2022 ASHG Invited Session Schedule

as of June 2022

Tuesday, October 25 4:30 – 6:00 pm	Friday, October 28 8:30 – 10:00 am
Session Title: Demographic history, natural selection, and disease risk in diverse global biobanks **Topic:** Evolution and Population Genetics **Track:** Basic/Fundamental/Translational	**Session Title:** The impact of ascertainment, phenotyping, and population structure on human genetic research **(Panel)** **Topic:** Statistical Genetics and Genetic Epidemiology **Track:** Basic/Fundamental/Clinical
Session Title: New advances in computational genome interpretation: From prediction to the clinic **Topic:** Bioinformatics and Computational Approaches **Track:** Basic/Fundamental/Clinical	**Session Title:** To report or not to report: The quandary of variants of uncertain significance (VUSs) **(Panel)** **Topic:** Molecular and Cytogenetic Diagnostics **Track:** Clinical
Session Title: Genome mapping technologies – Enabling next-generation cytogenetics **(Panel)** **Topic:** Molecular and Cytogenetic Diagnostics **Track:** Clinical	**Session Title:** Novel preclinical models of Down syndrome elucidate the complex genetic etiology of neurodevelopmental phenotypes **Topic:** Complex Traits and Polygenic Disorders **Track:** Basic/Fundamental/Translational
Session Title: Genomic perspectives on biological sex **Topic:** Molecular Effects of Genetic Variation **Track:** Basic/Fundamental/Translational	**Session Title:** Long-read RNA-seq to illuminate splice-driven mechanisms of human genetic diseases **Topic:** Molecular Effects of Genetic Variation **Track:** Basic/Fundamental/Translational
Session Title: COVID-19 in the post-pandemic era: Long COVID, vaccine response, and beyond **(Panel)** **Topic:** Complex Traits and Polygenic Disorders **Track:** Basic/Fundamental/Clinical	**Session Title:** Upset the set up: Moving from community engagement to community empowerment **(Panel)** **Topic:** Genetic Counseling, ELSI, Education, and Health Services Research **Track:** Ethical, Legal, Social Issues/Diversity, Equity and Inclusion
Session Title: Mosaicism, vascular anomalies, and emerging therapeutics: Models for using the rare to understand the common **Topic:** Precision Medicine, Pharmacogenomics, and Genetic Therapies **Track:** Basic/Fundamental/Translational	

ASHG 2022 Invited Sessions (as of June 2022)

Tuesday, October 25, 4:30 – 6:00 pm

Demographic history, natural selection, and disease risk in diverse global biobanks

Moderators: Arjun Biddanda, PhD, 54Gene; Alicia Martin, PhD, Massachusetts General Hospital

Session Type: Scientific/Education
Topic: Evolution and Population Genetics
Track/Audience: Basic/Fundamental/Translational

Large-scale collections of genotypic and phenotypic data have become a standard in the field of genomics, enabling rapid acceleration of discoveries into the genetic architecture of populations and facilitating the discovery of novel disease targets. While biobanks in cohorts of European ancestry have been available for a number of years (e.g. UK Biobank), there are rapidly growing biobanks in multiple regions around the world, yielding insight into both disease risk and adaptation in diverse populations. Insights from these efforts will inform our understanding of the genomic drivers of disease risk. Here, we focus on these recent biobanking efforts in diverse and under-represented populations and the insights they offer into fine-scale demographic history and adaptation, with an outlook on direct links to phenotypic association. The speakers in this session each highlight relevant biobanks across regions of the world that have traditionally been underrepresented, emphasizing the value in curating genomic and phenotypic datasets from diverse populations. A focus in each talk will also be to highlight data-sharing protocols, providing a broader understanding of how external researchers may interact with data from diverse populations.

