa (RP) cause irreversible retinal cell death and progressive vision loss in millions of people across the world. Subretinal transplantation of cells is a promising experimental method for their treatment. Here, we tested the efficacy of transplantation of (Eyecyte-RPE) RPE cells to rescue photoreceptors and visual function in the RCS rat model of retinal degeneration.

**Methods:** We have successfully generated retinal pigment epithelial (RPE) cells from human iPSC and characterized them wrt their identity, purity and potency. Transplantation of 50K or 100K cells into the subretinal space was performed as a suspension in RCS rats; BSS+ served as controls. Optomotor tracking was used to measure visual acuity of all animals. Half the animals were sacrificed at P60 and the other half at P90.

**Results:** All the experimental animals showed successful delivery of cells and bleb formation. Optomotor tracking thresholds were rescued in each cell treated dose groups over that of control animals. Histological analysis revealed significant photoreceptor protection above that of controls at both sacrifice ages in both cell dose groups. Quantification of cone counting revealed a significantly higher number of cones in cell treated groups compared with control eyes, most evident at P90. Approximately 10% of the transplanted RPE cell markers expressed Ki67, a cell proliferation marker.

**Conclusion:** When transplanted into the subretinal space of RCS rats, Eyecyte-RPE delayed the loss of visual acuity in the RCS rat over that of controls at all ages tested. Rod and cone photoreceptors were rescued in the area of the grafts for up to 70 days post-transplantation. RPE transplantation is a promising treatment for degenerative retinal diseases.

**Conflict of interest disclosure:** The following conflict(s) of interest must be disclosed:
Rajani Battu is/are stock shareholder of Eyesystems Research Private LTD
O13: Proteomics profiling of retinoblastoma derived exosomes

Angela Galardi

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8. Hopital Ophtalmique Jules Gonin - Fondation Asile Des Aveugles, Lausanne, Switzerland

Purpose: Retinoblastoma (RB) is the most common intraocular cancer of childhood. Despite recent advances in conservative treatment have greatly improved the visual outcome, local tumor control remain difficult in presence of massive vitreous seeding. Thus, the identification of new biomarkers is crucial to design more effective therapeutic approaches. Traditional biopsy has long been considered unsafe in RB, due to the risk of extraocular spread. Exosomes, nano-sized vesicles containing nucleic acids and proteins, represent an interesting alternative to detect tumor-associated biomarkers. The aim of this study was to determine the protein signature of exosomes derived from RB tumors (RBT) and vitreous seeding (RBVS) primary cell lines.

Methods: Exosomes from 4 RBT (HSJD-RBT1, HSJD-RBT2, HSJD-RBT5, HSJD-RBT14) and 3 RBVS (HSJD-RBVS1, HSJD-RBVS3, HSJD-RBVS10) cell lines were isolated by high speed ultracentrifugation. Vesicles number and size were confirmed by NanoSight and Scanning Electron Microscopy. Protein content was analyzed by bicinchonic-acid assay and high resolution mass spectrometry.

Results: A total of 5404 proteins were identified. Among those, 1940 and 409 were exclusively expressed in exosomes from at least one RBT and one RBVS respectively. 3055 proteins were in common between the two groups. Gene Ontology analysis identified proteins primarily involved in unfolded protein response, metabolic processes and cellular response to hypoxia in both groups. Only in RBT-exosomes were found proteins involved in neuronal development, vesicular traffic, oxidative metabolism, ion channels and transport. Lastly, we found 15 proteins exclusively expressed in all RBT-derived exosomes (e.g SNAP25, NCAN, ABI2) and 6 proteins in RBVS-derived exosomes (e.g integrin beta-3, PSMB6, GALK1, CREBBP).

Conclusions: This work suggests that the proteomic profiling of RB-derived exosomes could reflects the signature of the primitive tissue and may be considered as potential tumor biomarkers.

Conflict of interest disclosure: none
Clinical features and molecular basis of X-linked retinoschisis: From mechanism to therapy

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Purpose: To describe X-linked retinoschisis disease (XLRS) and our gene therapy treatment efforts. XLRS is a monogenic retinal dystrophy with a complex phenotype that includes retinal structural defects resulting in schisis cavity formation. A prominent feature of XLRS disease historically has been the selective reduction of the electroretinogram b-wave but not a-wave. While the b-wave loss frequently is considered a curiosity, it signifies a fundamental facet of XLRS disease, namely a failure of synaptic transmission from photoreceptors to the depolarizing bipolar cells (DBCs).

Methods: We studied the molecular basis of XLRS pathology and are conducting a gene therapy trial. In probing the molecular basis of this condition, we found that the retinoschisin \( RS1 \) molecule is required for proper localization of signaling molecules in the post-synaptic dendritic inputs to the DBCs. The absence of \( RS1 \) protein in XLRS disease results in deficient visual signal transmission despite normal photoreceptor function. Hence the XLRS phenotype overlaps Congenital Stationary Night Blindness (CSNB). Providing normal \( RS1 \) protein by gene therapy restores the b-wave in the \( RS1 \)-KO mouse model and, if extended to the human condition, presumably will at least partially correct the visual failure. We initiated a Phase I/IIa human XLRS gene therapy trial (Feb 2015; ClinicalTrials.Gov NCT02317887). Our clinical scAAV8-hRS/IRBP-RS1 vector contains the human \( RS1 \) cDNA and a tissue-specific \( RS1 \) promoter plus an IRBP enhancer. Pre-clinical studies indicated that “a fully normal level of \( RS1 \) expression” was not necessary for therapeutic effect in the XLRS mouse. We have dosed eleven subjects at 1e9 to 3e11 vg/eye. The primary outcome is safety, and secondary outcomes include monitoring for treatment benefit, with visual acuity and fields, ERG responses and retinal structure by OCT imaging. In one subject dosed at 1e11 vg/eye, we observed complete closure of macular schisis cavities two weeks later. We are dosing additional subjects and evaluating possible functional benefits.

Discussion: Currently we are exploring methods to ameliorate the ocular inflammatory response we observe following intravitreal administration of the vector, while monitoring the formation of anti-AAV and anti-\( RS1 \) antibodies. Results will be described.

Conflict of interest disclosure: None
Session 4

Biomarkers for Substantiating Success in Treatment
T09: AAV2-hCHM subretinal delivery to the macula in choroideremia: Performance of outcome measures

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Purpose: To assess preliminary safety and efficacy data of the investigational subretinal delivery of a recombinant adeno-associated virus serotype 2 (AAV2) vector carrying a human REP1-encoding cDNA in choroideremia (CHM).

Methods: Ten subjects with CHM (ages 26-57 years at injection), received uniocular subfoveal injections of low dose (up to 5x10^10 vector genome (vg) per eye, n=5) or high dose (up to 1x10^11 vg per eye, n=5) AAV2-hCHM. Patients were evaluated pre- and post-operatively at study-defined follow up visits for 2 years. Ocular safety was assessed by ophthalmic examination, perimetry, spectral domain optical coherence tomography (SD-OCT) and short-wavelength autofluorescence (SW-FAF) and by conventional automated perimetry and microperimetry.

Results: There were no surgery-related complications or unexpected adverse events. By two years visual acuity (VA) returned to baseline in all but one patient who slowly recovered to -17 letters of baseline. With the exclusion of this patient, mean VA letter counts differences (2 year minus baseline) were similar in injected (-1.7 letters) compared to uninjected (-0.3 letters) eyes. Two patients showed greater VA counts (5-6 letters) in the injected eye compared to baseline and to the uninjected control. Mean sensitivity by microperimetry changed minimally in injected (mean±SD= -0.7±0.75dB) and uninjected (-0.3±0.59 dB) eyes. There were no significant differences between injected and uninjected eyes in absolute dark-adapted cone-mediated sensitivities at the fovea or within the central 30° of eccentricity. There was a slightly slower mean rate of reduction of the IS/OS band horizontal extent in injected eyes (-69±59μm/year) compared to uninjected eyes (-96±67μm/year), which corresponded in extent to the areas of SW-FAF. There were no obvious dose-dependent relationships.

Conclusions: VA in 9/10 subjects was unchanged (less than ±10 letters difference from baseline) after the subfoveal injections of AAV2-hCHM and in uninjected eyes at 2 years of follow-up. Acute (~72 hours) localized foveal thinning and slow, partial recovery of VA in one patient suggests non-vector related individual vulnerability to the subfoveal injection. Residual islands of relatively preserved retina continued to shrink in both injected and uninjected eyes. Longer observation intervals are required to better evaluate the significance of these observations.

Support: Spark Therapeutics Clinical Trials Agreement, National Institutes of Health (NEI-K12EY015398-10, NIH R01EY028601), Research to Prevent Blindness, Foundation Fighting Blindness, Hope for Vision, Macula Vision Research Foundation, the Paul and Evanina Bell Mackall Foundation Trust, and The Pennsylvania Lions Sight Conservation and Eye Research Foundation. Clinical Trial Registration: NCT02341807

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
F Spark Therapeutics (AMM); P (JB); S GenSight Biologics, Spark Therapeutics (JB); C Sanofi (JB); F Biogen, Limelight Bio (JB). Jason - Beam therapeutics, Sanofi, Editas Medicine, Gensight, Blue Cross Blue Shield (Consultant for all) Eric - Spark (F)
T10: Plasticity and its limits - Cortical visual field representations in achromatopsia

Michael Hoffmann¹

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Purpose: Achromatopsia is a rare inherited disorder rendering cones dysfunctional. As a consequence there is a congenital absence of visual input from the foveal cones to the visual cortex, which prompts the question of remapping of the foveal representation in achromatopsia [1]. Such remapping might interfere with gene-addition approaches that are currently pursued to restore cone function.

Methods: In a multi-center approach a cohort of 18 participants with achromatopsia (CNGA3⁻/⁻ or CNGB3⁻/⁻) was compared to 18 controls. fMRI-based eccentricity and population receptive field (pRF) mapping data were acquired for both scotopic and photopic conditions (2.5 x 2.5 x 2.5 mm³ resolution at 3 Tesla; Prisma Siemens or GE Healthcare; stimulus diameter: 16°) and projected onto the cortical surface of anatomical scans (T1 MPRAGE: 1 mm³). Anatomically defined [2] central (0° – 4°) and paracentral (4° – 8°) V1-ROIs were compared in terms of (i) activated proportion and (ii) their average eccentricity representation to assess alterations in achromatopsia related to remapping of the foveal representation, i.e. via the identification of a significant interaction of GROUP and ROI. All analyses were performed for all patients (RODall) and for a subset with electroretinographically confirmed normal rod function (ROD+, n=12).

Results: In terms of activated V1-proportion, no interaction of ROI and GROUP was evident, neither for RODall and ROD+. In terms of V1-eccentricity representation, a significant interaction of ROI and GROUP was evident for RODall and ROD+ for scotopic stimulation (p=0.0018 and p=0.03, respectively), associated with an increase of the mean eccentricity of the central ROI by around 1°.

Conclusion: Sizeable remapping of the primary visual cortex does not appear to be a general feature in our achromatopsia cohort. The relation to previous reports [1] and the relevance of our findings for gene-therapeutic interventions will be discussed.

References:

Conflict of interest disclosure: none
T11: High-resolution retinal imaging analysis in female carriers of choroideremia

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Purpose: Choroideremia is an X-linked disease that causes degeneration in choriocapillaris, retinal pigment epithelium (RPE) and retinal photoreceptors. Heterozygous female carriers of choroideremia typically do not have any visual symptoms but often have severe funduscopic changes. The purpose of this study was to characterize the cone photoreceptor mosaic and choroidal morphology of these carriers.

Methods: This research was a clinical case series study. Six genetically identified female carriers of choroideremia from four different families were included. Each patient underwent a comprehensive ophthalmic examination, including: full-field electroretinography (ERG), color fundus photography, subfoveal choroidal thickness (SFCT) measured with spectral-domain optical coherence tomography (OCT), and cone photoreceptor density assessed using an adaptive optics (AO) retinal camera at temporal eccentricities ranging from 2 to 8 degrees. SFCT and cone density findings were compared to control data previously obtained in a group of healthy subjects.

Results: Carriers’ age ranged between 10 and 66 years. Best-corrected visual acuity was equal to or higher than 20/20. With conventional fundoscopy, severe retinal depigmentation was observed in one carrier and scattered depigmentation was present in 3 other cases. However, in all patients, SFCT was within normal limits, and cone photoreceptor density values measured with AO imaging did not significantly differ from those found in healthy controls.

Conclusions: The findings indicate that despite the presence of distinctive depigmentation of the retinal pigment epithelium in female carriers of choroideremia, their cone photoreceptor density and SFCT are well-preserved. Therefore, unlike conventional fundoscopy, both OCT and AO imaging provided objective assessments that were consistent with visual performance findings.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
Kiyoko Gocho received grants or research support from Kaken Grant type(C) No.18K09426
Spouse of Kiyoko Gocho is CEO of Imagine eyes
O14: Multimodal imaging of patients with Best Vitelliform Macular Dystrophy (BVMD): a 4-year follow-up study

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Purpose: To test the hypothesis that imaging biomarkers can be used to measure outcome in upcoming Best Vitelliform Macular Dystrophy (BVMD) treatment trials.

Methods: A retrospective analysis of 31 patients (59 eyes) from 27 families with a clinical and genetic diagnosis of dominant BVMD was performed. Three eyes were excluded from analysis due to poor image quality. SD-OCT, SW-AF and NIR-AF images were taken at the same visit. A second set of imaging was performed in 15 patients (30 eyes). The diameter of the lesion measured by the two different autofluorescence techniques were correlated with the measurements made by SD-OCT. Central macular thickness, foveal height of the lesion and foveal outer nuclear layer (ONL) thickness were measured by SD-OCT. Likewise, ONL thickness at temporal (T-ONL) and nasal (N-ONL) limits of the lesion and at 500 µm from the border of the lesions (5T-ONL and 5N-ONL) towards the healthy retina were evaluated. In addition, the area of the macular lesion was manually measured on both SW-AF and NIR-AF. Comparative statistics was used to calculate differences between the calculated means. The Pearson correlation coefficient was used to evaluate the relationships between each imaging modality.

Results: Among 59 eyes, one eye classified in the pre-vitelliform stage did not exhibit a lesion after 2 years of follow-up but revealed a hypoautofluorescent signal on NIR-AF that was not observed on SW-AF. The mean follow-up time was 4.11±0.54 years. Significant positive correlations were found among SD-OCT, SW-AF, and NIR-AF when used to measure lesion diameter (P<0.001). Distinct regions of the lesions, namely T-ONL, N-ONL, 5N-ONL, decreased in thickness by -3.83±2.26 µm/year, -5.03±2.01 µm/year, -5.11±2.69 µm/year, respectively, over time. No progression was observed in the diameter and area of the lesion as measured by each imaging modality.

Conclusion: NIR-AF appears to have greater sensitivity to the early pre-vitelliform stage in BVMD. As significant changes were observed in the ONL of the lesions over time, our data suggests that ONL measurements may be used as an anatomical outcome measure for clinical trials. Future studies should include parameters such as microperimetry, which may additionally serve as a form of functional outcome measure for BVMD.

Conflict of interest disclosure: none
O15: Characterization of the Brazilian ARSACS phenotype: clinical, ophthalmological, neuroimaging, and genetic features of fourteen cases

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Background: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare, progressive neurodegenerative condition described in Charlevoix-Saguenay region, where it causes spasticity, ataxia and peripheral neuropathy (1). Retinal nerve fiber layer thickening is present in most Canadian cases (1,2). Cerebellar atrophy and linear pontine hypointensities on MRI support diagnosis (3). More than 200 mutations in the causative gene, SACS, have been reported throughout the world, and distinct ARSACS features occur in non-Canadians individuals. Phenotype characterization is important to understand molecular pathogenesis and improve accuracy in diagnosis.

Methods: Magnetic resonance imaging of the skull, retinography and optic coherence tomography (OCT) were performed in fourteen consecutive cases of genetically confirmed ARSACS. Detailed neurological history and examination were recorded. We obtained informed consent from all patients, and approval by Ethics Committee.

Results: We included 14 patients (10 females) from 10 families (age range 16-57 years). Age at onset was within the first decade in twelve cases, 11 years in one and 44 in another. All had ataxia, peripheral neuropathy and spasticity. One had learning disability and psychosis at the age of 23. Retinal nerve fiber hypertrophy in OCT was seen in 12/13. Cerebellar atrophy (14/14), biparietal atrophy (13/14), and linear pontine hypointensities (13/14) were the most consistent radiological signs. Genetic analysis revealed 16 different SACS gene mutations and thirteen novel variants.

Conclusions: Retinal and neuroimaging changes are common feature in Brazilian ARSACS. OCT and MRI may provide useful clues during diagnostic work-up of spastic ataxias.

Conflict of interest disclosure: none
O16: Retinal implantation with Argus II artificial retina in 3 patients with Bardet-Biedl syndrome

Fouzia Studer

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Purpose: Bardet-Biedl syndrome is an emblematic ciliopathy that associates mainly early onset retinal degeneration, obesity, polydactyly, kidney dysfunction, inconstant intellectual deficiency and other rarer features. No specific therapy exists today to treat the retinal degeneration that is usually severe and of early onset with most patients being legally blind. We report here 3 patients with Bardet-Biedl syndrome (BBS) who were implanted with the Argus II retinal implants.

Methods: Three BBS patients followed by the CARGO with severe retinal degeneration were eligible for an artificial retina by implantation with an ARGUS II retinal implant (Second Sight) on one eye. All of the patient were implanted thanks to the “Forfait d'innovation” research program. Molecular diagnostic was assessed with clear biallelic pathogenic variations in various genes: patient 1 in BBS10 c.[271dupT];[273C>G], p.[Cys91Leufs*5];[Cys91Trp], patient 2 in BBS5 c.[413G>C];[413G>C], p.[Arg138Pro];[Arg138Pro] and patient 3 in BBS1 c.[1169T>G];[1215insN], p.[M390R];[?]. After surgery they benefited a rehabilitation program and where evaluated at a common stage of the procedure.

Results: We will present the visual functional benefits for each patient with a specific focus to the evolution of their skills as well as their clinical and imaging data. Overall, after intensive rehabilitation work each patient disclosed objective and functional improvement.

