

**213 Genotype-phenotype correlations, prevalence studies and novel gene defects**

Monday, May 08, 2017 8:30 AM–10:15 AM

Room 314 Paper Session

**Program #/Board # Range:** 1237–1243

**Organizing Section:** Biochemistry/Molecular Biology

**Program Number:** 1237

**Presentation Time:** 8:30 AM–8:45 AM

**Reinspection of FEVR based on exome sequencing: a common disease with extremely variable phenotypes**

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**Purpose:** Familial exudative vitreoretinopathy (FEVR) has been described as a rare hereditary disease with variable phenotypes based on study of families with typical signs. This study is to explore to what extent such variable phenotypes might be and the presumed prevalence of FEVR based on frequency of potential pathogenic mutations (PPM).

**Methods:** A cohort of 2429 Chinese probands with different forms of hereditary retinal diseases (HRD) other than FEVR were collected from our clinic and their genomic DNA was analyzed by whole exome sequencing. Variations in genes known to be associated with FEVR, such as FZD4, LRP1, TSPAN12, KIF11, NDP, etc, were collected and analyzed by multiple informatics analysis in order to identify PPM. Reexamination of clinical data as well as probands and available family members was carried out to identify key signs of FEVR in these patients with PPM but with other forms of HRD. Data from controls and online database were used to filter out unlikely PPM.

**Results:** Totally, PPM in FEVR-related genes were detected in about 6.7% of the 2429 probands. About half of the mutations were previously reported to be causative for FEVR. Comparing the PPM with data from controls and online database, about half of the PPM (mostly frequently reported ones) might not be causative, which has been further supported by reexamination of the patients and controls. For the rest half of the PPM, clinical data and fluorescein angiography demonstrated typical signs of FEVR although they were clinically considered as other forms of HRD, such as early-onset high myopia, cone-rod dystrophy, juvenile retinal detachment, macular degeneration, macular hypoplasia, glaucoma, etc. Taking into account of the high prevalence of the HRD, the presumed prevalence of FEVR might be more than 1 in 2000 based on the frequency of PPM detected.

**Conclusions:** The results not only greatly expand the phenotypic variation of FEVR based on genotypes but also indicate FEVR as a common disease. Recognizing signs suggestive for FEVR may facilitate the clinical diagnosis and management. Gene diagnosis based on systematic genetic analysis may reveal unexpected molecular basis for atypical diseases while provide useful information for clarifying false positive results.

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**Presentation Time:** 8:45 AM–9:00 AM

**The Israeli Inherited Retinal Diseases Consortium (IIRDC): Mapping Inherited Retinal Diseases in the Israeli Population**

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**Purpose:** Inherited Retinal Diseases (IRDs) are the most genetically heterogeneous conditions in humans, with over 250 causative genes identified to date, and more causative genes that are yet unknown. The unique structure of the Israeli population makes it an excellent resource for finding new causative genes for IRD and for studies of new therapies designed for specific IRD populations. The purpose of the study is to recruit, clinically characterize, and genetically diagnose the majority of Israeli patients with IRD.

**Methods:** A consortium, IIRDC (the Israeli IRD Consortium) was established that covers the whole of Israel and includes 6 genetic centers, 5 units for clinical electrophysiology of vision, and a bioinformatics lab. The clinical centers diagnose and characterize the phenotype of the IRD patients, who are then referred to the genetic centers, whose role is to seek the causative genes and mutations. The bioinformatic center analyzes data from next generation sequencing performed by the genetic centers. Ophthalmologic analysis includes visual acuity testing, visual field, electroretinography, and imaging.

**Results:** Our cohort of recruited IRD families currently contains over 2000 families with various phenotypes, the most prevalent being retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), cone-rod degeneration (CRD), and Usher syndrome. We performed different genetic analyses on this set of patients including genotyping of founder mutations, homozygosity mapping, and whole exome sequencing and were able to identify the cause of disease in about 45% of families. The most common causative genes are FAM161A, ABCA4, USH2A, and EYS. Since the establishment of IIRDC, we were able to accelerate the rate of recruitment. In addition, IIRDC members identified a number of novel IRD-causing genes (CEP78, CEP250 and HGSNAT) and founder mutations in known genes.