Speakers:

Inferring population size dynamics of Niger-Congo speakers using deep whole genome sequences. Ananyo Choudhury, PhD, University of the Witwatersrand
Pan-Arab genome wide genotyping array and its associated reference panel: Empowering the region with the necessary tools for increasing diversity in genetic studies. Radja Badji, PhD, Qatar Foundation
Nationwide biobank in Mexico unravels demographic history and complex trait architecture from 6,000 genomes. Mashaal Sohail, PhD, National Autonomous University of Mexico
Leveraging fine-scale population structure in health systems. Gillian Belbin, PhD, Icahn School of Medicine at Mount Sinai

Tuesday, October 25, 4:30 – 6:00 pm

New advances in computational genome interpretation: From prediction to the clinic
Moderators: Constantina Bakolitsa, PhD, UC Berkeley; Predrag Radivojac, PhD, Northeastern University

Session Type: Scientific/Education
Topic: Bioinformatics and Computational Approaches
Track/Audience: Basic/Fundamental/Clinical

Computational methods offer a potentially powerful approach for exploring genomic data, but their reliability and clinical utility have not been established. This session will highlight recent advances in the evaluation of computational method performance in a range of settings, as assessed by the Critical Assessment of Genome Interpretation (CAGI), a community experiment in variant impact prediction. Over the past decade, CAGI has informed new guidelines for genome interpretation, as well as ethical principles of the handling of human data. Using data from ClinVar, Dr Pejaver will present a sophisticated new approach for calibrating the performance of any computational model so that their readouts are interpretable in terms of ACMG/AMP variant classification (B, LB, LP, P). His analysis indicates that for several methods, Moderate and Strong evidence levels are justified for a subset of variants. Dr Stenton will discuss the application of diagnostic algorithms in the discovery of disease-causing variants in children with suspected rare, Mendelian disorders, as part of her assessment of the CAGI6 challenge involving a Rare Genomes Project cohort. Multiple predicted variants in this challenge were deemed diagnostic or are being pursued for functional validation and further analyses, indicating a powerful synergy between clinicians and computational experts in advancing the field of clinical genome interpretation. Dr Chun will present an evaluation of the CAGI6 PRS challenge, with real and simulated datasets from four complex phenotypes (T2D, IBD, CAD and cancer). Privacy and sample size limitations as well as covariate effects and the lack of transferability between different populations make this a difficult area for genome interpretation. However, one group outperformed state-of-the- art PRS methods in IBD, suggesting potential for use in the clinic. While these exciting advances bring the field of genome interpretation closer to the promise of personalized medicine, the risks of dealing with secondary findings and privacy violations increase. In the final talk, Dr Fullerton , will discuss the ethical considerations of new information generated by computational methods and current approaches and challenges to responsible data stewardship, in the dynamic balance between human participant protection and data access for research.

Speakers:

Evidence-based calibration of computational tools for missense variant pathogenicity classification. Vikas Pejaver, PhD, Icahn School of Medicine at Mount Sinai
Performance of diagnostic methods in identifying disease-causing variants: assessment of the Rare Genomes Project CAGI challenge. Sarah Louise Stenton, PhD, Broad Institute of MIT and Harvard
Progress in complex phenotype prediction: the CAGI6 PRS challenge. Sung Chun, PhD**,** Boston Children's Hospital
Ethical challenges in the era of genomic medicine: lessons from CAGI. Stephanie M. Fullerton, PhD, University of Washington

Tuesday, October 25, 4:30 – 6:00 pm

Genome mapping technologies – Enabling next-generation cytogenetics
Moderators: M Anwar Iqbal, PhD, University of Rochester Medical Center; Nikhil Sahajpal, PhD, Augusta University

Session Type: Scientific/Education
Topic: Molecular and Cytogenetic Diagnostics
Track/Audience: Clinical