Conclusion/Significance: We show that retinal implantation can benefit to patients with advanced and severe retinal dystrophy in a syndromic context such as BBS. The follow up will be of prime importance to assess the benefits on the long-term.

Conflict of interest disclosure: none
Session 4

Associated Posters
P15: Analysis of outer retinal layer alterations in patients with *RPE65* deficiency using Optical Coherence Tomography A-scan-analysis

Özgün Tanrikulu

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**Purpose:** Biallelic mutations in the *RPE65* gene cause early functional and morphological changes of the outer retina. Mutation dependent progression presents either as early onset neurodegeneration (severe, LCA, EOSRD) or by minor changes to the layer boundaries ("RP" type). The aim of this study was a further characterization of changes in the outer retinal layer thickness from RPE to ellipsoid zone (EZ) and external limiting membrane (ELM) by SD-OCT-A-scan (spectral-domain optical coherence tomography) analysis compared to healthy controls. Furthermore, layer thickness was correlated with best corrected visual acuity (BCVA).

**Material/Methods:** Twenty-five patients with biallelic mutations in *RPE65* were evaluated. Inclusion criteria required SD-OCT-scans with continuously distinguishable outer retinal layers covering the fovea. Recordings from 28 eyes of 15 patients fulfilled both criteria. SDOCT- A-scans were analyzed at defined distances (250 μm to 500 μm) from the foveal center. Corresponding BCVA to each scan was retrieved from the patient files. The patients were assigned to a juvenile patient group [n=7, 13 SD-OCT-scans, range: 4-10 years], and an adult patient group [n=8, 15 SD-OCT-scans, range: 15-24 years]. Healthy control subjects were assigned to a juvenile control group [n=10, 10 SD-OCT-scans, range: 4-10 years], and an adult control group [n=10, 10 SD-OCT-scans, range: 13-29 years]. The distances between A-scan-peaks of RPE to ELM, RPE to EZ, EZ to ELM were measured with a customized MATLAB application, assuring measurements in vertical axis.

**Results:** The layer thicknesses between RPE to ELM, RPE to EZ, and EZ to ELM were significantly shortened in the foveolar region in both patient groups compared to the corresponding control group. There was a significant positive correlation of layer thickness with BCVA in all patients at full layer stratification.

**Discussion:** In patients with biallelic *RPE65* mutations, photoreceptors show structural abnormalities already at an early age detected by SD-OCT fine-structure analysis. Ongoing degeneration likely results in significant shortening of the foveolar photoreceptor layers on SD-OCT-A-scans. A positive correlation between BCVA and the distances of the photoreceptor layer peaks could be a read-out parameter even at preverbal age to monitor disease progression in natural history and subretinal gene addition therapy with Luxturna.

**Conflict of interest disclosure:** none
Session 5

Luxturna Therapy – Recent Developments
T12: Voretigene Neparvovec for RPE65-Related Inherited Retinal Dystrophies: the Philadelphia Experience

Bart P Leroy¹

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Purpose: to illustrate our experience with voretigene neparvovec for RPE65-related inherited retinal dystrophies (IRD) at the Children's Hospital of Philadelphia and Scheie Eye Institute of the University of Pennsylvania.

Methods: patients with RPE65-related IRDs underwent pre- and postoperative evaluations including best-corrected visual acuity, Goldmann visual fields, full-field sensitivity testing, full-field flash electroretinography and imaging with blue and infrared reflectance and autofluorescence imaging as well as spectral-domain optical coherence tomography.

Results: at this time, 9 individual patients have been treated with voretigene neparvovec. All have significant improvements in several parameters.

Conclusions: voretigene neparvovec is a safe and efficient treatment, which significantly improves quality-of-Life for patients with RPE65-related IRDs.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
The authors received research support grants and travel grants from Spark Therapeutics & Novartis Pharma
T13a: How long does gene therapy last? 4 Year followup and adult versus pediatric outcomes of Phase 3 Voretigene Neparvovec Trial in RPE65–Associated LCA/Inherited Retinal Disease

Arlene Drack¹

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Introduction: Voretigene neparvovec (VN) gene therapy improves ambulatory navigation, light sensitivity, and visual field in subjects with RPE65–associated Leber Congenital Amaurosis /Inherited Retinal Disease.¹ We report Year 4 results for original intervention (OI) subjects, Year 3 for delayed intervention (DI), and Y1 results by age <=10, 11-17, or > 18 years at treatment.

Methods: Subjects were randomized to either original intervention (OI: bilateral subretinal VN at baseline) or delayed intervention (DI: VN after 1 year). Primary endpoint was change in bilateral performance on the Multi-Luminance Mobility Test (MLMT). One of the secondary endpoints was change in full-field light sensitivity threshold (FST) testing.

Results: At Y1, there were no statistically significant differences in MLMT between subjects aged ≤10 (n=13), 11–17 (n=7), and ≥18 years (n=9), however FST was statistically significantly better in those treated at 11-17 vs. ≥18 years. Mean changes in MLMT at Y1 were maintained at Y4 for OI and Y3 for DI. When compared to Y1, 5 subjects (ages at treatment 4, 6, 11, 11, and 34 years) lost a light level while 1 subject (age at treatment 16 years) gained a light level. No subject declined below baseline. One subject had a retinal detachment detected at Y4.

Discussion: Amblyopia may not be a major hindrance to gene therapy treatment but loss of photoreceptors over time may affect outcome.

Conclusions: Functional vision is stable in 24 of 28 (86%) patients from one year post-treatment through the duration of follow-up.

References:

Funding Statement: This study was sponsored by Spark Therapeutics.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
Arlene Drack reports grants from Spark Therapeutics, ProQr, RETrophin and educational fees from Retrophin. Stephen Russell reports consulting fees and grants from Spark Therapeutics, Inc. Jean Bennett reports grants from the Foundation Fighting Blindness, NIH, and Spark Therapeutics, Inc. Zi-Fan Yu and Amy Tillman provided statistical consulting to Spark Therapeutics, Inc. through their employer, Statistics Collaborative, Inc. Katherine A. High, Thomas Ciulla, Daniel Chung, and Kathleen Z. Reape are employees of Spark Therapeutics, Inc. and hold equity in the company. Albert M. Maguire reports grants from the Foundation Fighting Blindness and Spark Therapeutics, Inc.
T13b: Electrophysiology following subretinal treatment with voretigene neparvovec (Luxturna)

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Purpose: In animal models of RPE65-mutation associated IRD, ERG response may be restored after subretinal treatment with voretigene neparvovec (Luxturna) but similar recovery has not been documented in humans, even when measures of functional vision such as mobility course and FST improve. We instituted a protocol of electrophysiology testing in patients with LCA to detect if ERG recovers.

Methods: Two female children with RPE65-mutation associated LCA received a battery of electrophysiologic testing including full field ERG, multifocal ERG, and flash VEP in addition to standard clinical studies.

Results: Both patients were 4-years-old at time of treatment. Patient 1 had essentially non-recordable full field and multifocal ERG after treatment but recordable flash VEP. Visual acuity was 20/40 OU after treatment. Patient 2 had essentially nonrecordable flash ERG and flash VEP before treatment, and almost normal amplitude full field ERG and flash VEP after treatment. Visual acuity was 20/100+1 OD and 20/80-1 OS.

Conclusions: Some patients have a marked improvement in electrophysiology following Luxturna. Based on a small sample, flash VEP may be more consistently improved than ERG. Long term follow up may aid in assessing durability of response.

Conflict of interest disclosure: none
T14: Our experience with gene therapy approaches for RPE65 inherited retinal diseases

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LCA/Retinal dystrophy caused by mutations in the RPE65 gene is the first ocular disease treated successfully with gene therapy in phase I/II and III clinical trials. The results obtained in the clinical trials led to the recent approval of the drug voretigene/neparvovec, named Luxturna, by EMA and FDA. Our experience in phase I/II clinical trial of gene therapy in five Italian patients affected by RPE65 LCA-Retinal dystrophies will be reported showing the results in terms of safety and efficacy. Finally, on the basis of our experience, critical issues arisen in gene therapy clinical trials will be discussed.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed: Francesca Simonelli received honorary or consultation fees from Spark Therapeutics, Inc.
T15: Country specific problems to get started with EMA-approved gene therapy with Luxturna

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Purpose: to report our experience at a designated Luxturna treatment center in Germany preparing to treat the first patients with IRDs associated with biallelic mutations in RPE65.

Methods and

Results: Introduction of new therapies requires a complex process in Germany. First, approval by a procedure called NUB – Neue Untersuchungs- und Behandlungsmethoden (new examination and treatment methods) has to be obtained prior to getting approval by the individual health insurance companies of the selected patients. In parallel, the infrastructure for preparing the drug have to be established at the pharmacy of the university clinic. Due to the novel character of the therapy, uncertain legislation with regard to how to handle gene therapeutic medication, and the lack of experience of the involved personnel, establishing a dedicated room and putting trained personnel in place at the pharmacy can become a major hurdle. Furthermore, as the volume of the ready-to-use preparation of Luxturna® is about 5 times the actual substance injected at the level of the interface between RPE and neuroretina, health insurance companies are considering to suggest the usage of one vial for more than one patient.

Conclusion: Approval of a new medication by the EMA does not mean that clinical centers can start immediately with treating patients in Germany but a number of issues need to be solved.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed: Birgit Lorenz received honorary or consultation fees from Novartis Pharma, Switzerland
T16: The post-authorization safety study of voretigene neparvovec-rzyl

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Following its marketing approval by the FDA in 2017, voretigene neparvovec-rzyl has been administered exclusively at designated Ocular Gene Therapy Treatment Centers (OGTTCs) in the United States (US). This model not only supports the safe storage, preparation and administration of this novel gene therapy, but also facilitates the review of product safety in a larger population than was available in the clinical development program. More than 20 vitreoretinal surgeons are now trained in the administration procedure at ten OGTTCs in the US – compared to 5 surgeons (2 primary, 3 secondary) at two trial sites during the clinical development of voretigene neparvovec-rzyl. The Post-Authorization Safety Study (PASS) is a multicenter, longitudinal, observational safety registry study for patients treated with voretigene neparvovec-rzyl; the planned US enrollment is ≥40 participants and patients will be followed for a period of 5 years. The purpose of the PASS is to evaluate the long-term safety profile of voretigene neparvovec-rzyl for the 5-year post-administration period; all adverse events, information about pregnancy outcomes, and ophthalmic examination results will be collected. Prior to the enrollment of subjects into the PASS, spontaneously reported adverse events occurring during the first year of availability in the US have been collected, summarized and reviewed, and compared to observed rates in the clinical trial. The PASS will collect additional safety data as patients are enrolled in the study.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
Daniel Chung is stock shareholder of Spark Therapeutics, Inc.
Ellsworth Lecture 2019

Retinoblastoma around the world in 2019
Laurence Desjardins
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Children with retinoblastoma face very different situations and problems according to the place where they are born. In developed countries survival is excellent and conservative management has made significant improvement with intraarterial and intravitreal chemotherapy. Nevertheless we observe a worrying increase of metastasis in unilateral retinoblastomas due to excessive indications of conservative management versus enucleation. In developing countries survival is still poor due to late diagnosis and lack of hospital structures able to treat the patients with also financial difficulties for the parents. This is particularly true in sub saharan africa while South America, cChina and Asia have already improved the quality of diagnosis and care in many countries. The AMCC programm aims to improve diagnosis and treatment of retinoblastoma in Sub Saharan Africa where the natality is still very high (4,9) with approximatively one thousand cases of retinoblastomas each year. It includes a programm for early diagnosis, training of oncopediatrician, ophtalmologists and pathologists who come to stay in Curie Institute, training for prosthesis making and financial support for medical equipment and drugs (through the GFAOP). It also implies common treatment protocol and precise registry of all cases in a common data base. This program was supportde by Sanofi Espoir, Retinostop, Curie Institute and now by a swiss foundation. It is implementing in francophone and some anglophone sub Saharan African countries. Some of the centers who have the largest number of children will finally become themselves training centers for other countries.

Conflict of interest disclosure: none
Session 6

Precision Care for Children with Retinoblastoma
T17: Proteomics for biomarker identification in retinoblastoma liquid biopsy

Angela Di Giannatale¹

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Purpose: Retinoblastoma represents the most common intraocular malignancy of infancy and childhood. Although several tumor biomarkers have been evaluated in RB, new prognostic biomarkers, therapeutic targets and new candidates that are predictive for response to therapy are needed. In the majority of pediatric cancers, invasive techniques are necessary to validate the mutational status and/or determine the activation of specific pathways. Nevertheless, in RB the biopsy of the primary tumor is not feasible because of the risk of tumor intraocular dissemination. Tumor release molecular information into the circulation through nucleic acids, proteins, and tumor-derived extracellular vesicles that circulate in biologic fluids such as plasma and cerebrospinal fluid (CSF). In particular, exosomes, nanosized vesicles released from various cells, have been described to contain many molecules representative of the primary tumor.

Methods: Proteins and peptides are promising biomarkers since they are functionally involved in biological processes and their expression levels variate in different tumors. In our studies we performed proteomic analysis of biological liquid derived from RB patients (humor aqueous, plasma and CSF). Furthermore, we isolated exosomes released from retinoblastoma cells lines and evaluated protein content.

Results: We identified proteins involved in specific cellular process such as cellular adhesion, metabolic processes, neuronal development and vesicular trafficking. The evaluation of different timepoints showed how the treatment modify the protein content in biological fluids of these patients.

Conclusions/Significance: Our innovative approach could be used as a non-invasive method, in alternative to tissue biopsies. The liquid biopsy may facilitate the definition of prognostic subgroups through the identification of diagnostic, prognostic and/or predictive biomarkers to guide patient management.

Conflict of interest disclosure: none
T18: The current and future role of cell free DNA analysis in the management of retinoblastoma

Trevor Cole

West Midlands Regional Genetics Service, Birmingham Women’s and Children’s NHS Foundation Trust, Birmingham UK (BWCNHSFT) and Birmingham Health Partners and on behalf of the Birmingham National Retinoblastoma Service and the West Midlands Regional Genetics Laboratory (BWCNHSFT)

Forty percent of all cases of Retinoblastoma have a germline mutation and are at very high risk of bilateral disease, second non-ocular cancers, and induction of second cancers secondary to radiotherapy and may be in families associated with a significant risk of with further affected first degree relatives (siblings and offspring). 60% of cases are not inherited and two somatic $RB1$ gene mutations occur after conception and are at low risk of bilateral disease, non-ocular second tumours and having affected first degree relatives. Definitive proof that both $RB1$ gene mutations are somatic requires a source of tumour DNA for analysis. With newer chemotherapeutic regimes and local treatment enucleation for unilateral retinoblastoma has decreased by approximately 50% in our practice, which would have prevented obtaining definitive somatic results. We have now shown that informative molecular results can be obtained from cell free DNA (cfDNA) obtained from anterior chamber aqueous fluid. This cfDNA can also be utilised for real time monitoring of additional somatic events and with the potential alignment of these findings with the clinical behaviour and improving prognostication and future management decisions. Furthermore we would propose that investigation of the cerebrospinal fluid, another source of cfDNA from a fluid present in a “protected compartment”, could be utilised to assess and monitor possible CNS disease. In addition we have now reported 6 cases in the West Midlands where pre-natal cfDNA testing (undertaken on a standard maternal sample in mid-trimester) has provided a validated non-invasive predictive answer long before delivery. This has significant benefits in the quality of family care and in service delivery planning, which we suggest, outweighs any short term laboratory costs.

Conflict of interest disclosure: none
T19: Disruptive innovations to reach precision retinoblastoma care

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**Purpose:** To describe innovative therapies with potential to improve care for intraocular retinoblastoma.

**Methods:** We describe two innovative “disruptive” technologies to reduce duration and intensity of toxic therapies to save eyes with advanced intraocular retinoblastoma for evaluation in clinical trials: vitrectomy/resection (PPV) of active tumor and delivery of chemotherapy via an episcleral device (Chemoplaque).

**Results:** Since 2013, PPV for residual active tumor or recurrent tumor after primary chemotherapy (IV or IAC) was performed with procedures to enhance safety on 489 eyes of 454 children. Retinoblastoma-specific mortality was 4% (2% related to PPV eye); 2% of patients are lost-to-follow-up; salvaged were 87% of eyes (minimum 2-year follow-up). Health Canada authorized compassionate “First in Human” use of the FDA-approved Chemoplaque (0.6 mg topotecan, glued to sclera) for two patients with refractory retinoblastoma in their only remaining eye. No ocular or systemic toxicity was observed. All 30+ small distributed tumors of Patient One disappeared within 28 days (complete remission, CR); the large primary calcified tumor regressed but recurred; standard therapies attained CR at one year. Patient Two had very resistant tumors to all standard therapies including external beam radiation; initial apparent complete regression of intra-retinal and vitreous disease at day 130 was followed by recurrence for which enucleation was performed to reduce risk to life; pathology was pT1.

**Conclusions/Significance:** Prospective clinical trials are necessary for both PPV and the Chemoplaque to establish their role in control of advanced intraocular retinoblastoma and reduce the duration and number of invasive therapies needed to save eyes.

**Conflict of interest disclosure:** none
T20: Optimizing focal laser photocoagulation therapy for retinoblastoma
Sameh Soliman
Hospital For Sick Children, Toronto, ON, Canada

**Purpose:** To describe optimizing techniques of laser photocoagulation in retinoblastoma utilizing optical coherence tomography (OCT) guidance.

**Methods:** OCT scanning of the intended treatment area was performed during examination under anesthesia. Embedded OCT software tools (calipers on variable frames) were studied in multiple cube scans (vertical and horizontal) and plotted on the red-free image to determine both extent and relevant measurements. Red-free images were compared to colored fundus photos for localizing anatomical landmarks (vessels, vessel branching, fovea or optic disc).

**Results:** In perifoveal tumors, laser Photocoagulation avoids the foveal center and perifoveal area by starting from crescent-shaped anti-foveal edge including outer tumor boundary with the adjacent retina and moving closer to the fovea in subsequent sessions. In invisible and subclinical tumors, calipers determine tumor location and anatomical landmarks proposed the location on the fundus photo and a single laser (532 nm) burn was fired in that proposed location. OCT showed tumor-laser burn relation and laser treatment was continued accordingly. A post-laser OCT ensured complete tumor treatment. A similar technique was utilized in tumor scar recurrences.