**Conclusions:** This is a unique consortium given the nationwide coverage. The immediate expected outcomes include an epidemiological overview of IRD distribution and etiology in the Israeli population, identification of novel causative genes and mechanisms, and genotype-phenotype correlations. The main expected long-term outcome is a significant reduction in the prevalence and “disease load” of IRD in Israel, achieved by a combination of prevention and treatment.

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**Presentation Time:** 9:00 AM–9:15 AM

**Mutation spectrum of a French cohort with autosomal recessive bestrophinopathy**

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**Purpose:** In 2008, Burgess et al. reported a peculiar retinal dystrophy designated as autosomal recessive bestrophinopathy (ARB, MIM #611809) in which atypical retinal abnormalities were associated with an abolished light rise in the Electrooculogram (EOG), a common electrophysiological feature with Best disease (MIM #153700). The phenotype, associated with biallelic *BEST1* mutations, is however more severe with variable degrees of full field electroretinogram (ERG) abnormalities, neurosensory retinal detachment, intra retinal cysts and yellowish flecks. The purpose of our study was to genetically characterize a cohort of patients with typical phenotypic feature and attempt a phenotype/genotype correlation.

**Methods:** Patients with a presumed diagnosis of ARB were reviewed. Subjects underwent full ophthalmic examination. Informed consent was obtained from each patient and available family members. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Sanger sequencing of all 11 exons and flanking region of *BEST1* (NM\_004183.3) was applied to patients' DNA with a presumed clinical diagnosis of ARB and available family members.

**Results:** Thirteen patients from 12 families with a diagnosis of ARB were selected in this study. Patient's age at time of examination ranges from 8 to 58 with an average age of 30. Best corrected visual acuity on the ETDRS chart ranges from light perception to 20/25; 55% of the patients were hyperopic and 3 of them had history of closed angle glaucoma; 67% of the patients had generalized retinal dysfunction with a majority affected rod responses more than cone. Regarding genetic screening, 5 of the patients carried compound heterozygous and 7 (2 including siblings) were homozygous for likely disease causing mutations. These variants include 10 missense among which 5 are novel, 3 nonsense with one novel, 2 small deletions which are all novel and one small already reported insertion. One of the novel missense variant (c.91C>A p.Leu31Met) was found at the homozygous status in the two affected siblings and in one unrelated subject, all originating from Morocco which may suggest a founder effect.

**Conclusions:** Our study identifies novel *BEST1* variants underlying ARB. Further 3D modeling and *in vitro* assays will be needed to better understand functional consequences of these variants to contribute to a better understanding of this disorder.

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**Presentation Time:** 9:15 AM–9:30 AM

**Frequent hypomorphic alleles solve 80% of late-onset ABCA4 disease and distinguish it from age-related macular degeneration**

Rando Allikmets<sup>1</sup>, Jana Zernant<sup>1</sup>, Frederick T. Collison<sup>3</sup>, Gerald A. Fishman<sup>3</sup>, Yuri V. Sergeev<sup>2</sup>, Kaspar Schuerch<sup>1</sup>, Janet R. Sparrow<sup>1</sup>, Stephen Tsang<sup>1</sup>, Winston Lee<sup>1</sup>. <sup>1</sup>Ophthalmology, Columbia University, New York, NY; <sup>2</sup>OGVFB, National Eye Institute, Bethesda, MD; <sup>3</sup>Chicago Lighthouse for the Blind & Vis Impaired, Chicago, IL.