The current standard-of-care methods (karyotype; FISH; microarray) for the detection of structural variations (SVs) and copy number variants (CNVs) are low resolution (karyotype), targeted and require prior knowledge (FISH), or cannot detect balanced SVs nor indicate the location and orientation of duplicated segments of the genome (microarray). This session will introduce the audience to genome mapping technologies and focus on evidence-based clinical utilization of one of them, namely, optical genome mapping (OGM) - an emerging next- generation molecular and cytogenetics tool for comprehensive structural variant (SV) analysis. This session will involve four pioneers – they will share their experience on how genome mapping techniques, with a focus on OGM in particular, are beginning to revolutionize (molecular) cytogenetics. The speakers will also discuss the utilization and limitations of short and long read sequencing (srWGS and lrWGS) to detect SVs in the light of their different studies and the literature. The first speaker, Dr. Tuomo Mantere, will introduce the topic by a brief historic overview of genome mapping technologies, discussing the fundamentals of genome mapping as well as an overview of existing platforms in particular, OGM, as well as long read sequencing technologies. The second speaker, Dr. Laila El-Khattabi, will show how OGM can be applied to constitutional diseases by enabling the most comprehensive SV detection of chromosomal aberrations including translocations, micro-deletions and –duplications, as well as repeat expansions. She will also show results from her study comparing OGM and srWGS performance in detecting SVs. The third speaker, Dr. Rashmi Kanagal-Shamanna, will demonstrate an integrated approach of using OGM and targeted NGS for comprehensive genomic evaluation of hematological malignancies. Finally, the fourth speaker, Dr. Adam Smith, will share the prevailing current opinion on "Global Evolution of Cytogenetic Testing" and development of clinical guidelines for molecular testing from "technology- centric" classifications (e.g. karyotype based) to more "biology-centric" as approaches to testing evolves.

Speakers:

Principles of genome mapping and long-read sequencing technologies for structural variant detection. Tuomo Mantere, PhD, University of Oulu
Optical genome mapping allows for comprehensive and efficient detection of constitutional chromosomal aberrations. Laila El-Khattabi, PharmD, Paris University Hospitals
Integrated genomic evaluation using optical genome mapping combined with targeted NGS in hematological malignancies. Rashmi Kanagal-Shamanna, MD, The University of Texas, MD Anderson Cancer Center
How genome mapping technologies will change clinical cytogenetics practice. Adam Smith, PhD, University Health Network and University of Toronto

Tuesday, October 25, 4:30 – 6:00 pm

Genomic perspectives on biological sex
Moderators: Armin Raznahan, MD/PhD, NIMH Intramural Research Program, NIH; Christine Disteche, PhD, University of Washington

Session Type: Scientific/Education
Topic: Molecular Effects of Genetic Variation
Track/Audience: Basic/Fundamental/Translational

There is growing awareness of the importance of considering sex as a biological variable, and this need intersects with Human Genetics at several fundamental levels. First, genetic differences are foundational to the distinction between XX females and XY males in humans and all other placental mammals. This defining karyotypic sex-difference reflect millions of years of sex-biased genome evolution and leads to profound sex-differences in genome-wide regulation and function. As such, biological sex is a dominant source of naturally occurring genomic variation amongst humans and needs to be taken into account when wanting to understand health- and disease-related outcomes in humans. Second, biological sex is intimately related to the societal construct of gender, and both these factors interact to shape many phenotypes of interest to Human Genetics as well as the ways in which these phenotypes are underpinned by genetic and environmental factors (as well as gene-environment interactions). Third, the accelerating use of modern research methods to tackle the above two considerations has made genomic research on sex-differences a hot bed of methodological innovation that carries broader utility in Human Genetics. This Invited Session will bring together cutting-edge multidisciplinary research that unpacks the bivalent connections between biological sex and Human Genetics. We not only provide practical pointers that will help all researchers best-incorporate sex into their basic and clinical genetic studies, but we will also showcase the how modern genetic and genomic research methods are dramatically advancing our understanding of sex as a biological variable (and vice versa). Special attention will be paid to: (i) surveying sex-differences in gene expression and how these vary between species, individuals, tissues and cell-types; (ii) identifying how sex- differences in gene dosage and genome regulation can serve to both create and mask sex-differences in gene- expression; (iii) identifying intersections between sex-biased genome function intersects and the biology of risk for diverse human diseases; and (iv) underlining the importance of sex-stratified analyses for identifying genetic risk factors for human disease.

