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Session Topic Area: 22. Therapy for Genetic Disorders

Session Content: Scientific

Session Title: Gene discovery, genetic counseling, and clinical care of patients with inherited retinal diseases

Session Description:
Inherited retinal diseases (IRDs) comprise a heterogeneous group of retinal degenerations, including retinitis pigmentosa, choroideremia, Leber congenital amaurosis (LCA), and other dystrophies. These disorders exhibit remarkable genetic heterogeneity as well; mutations in numerous genes can cause retinal diseases that exhibit dominant, recessive, or X-linked patterns of inheritance. The catalogue of pathogenic mutations and disease- associated genes for IRDs has grown considerably over the past two decades, fueled by both technological advances (i.e., next-generation sequencing) and well-established genetic testing programs. However, our knowledge of the molecular mechanisms linking pathogenic mutations to distinct clinical phenotypes has advanced relatively slowly. There remains a pressing need for innovative approaches to functionally validate genetic discoveries, and to incorporate that information into patient counseling and clinical care. This session brings together a diverse panel of experts in gene discovery, molecular characterization, genetic counseling, and treatment for inherited retinal diseases. Together, they will provide an overview of the current state of research in IRDs and use it as a context to discuss the best practices for transforming genetic discoveries into personalized precision medicine.

Session Rationale:
Among the many classes of genetic disorders, IRDs offer several key advantages as a model system for gene discovery, functional validation, genetic counseling, and individualized treatment. First, the genetic heterogeneity within IRDs encompasses a broad set of genes, inheritance patterns, and disease pathways. While the number of patients affected by a single one of these may be small, they provide a wider set of options for targeted therapies. Second, IRDs typically affect only a single tissue (the retina). Although the genes implicated in these disorders are involved in a variety of pathways, many share a molecular phenotype: high (and often transcript-specific) expression in retinal tissue. This offers a compelling avenue of experimental approaches to functionally validate new candidate disease genes.

Third, the fact that most IRDs are not life threatening allows for long-term studies and recruitment from an actively engaged patient population. Thanks to decades of work to identify the genes and mutations responsible for IRDs, more than half of patients who undergo routine genetic testing receive a definitive molecular diagnosis. This success, combined with the customary slow onset of many retinal disorders, suggests that new therapeutic interventions that could dramatically improve the quality of life for thousands of patients. Indeed, one form of LCA was among the first recessive disorders to undergo clinical trials for gene replacement therapy.

We believe that this session therefore would appeal not only to groups working on retinal diseases but also to the wider community of researchers, genetic counselors, and clinicians who seek to translate genetic discoveries into improved clinical care.

Learning Objectives
1. Understand the clinical characteristics of IRDs as well as our current knowledge on the mutations and genes associated with them.
2. Describe state-of-the-art approaches to the discovery, characterization, and functional validation of disease genes.
3. Explain the utility and challenges of incorporating genetic testing and genetic counseling into clinical care.
4. Discuss the potential for gene replacement, stem cell therapy, and genome editing to dramatically improve treatment for retinal degenerations.

Attendee Benefits:
In this session, the audience will learn about state-of-the-art approaches for gene discovery, functional validation, genetic counseling, and therapeutic intervention for human genetic disorders. They will hear speakers who represent some of the top research groups and clinical sites in the world for inherited retinal disorders. The presentations will include current, cutting-edge approaches to ophthalmic genetics research and experimental therapeutics. Even so, audience members need not work in the field of retinal disease research to benefit from this session. The principles and strategies discussed here are broadly applicable as we leverage the results of genetic discovery to improve disease outcomes and clinical care.

Target Audience:
This session will have particular appeal to researchers studying the genetics of vision disorders and clinicians interested in cutting-edge therapeutic approaches. It will also include topics relevant for human and population geneticists, genetic counselors, and students or trainees in biomedical fields.