**Conclusions:** OCT guided photocoagulation can optimize visual outcome by reducing scar size, preventing surface traction and migration and avoiding foveal center.

**Conflict of interest disclosure:** none
O17: Retinoblastoma treatment in the age of intra-vitreal and intra-arterial chemotherapy: the UCSF experience

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Purpose: To determine (1) how UCSF retinoblastoma ocular salvage rates have changed since the implementation of intra-vitreal and intra-arterial chemotherapy, (2) treatment needed to achieve remission for each ICRB group, and (3) visual acuity post-treatment.

Methods: Retrospective review of 70 patients treated since 2013. Remission is defined as no recurrence for =3 months since last treatment.

Results: 100 eyes of 70 patients (43% bilateral disease) were included. RB1 germline status was negative, positive, or mosaic in 50%, 46%, and 4% of patients, respectively. The number of eyes in each ICRB Group (A-E) and the ocular salvage rates at a mean of 28 months were: A (n=14, 100%), B (n=18, 100%), C (n=9, 78%), D (n=26, 62%), and E (n=33, 12%). Relative to UCSF historic rates (1990-2012), salvage rates improved for Group D (44% vs. 8%, chi-squared test, p=2.4 x10-12) and Group E eyes (9% vs. 6%, p=0.00014). Figure-1 summarizes the type and number of treatments administered for eyes in remission for each ICRB Group, highlighting efficacy of intra-arterial chemotherapy in advanced disease. This information was used to develop a standardized retinoblastoma treatment protocol at UCSF. Most Group A-C eyes in remission retained excellent visual acuity (20/20-20/60), though some with macular tumors had acuity ranging from 20/200 to light perception. Three Group D eyes achieved acuity better than 20/700, but the remainder of Group D and E eyes in remission had poor acuity (hand-motion or counting-fingers).

Conclusions: UCSF retinoblastoma ocular salvage significantly improved with intra-vitreal and intra-arterial chemotherapy.
Figure 1: Type and average number(s) of each therapy to achieve eye remission, by ICRB Group

Eye remission = has not required treatment of any kind for 3 or more months, with no evidence of recurrence
Number that achieved remission per ICRB group: A (n=13), B (n=15), C (n=6), D (n=6), E (n=3)
SC systemic chemotherapy; IAC intra-arterial chemotherapy; IVC intra-vitreal chemotherapy
p-value represents analysis of variance of the means (ANOVA)

Conflict of interest disclosure: none
O18: Screening for pineal trilateral retinoblastoma revisited: a meta-analysis

Marcus De Jong¹

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Purpose: Objectives of this study were to determine until what age children are at risk for pineoblastoma, whether the onset of pineoblastoma is linked to the age at which eye tumors develop and the lead time between a detectable tumor and symptoms. Up to 4% of patients with retinoblastoma are at risk for pineal trilateral retinoblastoma (pineoblastoma). Early detection and proper treatment is essential for survival. Current evidence is unclear on the usefulness of screening for pineoblastoma and, if so, until what age.

Methods: We conducted the study according to the MOOSE guideline for reporting meta-analyses of observational studies. We searched PubMed (Medline) and Embase between January 1, 1966 and February 27, 2019 for published literature. Inclusion of all articles was performed separately and independently by two authors. Articles reporting patients with trilateral retinoblastoma with last known survival status and follow-up data were considered. Two authors independently each extracted the data from all included articles. Discrepancies were resolved in consensus. The Mann-Whitney U test was used to compare subgroups. Pearson’s r was used to calculate a correlation between two continuous variables.

Results: In total 138 pineoblastoma patients were included in the analysis. Ninety-five percent of patients with asymptomatic pineoblastoma (21/22) were diagnosed before 40 months (median 16 months, IQR 9–29). Age at pineoblastoma diagnosis was independent of age at intraocular retinoblastoma diagnosis (testing for dependency: P > 0.4). The lead time between asymptomatic and symptomatic pineoblastoma was ~1 year. From this, we calculated that for a screening program with 1 MRI scan every 6 months after retinoblastoma diagnosis (~6 months of age) until the age of 3 years, at least 311 scans would be required to detect 1 pineoblastoma.

Conclusion: This study suggests that retinoblastoma patients are at risk for pineoblastoma within a narrower time period than previously assumed and the age of retinoblastoma diagnosis, laterality and previous treatment have no influence on the age of pineoblastoma diagnosis. Screening would require numerous MRI scans to diagnose 1 pineoblastoma and even more to save 1 life, but does seem to be cost-effective.

Conflict of interest disclosure: none
O19: A human organoid-based model for retinoblastoma

Julia Menges
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Retinoblastoma is the most common tumor of the eye in early childhood and is caused by biallelic inactivation of the retinoblastoma gene RB1. Efforts to model retinoblastoma in mouse were not satisfactory as the mutation of RB1 alone is not sufficient for tumor formation, indicating that the development of retinoblastoma in these two species follows different routes. Therefore, we have created a human cell-based model for retinoblastoma using organoid technology. Using the CRISPR/Cas9 system we have generated H9 hESCs carrying a mutation in exon 3 (close to the splice donor site) either on one or both RB1 alleles. By now, we have characterized 10 heterozygous, one compound heterozygous and one homozygous clone by DNA, RNA and protein analysis. For comparative differentiation into retinal organoids we have used the H9 hESCs as well as clones G12LS and C7, heterozygous and homozygous for the RB1 variant c.374_380del (LRG_517t1), respectively. The variant results in a premature stop codon on protein level (p.Glu125Valfs*9). Generated retinal organoids contain mature photoreceptors (rods and cones) in the outer layer and ganglion cells, Müller glia cells, amacrine cells and horizontal cells in the inner layer. Presence of different cell layers in the retinal organoids was analysed by immunocytochemistry. RB1 wildtype, G12LS RB1<sup>+/−</sup> and C7 RB1<sup>−/−</sup> organoids stained positive for ganglion cells, immature photoreceptors and cone photoreceptors on day 35, 61 and 96 of differentiation, respectively. Immunostainings on day 126 indicated enhanced proliferation, a decrease in rod photoreceptors and horizontal cells and absence of amacrine cells in C7 RB1<sup>−/−</sup> organoids. In addition, over time the neural retina layer of C7 RB1<sup>−/−</sup> organoids took on a loose and disordered appearance. Overall, the presence of cones in our organoid-based model demonstrates its applicability for studies in retinoblastoma research as these are the presumed cell-of-origin of retinoblastoma. Moreover, we could detect first differences between the wildtype and RB1 knock-out organoids. Expression analyses of markers specific for the different retinal cell layers via qPCR and FACS are ongoing.

Conflict of interest disclosure: none
O20: New retinoblastoma cell culture establishment and drug resistance assessment

Alexander Tsygankov¹
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2. N.N. Blokhin National Medical Research Center Of Oncology, Moscow, Russian Federation

**Purpose:** An attempt to create a primary retinoblastoma cell culture and evaluation of drug resistance to chemotherapy.

**Methods:** The study included 19 patients aged 6-64 months (27.9±17.4). In 6 patients (31.6%) bilateral disease was noted, in 13 (68.4%) - monolateral. In 18 patients (94.7%), group E retinoblastoma was detected. In all cases, enucleation was performed, while in 94.7% of cases a low-differentiated retinoblastoma was defined. Samples of tumor tissue were taken to obtain a cell culture, followed by a study of drug resistance and cell metabolic activity (MTT-assay).

**Results:** In four cases it was possible to obtain surviving adhesive retinoblastoma primary cultures. Cytological verification was carried out. For bilateral lesions, primary cultures were obtained more often (4/6), whereas in monolateral lesions, the cells did not survive (0/13) (p=0.003). A statistically significant relationship with the age of patients (p=0.33) and the presence of calcinates in the tumor according to ultrasound data (p=0.26) was not revealed. The performed MTT-assay showed no differences in the sensitivity of cell cultures to irinotecan and ifosfamide. Significant differences in stability between cultures were obtained only for oxaliplatin and ascorbic acid.

**Conclusions:** We describe the first domestic experience in obtaining the cellular culture of retinoblastoma and assessing chemosensitivity to various drugs. Performing an MTT-assay with an evaluation of drug resistance can be used both in clinical practice to refine the chemotherapy regimen with registered drugs and to develop new approaches to retinoblastoma treatment in assessing the resistance of tumor cells in vivo in animal models.

**Conflict of interest disclosure:** none
O21: Delay in the diagnosis of retinoblastoma: the role of parents and practitioners

Jaclyn White
Gole, Glen
Queensland Children's Hospital, Brisbane, QLD, Australia

Purpose: Early diagnosis of retinoblastoma is essential for patient survival and the preservation of sight. The ability of parents and primary healthcare practitioners to recognise common presenting signs and symptoms is crucial in minimising time to diagnosis.

Methods: Over a period of 11 years (2008-2019), the parents of 37 patients diagnosed and treated for retinoblastoma in Queensland were interviewed and asked a series of standard questions which focused on their child's referral pathway. Particular attention was paid to the 'diagnostic lag period', the time from when signs or symptoms were first detected by a parent, to when a definitive diagnosis of retinoblastoma was made by an experienced consultant ophthalmologist. The number and type of healthcare professionals consulted prior to diagnosis was also noted.

Results: The most common presenting symptom was leukocoria (54%), followed by strabismus (27%), suspected poor vision (including apparent inability to fix and follow, and nystagmus) (11%) and heterochromia iridis (5%). One child was diagnosed antenatally on account of a positive family history. The average ‘parental lag period’ (time from when the child was first noticed to be symptomatic to when advice from primary healthcare professional (PHP) was sought) was 3.58 months (Range = 0-18 months). The average ‘practitioner lag period’ (time from primary care consultation to definitive diagnosis by a consultant ophthalmologist) was 3.55 weeks (Range = 0-9 months). In 70% of cases, general practitioners were the first PHPs consulted. In only 13 of the 37 (35%) cases was an urgent referral to an ophthalmology service issued at the initial consultation. In 10 cases, 2 or more primary care consultations were needed to secure an urgent ophthalmic referral.

Conclusion: Parents and primary care practitioners require greater education about the presenting signs and symptoms of retinoblastoma.


Conflict of interest disclosure: none
Session 6

Associated Posters
P16: Bilateral retinoblastoma with 13q-syndrome in a patient carrying an X;13 balanced translocation without rearrangement of the RB1 gene
Hiroyoshi Hattori

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2. Division Of Molecular Genetics, Institute For Comprehensive Medical Science, Fujita Health University, Toyoake, Japan
3. Department Of Ophthalmology, National Hospital Organization Nagoya Medical Center

Background: Retinoblastoma with 13q- syndrome generally exhibits the structural deletion of RB1 gene which is responsible for the disease. However, several patients including our case carrying a constitutional X;13 balanced translocation, who seem to maintain the normal RB1 structure, have been reported. Our purpose is to investigate whether retinoblastoma and other symptoms in our patient can be accounted for by the functional impairment such as X-inactivation. Patient: The patient was diagnosed with retinoblastoma in the left eye at age 18-month and in the right eye with 4-month lag time. Before the onset, medical checkup revealed poor weight gain at 1 month old and developmental retardation afterwards. Chromosomal analysis revealed reciprocal translocation of chromosome X-13[46,X,t(X;13) (q27;q12.3)]. She was diagnosed with retinoblastoma (Group D1) unpredictably when she underwent brain MR imaging for developmental delay screening. She was treated with 4 cycles of systemic chemotherapy (vincristine, etoposide, and carboplatin), in addition to intra-arterial chemotherapy and the laser transpupillary thermotherapies. Initial cycles of chemotherapy resulted in prolonged renal tubular disorder and constipation. She eventually relapsed in the left eye and received enucleation at the age of 4. She could not speak at the age of 6, manifesting severe speech and language disorder and developmental retardation.

Methods and Results: The genetic testing in this study was approved by the ethics committee. Blood samples were obtained with informed consent from the parents in the multiple sessions of genetic counselling. FISH analysis revealed the breakpoint of 13 chromosome was 12 to 15 Mb upstream of the RB1 locus. Sequencing analysis confirmed no copy number change nor nucleotide variation in the RB1 gene. HUMARA assay found the derivative X chromosome was inactivated in a few cells. Higher methylation frequency showed around RB1 promotor region than in a healthy control.

Conclusions: Our analysis indicated that the X-inactivation caused single allelic inactivation of RB1 gene, at least, in part of the cells, suggesting the 1st-hit of retinoblastoma genesis without disrupting gene structure itself. Haploinsufficiency of 13q chromosome affected by the X-inactivation would be associated with other symptoms of the patient.

Conflict of interest disclosure: none
Session 7

Clinical Studies in Gene Therapy II
T21: Gene therapy for X-linked retinitis pigmentosa caused by mutations in \textit{RPGR}

Robert MacLaren

Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Mutations in \textit{RPGR} probably account for more causes of severe retinitis pigmentosa than any other gene in the European population. Although the \textit{RPGR} cDNA is under 3.5 kb and therefore encodable with the expression cassette of adeno-associated viral (AAV) vectors, cloning this sequence has proved to be highly challenging. A repetitive purine rich region in the splice variant ‘\textit{RPGR-ORF15}’ required for photoreceptor function is prone to insertions and deletions and a splice donor site within the ORF15 sequence remains prone to secondary splicing when the mRNA is read from the AAV genome in transduced photoreceptor cells. Recently the research group in Oxford used codon changes to stabilise the RGPR gene, which led to the first gene therapy clinical trial for X-linked retinitis pigmentosa caused by \textit{RPGR} in 2017. The trial is now led by Nightstar and includes countries in the UK and Europe. In this lecture I will give an overview of the basic science leading up to the trial and share some preliminary results showing improved visual function.

\textbf{Conflict of interest disclosure:} The following conflict(s) of interest must be disclosed:

Robert Maclaren
- received grants or research support from Biogen Inc.
- received honorary or consultation fees from Biogen Inc., Novartis Pharma, and Allergan
- participated in a speaker’s bureau sponsored by Biogen Inc., Novartis Pharma
- is the named inventor on several patents which are owned and licensed out by the University of Oxford.
T22: Surgical challenges and outcomes with voretigene neparvovec (Luxturna)

Stephen Russell¹
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2. University Of Iowa, Dept Of Ophthalmology And Visual Sciences, Institute For Vision Research, Iowa City, IA, USA

**Purpose:** To present and discuss several post-FDA surgical interventions involving voretigene neparvovec and discuss related study cohort outcomes

**Methods:** Pre-, intra- and post-operative findings in selected patients that have received voretigene neparvovec for biallelic RPE65-mutation associated Leber’s Congenital Amaurosis (LCA) will be presented and discussed that illustrate non-trial related surgical or evaluation challenges.

**Results:** Subjects will include bleb-related retinal detachment and repair, pre-operative evaluation of full-field light sensitivity (FST) -incapable patients, FST deterioration following injection and use of intraoperative ocular coherence tomography (OCT).

**Conclusions:** Surgical evaluation and management of biallelic RPE65-mutation associated LCA patients post-FDA and EMA approval requires a more comprehensive clinical approach than was needed within the phase 3 trial. Complications and side effects not observed in the phase 1 and 3 voretigene neparvovec studies have been observed. With additional US and European treatments, more diverse surgical and geographic experiences will provide broader safety and efficacy profiles.

**Conflict of interest disclosure:** The following conflict(s) of interest must be disclosed:

Stephen R. Russell
- received grants or research support from Spark Therapeutics, Inc. and ProQR Therapeutics N.V.
- received honorary or consultation fees from Novartis Pharmaceuticals Corporation
- is stock shareholder of IDx Technologies Inc.
Session 7

Associated Posters
P17: Intravitreal Ranibizumab (Lucentis®) in the treatment of non-leaking macular cysts in retinal dystrophy

Ammar Alfarsi

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2. Ophthalmology Department, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman
3. Armed Forces Hospital Eye Center, Muscat, Sultanate of Oman

Methods: This is a prospective cohort study followed by a non-controlled, nonrandomized, non-blinded quasi-experimental trial, conducted on patients >18 years, diagnosed with retinal dystrophy and non-leaking macular cysts between January 2015 and July 2018 in one center (Sultan Qaboos University Hospital). Phase 1: Patients with best-corrected visual acuity (BCVA) ≤ 0.5 received carbonic anhydrase inhibitors (CAI) (oral acetazolamide 500 mg/day or topical brinzolamide twice daily) and followed-up for three months. Phase 2: Patients who did not show an adequate response with CAI, were invited to receive three 0.5 mg IVR injections at monthly intervals. Efficacy was predetermined as a significant reduction (> 10%) of the central macular thickness (CMT) with/without improvement (> 1 line) in BCVA. Presence of any complication was noted. The mean reduction in CMT with IVR treatment was analyzed using Wilcoxon signed ranks test based on positive ranks. Correlation between BCVA and CMT was assessed using Spearman’s rho correlation coefficient. The study was approved by the institutional research and ethics committee.

Results: 21 eyes of 13 patients with retinal dystrophy (8 males and 5 females) with a mean age of 23 years ±5 (SD) were recruited. Phase 1: 9 eyes of 7 patients with BCVA ≤ 0.5 received CAI. 3 eyes of 2 patients (33%) showed a positive response to the treatment. A mean reduction of 19% in the CMT compared to pretreatment levels was observed. Phase 2: 6 eyes of 5 patients with BCVA ≤ 0.5 who did not respond to CAI treatment received IVR injections. All eyes (100%) showed a positive response to the treatment. A mean reduction of 42% in the CMT was observed compared with pretreatment values (p < 0.05). 1 patient showed improvement in BCVA by 2–4 lines in both eyes; no change was seen in others. A moderate negative correlation was found between BCVA and change in CMT (r = 0.432; p = 0.467). 4 patients (57%) showed intolerance to oral CAI. No ocular or systemic complication was noted following IVR injections.