Speakers:

The impact of sex on gene expression and its genetic regulation across human tissues. Barbara Stranger, PhD, Northwestern University
Linking X-Y gametologue co-expression patterns to sex differences in disease. Armin Raznahan, MD/PhD, NIMH Intramural Research Program, NIH
X chromosome regulation and gene expression in stem cell derivatives. Christine Disteche, PhD, University of Washington
The influence of common X-linked genetic variation on neuroanatomical variation in humans. Travis Mallard, PhD, Massachusetts General Hospital

Tuesday, October 25, 4:30 – 6:00 pm

COVID-19 in the post-pandemic era: Long COVID, vaccine response, and beyond
Moderators: Eva Schulte, MD/PhD, University of Munich; Shefali Verma, PhD, University of Pennsylvania

Session Type: Scientific/Education
Topic: Complex Traits and Polygenic Disorders
Track/Audience: Basic/Fundamental/Clinical

The SARS-CoV-2 pandemic has affected all of our lives over the past two years. Immense research efforts have led to an unprecedented depth of knowledge about SARS-CoV-2 and COVID-19. This session will showcase some of the work that has been performed with the aim of furthering our understanding of the interaction between SARS- CoV-2 and its human host with a special focus on the host genetics aspects. It will highlight host genetic aspects surrounding COVID-19 that are sure to play an important role during years to come, including vaccine response and longCOVID. Andreas Pichlmair introduces the topic by showing how a combination of multimodal proteomics and network analyses can be used to understand how viral and host proteins interact in bringing about COVID-19. Next, Tomoko Nakanishi will discuss how rare and common host genetic risk factors, identified in studies conducted by large global consortial efforts like the COVID-19 Host Genetics Initiative (COVID-19 HGI), relate to the clinical presentation of COVID-19 and how host genetics could influence the clinical management of individuals with COVID-19. Liz Cirulli will depict the interaction between reactions to mRNA-based COVID-19 vaccines and host genetic aspects by highlighting a recently identified link between HLA genotypes and vaccine tolerance. Finally, addressing potential long-term consequences of the pandemic, Hanna Ollila will describe a large ongoing effort to understand the genetic underpinnings of post COVID-19 symptoms like LongCOVID by genome- wide association studies. Together, these presentations will present the audience with a great overview of the emerging understanding of the genetic aspects of virus-host interaction in COVID-19 and its continued everyday relevance to diverse clinical phenotypes during the third year of the pandemic.

Speakers:

Multi-omics analysis to identify molecular determinants of virus-host interaction in SARS-CoV- 2 infection. Andreas Pichlmair, PhD, Technical University of Munich

Clinical implications of COVID-19 genetics. How can we use genetic risk to improve patient care? Tomoko Nakanishi, MD, McGill University

Genetics of vaccine side-effects. Elizabeth Cirulli, PhD, Helix

Lessons learned from the Long COVID Working Group of the COVID-19 Host Genetics Initiative–Understanding genetic risk factors for Long COVID. Hanna Ollila, PhD, University of Helsinki

Tuesday, October 25, 4:30 – 6:00 pm

Mosaicism, vascular anomalies, and emerging therapeutics: Models for using the rare to understand the common
Moderators: Sarah Sheppard, MD/PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; James Bennett, MD/PhD, Seattle Children's Research Institute

Session Type: Scientific/Education
Topic: Precision Medicine, Pharmacogenomics, and Genetic Therapies
Track/Audience: Basic/Fundamental/Translational