The competencies and attributes the session will address:
Patient Care
Medical Knowledge Practice-Based Learning
Interpersonal and communication skills

Speaker 1: Stephen P. Daiger
Presentation Title: Gene discovery and mutation detection in families with dominant retinitis pigmentosa Presentation Content: Retinitis pigmentosa (RP) accounts for half of inherited retinal diseases and dominantly- inherited disease accounts for a substantial fraction of RP families. Dominant RP families are optimal for genetic studies because segregation within families allows for gene mapping, and pathogenicity of potential disease- causing variants can be assessed by comparing affected and unaffected individuals. Currently, targeted retinal- capture NGS can identify the disease-causing mutation in 60% to 80% of families with dominant RP, depending on the population tested. The remaining families without detectable mutations suggest existence of novel RP genes, but mutations in known genes that are not easily detected by current methods are likely too. We present results of multiple approaches to gene discovery and mutation detection in a cohort of over 260 dominant RP families, resulting in a high detection rate and identification of novel genes, but also frustrating failure to detect mutations in several large families. Our experience illustrates the strengths and limitations of current approaches.

Speaker 2: Kari E. Branham
Presentation Title: Integrating genetic testing into the inherited retinal disease clinic
Presentation Content: Advances in gene identification in the field of inherited retinal diseases have allowed clinical genetic testing to become an essential aspect of comprehensive clinical care for patients affected with these conditions. Genetic testing allows for genetic confirmation of disease, accurate inheritance counseling, enrollment in clinical treatment trials, and can guide appropriate screening/management of patients affected with syndromic forms of retinal disease. As with other genetic disease specialties, inherited retinal disease clinics have undergone a transition from genetic testing which was once only through research studies, to clinical testing of single disease specific genes, to testing for large multigene panels. Over the last ten years, the University of Michigan's Kellogg Eye Center has ordered clinical testing on several hundred patients and arranged for testing on more than a thousand additional patients through the eyeGENE research program and other research collaborations. With the use of newly developed NGS multigene panel based tests, approximately 50% of our patients with inherited retinal disease will have the genetic basis for their disease identified. The successes and challenges of the integration of genetic testing and genetic counseling into an inherited retinal disease clinic will be presented with case examples.

Speaker 3: Val Sheffield
Presentation Title: Functional validation and genetic intervention for retinal disease genes
Presentation Content: High-throughput sequencing technologies have fueled rapid improvements to mutation detection and gene discovery for inherited retinal degenerative diseases (IRDs). However, there remains a pressing need for functional validation of new mutations and candidate disease genes to credential their role in retinal degeneration. Some potential avenues of treatment, such as gene replacement therapy for recessive diseases only require knowledge of a patient's disease gene. Other approaches like CRISPR/Cas9 genome editing require precise information about the pathogenic mutation(s). In this presentation it will be demonstrated that patient specific
iPSC derived eyecups can be used to evaluate the pathophysiology of novel genetic variants in patients with specific forms of retinal degeneration. It will also be demonstrated that such data can be used to develop gene augmentation and CRISPR corrected autologous photoreceptor cell replacement strategies in a non-profit academic GMP facility, even for rare diseases. The approach described is in keeping with the goals of the Precision Medicine initiative and the need for execution strategies.

Speaker 4: Eric Pierce
Presentation Title: From gene discovery to clinical trials for inherited retinal diseases
Presentation Content: Inherited retinal degenerations (IRDs) are important causes of vision loss. They are also genetically diverse, with over 250 IRD disease genes identified to date. Several clinical trials have demonstrated the potential of gene augmentation therapy to be used to treat IRDs. Specifically, adeno-associated virus (AAV) mediated gene augmentation therapy for the genetic subtypes of IRD caused by mutations in the RPE65 and CHM genes have demonstrated visual benefit in clinical trials. Clinical trials of gene therapies for several additional genetic subtypes of IRD are in progress (NCT02416622, NCT01505062, NCT02341807, NCT01461213, NCT02610582, NCT01482195, NCT02317887, NCT01367444). There is thus great interest in extending the use of gene and genetic therapies to treat many genetic forms of IRD. In order to achieve this goal, genetic diagnostic testing needs to be applied broadly for patients with IRDs. This presentation will discuss the use of genetic testing in patient care, including the integration of clinical workup, different types of genetic diagnostic testing, data analysis, and follow- up including resolution of pathogenicity. Data from recent studies of panel-based tests and exome sequencing to identify genetic causality will be presented. Similarly, data from informatic and empiric methods to evaluate pathogenicity of identified variants will be discussed.