Conclusions: Patients with retinal dystrophy and non-leaking macular cysts who do not respond to CAI treatment showed a significant reduction in CMT following IVR injections. A corresponding visual benefit was observed, but this was not statistically significant. No complications from IVR were observed. Further studies with more patients and longer follow-up are warranted to ascertain the efficacy and safety of this treatment modality.

Conflict of interest disclosure: none
P18: Laser photocoagulation for hemorrhagic retinopathy in a newborn with Norrie disease
Monika Andrassi-Darida¹
Preising, Markus²; Stieger, Knut²; Lytvynchuk, Lyubomyr¹, ²; Friedburg, Christoph¹, ²; Lorenz, Birgit¹, ²
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2. Dept. Of Ophthalmology, Justus-Liebig-University Giessen, Germany

Purpose: To report the functional and anatomical outcome 10 months after diode laser photocoagulation (DLC) at birth in a case of Norrie disease with hemorrhagic retinopathy.

Methods: A newborn from a family with Norrie disease (7 affected males) was referred to us for examination immediately after birth. Transpupillary DLC of the avascular peripheral retina was performed on the second day of life. Functional and morphological follow-up included (1) preferential looking testing, (2) retinal imaging by wide-field colour and monochromatic fundus photography and angiography, OCT and (3) full-field ERG. Measurement of VEGF concentration in blood samples and aqueous humour from the anterior chamber was performed as well as molecular genetic testing.

Results: At presentation an extensive intraretinal bleeding was diagnosed on the posterior pole with avascular periphery. Bleeding completely resolved in both eyes after DLC but macular atrophy RE and a recurrent moderate extramacular vitreous hemorrhage LE developed. Hand-held SD-OCT showed (1) in the beginning subretinal subfoveal fluid, that resolved after laser, and (2) a prepapillary and intraretinal peripapillary fibrosis (LE>RE), with progressive dragging of the macula in the LE. Fluorescein angiography at age 6 months showed a leaking network of telangiectatic intraretinal vesels peripapillary, unchanged at follow up examinations. At the last examination at 10 months grating visual acuity was 20/1200 RE and 20/1600 LE and cycloplegic refraction was RE -3.25 sph/-4.74 cyl/70° and LE -3.75 sph/-4.25cyl/180°. A reduced cone and rod function was detected by full-field ERG in the RE. As VEGF levels were not significantly elevated, an anti-VEGF injection was considered not to be appropriate. Molecular genetics identified a a novel mutation in the NDP gene: p.C95F (c.284G>T).

Conclusions: Diode laser photocoagulation of the avascular retina, as reported in rare case reports, had a protective effect on the retina in the first months of life. Persistent extensive intraretinal leakage can be expected to be a risk factor for later retinal changes requiring close multimodal monitoring.

Conflict of interest disclosure: none
P19: Enhancing glycolytic metabolism with gene therapy and a small molecule drug attenuates neurodegeneration

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**Purpose:** To determine the mechanism of attenuation of the neurodegeneration process in retinitis pigmentosa (RP) by enhancing glycolytic metabolism in photoreceptors using gene therapy and a small molecule drug.

**Methods:** To enhance glycolytic metabolism using gene therapy, we created an RP mouse model harboring a Vhl gene that can be exclusively excised in rod photoreceptors using tamoxifen-inducible genetic scissors. We systematically injected tamoxifen in 7-, 8-, and 10-day old RP mice to induce Vhl knockout, reprogram the metabolism towards glycolysis, and assess the neuroprotective effects in rod photoreceptors using electroretinography (ERG), histology, immunostaining, and mass spectrometry. To determine whether these neuroprotective effects can occur using a small molecule drug, we orally administered an FDA-approved small-molecule VHL inhibitor to Pde6b RP mice every two days from postnatal day 5 and evaluated the effects using histology and mass spectrometry.

**Results:** Based on histology and immunostaining, we observed increased outer nuclear layer (ONL) thickness and preserved rod and cone photoreceptors in the tamoxifen-injected mice. ERG showed that the retinal function was well preserved after increasing glycolytic metabolism in rods. In RP mice that were administered the small molecule drug, glycolytic metabolism increased in the retina, resulting in increased ONL thickness representing preserved photoreceptors as shown by histology.

**Conclusions:** Metabolic reprogramming through gene therapy and repurposing of a small molecule drug increases glycolytic metabolism, leading to structural and functional perseveration of the retina in a preclinical model of RP.

**Conflict of interest disclosure:** none
P20: Individual treatment of an infant with severe conjunctivitis lignosa (CL) and other systemic manifestations of plasminogen deficiency, caused by a compound mutation of the PLG gene

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Introduction: Plasminogen deficiency is an inherited autosomal recessive rare disease. It leads to increased deposition of fibrin, causing ligneous, ‘wood-like’ growths on all mucous surfaces. Those may lead to bronchial obstruction, LC and hydrocephalus. Spinal fluid drainage via ventriculoperitoneal shunt can be complicated by peritoneal ligneous membranes. Formation of membranes is triggered by infection and injuries. Invasive treatments should be avoided as much as possible. Currently, there is no FDA approved treatment available.

History: The patient was born at 35 weeks gestational age by caesarian section due to increasing hydrocephalus occlusus. A ventriculoperitoneal shunt was implanted 10 days later. Spinal fluid drainage was insufficient due to peritoneal insufficiency which led to significant ascites. At 3 months she developed LC, suffering constant pain and irritation of both eyes. The ophthalmologist measured a baseline plasminogen residual activity of 13 – 30%. Eye membranes were treated conservatively with antibiotic, steroid and heparin eye drops. They were finally surgically removed (3x) in order to avoid amaurosis and consecutive blindness. Steroid eye drops caused glaucoma in both eyes. At 9 months the baby was failing to thrive, refusing any nourishment, except hourly breast milk. Genetic examination revealed an inherited compound variant of the PLG gene.

Treatment: At 9 months we started the patient on an experimental treatment with intravenous Ryplazim™ (human plasminogen). Her condition improved immensely, as previously published1. After 15d the LC had completely vanished, ascites was decreasing, and age appropriate food intake was established a few weeks later. Initial treatment frequency of 6,6mg/kgbw (q48h) was reduced to (q5d) after resolution of symptoms. Residual Plasminogen activity @24h after plasminogen infusion was 100%, @48h 45%, @5d 20%. Treatment breaks led to recurrent LC after 5 days and increasing amounts of ascites. The drug is administered at home by the mother via a port catheter.

Conclusion: Congenital plasminogen deficiency is a possibly life threatening and painful disease. Patients with hydrocephalus occlusus and LC should be tested for plasminogen activity. Current therapy options cannot assure acceptable quality of life. Treatment with Ryplazim™ (human plasminogen) is relatively easy, safe and very effective.


Conflict of interest disclosure: none
Session 8

Secondary Cancer and Survival in Retinoblastoma
T23: The impact of the type of predisposing RB1 variants on the incidence of malignancies

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Purpose: Survivors of heritable retinoblastoma carry a high risk to develop other malignancies later in life. The incidence of these second malignancies is significantly raised after external beam radiotherapy (EBRT). We aimed to analyze the impact of the type of the predisposing RB1 gene variant on the incidence of SPM with and without previous irradiation.

Methods: From 1940 to 2008, 655 national patients were treated for heritable retinoblastoma at the German referral center. Complete information on second primary malignancies until 2012 and data on constitutional RB1 variant were available for 317 patients (48.3%).

Results: SPM occurred in 51 of 317 survivors of heritable retinoblastoma. After irradiation, the cumulative incidence ratio (per 1,000 person years) of SPM was 10.2 (95% confidence interval 7.3-13.9) and was not influenced by type of constitutional RB1 mutations. In non-irradiated retinoblastoma survivors, the cumulative incidence ratio of SPM was lower compared to the irradiated patients (IR 3.6 [1.7-6.7]; p< 0.005). Without previous irradiation, SPM were only observed in patients with high penetrance RB1 variants and no SPM was reported in survivors with somatic mosaicm of RB1 gene or in survivors with low penetrance RB1 variant. The type of tumors in non-irradiated heritable retinoblastoma survivors were diverse and comprised of three soft tissue sarcoma, one hematological malignancy, three mamma carcinoma, one bronchial carcinoma, one melanoma and one brain tumor.

Conclusion: The influence of the type of predisposing RB1 variant on the incidence of SPM in our cohort was only evident without previous radiotherapy treatment. After external beam radiotherapy, all survivors of heritable retinoblastoma were at risk for second cancers regardless of the constitutional RB1 genotype.

Conflict of interest disclosure: none
T24: Retinoblastoma and second primary malignancies: a Dutch overview and update
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Due to their genetic predisposition (RB1 mutation), the heritable retinoblastoma (Rb) patient is at risk for the development of second primary malignancy (SPM). Throughout their lives, survivors of heritable retinoblastoma are susceptible to various but discrete types of SPMs. This risk of developing SPMs is increased even further by therapy like external beam irradiation and this in combination with chemotherapy. Survival from Rb exceeds 95% in high and middle income countries. While no significant changes in mortality were found for non-heritable Rb survivors, due to SPMs heritable Rb survivors in the Netherlands have a significantly increased standardized mortality ratio (SMR) of 12.8 (95% CI: 9.6-16.5). Consequently, SPMs are now the leading cause of death in patients with heritable retinoblastoma. Patients with SPMs that survive after treatment are at risk for third, fourth and fifth malignancies. The risk of a third primary malignancy was increased 8-fold in Dutch patients that have suffered an SPM (SIR=8.5 (95% CI: 3.7-16.7) ) and the Absolute Excess Risk (AER) increased to 202 excess malignancies per 10,000 person years. The Dutch nationwide retinoblastoma cohort has recently been updated (1945-2017) and now contains 910 Rb patients of whom 524 non-heritable and 386 heritable. Among the heritable patients 98 SPMs were diagnosed with a SIR of 10.4 (95% CI: 8.4-12.7) for all malignancies combined and an AER of 85.5. With extended follow-up the risk for sarcomas of soft tissue (SIR=149.6 (95% CI 91.4-231.0) ) and bone and joint (SIR=188 (95% CI 107.7-305.8) ) remains high in this group. When looking at therapy, radiotherapy (SIR 11.9 (95% CI 8.9 - 15.6) ) and radiotherapy combined with chemotherapy (SIR 20.8 (95% CI 13.5 - 30.7) ) show a significantly higher risk for all malignancies compared with local therapy and/or enucleation (SIR 4.7 (95% CI 2.7 - 7.5) ) while the risk from sole chemotherapy (SIR 11.3 (95% CI 1.6 - 48.2) ) is based on two events alone. The next step is to pool our data with other international retinoblastoma cohorts in the IRISC (International Retinoblastoma and Second Cancer) consortium in order to have sufficient power to better identify factors responsible for SPM development.

Conflict of interest disclosure: none
O22: Understanding and predicting tumor risk in heritable retinoblastoma
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Purpose: Risk of retinoblastoma and other tumors is not the same in all individuals with a heritable predisposition. This heterogeneity may be exploited to adjust the timing and extent of examinations for early detection of tumors to individual risk profiles. As a prerequisite for individualized patient management, observable risk factors must be identified and a model that describes the joint effect of these parameters has to be developed. These models must also provide information on the credibility of predictions.

Methods: Multilevel Bayesian data analysis was chosen as the principle framework for statistical inference of tumor risk. The first level of analyses within this framework was aimed at modelling retinoblastoma penetrance.

Results: A structured database for genotype and phenotype data was established and populated with published and unpublished data. The current data set includes 85 families with at least one instance of incomplete penetrance (founders excluded). Most RB1 variant alleles segregating in these families have previously been classified as “low penetrance mutations” but there are notable exceptions. Parent-of-origin of the variant allele has an effect on penetrance but this effect is also variable. Thus it appears that a model for explanation of tumor risk that is restricted to variant effect data and parent of origin misses some variables. The contrast of posteriors for inter- and intrafamilial penetrance suggests genetic variation in cis to the RB1 as a candidate. However, as the families included in the analyses are from diverse genetic backgrounds, genetic variation in trans is not implausible.

Conclusions and outlook: There are great hopes that examination schedules for early detection of tumors can be improved by individualized prediction of tumor risk. Our approach, multilevel Bayesian data analysis, provides the conceptional framework and tools to extract a maximum of information relevant to individual risk from observable data.

Conflict of interest disclosure: none
O23: Study of genetic predisposition to uveal melanoma

Mohamed Abdel-Rahman¹

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Purpose: The aim of this study was to identify germline mutations in cancer susceptibility genes in uveal melanoma (UM) patients with strong personal and/or family history of cancer.

Methods: A total of 164 UM probands, including 33 with familial UM, were studied. Germline mutation and large deletion in BAP1 were assessed by direct sequencing and multiplex ligation probe amplification (MLPA), respectively. Whole exome sequencing and cancer gene panel testing were carried out on patients with no detectable BAP1 alterations. Functional validation was carried out by combination of genomic and proteomic studies.

Results: We identified actionable pathogenic variants in nine known hereditary cancer predisposition genes BAP1, PALB2, MLH1, MSH6, CHEK2, SMARCE1, ATM, BRCA1 and CTNNA1 in 18 patients, including 9/33 (27.3%) with familial UM and 9/131 (6.9%) of UM patients with strong personal and/or family history of cancer. Seven patients had pathogenic variants in BAP1, one had a whole BAP1 gene deletion, three had pathogenic variants in CHEK2, two in PALB2, while variants in the other genes each occurred in one patient. Biallelic inactivation of BAP1, PALB2 and MLH1 was observed in tumors from the respective patients. The frequencies of pathogenic variants in BAP1, PALB2, MLH1 and SMARCE1 in UM patients were significantly higher than the observed frequencies in non-cancer controls [p= 5.7 -18, OR: 940 (198-4460); p=0.03, OR: 7.6 (1.9-31); p=0.048, OR: 21.9 (2.9-167); p=0.0012, OR: 1770 (108-28984), respectively].

Conclusions: Together with published data, the study provides definitive evidence of gene/disease association of germline BAP1 with predisposition to UM, as well as, moderate evidence for germline mutation in PALB2 and MLH1. It also identifies several other candidate susceptibility genes. The results suggest locus heterogeneity in predisposition to UM. Genetic testing for hereditary predisposition to cancer is warranted in UM patients with strong personal and/or family history of cancers.

Conflict of interest disclosure: none
O24: Prognostic information for mosaic and high penetrant carriers of RB1 mutations

M. Ashwin Reddy

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**Purpose:** The role of mosaicism in Retinoblastoma (Rb) is increasingly being recognised as molecular genetic tests become more sensitive. Previous studies have been based upon disease eye ratio and not shown striking differences between mosaic and heterozygous RB1 mutation carriers. Providing information regarding laterality and tumor number for mosaic and heterozygous RB1 mutation carriers would be helpful for clinicians and parents.

**Methods:** A retrospective analysis of mosaic and heterozygous RB1 mutation carriers (low penetrant (LP) and high penetrant (HP) ) from 1992 to 2017 was conducted. Tumor number per eye was assessed in patients classified with mainly A, B and C tumors using the International Intraocular Retinoblastoma Classification system. Patients with D or E group eyes were assessed based upon age at diagnosis.

**Results:** Data were analysed for 107 patients, 64 were full germline familial patients (53 HP and 11 LP) and 43 mosaic patients. 25% of high penetrant patients were unilateral at presentation and 9 of 13 (69%) developed tumors in their previously unaffected eye. 72% of mosaic patients were unilateral and only 1 of 31 (3%) developed tumors in their unaffected eye. Age at diagnosis was higher in mosaic patients (median 16 months range 2-117) than HP patients (median 7 range 2-33) (p<0.001). Tumor number per eye was lower in mosaic patients (median 1.5 tumors range 1-6) than highly penetrant patients (median 3 range 1-8) (p=0.009). There were only 3 gaugeable eyes regarding tumor number with LP.

**Conclusion:** This is the first study to provide prognostic information in the form of tumor number. Children with mosaicism have fewer tumors in eyes with Rb compared to HP carriers and are more likely to remain unilateral.

**Conflict of interest disclosure:** none
O25: Outcomes of RB1 Gene Testing from blood samples of 113 Retinoblastoma survivors and their families (398 in total) collected on a single day at Aravind Eye Hospital, Coimbatore, India

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Purpose: To report the outcomes of RB1 gene testing of blood samples from 113 retinoblastoma survivors and their family members (398 in total), collected on a single day at Aravind Eye Hospital, Coimbatore, India.

Methods: During the world retinoblastoma week celebration, blood samples of 113 retinoblastoma survivors along with their immediate family members were collected on a single day on 13th May 2017 after taking an informed consent and documenting a detailed family history along with pedigree chart. Ethics committee approval was taken. Overall 398 blood samples were collected of which 113 samples were of known retinoblastoma survivors and 285 of their family members. DNA was extracted and stored at -200 C after initial quality check. RB1 gene mutation analysis was performed by Sanger Sequencing. Large deletions and duplications were analyzed by Multiplex Ligation dependent Probe Amplification. Genetic counseling was given to all the cases two years later on 18th May 2019 during this year’s world retinoblastoma week celebration.

Results: Of the 113 cases, 65 were unilateral and 48 were bilateral. Totally 60 germline mutations were identified. Inherited germline mutations were identified in all the affected family members in 5 families with known clinical history of retinoblastoma, in 12 patients (5 bilateral and 7 unilateral), mutations were identified in a family member other than proband, however they did not had RB. De novo germline mutation were identified in 34 patients (29 bilateral and 5 unilateral). In 9 families, only one parent was available for analysis and hence those 9 germline mutations could not be categorized as inherited or de novo. 9 germinal mutations were not know whether it is de novo or inherited (8 bilateral and 1 unilateral). Two novel nonsense mutations causing truncated RB1 protein was identified in our patients.

Conclusion: Overall, mutations were identified in 47/48 (98%) and 13/65 (20%) in bilateral and unilateral patients respectively, which indicates the highest mutation detection rate. The need for continuous surveillance in patients and family member with RB1 mutations were explained. Reduced risk of retinoblastoma in siblings and offspring was a greater relief for families (57%) with no RB1 mutations.