**Purpose:** Variation in the *ABCA4* gene is causal for, or associated with, a wide range of phenotypes from early-onset Mendelian retinal dystrophies to late-onset complex disorders such as age-related macular degeneration (AMD). However, a significant fraction of the disease-associated genetic variation has remained elusive thereby complicating assessment of the role of monoallelic and biallelic variants in clinically confirmed disease.

**Methods:** All 645 study subjects diagnosed with *ABCA4* disease underwent complete ophthalmic examinations, including autofluorescence (AF) imaging with cSLO and SD-OCT scans. The *ABCA4* gene and locus sequencing were performed using the Illumina TruSeq Custom Amplicon protocol followed by confirmation of variants by Sanger sequencing. The possible effect of *ABCA4* variants was assessed with prediction algorithms via Alamut and the allele frequencies of all variants were compared to the gnomAD database or the 1000 Genomes Project database. Protein unfolding propensities for selected *ABCA4* variants were evaluated with the unfolding mutation screen.

**Results:** We determined that some *ABCA4* variants, previously considered benign due to high minor allele frequency (MAF 2-7%) in the general population, account for a large fraction of missing pathogenic alleles, particularly in monoallelic cases. We show that a hypomorphic c.5603A>T (p.Asn1868Ile) variant with MAF ~7% in the general population accounts for a large fraction of missing pathogenic alleles. It explains >50% of monoallelic cases, ~80% of late-onset cases and distinguishes *ABCA4* disease from AMD. We also identify intragenic modifying effects of another, c.2588G>C (p.Gly863Ala), allele and describe distinct clinical phenotype(s) conferred by these alleles.

**Conclusions:** Our findings substantiate the causality of frequent missense variants and their phenotypic outcomes as a significant contribution to *ABCA4* disease and its clinical presentation.

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**Presentation Time:** 9:30 AM–9:45 AM

***In silico* functional meta-analysis of 5,962 *ABCA4* variants in 3,928 Stargardt disease and cone-rod dystrophy cases**

Frans P. Cremers<sup>1,7</sup>, Stephanie Cornelis<sup>1,7</sup>, Nathalie Bax<sup>2,7</sup>, Jana Zernant<sup>3</sup>, Rando Allikmets<sup>3</sup>, Andreas Fritsche<sup>4</sup>, Johan den Dunnen<sup>5</sup>, Muhammad Ajmal<sup>6</sup>, Carel C. Hoyng<sup>2,7</sup>. <sup>1</sup>Human Genetics, Radboud university medical center, Nijmegen, Netherlands; <sup>2</sup>Ophthalmology, Radboud University Medical Center, Nijmegen, Netherlands; <sup>3</sup>Ophthalmology, Columbia University, New York, NY; <sup>4</sup>Norwegian University of Science and Technology, Trondheim, Norway; <sup>5</sup>Clinical Genetics and Human Genetics, Leiden University Medical Center, Leiden, Netherlands; <sup>6</sup>Biosciences, COMSATS Institute of Information Technology, Islamabad, Pakistan; <sup>7</sup>Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, Netherlands.

**Purpose:** Variants in *ABCA4* are associated with autosomal recessive Stargardt disease (STGD1) and cone-rod dystrophy (arCRD). The clinical outcome depends on the severity of the two variants. To provide an accurate clinical prognosis and to select patients for novel treatments, it is important to assess the functional significance of non-truncating *ABCA4* variants. Employing a meta-analysis of the published *ABCA4* variants and associated phenotypes, we aimed to functionally classify the variants.

**Methods:** We collected all *ABCA4* variants from 3,928 retinal dystrophy cases published up to 2015 in a Leiden Open Variation Database ([www.LOVD.nl/ABCA4](http://www.LOVD.nl/ABCA4)). The frequencies of *ABCA4* variants were compared between 3,270 Caucasian STGD1/arCRD cases and 33,370 non-Finnish European control individuals. We performed *in silico* predictions on the functional effects of missense and non-canonical splice site variants. We also analyzed the homozygous occurrence of variants and the age of onset of affected persons. Based on this information and the American College of Medical Genetics and Genomics (ACMG) guidelines, all variants were classified according to their pathogenicity.