This session will focus on the role of mosaic activating pathogenic variants in development malformations of the blood and lymphatic vascular systems. Recent reports of very low level somatic variants in well-known oncogenes as a cause of vascular malformations- a non-neoplastic congenital disease- has led to an explosion of research addressing three primary questions spanning basic science signaling mechanisms all the way to clinical trials: 1) how do such a small number of mutant cells non-cell autonomously induce wild-type cells to become part of the vascular malformation?; 2) what are the diagnostic methods to detect such low level pathogenic variants in individuals with vascular malformations?; and 3) can we repurpose drugs designed to treat cancer for individuals with vascular malformations? Dr. Miikka Vikkula, a human geneticist, long-term ASHG member and a leader in the field, will open the session by describing the current landscape of vascular malformations and strategies to identify the etiology in undiagnosed cases. Dr. Ralitsa Madsen, an early-stage investigator, will then describe her in vitro approaches understanding PI3K-AKT signaling and pathway cross talk using precision human induced pluripotent stem cell (hiPSC) models. Dr. Michael Dellinger, a mid-stage investigator will follow with his work developing and treating a KRAS-driven mouse model for Gorham Stout Disease (a complex lymphatic anomaly with loss of adjacent bone). Finally, the session will end with Jill Dayneka, a combined medical and MPH student, who will discuss the safety and efficacy of MEK inhibitor therapy for vascular malformations.

Speakers:

A novel genetic cause for central conducting lymphatic anomaly. Miikka Vikkula, MD/PhD, de Duve Institute, UCLouvain
Towards a quantitative understanding of genetic PI3Ka activation. Ralitsa Madsen, PhD, University College London
A MEKINIST-ic approach to target abnormal lymphatics in Gorham-Stout disease. Michael Dellinger, PhD, UT Southwestern Medical Center
MEK inhibition for the treatment of RAS-pathway related vascular malformations. Jill Dayneka, BA, Tulane University

Friday, October 28, 8:30 – 10:00 am

The impact of ascertainment, phenotyping, and population structure on human genetic research
Moderators: Renato Polimanti, PhD, Yale University; Loic Yengo, PhD, The University of Queensland

Session Type: Scientific/Education
Topic: Statistical Genetics and Genetic Epidemiology
Track/Audience: Basic/Fundamental/Clinical

Large-scale genome-wide association studies are providing an unprecedented amount of information to understand the complex dynamics underlying genotype-phenotype associations. This session will showcase novel methods and results regarding the impact of ascertainment, phenotyping, and population structure on gene discovery and polygenic characterization of human traits and diseases. The first speaker will explain the impact of participation bias and non-response behaviors on the interpretation and the generalizability of large-scale genome-wide association studies. His analyses demonstrate that these biases are genetically correlated with education, health, and income although unique genetic effects were also observed. Next, the second speaker will show how assortative mating due to socioeconomic status affects the polygenic architecture of psychiatric traits and disorders assessed in the UK Biobank. Her research underlines that socioeconomic status should be carefully modeled when investigating the polygenic architecture of phenotypes related to mental health. Our third speaker will present the consistent correlation of year of birth with polygenic scores for different health conditions and quantitative traits in participants recruited by multiple biobanks within the PsycheMERGE network. Her findings highlight that this phenomenon is likely due to a combination of factors, such as differences in population structure by birth cohort and changing ascertainment bias within the medical system over time. Finally, our fourth speaker will introduce a novel method to assess ascertainment biases through the analysis of individual- level array-genotyped data and genome-wide association statistics. Specifically, he will show how comparing the empirical distribution (mainly statistical moments) of multivariate distributions of polygenic scores with that expected for a randomly ascertained sample can provide evidence of different types of ascertainment.

