ARVO 2017 Annual Meeting Abstracts

501 Genes and disease: How knowledge of genetics can guide treatment, now and in the future
Thursday, May 11, 2017 8:30 AM–10:30 AM
Ballroom 3 Symposium
Program #/Board # Range: 5102–5108
Contributing Section(s): Anatomy and Pathology/ Oncology, Cornea, Eye Movements/Strabismus/Amblyopia/Neuro-Ophthalmology, Glaucoma, Retina, Retinal Cell Biology

Program Number: 5102
Presentation Time: 8:35 AM–8:50 AM
Gene discovery and Mendelian retinal degenerations
David Valle. Inst Genetic Med, Johns Hopkins, Baltimore, MD.
Presentation Description: Over the last decade robust genomic and genetic methods to identify the genes and variants responsible for Mendelian phenotypes have been developed. These advances have lead to the elucidation of the molecular basis of many, previously unexplained retinal degenerations. Each discovery not only provides the opportunity for precise molecular diagnosis, prognosis and counseling but also implicates a particular biological system important for retinal development and function. As we accrue this information, we can expect to synthesize it to provide general principles on retinal development and function. My talk will take stock on where we stand in the growth of this knowledge.
Commercial Relationships: David Valle, None
Support: 2UM1HG006542

Program Number: 5103
Presentation Time: 8:50 AM–9:05 AM
Genetic basis of complex macular disease: interactions between genes and environment
Caroline Klaer1,2. Ophthalmology and Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands; 2Ophthalmology, Radboudumc, Nijmegen, Netherlands.
Presentation Description: Complex macular disease is influenced by both environment and genes. The presentation will give an overview of the current knowledge. Does lifestyle influence the disease risk or treatment response and what is the value of genetic testing?
Commercial Relationships: Caroline Klaer, Novartis (C), Topcon (C), Thea Pharma (C), Bayer (C)
Support: EU Grant 648268, EU grant 634479, Dutch government (NWO) grant 91815655

Program Number: 5104
Presentation Time: 9:05 AM–9:20 AM
Autophagy genes and new insights into the pathogenesis and treatment of glaucoma
John Fingert1,2. Ophthalmology, University of Iowa, Iowa City, IA; 2Stephen A. Wynn Institute for Vision Research, University of Iowa, Iowa City, IA.
Presentation Description: Genetic studies of normal tension glaucoma have detected mutations or variations in three genes known to participate in autophagy, an important catabolic biological process. Autophagy is an ancient cellular response to nutritional deprivation, accumulating cytoplasmic proteins, or intracellular pathogens. Autophagy also has a role in the pathophysiology of several neurodegenerative diseases. Most recently, mutations in several genes that regulate autophagy (TBK1, OPTN, and TLR4) have been linked with normal tension glaucoma. Studies of TBK1 and OPTN with transgenic mice and patient-derived induced pluripotent stem cells suggest that aberrant regulation of autophagy is a cause of retinal ganglion cell death and some cases of normal tension glaucoma. These genetic studies have provided new insights into glaucoma biology and suggest that targeting TBK1, OPTN and/or autophagy with drugs may have great potential as a novel glaucoma therapy.
Commercial Relationships: John Fingert, Regeneron (F)
Support: NEI RO1 EY023512, NEI R21 EY026207, NEI RO1 EY025647, NEI RO1 EY017673, NEI RO1 EY022305, and Regeneron, Inc.

Program Number: 5105
Presentation Time: 9:20 AM–9:35 AM
Toward genome editing to treat inherited autosomal dominant eye disease
Tara Moore1,2. Biomedical Sciences, University of Ulster, Coleraine, United Kingdom; 2Avellino Labs, San Francisco, CA.
Presentation Description: The presentation will describe development of CRISPrCas9 for mutant allele gene editing for a number inherited autosomal dominant eye diseases namely Corneal dystrophies. A number of animal models will be shown including a corneal bioluminescent mouse model and MECD and FECD mouse model. It will show various efficacies and specificities for the mutant allele depending on the guide RNA, it will compare a number of CAS9 and will show effective gene editing in vitro, invivo and in DNA from patient cells. It will compare this form of treatment to siRNA use in vivo.
Commercial Relationships: Tara Moore, Avellino Labs (E), Ulster University (E)
Support: Avellino Labs USA, Fight for Sight UK

Program Number: 5106
Presentation Time: 9:35 AM–9:50 AM
Molecular genetics of choroidal melanoma: Impact on prognosis and therapies
Emine Kille. Dept of Ophthalmology, Erasmus University, Rotterdam, Netherlands.
Presentation Description: In uveal melanoma (UM) non-random chromosomal aberrations occur and correspond to patients’ prognosis. From all chromosomal tests monosomy 3 with or without a gain of chromosome 8q was the most solid indicator for development of metastasis. Nevertheless, mutations in UM specific genes, such as BAP1, SF3B1 and EIF1AX are nowadays more solid and also used to predict survival. Patients with BAP1 mutations have the worst prognosis (<4y metastasis). Tumors with SF3B1 mutations predict an intermediate risk of developing, often late (7-10y) and patients with EIF1AX mutations seldom develop metastases. Mutational screening can be cumbersome and copy number variation patterns throughout the genome correspond with the specific mutations. This enables us to predict a specific mutation on the chromosomal profile. All new developments in the molecular genetic field changes in the treatment strategies will be expected. Treatment of patients based on the molecular profile of their tumor will enable us to select patients at high risk and give superior results on treatment outcome.
Commercial Relationships: Emine Kille, None

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loss for less than a year received the low (n=3) or medium dose (n=3). Clinical testing included ETDRS visual acuity, visual fields, OCT, pattern ERG and neuroophthalmic examinations. GEE methods were used for longitudinal analyses. When improvement of visual acuity in injected eyes was compared to fellow eyes using all measurements from day 1 through month 18, injected eye improvement was significantly greater than fellow eye improvement (p=0.039). A post-hoc comparison found the differences between study eye minus fellow eye improvement in gene therapy patients (0.69 logMAR units) was greater than that of the natural history (0.21 logMAR units) (p=0.012) (JAMA Ophthalmol 132:428-436). 0.1LogMAR=5 EDTRS letters. Two patients developed asymptomatic uveitis that resolved without treatment. One was treated with low dose, the other with medium dose. Two additional patients with <20/200 vision loss in one eye were treated before loss of vision in the fellow eye. For one with 5 letters in the bad eye, low-dose did not prevent a drop from 80 to 60 letters at month3 and to 5 letters at month6. In another unilateral case the fellow eye increased to 84 letters at month3 relative to 77 letters at entry. No difference between eyes in outcomes of other visual function measures was detected. Virus was not detected in blood. Nabs to AAV were detected in all patients before and after treatment.

**Commercial Relationships:** John Guy, U.S. Patent No. 7,405,284 (P), U.S. Patent No.: 8,278,428 (P)
**Support:** NEI 1U10EY023558 (Guy) 1U10EY024247 (Feuer)
**Clinical Trial:** NCT02161380