**Results:** 316 of 913 *ABCA4* variants, were found to be significantly enriched in Caucasian STGD1/arCRD cases. We predicted 81 missense variants to have a (moderately) severe pathogenic nature and 30 variants to be benign. Assessing the homozygous occurrence of frequent variants in STGD1/arCRD cases based on the allele frequencies in control individuals, confirmed the mild nature of the p.[Gly863Ala, Gly863del] variant and identified 3 additional mild variants (p.Ala1038Val, c.5714+5G>A, p.Arg2030Gln). Based on these data, *in silico* analyses and the ACMG guidelines, we provide pathogenicity classifications for all variants.

**Conclusions:** Our meta-analysis and application of the ACMG guidelines allowed us to classify all *ABCA4* missense variants on the 5-tier scale from benign to pathogenic and to predict their functional effect. We share these results through the LOVD database thereby facilitating direct variant annotation, e.g. for diagnostic application. The next challenge is to promote *ABCA4* variant sharing by diagnostic centers to further enhance the value of the database and to allow classification of variants for which there is currently not sufficient data for reliable classification.

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**Presentation Time:** 9:45 AM–10:00 AM

**Homozygosity mapping-guided exome sequencing in LCA patients of consanguineous origin reveals mutations in known genes and a novel candidate gene**

Basamat Almoallem<sup>1,2</sup>, Kristof Van Schil<sup>1</sup>, Laila Jeddawi<sup>3</sup>, Bart P. Leroy<sup>4,1</sup>, Frauke Coppieters<sup>1</sup>, Elfride De Baere<sup>1</sup>. <sup>1</sup>Center for Medical Genetics, Ghent University and Ghent University Hospital, Ghent, Belgium; <sup>2</sup>Department of Ophthalmology, King Abdul-Aziz University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia; <sup>3</sup>Pediatric Ophthalmology Division, Dhahran Eye Specialist Hospital, Dhahran, Saudi Arabia; <sup>4</sup>Department of Ophthalmology, Ghent University Hospital, Ghent, Belgium.

**Purpose:** Leber congenital amaurosis (LCA) is the most severe autosomal recessive inherited retinal dystrophy (IRD) accounting for 5% of childhood blindness. To date, 70% of LCA cases can be explained by mutations in one of the 23 known LCA genes. Here we aimed to identify the underlying genetic cause of LCA in 15 Saudi-Arabian families with reported or suspected consanguinity.

**Methods:** A total of 20 probands, ranging between 2–9 years old, were clinically diagnosed with LCA or early-onset IRD. The genetic workup consisted of homozygosity mapping followed by targeted next generation sequencing (NGS) or Sanger sequencing, combined or not with whole exome sequencing (WES). Co-segregation could be demonstrated for all identified mutations.

**Results:** Overall, we identified 13 putative pathogenic homozygous mutations in 10 known IRD genes in 14/15 (93.3%) of the studied families, six of which are novel. Eight of these genes were known LCA genes: *CRB1* (3/15, 20%), *RPGRIP1* (2/15, 13.3%), *SPATA7* (2/15, 13.3%) and *CABP4*, *CEP290*, *GUCY2D*, *MERTK*, *RDH12* (1/15, 6.7% for the latter five) respectively. Specifically, the recurrent *RPGRIP1* mutation c.1007delA p.(Glu370Asnfs\*5) is a reported potential founder mutation in the Saudi population (Khan et al. 2014). Moreover, mutations were found in *ATF6* and *ALMS1* (1/15, 6.7% for each), known to be implicated in autosomal recessive achromatopsia and in Alström syndrome, respectively. In two affected sibs with LCA and autism, we identified a novel nonsense mutation c.3283C>T p.(Arg1095\*) in the *Regulating Synaptic Membrane Exocytosis 2* (*RIMS2*) gene (NM\_001100117.2), located in the largest autozygous region of 25 Mb. *RIMS2* was found to be expressed in human retina and in cerebral cortex, which might be consistent with the phenotype observed in the sibship. A mutation in a paralog *RIMS1* was previously reported in autosomal dominant cone-rod dystrophy (CORD7; MIM 603649), implicating a protein with a synaptic function in retinal disease.