Speakers:

Human genetics provides insights into participation to research studies and nonresponse to questionnaires. Andrea Ganna, PhD, Institute for Molecular Medicine Finland
The impact of socioeconomic status in the polygenic risk of psychiatric traits and disorders: evidence of assortative mating in UK Biobank. Brenda Cabrera Mendoza, MD/PhD, Yale University
Year of birth bias in the association of polygenic score within the PsycheMERGE network. Maria Niarchou, PhD, Vanderbilt University
Using polygenic scores distribution to detect ascertainment in observational studies. Adrian Campos, PhD, The University of Queensland

Friday, October 28, 8:30 – 10:00 am

To report or not to report: The quandary of the variants of uncertain significance (VUSs)
Moderators: Heidi Rehm, PhD, Massachusetts General Hospital; Shawneequa Callier, JD, George Washington University

Session Type: Ethical, Legal, and Social Issues
Topic: Molecular and Cytogenetic Diagnostics
Track/Audience: Clinical

An increasing percentage of the population is getting genetic testing as a diagnostic test based on symptoms, or as a risk assessment through population screening, or due to family history of a known or suspected genetic disease. As the indications for testing and the number of genes tested expand, so does the potential for variants of uncertain significance (VUSs) to be detected and returned to individuals. Additionally, the prevalence of VUSs are disproportionately higher in underrepresented minority populations due to both the paucity of literature in affected individuals from these populations and a lack of representation in databases. To date, most laboratories do not report VUSs in the context of population screening but do report VUSs for diagnostic testing given the potential to follow-up. This includes resolving VUSs if other family members are available for segregation studies, using clinical tests to inform a VUS, or waiting for additional data that may be generated over time. However, there are increasingly blurry lines between these testing paradigms and a need to engage the community in dialogue around when it is appropriate to return a VUS, when returning a VUS may do more harm than good, and how to guide clinical laboratory practices that are not labor intensive. For example, should a healthy individual seeking cancer risk screening have VUSs returned in their report? Some say no, others say yes, others feel it is context dependent. If an unaffected individual is part of a large family with many individuals segregating features of an inherited cancer syndrome, and follow-up segregation testing could be informative, then some would argue yes. For another unaffected individual whose family has no clear features of a condition and all affected family members are deceased, the utility of returning a VUS may be minimal and the potential for harm higher. Furthermore, not all VUSs are created equal and up to 90% of VUSs are eventually downgraded to Likely Benign. Some VUSs have substantial evidence towards pathogenicity but fall slightly below the line for classification as Likely Pathogenic. Yet the majority of VUSs have no evidence, some being found in population databases but at a frequency that is not quite sufficient to classify as Likely Benign. Should there be policies that distinguish these types of VUSs; should policies for return of VUS results incorporate these subcategories; and should laboratories be expected to subcategorize VUSs?

Speakers:

Challenges of communicating VUSs from genetic testing results. Andrea Hanson-Kahn, MS, Stanford University Medical School
The landscape of VUSs in a large clinical cohort undergoing molecular testing for hereditary disease. Dianalee McKnight, PhD, Invitae
Not all VUSs are created equal. Heidi Rehm, PhD, Massachusetts General Hospital
Reporting and return of results involving VUSs: Opinions from genetics providers. Sulagna Saitta, MD/PhD, David Geffen School of Medicine at UCLA

Friday, October 28, 8:30 – 10:00 am

Novel preclinical models of Down syndrome elucidate the complex genetic etiology of neurodevelopmental phenotypes
Moderators: Summer Thyme, PhD, The University of Alabama at Birmingham; Anna Moyer, PhD, Johns Hopkins School of Medicine

Session Type: Scientific/Education
Topic: Complex Traits and Polygenic Disorders
Track/Audience: Basic/Fundamental/Translational