Conflict of interest disclosure: none
O26: Type of \textit{RB1} mutation and age at diagnosis of familial retinoblastoma screened from birth

\textbf{Milo van Hoefen Wijsard$^1$}

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\textbf{Purpose:} Currently, the guidelines for screening children at risk for familial retinoblastoma (Rb) are a balance between early detection and the least exposure to potentially harmful and expensive diagnostics (general anesthesia). If \textit{RB1} mutation type influences the time of Rb tumor presentation, personalized screening based on germline mutation could reduce unnecessary exposure to anesthesia. The aim of this study is to explore the genotype-phenotype relation between the germline \textit{RB1} mutations and the age at detection of the first Rb tumor.

\textbf{Methods:} All patients at risk for familial Rb who were screened from birth and with a known \textit{RB1} gene mutation from nine study centers were included in this study. Patients were categorized by mutational type based on its effect on the \textit{RB1} protein and its presumed penetrance based on previous literature: Truncating, Altered Splicing, Large Deletions, Missense and regulatory variant mutations. We compared median time to a first Rb tumor between the groups using survival analyses and Log-Rank testing.

\textbf{Results:} One-hundred-forty-one (141) patients from 115 families were included. After a median follow-up of 6.6 years, 128 patients developed at least one Rb tumor while 13 patients did not develop any Rb tumor. In Truncating mutations (median time to a first Rb tumor \textit{MTFT} (95\%CI) = 19 days (10-28) ) and Large Deletions (\textit{MTFT} = 20 days (11-29) ) first Rb tumors occur sooner and more often than in Altered Splicing (\textit{MTFT} = 65 days (0-202) ) and Missense and regulatory variant mutations (\textit{MTFT} = 220 days (0-726) ) (Log-Rank; \textit{p}<0.03). Although the difference in time to a first Rb tumor is significant the majority of first tumors still present in the first 2 months.

\textbf{Conclusion:} Low penetrance \textit{RB1} mutations not only lead to less cases of Rb but the first Rb tumor also occurs significant later in time. Still half of first Rb tumors are diagnosed within the first two months, this underscores the importance of early and regular screening in familial Rb, even in patients with a low penetrance mutation.

\textbf{Conflict of interest disclosure:} none
Session 8

Associated Posters
P21: Patient-reported outcome measures for retinoblastoma: a scoping review

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Purpose: Retinoblastoma is a childhood retinal cancer with lifelong consequences such as vision loss and secondary cancer risks. Patient-reported outcome measures (PROMs) are instruments that measure outcomes related to health directly reported by patients. The purpose of this study was to determine which PROMs have been used for retinoblastoma, pediatric ophthalmology and pediatric oncology, and to assess their overall composition and quality.

Methods: A scoping review, conducted with the help of an information scientist, was performed on October 10, 2018 in MEDLINE and Embase. It included the keywords “Patient-Reported Outcome”, “exp retinoblastoma”, “exp Ophthalm”, “exp Neoplasm”, in studies on populations aged 0-18 published after 2004 (inclusive). Manuscripts were included if they were in English and reported on retinoblastoma, pediatric oncology or pediatric ophthalmology PROMs. Manuscripts were excluded if they reported on the process of PROM development only or were grey literature. Individual PROMs identified were from included manuscripts and categorized by patient involvement, construct measured and domains assessed. PROMs were assessed for their quality using the good measurement property checklist provided by the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN).

Results: The database searches identified 523 unique manuscripts, of which 32 were unavailable and 138 were abstracts only. Full-text review of the remaining 353 articles yielded 95 manuscripts that met inclusion criteria. The 95 identified manuscripts reported on 152 unique PROMs: 1 used for retinoblastoma, 56 used in pediatric ophthalmology broadly, and 95 used in pediatric oncology. The COMSIN analysis identified 8 PROMs with strong overall validity, all of which were patient-derived. The one retinoblastoma-specific PROM scored poorly for overall quality and did not assess two of the most commonly assessed domains; functioning and visual ability.

Conclusion: Retinoblastoma-specific PROMs are rare, and there is no patient-derived PROM for retinoblastoma. Survivors of retinoblastoma are motivated to participate in research and this is an opportunity to inform the development of a patient-derived PROM for retinoblastoma. Aligning how clinicians and research teams evaluate treatment success, with what patient's value in their own health outcomes, holds promise to improve healthcare delivery, for better vision and health outcomes.

Conflict of interest disclosure: none
P22: Should postlaminar optic nerve tumor invasion into the outer layers be considered a risk-factor for leptomeningeal spread of retinoblastoma? 
A case report and review of the literature

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Purpose: To discuss whether invasion into the outer layers up to the pia mater of the postlaminar optic nerve should be considered a risk factor for developing metastases in retinoblastoma.

Methods: This study reports a case of a boy aged 6 years who was diagnosed with unilateral retinoblastoma, subsequent MRI was performed. After enucleation the eye was assessed histopathologically.

Results: MRI showed a tumor of 20 mm with retinal detachment (figure 1, pre- and postcontrast T1 images). Almost the entire retina was invaded by tumor cells. The distal part of the postlaminar optic nerve showed contrast enhancement and the distal part of the nerve was thickened to 3.2 mm, versus 2.7 mm contralateral (figure 1d-e). It was decided to enucleate the eye. The enucleated specimen included 10 mms of optic nerve with 3 mm of postlaminar invasion (i.e., free resection margin). Therefore, it was decided that no further diagnostics were warranted, such as evaluating cerebrospinal fluid for malignant cells. MR images correlated with histopathology: tumor reaching the outer layers of the thickened distal postlaminar optic nerve up to the pia mater, see figure 1f-g. Following protocol this patient received six courses of adjuvant systemic chemotherapy. Unfortunately, after five months this patient returned with leptomeningeal spread of the tumor and died quickly thereafter.

Conclusion: A resection margin with tumor cells is recognized as a risk factor for metastasis, but perhaps the proximity of tumor cells to the leptomeninges should also be judged increased risk for metastatic spread.
Figure 1.

Conflict of interest disclosure: none
P23: Long-term follow-up after retinoblastoma: secondary malignancy

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**Purpose:** To estimate the incidence and the time of the occurrence of second malignant tumors (SMT) among survivors of retinoblastoma.

**Methods:** We evaluated the therapeutic modality used to manage the tumor, the occurrence of any second malignancy, and current follow-up on 162 patients with follow-up period more than 9 years. Patients received various chemotherapy courses with different regimens. Each patient or a parent or a spouse of the patient was asked about the patient’s current health and occurrence of SMT. Data on the past medical treatment was obtained from archival documents. Follow-up was recorded as the time interval between retinoblastoma diagnosis and last communication or documented death. The type and location of all known SMT were recorded. When it is possible, histopathological examination was performed.

**Results:** Second nonocular malignant tumors occurred in 8 patients (4.9%) treated for retinoblastoma from 1986 to 2008. The period between the start of treatment and the occurrence of a SMT averaged 10-15 years. Two patients died. A patient who received prospidin in childhood developed a parotid sarcoma after 27 years of retinoblastoma diagnosis. He died due to metastatic disease. The second patient, who received Vincristine, Cyclophosphane and Carboplatin, died due to osteosarcoma 9 years after starting treatment. Two patients had urinary bladder leiomyosarcoma. In one of them and his mother, a genetic study revealed homozygous mutations in the Q433P locus of the \( RB1 \) gene in both of them, indicating hereditary retinoblastoma. Mutations in this locus are associated with the development of SMT in patients with retinoblastoma localized in the urogenital system. One patient with a hereditary retinoblastoma developed an osteosarcoma of the lower limb 9 years after treatment, then he developed thyroid cancer at the age of 24, then developed sarcoma of shoulder soft tissues. In one case, a histiocytoma was detected. Cervical cancer was detected in one case after 18 years.

**Conclusion:** The findings suggest the need for regular life-long follow-up of patients due to the high risk of developing SMT. Molecular genetic studies are needed to determine the risk of a SMT in accordance with literature data and the OMIM database.

**Conflict of interest disclosure:** none
Session 9

Patients in Focus
T25: What could be the EYE-EYE role in Rare Eye Diseases care in Europe?

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ERN-EYE, dedicated to Rare Eye Diseases (RED), constituted by 29 healthcare-providers from 13 Member States, with important interactions with patient groups (European Patient Advocacy Groups noticeably), is organized to cover all RED conditions in four thematic groups: retinal RED, neuro-ophthalmology RED, paediatric ophthalmology RED & anterior segment RED. Moreover, six transversal working groups are addressing issues common to the four main themes. The objectives of ERN-EYE are wide, mainly patient-centered, with patients’ diagnosis and care improvement across EU, registry strategy, education and training program and development of guidelines noticeably. The working group dedicated to paediatric Rare Eye Diseases is currently working on all these topics. The creation of a virtual Clinic, EyeClin, to better diagnose and treat patients is the cornerstone of ERN-EYE. EyeClin was built thanks to a Clinical Patient Management System (CPMS) common for all ERNs and provided by the EC, in addition to a customized eye-dataset to fit ERN-EYE needs specifically. All experts registered had declared their field of expertise to help users to request their help. Each specialty is clearly represented in the system and the paediatric group organizes specific regular meeting to discuss difficult cases. The launching of EyeClin bring expertise to a large number of RED-affected EU citizens and stimulate their participation to initiatives generated or recognized by ERN-EYE such as nourishing registries, empower research, stimulate trials.

As we are in the middle of the 5 first years of the projects, a lot of initiatives are currently being developed. All our communication is centralized on a dedicated website www.ern-eye.eu.

Conflict of interest disclosure: none
T26: Clinical and genetic characteristics of East Asian patients with inherited retinal disorders

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**Purpose:** Ethnic variability of the clinical and genetic features of inherited disorders is crucial to understand Mendelian hereditary disorders. East Asia Inherited Retinal Disease Society (EAIRDs; https://www.fujinamik.com/east-asia-inherited-retinal-society) was established in 2016 to understand the etiology of IRD in a large cohort of East Asian patients assumed to have similar genetic background. 64 institutes from 5 countries are included; Japan, Korea, China, Singapore, Australia, associated with Japan Eye Genetics Consortium (JEGC), Korean Eye Genetics Consortium (KEGC), and Chinese Global Eye Genetics Consortium (CEGC).

**Methods:** Clinical information and gDNA samples were collected after obtaining informed consent in each country and subjects with available clinical and genetic data were registered to EAIRDs online database. Over 3000 patients with IRD have been registered to EAIRDs online database.

**Results:** The EAIRDs cohort included retinitis pigmentosa, macular dystrophy or cone (-rod) dystrophy, occult macular dystrophy, Stargardt disease, Leber congenital amaurosis, cone dysfunction syndrome, congenital stationary night blindness, and others. The causative genes for IRD were EYS, RP1L1, USH2A, ABCA4, BEST1, CRX, GUCY2D, PRPH2, RPGR, CYP4V2, RP1, RS1, SAG, RHO, CACNA1F, CHM, RDH5, PDE6C, POC1B, PROM1, CAGA1, CNGA3, CRB1, and others.

**Conclusions:** Clinical and genetic heterogeneity has been documented in an East Asian cohort with IRD. Disease-causing variants which are not found in the other ethnicity are frequently revealed, which suggests the distinctive genetic background of East Asian population. This international cohort survey provides an epidemiologic evidence of East Asian IRD, which promotes patients’ care and therapeutic trials in East Asia.

**Conflict of interest disclosure:** None
T27: Achieving meaningful patient research partnership: Development of the Canadian Retinoblastoma Research Advisory Board

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Introduction: Research on retinoblastoma survivors indicates that the disease has lifelong effects on daily life regardless of prognosis. Our prior research shows that retinoblastoma survivors and their families keenly interested in being involved in retinoblastoma research. In response to this, we developed The Canadian Retinoblastoma Research Advisory Board (CRRAB) as a way to generate meaningful and sustained involvement of patients in research.

Methods: CRRAB was created in 2016. It is composed of a general membership including people affected by retinoblastoma, clinicians, allied healthcare providers, researchers, engagement experts and policymakers. Led by a steering committee elected at an annual general meeting, three smaller working groups meet monthly by teleconference to lead tasks related to patient engagement, research advisory and priority setting/research development. To inform implementation of CRRAB and its activities, we conducted focus groups to uncover patient knowledge, experiences and preferences about research. Discussions were transcribed verbatim and analysed by thematic analysis.

Results: CRRAB resulted in the development of: a prospective ‘Research Registry’ of people willing to engage in research; the launch of a ‘Retinoblastoma Champions Program’; social media channels to disseminate research findings and opportunities; and a ‘Top 10’ list of jointly identified research priorities. Findings indicated that patients viewed their experiential knowledge as valuable to improving care and directing research and distinct from theoretical knowledge of the cancer held by clinicians. Patients recognized gaps in their theoretical knowledge of retinoblastoma, and wished this education to be provided from trusted sources. Patients were willing and motivated to engage in research as more than study subjects (a role many had experience with), but noted barriers (i.e. time, compensation, training).

Conclusions: CRRAB serves as an effective medium to generate new knowledge from the patient perspective, and translate this information into sustainable long-term patient engagement. We consider the findings suggestive of a novel role for research engagement: addressing patient educational needs through the establishment of trusted connections with researchers. The findings will be used to refine CRRAB activities to provide research engagement opportunities that meet the needs of patients.

Conflict of interest disclosure: none
T28: DEPICT HEALTH "full view for life" for circle of care including families will empower research

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**Purpose:** To reach the 9,000 children newly diagnosed with retinoblastoma each year (globally 70% die, with resources and knowledge >95% survive), we aim to facilitate collaborative care and research through a retinoblastoma-specific database and make retinoblastoma a zero death cancer. The paucity of quality evidence for retinoblastoma care due to disease complexities confounds conventional clinical trials.

**Methods:** DEPICT HEALTH v1 facilitated clinical care and research in one center for years. The core of DEPICT HEALTH (now hosted globally using high-performance cloud computing) is a language-independent timeline graphically displaying data (See Figure).

**Results:** The International Retinoblastoma Consortium (IRbC) established a governance process for DEPICT HEALTH that includes Steering, Operations and working Committees, modeling participation of every collaborating Center of Excellence. Centers join with service agreements; children/parents provide consent for use of DEPICT HEALTH for clinical communication across their care Center, enroll others (family, doctors) to view, and separately consent for Open research on their child’s coded data. Each Center receives their own patients’ data for research; other Centers and researchers will apply to IRbC for collective coded data for ethics approved projects and be encouraged to collaborate. Artificial Intelligence/machine learning on DEPICT HEALTH Real World Data can improve speed and quality of clinical research.

**Conclusions/Significance:** The DEPICT HEALTH model is uniquely suited to enhance retinoblastoma standard clinical care by supporting multidisciplinary teams and facilitate innovative future research by access to point-of-care data from children everywhere.

**Conflict of interest disclosure:** none
T29: The PRO RETINA patient registry

Franz Badura
ProRetina Deutschland e.V.

The PRO RETINA patient registry aims to minimize the timespan between recruiting patients and conducting a new clinical study. The goal of this patient registry is to encourage as many affected people as possible to provide clinical and genetically data. Therefore, the patient registry can help to establish new therapeutic concepts and options for rare inherited retinal diseases. Due to the lack of therapy perspectives, many patients do not contact a phisican, as this does not appear promising to them. Medical centres, clinical trial centres and affected persons will be contacted and receive information about the patient registry. Registered patients, who are interested in clinical studies, will obtain informations via the patient registry. Therefore, the patient data must be entered in the corresponding database for evaluation according to age, disease and genetic defect. The evaluated data are compared with databases of clinical studies. Suitable patients will be informed and advised about the possible clinical study.

Conflict of interest disclosure: none
Patients with inherited retinal degenerations dreamed for years to get therapies that would slow down or stop or even cure the disease. After many years of basic research, a huge amount of knowledge was achieved and the complexity of this disease, respectively of this group of disease became evident. Since 2005 the number of clinical trials increased exponentially and thus the hope of many patients and their families around the world. Gene therapy is a reality today for a few patients with a very rare form of IRD. With upcoming therapies and treatment trials patients have to face new challenges. So far in many countries genotyping was not considered to be necessary to diagnose an IRD, or even was unavailable. Patients that had received their diagnosis 10 years ago or earlier may have a different diagnosis or better name of their disease that they would get today. The descriptive name of the disease is today often replaced by the genotype or the disease is positioned into a new category: Early onset RP might be today called LCA, LCA10, LCA2, CEP209 or RPE65 thus adding to the patient's confusion. Therefore, it is challenging for patients to know whether a clinical trial or treatment option is addressing their own disease. Apart from diagnosis, patients have to consider very new questions: When should I be treated, should I let treat both eyes, what is the impact should there be a severe adverse effect, what happens if there will be a better treatment on the horizon?

What are we to expect from a treatment? What would be for me the best outcome and what would be the worst? These are questions that have to be discussed among patients in our community as well together with the specialists. However, with the excitement of new therapies, we should not forget all those, for which no treatment is available or even worse, where neither the diagnostic capacities nor the financial means are available to access treatments that would be available. We should not forget that auxiliary aids, low vision and rehabilitation are extremely valuable tools to help to master life with visual impairment or blindness.

The new therapies on the market are paving the way for future new treatment options and our society has to seek for a positive way to make them available also to those that had not the luck to be born in the highly industrialised world by addressing the disparities. Politicians world-wide have agreed on the sustainable goals 2030 with a clear commitment to the wellbeing of all and access to the health system for all. Let us together challenge politicians to answer to this goal by supporting people with inherited retinal degenerative diseases and let them have access to diagnosis, treatment and rehabilitation: In short to have equal access to the civil society.

Conflict of interest disclosure: none
Session 9

Associated Posters
P24: The Swiss Registry of Rare Eye Diseases

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Purpose: Establish a registry grouping all patients living in Switzerland and affected by rare eye diseases.

Methods: Informed consents were prepared in all national languages and in English to establish first a databank containing clinical, genetic and personal details of patients affected by rare eye diseases. Then, informed consents in compliance with the Swiss regulations about establishment of patient registries were implemented.

Results: The patient organization RETINA SUISSE acts as a sponsor of a database grouping clinical and molecular diagnosis of patients affected by rare eye diseases and living in Switzerland. This databank can be established thanks to a large collaboration between university eye clinics, state eye clinics and private practices located all over Switzerland. In a second step, the existing database is made compliant to a project of the Swiss Confederation, the Swiss Registry of Rare Diseases, coordinated by the KOSEK (KOordinationsstelle für SEltene Krankheiten) and located at the Institute for social and preventive Medicine of the University of Bern.