**Conclusions:** We identified 14 putative pathogenic mutations in all studied LCA families, demonstrating the power of autozygome-guided WES in a genetically heterogeneous consanguineous IRD cohort. Apart from mutations in known IRD genes (14/15; 93.3%), we uncovered *RIMS2* as a potential novel LCA gene.

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**Presentation Time:** 10:00 AM–10:15 AM

**Mutations in the X-linked gene *PRPS1* cause retinal degeneration in females**

*Alessia Fiorentino*<sup>1</sup>, *Gavin Arno*<sup>1,2</sup>, *Nikolas Pontikos*<sup>1,3</sup>, *Kaoru Fujinami*<sup>1,2</sup>, *Takaaki Hayashi*<sup>4</sup>, *Vincent Plagnol*<sup>3</sup>, *Michael E. Cheetham*<sup>1</sup>, *Takeshi Iwata*<sup>5</sup>, *Andrew R. Webster*<sup>1,2</sup>, *Michel Michaelides*<sup>1,2</sup>, *Alison J. Hardcastle*<sup>1</sup>. <sup>1</sup>UCL Institute of Ophthalmology, London, United Kingdom; <sup>2</sup>Moorfields Eye Hospital, London, United Kingdom; <sup>3</sup>UCL Genetics Institute, London, United Kingdom; <sup>4</sup>Department of Ophthalmology, The Jikei University School of Medicine, Tokyo, Japan; <sup>5</sup>Division of Molecular and Cellular Biology, National Institute of Sensory Organs, National Hospital Organization, Tokyo Medical Center, Tokyo, Japan.

**Purpose:** Retinal dystrophies show high genetic heterogeneity, with over 250 disease-causing genes identified. Additional genes remain to be discovered. We sought to identify the cause of retinal degeneration in unsolved cases.

**Methods:** Patients recruited to this study were mutation negative for known disease genes. Whole exome or whole genome sequence analysis was performed. Nonsynonymous, splice site, frameshift and nonsense variants with a minor allele frequency <0.1% were considered as candidates. Further prioritization was performed by combining data on sequence conservation, gene function and expression. Segregation analysis of variants by Sanger sequencing was performed where familial samples were available.

**Results:** In the first family, all affected females had patchy retinal degeneration and a tapetal reflex, with the female proband having an affected mother, consistent with dominant inheritance. Unexpectedly,

WES and segregation analysis revealed a rare missense variant in *PRPS1* (p.S16F). This variant was absent in Exac. Subsequently, three other unrelated female probands, with no affected male relatives, were found to have rare missense variants in *PRPS1* (p.R214W, p.R196W, p.R214P). Affected members of all four families showed an asymmetrical, non-contiguous retinopathy affecting both rod and cone photoreceptor function. Hearing impairment was present in 1 family.

**Conclusions:** Mutations in *PRPS1* are known to cause rare forms of non-syndromic sensorineural deafness, Charcot-Marie-Tooth disease and Arts Syndrome. Hearing loss is a common feature of these disorders, with affected males displaying phenotypic heterogeneity. In a previous report of one family with only affected females, a p.S16P variant was associated with variable degrees of optic atrophy, retinitis pigmentosa and neurological manifestations, including hearing loss, intellectual disability and peripheral neuropathy. These data highlight the unexpected finding of X-linked retinal degeneration in females caused by mutations in *PRPS1*. The asymmetry of the degeneration is similar to that seen in RPGR and RP2 and might be confused with an inflammatory retinopathy. Skewed X-inactivation and/or variable levels of PRS-I deficiency may contribute to the variability of disease.

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