Down syndrome is one of the most genetically complex conditions compatible with life. Subtle overexpression of 500+ chromosome 21 (HSA21) transcripts, many of which remain uncharacterized, results in intellectual disability and an increased risk of more than a dozen Down syndrome-associated phenotypes. The presence of extra genetic material also triggers global stress response pathways and developmental instability. Given the diversity of mechanisms by which trisomy 21 disrupts normal brain development, Down syndrome researchers must grapple with how to identify genes of major effect and prioritize which treatment strategies move forward to human clinical trials. This session will highlight cutting-edge methods for unraveling the genetic complexity of neurodevelopmental phenotypes across a range of animal and cellular models. Our first speaker will discuss a systematic screen of HSA21 orthologs in C. elegans. In contrast with mouse models, C. elegans offers an ideal platform for high-throughput and quantitative behavioral screening. Overexpression of several highly-conserved HSA21 orthologs causes behavioral defects, providing a crucial, first-pass characterization of understudied HSA21 orthologs in the nervous system. Our second speaker will present evidence that Dscam overexpression results in conserved presynaptic overgrowth phenotypes in Drosophila and Ts65Dn mice. The translation of a molecular phenotype from fly to mouse highlights the utility of invertebrate models for mechanistic studies, and, importantly, provides a hypothesis for how alteration of Dscam levels could contribute to neuropathology in Down syndrome, autism, and epilepsy. Our third speaker will present the development and characterization of two new transchromosomic models of Down syndrome. The TcHSA21RAT model recapitulates salient features of Down syndrome including learning and memory deficits, reduced brain volume, and abnormal cerebellar foliation. Refined behavioral assays in rat could help to prioritize which of the 20+ compounds tested in mouse models should proceed to clinical trials. Finally, our fourth speaker will discuss nuclear architecture in neural progenitors derived from human trisomy 21 iPSCs. Trisomic neural progenitors show global disruptions in chromatin organization that are reminiscent of senescence and can be rescued with senolytic drugs. These findings provide an additional mechanism by which aneuploidy stress could provoke shared phenotypes across trisomies.

Speakers:

Leveraging C. elegans for an unbiased screen of human 21st chromosome gene overexpression. Sophia Sanchez, BS/BA, University of Texas at Austin
Elevated levels of Down syndrome cell adhesion molecule cause presynaptic overgrowth in Drosophila and mouse models of Down syndrome. Bing Ye, PhD, University of Michigan
New genetic models of Down syndrome in mouse and rat. Roger Reeves, PhD, Johns Hopkins University
Down syndrome induced senescence disrupts the nuclear architecture and function of neural progenitors. Hiruy Meharena, PhD, UCSD

Friday, October 28, 8:30 – 10:00 am

Long-read RNA-seq to illuminate splice-driven mechanisms of human genetic diseases
Moderators: Gloria Sheynkman, PhD, University of Virginia; Peter Castaldi, MD, Brigham and Women's Hospital

Session Type: Scientific/Education
Topic: Molecular Effects of Genetic Variation
Track/Audience: Basic/Fundamental/Translational

Aberrant splicing underlies many human diseases, including cancer, cardiovascular diseases, and neurological disorders. The mapping of splicing quantitative trait loci (sQTL) has shown that genetic regulation of alternative splicing is widespread. However, the corresponding isoform or protein product associated with disease- associated sQTLs is largely unknown and unattainable with approaches such as short-read RNA-seq, which, frequently, cannot unambiguously characterize full-length transcript isoforms or offer allele-specific information. Furthermore, most sQTL interpretation performed today relies on mapping back to reference transcript annotations, which are incomplete, especially for disease contexts. Solutions to these issues may be found through integration of newly emerging long read sequencing technologies. Long read sequencing offers the capability to sequence full-length mRNA transcripts to more directly link sQTLs to disease-relevant protein alterations, in other words, a more accurate and efficient connection from DNA to protein, through context- specific transcript expression knowledge. Long read sequencing approaches allow for quantification of disease- associated isoforms and prediction of encoded proteins, which provides a path towards mechanistic understanding of disease. In this session, we will present the latest research that demonstrates how long read RNA-seq enables discovery and contextualization of complex alternative splicing contributing to disease pathophysiology. High-throughput long-read RNA-seq enables identification of thousands of novel isoforms that are entirely absent from existing annotations (GENCODE, RefSeq, etc.). We show how the resulting full-length transcript information reveals new sQTLs that were difficult to identify with only short read data. Further, with the ability to catalog the entire diversity of full-length transcript isoforms in genes known to have complex splicing, we are now able to query whether certain diseases express dominant isoforms across all patients, or whether the expressions are driven by patient-specific isoform expression. In all cases, speakers in this session will highlight the process by which long read RNA-seq identifies novel isoforms that could be implicated in disease progression, including disease subtype specific and patient-specific isoforms.