Significance: The pioneer eye module of the Swiss Registry of Rare Diseases will allow indefinite safe storage of clinical and molecular diagnosis of patients affected by rare eye diseases.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
Pascal Escher received honorary or consultation fees from Novartis Pharma, Switzerland
P25: The Canadian Retinoblastoma Research Registry

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Purpose: Retinoblastoma is an aggressive childhood eye cancer. Retinoblastoma patients (individuals affected by retinoblastoma, including parents/legal guardians) indicate they are deeply incentivized to keep abreast of research and help co-create it.

Methods: We initiated the Canadian Retinoblastoma Patient Engagement Strategy in response to the keen interest of the patient community to be involved in research. As part of this strategy, we created the Canadian Retinoblastoma Research eRegistry. The purpose of the eRegistry is to engage Canadian retinoblastoma patients with the research community. Registrants are invited to give permission to (Part A – Passive Participation) receive general information about retinoblastoma (e.g., lay summaries); and to (Part B – Active Participation) be contacted about specific research studies for which they (or their children) might be a suitable subject or team member (e.g., research assistant).

Results: Since it launched in November 2016, 65 people have agreed to participate in the Canadian Retinoblastoma Research Registry. All registrants enrolled in Part A and 62 (95.4 %) enrolled in Part B of the registry. Twenty-four (36.9%) of the registrants are retinoblastoma survivors and 44 (67.7%) of the registrants are the parent/legal guardian of someone diagnosed with retinoblastoma. Most of the registrants are 30 to 49 years of age (n=49) and women (n=52). Half of the registrants are from large urban centers. As part of enrollment, registrants are invited to share research topics of interest. Forty percent (n=26) of the registrants provided suggested research topic(s), including second cancers, vision, genetics, and psychological side effects of retinoblastoma.

Conclusion: These data indicate: (i) registrants are keen to receive both general information as well as invitations for specific research studies; (ii) targeted recruitment efforts may be required to reach younger people affected by retinoblastoma, males, individuals located outside of urban settings, and retinoblastoma survivors; and (iii) while all registrants are interested in general retinoblastoma research, almost half of the registrants have articulated specific research priorities.

Conflict of interest disclosure: none
P26: The top 10 retinoblastoma research priorities in Canada as determined by patients, clinicians and researchers

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Purpose: The purpose of this study was for retinoblastoma patients (including caregivers), clinicians and researchers to jointly determine the top 10 retinoblastoma research priorities in Canada.

Methods: An adaptation of the James Lind Alliance Priority Setting Partnership methodology was employed. In an online survey, retinoblastoma patients, clinicians and researchers were asked, “what questions about retinoblastoma would you like to see answered by research?”. A national Priority Setting Steering Committee was assembled to review and refine the list of survey responses. A final list of 30 retinoblastoma research questions were ranked, using the nominal group technique, by a group of patients, clinicians and researchers, during an in-person priority setting workshop. This resulted in consensus on the 10 retinoblastoma research priorities. An integrated knowledge translation approach was employed to disseminate and promote actualization of the priorities.

Results: A total of 175 retinoblastoma research questions were suggested by 59 survey participants. The top 10 retinoblastoma research questions fell into the following seven categories: Second Cancer (n = 2), Follow Up (n = 2), Psychosocial (n = 2), Treatment (n = 1), Diagnosis (n = 1), Miscellaneous (n = 1) and Global Health (n = 1). The early diagnosis of retinoblastoma was identified as the top retinoblastoma research priority in Canada. An in person co-creation workshop, led by a ‘parent in research’ and attended by clinicians, researchers and patients, was held to develop knowledge translation materials.

Conclusion: The list of priorities will serve as a resource for advocacy groups, research teams and funding agencies that focus on retinoblastoma or related fields. The inclusion of researchers as participants was a novel and valuable element in identifying research priorities valued also by clinicians and patients. Knowledge translation materials will be used to raise awareness and to inspire action towards actualizing the priorities among researchers, funders, and patients.

Conflict of interest disclosure: none
Biomarkers in IRDs: scientifically valid – clinically relevant

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**Purpose - Background:** The development of expensive therapies for inherited retinal degenerations (IRDs) requires at the same time the identification of novel biomarkers to quantify therapeutic effects unequivocally, and to demonstrate patient relevant improvements.

**Methods:** Comparative evaluation of morphological and functional biomarkers measured with sophisticated scientific set-ups and patient relevant parameters.

**Results:** IRDs are genetically and clinically extremely heterogeneous entities complicated further by their progressive nature. As rod and cone pathways may be affected with a different time course and at different degrees of severity, biomarkers measuring rod and cone distribution separately in their spatial distribution have been shown to be of particular value. Specific imaging methods visualize the morphology and specific metabolic features at high resolution, and allow correlation with functional parameters. Translation into patient relevant improvements by specific therapies can be difficult as some results may be statistically significant but not necessarily patient relevant. Novel functional tests such as sophisticated mobility tests with varying contrast and light levels have been shown to help close this gap. All methods have limitations as to application in infancy and early childhood.

**Conclusion:** Great advances have been made to show therapeutic effects that are relevant to patients. Future research should focus on the development of sensitive methods in very young children as some of the therapies are considered to be most effective at a very early age.

**Conflict of interest disclosure:** none
Session 10

Understanding Treatment Effects from Natural History Studies
Stargardt disease (STGD1; OMIM: 248200) is the most common juvenile macular dystrophy. It is inherited as an autosomal-recessive trait associated with mutations in the $ABCA4$ gene, and more than 1000 disease-associated variants have been reported. Clinically, STGD1 is characterized by fundus flecks in the retinal pigment epithelium (RPE) and by macular atrophic lesions. Visual acuity (VA) and central visual fields deteriorate progressively commonly leading to legal blindness in adulthood. Currently there is no approved treatment for STGD1. The international multicenter Progression of Atrophy Secondary to Stargardt Disease (ProgStar) study aimed to understand the natural history of disease progression to help determine appropriate outcome measures for future treatment trials. The primary aim was to assess the yearly rate of progression of STGD1 using the growth or the development of atrophic lesions as measured by fundus autofluorescence (FAF) imaging. Secondary aims include to assess the yearly rate of progression of STGD 1 using spectral-domain optical coherence tomography (SD-OCT) to measure the rates of retinal thinning and the loss of photoreceptors; to assess the yearly rate of loss of retinal sensitivity as measured by microperimetry (MP); to assess the yearly rate of VA changes; to correlate the presence and progression of morphological abnormalities in FAF and SD-OCT images with visual function as measured by MP and VA; to perform exploratory analysis of factors associated with STGD1, such as participants’ use of vitamin A supplementation and mutations in the $ABCA4$ gene.

It was found that the mean rate of best-corrected VA loss was clinically small at 0.55 letters on a standard ETDRS chart per year during two years. Patients were stratified by baseline VA and found to lose 1.3 letters/year ($p=0.07$) when starting with no visual impairment, to lose 1.9 letters/year ($p<0.001$) when starting with only mild visual impairment, to lose 0.6 letters/year ($p=0.002$) when starting with moderate visual impairment and to gain 0.7 letters/year ($p=0.02$) when starting with severe visual impairment at baseline. Eyes that showed abnormal FAF in the fovea deteriorated faster than eyes with normal FAF at baseline ($p<0.001$). The rate of VA change was not significantly associated with genotype group, age at baseline, sex, or race/ethnicity.

Additional details in attached PDF.

Conflict of interest disclosure: none
O27: Long-term follow-up, phenotypic and genetic spectrum of patients with juvenile X-linked retinoschisis in the Netherlands

Leo Hahn

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Purpose: Detailed genetic and clinical characterization of juvenile X-linked retinoschisis (XLRS) is essential to provide an accurate prognosis, and to identify clinical endpoints and the optimal intervention window for (gene) therapy. The aim of this retrospective observational clinical study was to describe the genotypic and phenotypic spectrum, and long-term clinical course in a large cohort of XLRS patients in the Netherlands.

Methods: Medical records of 173 affected males from 60 presumably unrelated families were reviewed for medical history, symptoms, best-corrected visual acuity (BCVA), ophthalmoscopy, visual field, full-field electroretinography and retinal imaging (fundus photography, spectral-domain optical coherence tomography, fundus autofluorescence). A causative RS1 mutation was identified in all families.

Results: Twenty-seven different RS1 mutations were identified in families, including 22 missense (81%), 3 frameshift (11%), 1 splice site (4%) mutation and 1 exon deletion (4%). The c.214G>A mutation (33%) and a deletion of exon 3 (12%) were most frequently detected in families, representing 42% and 19% of the total patient cohort, respectively. The median age at last examination was 30 years (interquartile range [IQR] 16-46 years). Follow-up data were available for 120 patients, with a median follow-up time of 13 years (IQR 6-21 years). BCVA ranged from no light perception to 0.0 logarithm of the minimum angle of resolution (LogMAR) (median 0.68 LogMAR [IQR 0.40-0.91]). BCVA of the better eye was not significantly different at last follow-up visit when compared to the first visit (median 0.49 LogMAR [IQR 0.40-0.70] and 0.48 LogMAR [IQR 0.30-0.70] respectively, p=0.069). Older age correlated significantly with lower mean BCVA, as well as lower mean central macular thickness (Spearman’s r -0.47 p<0.001 and r -0.46 p=0.001 respectively). No significant difference was found in mean BCVA between patients with truncating and non-truncating RS1 variants (p=0.744).

Conclusion/Significance: A wide range of BCVA was seen in different age categories. Although there is a correlation between age and BCVA, BCVA remained relatively stable during follow-up in this study, suggesting a slow decline of BCVA. Our study demonstrates no genotype-phenotype correlation. Trends in BCVA suggest an optimal intervention window for therapy in the first decades of life.

Conflict of interest disclosure: none
O28: The disease course of rhodopsin (RHO)-associated retinitis pigmentosa (RP): a follow-up study

Xuan-Thanh-An Nguyen¹

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Purpose: In view of upcoming gene therapy trials, more insight into the natural disease progression in RHO-associated RP is required. A more detailed clinical disease profile will aid in the selection of eligible candidates, and the establishment of appropriate clinical endpoints for future gene therapy trials. In this retrospective cohort study, we provide a description of the clinical variability and the natural disease course in patients with RHO-associated RP in a longitudinal cohort.

Methods: We reviewed the medical records of patients with RHO-associated retinitis pigmentosa for symptoms, best-corrected visual acuity (BCVA), slit-lamp examination, fundus photography, Goldmann kinetic perimetry (V4e and I4e isopters), full-field electroretinography, spectral-domain optical coherence tomography and fundus autofluorescence imaging.

Results: One-hundred patients with RHO mutations were included for analysis. Mutations were located in the extracellular (n=64; 64%), transmembrane (n=20; 20%), or cytoplasmic (n=16; 16%) domains. The median age at which patients reached mild visual impairment (0.3 ≤ BCVA < 0.5) was 72 years. First occurrences of low vision were observed from the 3rd decade onwards, whereas severe visual impairment and blindness were seen from the 6th decade onwards. Mutations in the cytoplasmic domain were associated with worse age-adjusted BCVA (p=0.033), but did not alter the BCVA decline rate of 2% per year (p<0.001). Mutations in the extracellular domain were associated with a larger age-adjusted seeing retinal area (I4e) than those in the cytoplasmic (p=0.006) or transmembrane domains (p=0.006), but did not affect the yearly decline rate of the I4e seeing retinal area (5%; p<0.001). Visual function parameters correlated robustly with the thickness of the foveal photoreceptor-retinal pigment epithelium complex (p<0.001). Cystoid maculopathy (CME) was reported in 34/56 patients (61%).

Conclusions: RHO mutations result in a relatively mild form of retinitis pigmentosa. Mutations in the cytoplasmic domain are associated with worse visual function. The relatively late occurrence of blindness and slow rates of BCVA decline indicate a broad therapeutic window, but also warrants further exploration of alternative functional and structural parameters to assess treatment efficacy in upcoming clinical trials.

Conflict of interest disclosure: none
O29: Further evaluation of a simple perimetric approach to the differential diagnosis between blue cone monochromacy (BCM) and achromatopsia (ACHM)

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Purpose: Without the aid of sophisticated functional studies and molecular genetic testing, differentiating BCM and ACHM is challenging, especially in isolated male cases. Consistent with the fact that S-cones are spared in BCM, it has been shown that light-adapted chromatic (600 nm and 440 nm) automated perimetry is differentially affected in BCM (Luo et al. PLoS One 2015) and not in ACHM, but these techniques are available only in highly specialized Centers. Thus, we sought to develop a simpler perimetric approach to BCM/ACHM differential diagnosis.

Methods: Out of 25 molecularly confirmed cases, 10 subjects [4 ACHM (all CNGB3 gene deletions or mutations, 10-70 yo) and 6 BCM patients (3 OPN1LW/OPN1MW gene cluster or LCR deletions, and one with the p.C203R point mutation, 9-72 yo)] were tested. Automated perimetry was performed with a Humphrey 30-2 FASTPAC test, using fovea on, fluctuation and fixation/gaze control off options. Size-V stimuli were present with dilated pupils, after at least 3 min of background adaptation. To probe mainly S-cones, standard SWAP was used (blue stimuli on a bright yellow background). To probe mainly L-cones, an identical test was performed on a standard white background with red stimuli, custom-selected from the “change parameters” menu.

Results: Each BCM subject consistently exhibited markedly elevated to non-detectable thresholds to red-on-white stimuli and a range of normal to mildly elevated thresholds to blue-on-yellow stimuli, whereas each ACHM subject showed markedly elevated to non-detectable thresholds to both tests. Each pair of perimetries was completed within 45 to 50 minutes on both eyes, adaptation time included (about 10-12 min of active testing time per eye).

Conclusions: Our perimetric method allows for accurate differentiation between BCM and ACHM, and can be easily implemented in a routine eye care setting with minimal customization of standard testing routines. We plan to extend further our studies on this method in these congenital cone disorders to estimate test-retest variability, and investigate possible trends for changes in these chromatic thresholds over time, so as to determine if this simple testing method may also be a useful outcome measure in gene therapy trials.

Conflict of interest disclosure: none
O30: Longitudinal natural history study in patients with Retinitis Pigmentosa in preparation for gene therapy clinical trials

Francesco Testa¹

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2. Department Of Precision Medicine, University Of Campania "luigi Vanvitelli", Naples, Italy

Purpose: To evaluate natural history of Retinitis pigmentosa caused by mutations in several disease genes.

Methods: we retrospectively evaluated 139 patients with clinical diagnosis of RP and mutations in the following genes: - USH2A (27 patients); RHO (35 patients); CRB1 (22 patients); RP1 (20 patients); EYS (13 patients); RPGR (9 patients); PDE6A (8 patients); (5 patients). Clinical investigation included best-corrected visual acuity (BCVA), Goldmann visual field (GVF), fundus photography, and electroretinography. Longitudinal analysis was performed over a median follow-up time of 3 years.

Results: At the study baseline, at a mean age of 33.7 ± 16.0 years, the patients showed a BCVA of 0.6 ± 0.8 logMAR in both eyes. They showed, on average, a GVF area with III4e target size of 2,069 ± 2,312°² and of 2,138 ± 2,259°², respectively in right and left eyes. Our patients reached legal blindness based on BCVA (i.e., >1.0 logMAR in the better eye) at a median age of 55.8 ± 1.4 years, RP1 patients reached it 13 years later whereas CRB1 18 years earlier. Our patients reached legal blindness based on GVF (i.e. III4e area <314°²) at a median age of 31.8 ± 1.0 years, PDE6A, EYS and USH2A patients reached it about 5 years later whereas CRB1 and RPGR about 7 years earlier.

Conclusions: The results of our natural history study confirmed the heterogeneity of clinical phenotype and natural history in RP patients according to the causative genes. For that reason, natural history data are strongly required in order to design appropriately gene therapy clinical trials.

Conflict of interest disclosure: The following conflict(s) of interest must be disclosed:
Francesco Testa and Francesca Simonelli received honoraria or consultation fees from Sanofi (FS & FT), Spark Therapeutics (FS), and Bayer (FT)
Session 11

Gene and Cell based Therapies
T32: Photoreceptor transplantation into the mammalian retina

Marius Ader

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Human vision depends on light sensing photoreceptors in the retina and their degeneration results in permanent vision impairment and blindness. In mammals, photoreceptors cannot regenerate from endogenous cell sources and, therefore, strategies are currently explored using pre-clinical animal models to regain visual function via photoreceptor transplantation. While photoreceptor replacement represents a promising approach in late-stage retinal degenerative diseases, we also observed the transfer of cytoplasmic material between donor and host photoreceptors, that might represent a potential new route for retinal therapy development. Furthermore, 3D retinal organoids derived from pluripotent stem cells have been established for the generation of high numbers of transplantable mouse and human photoreceptors. In my talk I will present our recent data about the generation of stem cell-derived human cone photoreceptors, sorting-systems for photoreceptor enrichment, and their transplantation into mouse models of retinal degeneration.

Conflict of interest disclosure: none
T33: DNA repair mechanisms in photoreceptors

Knut Stieger
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**Purpose:** The advent of genomic editing technologies has opened new possibilities to target genes at endogenous genomic loci. However, gene editing requires maximum precision of DNA repair to avoid de-novo mutations at the target site. Currently, there is insufficient knowledge of the DNA repair machinery in postmitotic neurons, specifically in rod and cone photoreceptors. Consequently, efficient therapeutic DNA repair has so far not been achieved. In order to shed further light on the status of DNA repair mechanisms in photoreceptors, we studied the gene expression profile of DNA repair proteins and characterized DNA repair mechanisms following double strand break (DSB) induction in photoreceptors in vivo.

**Methods:** Expression profile and localization of several DNA repair proteins, including Ku80, yH2AX, 53bp1, Lig 1, 3 and 4 were studied in vivo in the retinae of several different model systems. Additionally, we have developed a mouse model (RPGR-KI mouse containing an homing endonuclease I-SceI site) and studied DNA repair events following DSB induction via AAV mediated gene transfer in vivo.