Speakers:

Long-read RNA-seq of human microglia reveals novel isoforms and elucidates Alzheimer's- associated genetic regulation of splicing. Jack Humphrey, PhD, Mount Sinai School of Medicine
Interpreting the effects of GWAS loci on splicing using long-read RNA-seq. Abdullah Abood, MS, University of Virginia
Evidence for high levels of mis-annotation of protein coding genes known to have an associated pseudogene revealed by long-read RNA-sequencing. Mina Ryten, MD/PhD, University College London
A more comprehensive landscape of RNA alterations in cancer with long-read sequencing. Angela Brooks, PhD, University of California Santa Cruz

Friday, October 28, 8:30 – 10:00 am

Upset the set up: Moving from community engagement to community empowerment
Moderators: Daphne Martschenko, PhD, Stanford University Medicine; Markia Smith, BS/BA, UNC Chapel Hill School of Medicine

Session Type: Diversity, Equity & Inclusion
Topic: Genetic Counseling, ELSI, Education, and Health Services Research
Track/Audience: Ethical, Legal, Social Issues/Diversity, Equity and Inclusion

The Black feminist creative bell hooks wrote that "to build community requires vigilant awareness of the work we must continually do to undermine all the socialization that leads us to behave in ways that perpetuate domination." Community engagement is often presented as a way to build a 'genomic inclusive' research community that promotes social justice in the field of human genetics. However, genetic research has largely retained, and perpetuated, historical societal structures of domination. It has done so through racist, ableist, and classist campaigns that promote data collection as the end point for community engagement, while ignoring both communities' immediate needs and the necessity of restructuring systems that preclude long term equitable implementation and sharing of benefits. Despite increasing calls for community engagement, incentives structures within the research enterprise make such work difficult. Ideals and assumptions about how to redress historical and often racist and paternalistic approaches by consulting with people or groups as equal partners in research can displace the realities of what it will take to create multi-faceted relationships that serve both scientific and community values. In response to these challenges and the promises of community engagement, the overarching objectives of this session are to: (1) examine ongoing efforts that break the mold of transactional community engaged research; and (2) explore remaining needs for community empowered research in genetics and genomics. It does so by bringing together diverse stakeholders in the field to consider the need to transition from community engagement to community empowerment. This session celebrates the voices of those who have been most harmed by scientific research by presenting solutions from Black, Indigenous, Disabled, and LGBTQIA+ communities. Importantly, this session moves beyond a discussion of whether and how dominant approaches to communicate engagement perpetuate inequality and the limited agency of underserved communities in human genetics to explore, along a number of dimensions, the social and ethical implications of such approaches. Alongside audience members, speakers will engage in a productive dialogue on how to sustainably empower and include communities who have been historically excluded and harmed by the antecedents of research in human genetics with the intention to upset the set up.

Speakers:

Decolonizing DNA through storytelling. Janina Jeff, PhD, Illumina
Bezos to bottlenecks: The chasm between scientific altruism & extraction from the amerindigenous. Joseph Yracheta, MS, Native BioData Consortium
LGBTQIA+ community engagement with genomic studies on same-sex sexual behavior: Lessons learned. Robbee Wedow, PhD, Broad Institute
From objects to subjects: Anti-ableism and community engagement in precision medicine research. Maya Sabatello, PhD, Columbia University