**Results:** We have observed unexpected localization of DNA repair proteins in retinal neurons, most importantly concerning Ku80, a key protein in the non-homologous end-joining (NHEJ) pathway. In vivo induction of DSBs at the I-SceI site following AAV mediated gene transfer resulted in sequence changes at the target site in up to 20% of cases, most often representing indel formations following NHEJ.

**Conclusion:** Unexpected localization of DNA proteins in photoreceptors indicates the presence of non-canonical DNA repair pathway mechanisms, which may explain the reported DNA repair deficiency in murine rod photoreceptors. However, frequency and character of sequence changes after DSB repair in vivo indicate that efficient repair of DSBs by NHEJ is possible.

**Conflict of interest disclosure:** none
T34: Forward programming of human stem cells to photoreceptors
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Center For Regenerative Therapies Dresden, TU Dresden, Dresden, Germany

**Purpose:** The replacement of photoreceptors represents a promising option to counteract retinal degenerative diseases. However, for a viable cell therapeutic intervention, one requires human photoreceptors in high quantity and quality. While it is possible to obtain photoreceptors in low quantities by direct reprogramming from fibroblasts or from human stem-cell-derived 3D retinal organoids, an efficient 2D forward programming protocol to generate photoreceptors in vitro from human induced pluripotent stem cells (hiPSCs) needs to be established.

**Methods:** Forward programming relies on the ability of transcription factors (TFs) to activate distinct differentiation pathways in stem cells. Aiming to find TF combinations that drive efficient differentiation of stem cells into photoreceptors, we performed a TF-library-on-library screen. A conditional fluorescent photoreceptor hiPSC reporter line was transduced with lentiviral particles each carrying one of 16 TFs known from in vivo photoreceptor development and with a comprehensive library consisting of 1748 human TFs.

**Results:** We sorted 87 fluorescent cells out of 8 million cells that were qPCR-tested for photoreceptor markers and sequenced to identify the overexpressed TFs at single cell resolution. 90% of the sorted cells were qPCR-positive for at least one of the tested photoreceptor-specific genes indicating the cell-type-precision of our screen. One validated TF combination -two known TFs and one unbiasedly-screened TF- led to a significant loss of the pluripotency marker TRA-1-60 and upregulation of the neuronal marker NCAM within 5 days of overexpression, indicating that cells are differentiating towards the neuronal lineage. Furthermore, fluorescence microscopy and flow cytometry detected high numbers GFP-positive cells suggesting the presence of photoreceptor-like cells. We are currently characterizing these cells in-depths.

**Conclusions/Significance:** Our data suggest that the known TFs were insufficient to drive photoreceptor differentiation, indicating that photoreceptor genesis from hiPSCs requires additional TFs. In-vitro-engineered photoreceptors might serve as donor material for cell transplantation to treat blindness or as biomedical testbeds as sufficient quantities can be generated within few days compared to hundreds of days if dissociated from 3D human retinal organoids.

**Conflict of interest disclosure:** none
O31: DNA repair after ISce-I mediated DSB in photoreceptors and RPE cells following AAV mediated gene transfer in vivo

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Purpose: Genome editing represents a potentially powerful tool to treat inherited retinal disorders. However, DNA sequence alterations during the repair process after DNA double strand break (DSB) induction are manifold and uncontrolled so far. This represents a serious safety issue in the development of therapeutic strategies. The purpose of this study was to characterize the DNA sequence alterations following a DSB repair on the X chromosome in photoreceptors and RPE cells after AAV mediated gene transfer in a mouse model for XLRP.

Methods: Two month old mice ((B6J.SV129-Rpgrtm1stie) were used. This mouse line contains an Isce-I target site downstream of the RPGR-ORF15 gene on the X chromosome. A total of 4 different AAV-vectors were applied. Fifty-six days after subretinal injection, eyes were harvested, retinae isolated, and the GFP-positive cell population enriched by FACS. PCR fragments were subjected to T7 surveyor assay and subsequently Sanger sequenced to detect DNA sequence changes at the target site.

Results: GFP expression was observed in all injected eyes. Following Sanger sequencing of PCR clones, we observed a high frequency of small deletions and single nucleotide substitutions (between 10 and 30% of all clones), most often located in the 5' region of the target site. Small insertions were outnumbered by deletions and substitutions. Larger DNA sequence modifications were also found, but to a much lesser extent. In retinae injected with an all-in-one vector containing the template in addition to the nuclease, we detected replacement of the I-SceI site by the HindIII site with low frequency, indicating the presence of HDR at the target site in addition to more frequent NHEJ events.

Conclusion: We successfully induced in vivo genome editing in photoreceptors and RPE cells following AAV-mediated gene transfer. Both, NHEJ and HDR were detectable. These data represent the basis for further studies regarding the occurrence of DNA sequence changes at target sites in retinal neurons in vivo.

Conflict of interest disclosure: none
O32: A Bioluminescence Resonance Energy Transfer based Sensor for the precise determination of non-homologous end joining DNA repair events

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Purpose: Endonuclease based, therapeutic genome editing is a powerful strategy to treat inherited retinal degenerations. However, specificity and efficacy analysis are crucial in early development. Therefore, we generated a bioluminescence resonance energy transfer (BRET) based sensor for measuring the activity of endonucleases in inducing DNA double strand breaks (DSBs) and quantifying DNA repair through non-homologous end joining (NHEJ).

Methods: The NHEJ sensor, which is expressed as a single molecule, consists of a luciferase domain and a GFP2 domain with a shuttle-cloning box inserted for the integration of any given endonuclease target sequence. The luciferase as an energy donor is acting as an internal standard with which the disruption of the reading frame with premature stop codons of the green fluorescent energy acceptor by indel formation can be measured. This results in a change of the BRET ratio, which corresponds to the endonuclease and NHEJ activity. The sensor was tested with different endonucleases (I-SceI, spCas9) in different cell lines (HEK293-T, ARPE19, etc.) in vitro.

Results: The sensor showed an endonuclease induced reduction of the BRET ratio in all cell lines tested. The measured reading output is endonuclease concentration, but not NHEJ sensor concentration dependent. The sensor/endonuclease system shows outstanding specificity. Furthermore, the NHEJ sensor was validated with a FACS based reporter system successfully and applied to measure NHEJ pathway protein knockouts.

Conclusion: The NHEJ sensor is a useful tool to answer important questions regarding endonuclease activity, NHEJ activity in a variety of different possible cell lines in vitro before the translation to in vivo experiments. This would shorten the development of strategies to treat inherited, retinal diseases.

Conflict of interest disclosure: none
Session 11

Associated Posters
P41: First steps to a MMEJ genome editing approach correcting CLN3/Cln3deltaEx7/8

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Purpose: Neuronal ceroid lipofuscinoses (NCL) are a heterogeneous group of autosomal-recessive neurodegenerative storage diseases. The clinical features include epilepsy, a progressive decline in motor skills, visual impairment and premature death. The juvenile form called CLN3 or Batten disease is characterized by a common homozygous 1.02 kbp deletion of exons 7 and 8 and an early degeneration of all retinal layers as the first presenting symptom. Since the description of CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR associated protein9) as a programmable tool generating genomic double strand breaks (DSBs), targeted genome editing strategies have become possible. With the use of homology directed repair (HDR) or microhomology mediated end joining (MMEJ) DNA repair pathways, the correction of this deletion seems to be possible by providing a wildtype (wt) DNA template after gRNA/Cas9 induced DSBs.

Methods: Eight guideRNA (gRNA) sequences were identified using ATUM (Newark, CA) within the human CLN3 and six gRNA sequences in murine Cln3 genomic region in intron 6 and intron 8. Target and gRNA oligonucleotides were hybridized and cloned into px459 (Addgene: #62988) and a bioluminescence biosensor (BRET) reporter vector. A MMEJ shuttle system with a fluorescent reporter was generated to study the MMEJ frequency. Additionally, a synthetic wt-template with fused exons 7 and 8 that also includes exons 6 and 9 as HDR homologous regions was synthesized and subcloned.

Results: All hybridized DNA fragments were cloned successfully into the reporter systems and the gRNA/Cas9 vector. Three highly active gRNA/Cas9 complexes were identified and characterized using the BRET biosensor in CLN3/Cln3 intron 6 and intron 8. Furthermore, the fluorescent reporter system demonstrated successful MMEJ integration using 5 basepair homologous regions flanking the target site, with a combination of two selected gRNAs.

Conclusion: Methods to study and improve the therapeutic genome editing strategy in vitro were generated in this study. With the identified gRNA sequences and the use of two templates with different homologous sequence sizes in vitro HDR and MMEJ assays can be performed with a murine Cln3deltaEx7/8 cerebellar precursor cell line and a human CLN3deltaEx7/8 cell line derived from pluripotent stem cells.

Conflict of interest disclosure: none
Poster Session

Microphthalmia – Anophthalmia – Coloboma – Developmental Failures
P27: Novel mutations in MFRP and PRSS56 genes associated to posterior microphthalmos

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**Purpose:** MFRP and PRSS56 genes can be responsible of nanopthalmos (NO) or posterior microphthalmos (PM). This study describe the detailed clinical and molecular findings in a series of five patients affected by PM from four unrelated families.

**Methods:** All patients underwent a complete ophthalmological and genetic evaluation. For proper and deep phenotypization a multimodal instrumental approach was used for all five cases: B-scan ultrasound, spectral domain optical coherence tomography (SD-OCT), fundus retinal imaging and anterior segment data was obtained. For each patient, molecular analysis of PRSS56 and MFRP genes was performed with NGS methodology and segregation analysis on parents and siblings was performed with Sanger sequencing.

**Results:** A very high hyperopia of +14.00D or more was the main refractive error and macular abnormalities was identified in all patients. Anterior chamber depth was within normal values, according to age, while total axial length was severely reduced in all patients. All phenotypes presented criteria for diagnosis of PM. Three patients carried compound heterozygous mutations in PRSS56 gene; in the other two patients, a homozygous and two compound heterozygous mutations in MFRP gene were detected.

**Conclusion:** Our study describes genotype in five patients with non-syndromic posterior microphthalmos, describing also new mutations in PRSS56 and MFRP, broadening the knowledge about morphological association for these genotypes.

**Conflict of interest disclosure:** none
P28: Mendeliome in patients with microphthalmia, anophthalmia and coloboma – results and challenges

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Microphthalmia, anophthalmia and coloboma are ocular malformations leading to severe health and social consequences for the life of the affected children. The etiology of these anomalies is complex, and includes environmental and genetic factors. In industrialized countries, ocular malformations are most often of genetic origin. Despite this manifest importance, the underlying genetic causes in patients often remain undetermined due to the complexity of these disorders, including high genetic heterogeneity and incomplete penetrance. The development of the next generation sequencing technology allows to test many genes in parallel and leads to improved genetic diagnosis. We performed next generation sequencing of gene panel including genes related with mendelian disorders (Mendeliome) in patients with microphthalmia, anophthalmia and coloboma. Twelve patients with syndromic and nonsyndromic forms of microphthalmia, anophthalmia and coloboma were tested in a trio with their parents. Only patients with bilateral anomalies were included. Mutations were identified in 5 patients (45%) affecting RAX, PTPN11, MED12, TFAP2A and RBP4 genes. The mutations in – MED12, TFAP2A and RBP4 were novel and were inherited from a normal parent. MED12 mutations underlay the X linked Ohdo syndrome which was inherited from the mother. TFAP2A variant was found in the mildly affected parent. The segregation of the mutation in RBP4 showed uncertain results. Our results show that the etiology of microphthalmia, anophthalmia and coloboma is complex and involves different genetic mechanisms. The presence of the mutations in normal parents makes the interpretation and subsequent communication of these results particularly challenging.

Conflict of interest disclosure: none
P29: Early onset severe retinal dystrophy with irido-chorioretinal coloboma with optic disc dysplasia and macular hypoplasia in one eye due to a heterozygous GDF6-mutation

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**Purpose:** To report on the phenotypes of a heterozygous c.607G>C (p.Asp203His) mutation of GDF6 in a severely affected girl and her father initially considered unaffected.

**Methods:** A comprehensive ophthalmological examination included Goldmann perimetry, color perception (Farnsworth D15), spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF, Heidelberg Spectralis), and electroretinography (full field, ffERG: Diagnosys LCC ESPION; multifocal, mfERG: EDI VERIS). Molecular genetic analysis was performed using next-generation sequencing (NGS) of gene panels for microphthalmia/anophthalmia/coloboma (MAC) and early-onset severe retinal dystrophies (EOSRD). Segregation was confirmed by Sanger sequencing.

**Results:** The index patient was referred to our department at the age of 12 years for an unusual form of EOSRD with chorioretinal coloboma. Originally, a CHARGE association had been suspected. Her visual acuity was right eye (RE) 3.2/20 and left eye (LE) counting fingers to hand motion. Visual fields were severely constricted, especially in the LE. Even saturated colors were confused significantly. The most obvious feature was an inferior irido-chorioretinal coloboma in both eyes including the optic disc, and the central fundus in the LE. No other relatives with coloboma were known. The infrared reflex was granular, on OCT the IS/OS line was absent and the outer retina was thinned. The photopic ffERG and the mfERG were below detection level. The patient later developed epilepsy, considered due to dysplasia of the cerebral cortex. She inherited the mutation from her father who had microesotropia and amblyopia LE. His ffERG and mfERG were within normal range with unremarkable IR-, FAF, and SD-OCT of the nerve fibre layer. However, the optic disc was unusual as a normal central artery was missing. Remnants of the hyaloid artery were visible on OCT. Her paternal cousin had died aged 16 due to a severe cardiac problem.

**Discussion:** GDF6 codes for a transcription factor. Haploinsufficiency can explain the phenotypic spectrum from severe ocular affection with chorioretinal coloboma, optic nerve and macular dysplasia, and dysplasia of the cerebral cortex to very minor optic disc abnormalities and even cardiac problems. Molecular genetics was key to identify the underlying genetic cause and to direct genetic counselling.

**Conflict of interest disclosure:** none
P30: Genotype phenotype correlation in a case series of nanophthalmos

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Purpose: Nanophthalmos is characterized by reduced eye size with limited axial length (<21 mm) and shallow anterior chamber depth (<3.0mm) leading to high hyperopia ranging from +8.00 to +25.00 diopters. Although an otherwise normal ocular function and anatomic organization is assumed, nanophthalmos may be associated with additional or secondary pathological ocular findings. Inheritance follows an autosomal dominant or recessive pattern, or appearance may be sporadic.

Methods: Patients with suspected nanophthalmos were investigated clinically including corneal topography, enhanced depth imaging optical coherence tomography (EDI-OCT), optic coherence tomography angiography (OCTA) of the macula, as well as autofluorescence and ultrasonographic imaging of the optic nerve head and full-field ERG where appropriate. Phenotypic characteristics were correlated with molecular genetic results, when available.

Results: A series of five patients of four unrelated families, aged between 3 and 63 years were identified. Isolated or syndromic presentations were found in 3 and 2 patients, respectively. In one patient a previously unreported association with Kenny-Caffey syndrome type 2 was identified with a de novo heterozygous missense mutation in FAM111A gene. The other syndromic patient was diagnosed with Aicardi-Goutières Syndrome with a novel homozygous missense mutation in the ADAR gene. Among isolated cases, two siblings showed a novel homozygous missense mutation in the MFRP gene and one patient presented with a novel homozygous missense mutation in PRSS56. Patients displayed a variety of ophthalmic findings. Signs at referral ranged from reduced vision, chorioretinal folds, reduced foveal depression, foveal subretinal fluid to recurring macula-involving bullous retinal detachment. One patient presented with narrow anterior chamber angle and pseudo-papilledema with prominent optic disc, but none of the patients had increased intraocular pressure or signs of glaucoma. One patient with MFRP mutation showed optic disc drusen and degenerative retinal alterations but supranormal photopic ERG responses.

Conclusion: A significant number of nanophthalmos cases are caused by mutations in different genes. The severity of ocular signs at referral seems not to correlate with the syndromic phenotype. Regular follow up is advised as nanophthalmos can lead to amblyopia and a range of secondary ocular pathologies. Intraocular surgery is demanding due to reduced bulbar size.

Conflict of interest disclosure: none
P31: Novel phenotype-genotype correlation with PEX6 gene in Saudi patients with Heimler syndrome

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Purpose: Peroxisome biogenesis disorders (PBDs; MIM# 601539) are heterogeneous disorders caused by defects in genes encoding proteins that are essential for peroxisomal matrix and membrane proteins. Heimler syndrome is one of PBDs that is caused by mutations in PEX1 and PEX6 genes. In this study, we aimed to fully characterize the clinical and molecular aspects of two Saudi probands who were diagnosed early as Usher syndrome.

Method: We set up a comprehensive clinical and molecular genetic workflow including detailed ophthalmological, audiological and systemic assessments followed by genome-wide SNP microarrays analysis and targeted PEX6 gene screening by Sanger sequencing.

Results: Clinically: both patients appeared dysmorphic with long faces, high forehead, short nose, small low set ears, and full lips. The ophthalmological assessment revealed advanced inherited retinal dysfunction represented by waxy pallor optic disc, attenuated vessels, RPE mottling with intraretinal bony spicules pigmentations and central foveal atrophic changes in both eyes. Moreover, both patients exhibited bilateral sensory neural hearing loss and amelogenesis imperfecta. Genetically: an autozygous block was identified on chromosome 6p21.1 encompassing PEX6 gene using SNP microarrays. Subsequently, novel variant chr6: 42946599; c.290T>G (p.Val97Gly) in PEX6 (NM_000287.3) was found. The identified variant co-segregated with the phenotype in both families and found to be classified as class 4 “likely pathogenic” according to ACMG guidelines.

Conclusion: Our study represents the first report of PEX6 associated Heimler syndrome in Saudi in the middle east and considered to be the third in the literature so far. This report describes novel PEX6 mutations in Saudi patients and highlights the importance of combining molecular diagnosis with the clinical findings. In addition, it also expands the knowledge of PEX6-related PBDs phenotype and the allelic spectrum for this gene.

Conflict of interest disclosure: none
P32: Microcephaly and chorioretinopathy associated with TUBGCP4 mutation

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Introduction: Microcephaly and chorioretinopathy (MCCRP) is a rare Mendelian autosomal recessive disorder that comprehends three types. The MCCRP type 3 (MCCRP3) (OMIM: 616335) is a neuro-ophthalmologic disorder that causes microcephaly and chorioretinopathy unrelated to congenital infection but related to mutations in the tubulin-gamma complex-associated protein 4 (TUBGCP4). This gene was recently described in one paper reporting four children with pathogenic variants in it.

Purpose: To study the clinical features of a Brazilian patient with pathogenic variants in the TUBGCP4 gene and segregation of the parents.

Methods: Retrospective study of a patient with a molecular diagnosis, cranial tomography, full-field electroretinography, magnetic resonance imaging, fundus examination, retinography, and red-free images of the proband and fundus images of the parents.

Results: The genetic testing found a synonymous pathogenic variant: c.1746G>T (p. Leu582=) (same found in all individuals with MCCRP3 previously described). The second pathogenic variant was a nonsense variant, c.1380G>A (p.Trp460*), previously unreported.

Conclusion: The role of TUBGCP4 is not well established in the cilium physiology. This disease may be part of the ciliopathy spectrum.

Conflict of interest disclosure: none
Poster Session

Glaucoma
P33: A case of childhood glaucoma with a combined partial monosomy 6p25 and partial trisomy 18p11 due to an unbalanced translocation

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Background: Chromosomal deletion involving the 6p25 region results in a clinically recognizable syndrome characterized by anterior eye chamber anomalies with risk of glaucoma and non-ocular malformations (6pter-p24 deletion syndrome or 6p25 deletion syndrome). We report a newborn infant case of childhood glaucoma with a combination of partial monosomy 6p25 and partial trisomy 18p11 due to an unbalanced translocation.

Materials and Methods: The clinical appearance and visual function parameters of the patient were determined from the medical records. To identify the chromosomal aberrations in the patient with clinically suspected 6p25 deletion syndrome, we performed a cytogenetic analysis (G-banding and Multicolor fluorescent in-situ hybridization; M-FISH) and array-based Comparative genomic hybridization (array-CGH) analysis.

Results: The patient was 0-year old girl. Corneal opacity of both eyes was observed after birth. She presented with right eye aniridia and left eye Peters anomaly and multiple malformations. The clinical features of the patient were similar to those seen in the 6p25 deletion syndrome. Familial history of glaucoma was not recognized. Cytogenetic analyses revealed a derivative chromosome 6 with its distal short arm replaced by an extra copy of the short arm of chromosome 18, resulting from an unbalanced translocation. The karyotype was designated as 46,XX,der(6) t(6;18) (q25;p11). Array-CGH analysis detected a 4.6 Mb deletion at 6pter to 6p25.1 and an 8.8 Mb duplication at 18pter to 18p11.22. To determine the breakpoint of the unbalanced rearrangement at the single base-level, we performed a long-range PCR for amplifying the junctional fragment of the translocation breakpoint. By sequencing the junctional fragment, we defined the unbalanced translocation as g.chr6: pter_4594783delinschr18: pter_8911541.

Conclusions: A phenotype corresponding to combined monosomy 6p25 and trisomy 18p11 presented as childhood glaucoma associated with non-acquired ocular anomalies resulting from aniridia and Peters anomaly and multiple malformations. To the best of our knowledge, this is the first report which clarified the breakpoint sequence of an unbalanced translocation in Japanese infant with childhood glaucoma.

Conflict of interest disclosure: none
P34: Genotypic and phenotypic characterization of childhood glaucoma

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Purpose: To investigate the genotype in patients diagnosed with childhood glaucoma and to correlate the genotype with the phenotype.

Methods: Patients diagnosed with childhood glaucoma from the department of ophthalmology at the University Hospital Zurich and Basel were included in this analysis. All patients received a comprehensive eye examination with a detailed assessment regarding glaucoma associated anterior and posterior segment pathologies. Genetic analysis based on whole-exome-sequencing was performed for each patient. Only variants with allele-frequency < 0.1 % were considered. Analysis of copy number variation was performed on sequencing data. Sanger sequencing was used for validation of the variants as well as segregation analysis. This study was approved by the Cantonal Ethics Committee of Zurich.

Results: A total of 17 patients of 13 unrelated families were identified with congenital (13/17), late onset open angle (1/17), secondary childhood glaucoma or glaucoma suspect associated with non-acquired ocular anomalies (3/17). Phenotype: Complete (no medications, IOP 5-21 mmHg) or qualified (glaucoma medication, IOP 5-21 mmHg) treatment success was evident in 5 and 8 patients, respectively. One patient had no light perception.

Genotype: Novel and recurrent missense and nonsense variants in the CYP1B1 gene were identified in 4 families with autosomal recessive pedigree. 2 families revealed heterozygous duplication of FOXC1 gene segregating in an autosomal dominant manner. In 8 cases of mainly sporadic appearance, variants in glaucoma-candidate genes are proposed.

Conclusion/Significance: Childhood glaucoma carries a broad phenotypic spectrum. (1) Genetic testing of glaucoma associated genes, including copy number variation analysis, can confirm diagnosis and allow genetic counseling for patients and their families. (2) Phenotype-genotype correlation of CYP1B1 mutations remain inconclusive suggesting the role of modifier genes and/or environmental factors on disease severity. (3) As our results reflect, for 10-40 % cases depending on population a genetic cause for childhood glaucoma can be identified. Sporadic cases often remain unsolved, highlighting the need for a better understanding of the pathomechanism and the genetic background of childhood glaucoma.

Conflict of interest disclosure: none
P35: Development of glaucoma after early cataract surgery in a case of oculo-facio-cardio-dental syndrome

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Introduction: Oculo-facio-cardio-dental syndrome (OFCD) is an X-linked dominant disorder which is lethal in men and is associated with microphthalmia, congenital cataract, and systemic complications including dysplasia of the teeth, and facial and cardiac septal defects. OFCD is caused by mutations in the BCOR (BCL-6-interacting coreceptor) gene, a POZ/zinc finger transcription repressor. It is required for germinal center formation and may influence apoptosis. We have examined a sporadic case with OFCD that developed refractory glaucoma after surgery for a congenital cataract.

Case report: A 12-year-old girl was born at full term without any adverse events during pregnancy. After birth, microphthalmia was noticeable in both eyes, and the diagnoses of microphthalmia, microcornea, and congenital cataract was made. At the first examination, the axial length was 18.2 mm OD and 16.5 mm OS, and the corneal diameter was 9 mm OD and 8.5 mm OS. Because of the dense cataract in both eyes, she underwent lensectomy bilaterally at the age of two-months. Four months later, she developed bilateral glaucoma. The glaucoma was refractory to anti-glaucoma medications, and several surgical interventions were required including a tube shunt operation in the right eye with full medications in both eyes. Presently, her best-corrected visual acuities are 0.1 OD and 0.8 OS, and her visual fields are retained at 30 degrees OU. She had a history of dental dysplasia and cardiac septal defect, which allowed us to diagnosis her with OFCD. Whole exome sequence (WES) for the patient and asymptomatic parents revealed a heterozygous de novo mutation p.R1480* in the BCOR gene.

Conclusion: Although a total of 43 different mutations of BCOR gene have been reported, a detailed visual function has been rarely reported after a long-term follow-up in eyes surgically-treated OFCD cases. Lensectomy for cataract during an early infancy was beneficial, however, careful management for possible complications including aphakic glaucoma is required to preserve the visual function. WES was useful for the correct diagnosis.

Conflict of interest disclosure: none
P36: The Robison D Harley, MD Childhood Glaucoma Research Network (CGRN) International Pediatric Glaucoma Registry

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**Purpose:** To report the status of an international centralized database for all forms of pediatric glaucoma to foster future genetic and clinical research worldwide.

**Methods:** The registry is governed by an Advisory Board made up with representation from CGRN and Wills Eye Hospital. Registry data is curated by AltaVoice (San Francisco, California), with much experience in developing secure HIPPA complaint rare disease registries. Each site enters patient data into the registry with local IRB/REB approval. Collected data include demographics, family history, birth history, presenting signs, history of prior surgery, ocular anomalies, presence of systemic disease, chromosomal aberrations, and subsequent interventions with outcome data. Diagnostic categorization is based on the Childhood Glaucoma Research Network (CGRN) taxonomy. Data for research purposes is available to any investigators with approval from an IRB/TREB approved protocol and the approval of the Advisory Board after a site has entered a minimum of 10 cases. Registry data can be linked to specimens in DNA banks if desired. The Wills-Jefferson DNA bank will accept specimens from around the world and offer access to these specimens for any researcher who is participating in the registry. We conducted a retrospective review of the first 312 patients enrolled into the registry since its first entry in June 2013. Statistical analyses were performed using Microsoft Excel software.

**Results:** Data has been entered by 14 active centers from 8 different countries. Males represented 56% of patients. Parental consanguinity occurred in 9.9% of the whole study sample with a suspected constricted gene pool in 13.7%. Family history of similar glaucoma was reported in 16.9% of patients. The median age at diagnosis was 9.5 months. The most common type of glaucoma was infantile onset primary congenital glaucoma (23.80%).

**Conclusion:** This registry has the potential to leverage significant advancement in understanding genetic aspects and treatment of pediatric glaucoma.

**Conflict of interest disclosure:** none
Poster Session

Foveal Hypoplasia
P37: Novel variant in SLC38A8 gene segregating with foveal hypoplasia in an autosomal recessive South Asian family

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Introduction: Mutations in SLC38A8 gene has been reported to be causal for foveal hypoplasia (FH), optic-nerve decussation defects and anterior segment dysgenesis (FHONDA) syndrome. We report a novel mutation in the SLC38A8 gene in a large two-generation non-consanguineous presumptively autosomal recessive (AR) south Asian family of north Indian ancestry presenting with FH, nystagmus, exotropia (XT) and low vision (LV) in the fifth and seventh of seven siblings (Figure 1 - Pedigree chart of recruited family).

Methods: Both parents of these seven siblings in this informative family, recruited from the ophthalmic outpatients department (OPD) of Lady Hardinge Medical College, New Delhi were deceased. Whole exome sequencing (WES) was performed on four of seven siblings [two affected and two unaffected] using Agilent V5 + UTR on an Illumina platform and the data analysed.

Results: WES based variant analysis and bio-informatic statistics demonstrated a homozygous stop-gain mutation in the SLC38A8 gene in the affected siblings, confirmed by Sanger sequencing. Optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) confirmed FH in them. Unaffected siblings had normal foveal contour on OCT but were heterozygous for the mutation.

Conclusion: Mutations in SLC38A8 resulting in the FHONDA syndrome is rare. Its causal role towards FH has been functionally validated in the medaka fish (Oryzias latipes). Heterozygous presence of the variant in asymptomatic siblings (parental phenotypes not available) may be considered as an indirect evidence of the disease-causing nature of this variant in a homozygous state in the absence of functional validation.

Conflict of interest disclosure: none
P38: Genotype-phenotype correlation in patients with albinism

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Purpose: Oculocutaneous albinism (OCA) causes significant vision loss, from mild to legal blindness. At least 15 genes (AR - OCA and X-linked -XLOA), are associated with albinism. We analyzed a cohort of patients presenting with presumed OCA/XLOA, who have undergone molecular genetic testing, to ascertain whether genotype-phenotype correlations exist.

Methods: IRB approved - retrospective chart review of all patients with clinical diagnosis of albinism, who underwent genetic testing, evaluated by the pediatric oculo-genetic service from 1980-2015. A clinical scoring system was developed for phenotype analysis ranging from 0 to 6 (6 = complete albinism phenotype). Genetic testing results were reviewed.

Results: 58 patients met the inclusion criteria. 18 patients (31%) had two disease-causing mutations found, 23 patients (40%) had one, 14 patients (24%) had no disease-causing mutations found in OCA/XLOA genes. Of the pathogenic mutations found 52.3% were in the OCA1 gene, 34% were in the OCA2 gene, 2.3% were in OCA4, 6.8% were in OA1, and 4.5% were in Hermansky Pudlak Syndrome (HPS) genes. 3 patients (with no OCA/XLOA mutations found) ultimately received different diagnoses. There was a significant difference in number of mutations found on genetic testing between patients with albinism scores of 3.5 and above and those with scores of less than 3.5 (Fisher Exact test, p < 0.001). Patients with one mutation found had significantly higher albinism scores than those with no mutations, and patients with two mutations had significantly higher albinism scores than those with one or none (p < 0.01). Better visual acuity was associated with lower albinism scores and fewer number of disease-causing mutations (p < 0.01).

Conclusions/Significance: Genotype-phenotype correlation is not strong in albinism patients. Many patients with a clinical diagnosis of albinism have only one plausible mutation found on genetic testing or none. These patients should be counseled about the possibility of another diagnosis masquerading as albinism, versus the presence of an occult mutation on the other allele. Prognosis based on specific mutations is not possible due to variability in phenotype, however albinism score may correlate with visual acuity and number of mutations identified. Genetic testing may diagnose unsuspected HPS.

Conflict of interest disclosure: none
P39: Correlation between genotype-phenotype in patients with autosomal dominant idiopathic foveal hypoplasia associated with PAX6 mutations

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Purpose: To determine the correlations between the genotype and phenotype in patients with autosomal dominant foveal hypoplasia (foveal hypoplasia 1) associated with PAX6 mutations.

Methods: Twelve patients with idiopathic foveal hypoplasia were studied. They consisted of two sporadic cases, eight patients of three families with autosomal dominant foveal hypoplasia, one member with familial corneal opacity, and one member with familial aniridia. Eyes associated with aniridia and corneal opacity were excluded, and thus, a total of 23 eyes were studied. Mutation screening for the PAX6 gene were performed, and detailed examinations including the measurement of the best-corrected visual acuity (BCVA), and slit-lamp biomicroscopy, ophthalmoscopy, fluorescein angiography, electroretinography (ERG), and optical coherence tomography (OCT) were performed.

Results: Six novel mutations, p.P20S, p.V78E, p.V83F, p.V256E, c.1032+5G>A, p.N365K and one known mutation, p.R128H in the PAX6 gene (NM_000280.4) were identified heterozygously in all families. These variants were located in the paired domain, or the DNA binding domain, or the 3' conserved region. Mutations p.P20S, p.V78E, and p.V83F were found in familial cases, and p.N365K was found in a de novo mutation. p.V256E and c.1032+5G>A were found in the families with aniridia and corneal opacity, respectively. The age of the patients varied from 1- to 68-years-of-age. The decimal BCVAs ranged from 0.05 to 1.2 with a median of 0.8. Two patients from one family with p.V78E had the worst BCVA of 0.05 and 0.1. The refractive errors ranged from +0.25 to -12.5 diopters with an average of -4.3 diopters in 16 eyes. Manifest nystagmus was present in 4 of 11 (36%) patients. Goniodysgenesis was found in 6 of 6 (100%) patients. Dark- and light-adapted ERGs were normal in the 3 patients tested. The OCT images showed that a foveal pit was present with persistent inner retinal layers in 5 patients of 3 families with the p.P20S, p.V256E and p.N365K mutations while foveal pit was absent in 7 patients of families with the other mutations.

Conclusions: There were genotype-phenotype relationships in patients with idiopathic foveal hypoplasia with PAX6 mutations in the OCT images and BCVA. Goniodysgenesis appeared to be consistent features regardless of the mutation type.

Conflict of interest disclosure: none
P40: Zebrafish, as a useful model to validate human eye candidate diseases genes

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Purpose: Around the world, millions of people suffer from an impaired vision or blindness and these numbers are still rising as life expectancy increases. Beside environmental factors, the main causes of eye diseases are related to genetics. Our goal is to identify the genetic factors contributing to eye diseases such as cataract and coloboma. To validate the candidate eye diseases genes, one valuable tool is the zebrafish model. Indeed, 84% of the already known human disease genes have orthologues in the zebrafish genome and at least 70% of the human protein-coding genes have at least one counterpart. Moreover, the zebrafish eye shares nearly all morphological and functional characteristics present in the human eye.

Methods: To identify the causative pathogenic mutation of a patient with an unknown genetic diagnosis, we perform either whole exome or whole genome sequencing. Subsequently, cellular biology experiments have been performed on patients’ fibroblasts to test the impact of the mutation on the cellular morphology and function. In addition, we develop zebrafish knockout or knockdown models for our candidate genes by using the CRISPR/Cas9 system or morpholinos to (1) validate the candidate genes as bona fide eye disease genes and (2) to study the pathophysiological mechanisms.

Results: Using next-generation sequencing approaches, we were able to identify two novel genes implicated in eye diseases when mutated (one for coloboma and one for cataract). The zebrafish model was able to reproduce the cataract phenotype seen in affected human, but failed to phenocopy the coloboma phenotype.

Conclusion: Zebrafish can be a very attractive model for the validation and characterization of human candidate eye disease genes. However, the zebrafish model also has its limitations. Due to the phylogenetic distance to humans, gene compensation, anatomical and functional differences, the zebrafish does not always fully recapitulate the human phenotype.

Conflict of interest disclosure: none
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Madhulatha Pantrangi, PhD

Madhulatha Pantrangi, Ph.D., joined PreventionGenetics in January 2013 as a Human Molecular Geneticist. Her portfolio focuses on eye disorders. While at PreventionGenetics, she has also served as DNA Banking Advisor. Dr. Pantrangi received her Ph.D. in genetics from the University of Delhi and her master’s in biotechnology from Pondicherry University, both in India. She completed a postdoctoral fellowship at the Marshfield Clinic Research Foundation.
Previous Meetings


2015 - Halifax, Nova Scotia, Canada

2013 - Ghent, Belgium

2011 - Bangalore, India

2008 - Strasbourg, France

2005 - Whistler, Canada

2003 - Paris, France

2001 - Ft. Lauderdale, USA

1998 - Geneva, Switzerland

1996 - Hobart, Australia

1994 - Niagara Falls, Canada

1992 - Siena, Italy

1990 - Calloway Gardens, USA

1988 - Lisbon, Portugal

1986 - Amsterdam, The Netherlands

1984 - Ghent, Belgium

1982 - San Francisco, USA

1980 - Jerusalem, Israel

1978 - Tokyo, Japan

1975 - Oxford, England