Proposed By: Simon E. Fisher

Proposed Moderator(s): Simon E. Fisher, Evan Eichler

Topic Area: 5. Evolution and Population Genetics

Session Content: Scientific

Session Title: Novel insights into human brain evolution from advanced genomics.

Session Description:
Dramatic advances in genomic technologies are shedding new light on the evolutionary origins of human-specific traits and how the relevant molecular pathways may be disturbed in related disorders. This session will showcase the extraordinary impact that cutting-edge molecular approaches are making on our understanding of the distinctive evolution, development and functions of the human brain. Evan Eichler (U. Washington) introduces the topic, showing how the latest sequencing methods help resolve the critical contributions of segmental duplications to the emergence of our species. Crucially, these genomic processes have at the same time put modern humans at high risk of neurodevelopmental disease, including autism, intellectual disability and epilepsy. Next, Wieland Huttner (MPI of Molecular Cell Biology and Genetics) describes how a sophisticated combination of comparative transcriptomics with functional analyses in model systems has identified human-specific genes, such as ARHGAP11B, that can be mechanistically linked to neocortical expansion. Our third speaker, Fenna Krienen (Harvard Medical School), discusses innovative work integrating spatial patterns of gene expression in the human neocortex with patterns of functional connectivity, as indexed by state-of-the-art neuroimaging. Her research uncovers a role for molecular modifications of upper cortical layers in the evolution of long-range connections in the human brain. Finally, Alex Pollen (UCSF) explains how his analyses of gene expression in single cells can be correlated with their position, morphology and cellular behavior during development. This approach has highlighted species-specific changes in radial glia gene expression that may help uncover what makes us human, and yield novel windows into brain disorders.

Session Rationale:
The evolution of the human brain is a fundamental question at the heart of modern biology. For many years this topic has been largely outside the reach of available methods, such that it has been hard to move beyond speculative stories. We are now in an exciting era where technical innovations at multiple different levels make it possible to carry out empirical studies on the molecular bases of human brain evolution. In particular, the advances in genomic technologies are allowing us not only to identify specific genetic factors that have contributed to human evolution, but to uncover the relevant mechanistic pathways in development and function of the brain. This session will be particular timely, incorporating recent advances in comparative genomics, DNA/RNA sequencing of single molecules, single cell transcriptomics, model systems and neuroimaging-based connectivity analyses. We highlight not only the excitement of the latest discoveries for explaining human evolution, but also the relevance of these findings for understanding the molecular genetic pathways underlying important neurodevelopmental diseases, including autism and epilepsy. Thus, this fills gaps in knowledge across multiple fields of human genetics, from evolutionary anthropology to developmental biology to medical genetics.

Learning Objectives
1. Define the main types of state-of-the-art genomic approaches that are being used for studying human brain evolution.
2. Relate genomic findings concerning human brain evolution to those from studies of major neurodevelopmental disorders.
3. Interpret how evolutionary changes in multiple molecular pathways have contributed to the unique expansion of the human neocortex.
4. Discuss the integration of complementary methods, such as genome sequencing, brain transcriptomics, model systems and functional neuroimaging, for shedding new light on the evolution of our species.

Attendee Benefits:
Attendees from diverse disciplines will gain an appreciation of the remarkable and exciting advances in evolutionary neurogenetics. They will understand how genomic tools can be successfully integrated with research methods at other levels (developmental biology, neuroimaging etc.) to yield much more than the sum of the parts, giving some of the first robust biological insights into very old questions about the emergence of Homo sapiens. Moreover, attendees will be able to relate the evolutionary findings to major issues in medical genetics, given that the pathways that are being identified appear to be implicated in a range of human neurodevelopmental disorders.

Target Audience:
This session will be of interest to a broad audience of ASHG2017 attendees from diverse backgrounds, since it explicitly integrates findings from evolutionary anthropology, clinical genetics, developmental biology and neurogenetics, all uniting around a focus of the latest developments in genomics technologies. We anticipate most interest from scientists interested in evolution, neurodevelopmental disorders, and human genomics. Nonetheless, the central question (the developmental and evolutionary origins of the human brain) is a very hot topic that cuts across fields. We have assembled a set of top speakers who have excellent abilities in making their findings accessible to non-experts.

The competencies and attributes the session will address: Medical Knowledge
Interpersonal and communication skills

Speaker 1: Evan Eichler
Presentation Title: Human evolution and disease by segmental duplication.
Presentation Content: Human duplicated sequences show extraordinary sequence complexity and are important sources for gene innovation and rearrangement associated with neurocognitive and neurodevelopmental diseases. I will present an overview of the evolution of great-ape segmental duplications, their copy-number variation in diverse human populations and their potential to form neofunctional paralogs through segmental duplication fusion and truncation. I will highlight examples of novel genes that have evolved within the human lineage that appear to have contributed to unique adaptive aspects of the human species including an increased density of excitatory/inhibitory synapses and the expansion of cortical neurons. Using single-molecule real-time sequencing technology, I will show how such complex regions can be resolved and show how radically these regions of our genome have changed and differ among human populations. Paradoxically, the duplication architecture complexity has led to a high background rate of copy-number variation mutations associated with neurodevelopmental disease (eg. autism, intellectual disability and epilepsy) in the human species suggesting that novel adaptations and increased disease burden are inextricably linked.

Speaker 2: Wieland Huttner
Presentation Title: The role of human-specific genes, notably ARHGAP11B, in neural stem cell amplification and neocortex expansion in development and evolution.
Presentation Content: Our group studies neural stem and progenitor cells in the context of the expansion of the neocortex in development and evolution. Two major classes of cortical stem/progenitor cells can be distinguished. First, stem/progenitor cells that reside in the ventricular zone, i.e. neuroepithelial cells, apical radial glia and apical intermediate progenitors, collectively referred to as apical progenitors. Second, stem/progenitor cells that reside in the subventricular zone, i.e. basal radial glia and basal intermediate progenitors, collectively referred to as basal progenitors. Neocortex expansion is thought to be linked to an increased abundance and proliferative capacity of basal progenitors. To gain insight into the genomic changes that underlie neocortex expansion, notably in humans, we have analyzed the transcriptomes of human versus mouse ventricular and subventricular zones, and of human versus mouse apical and basal radial glia. This led to the identification of the human-specific gene ARHGAP11B as a major player.
Specifically, ARHGAP11B promotes the generation of basal progenitors from apical radial glia and the subsequent basal progenitor proliferation, thereby increasing basal progenitor abundance. Moreover, ARHGAP11B is able to induce folding of the embryonic mouse neocortex, which normally is smooth. The ability of ARHGAP11B to amplify basal progenitors is based on a single C-to-G base substitution which creates a novel splice donor site, causing a reading frame shift and generating a human-specific 47-amino acid sequence that is thought to be key for basal progenitor amplification.

Speaker 3: Fenna Krienen
Presentation Title: Variation in gene expression across the human neocortex is associated with brain network organization.
Presentation Content: The expansion of the human neocortex has led to the emergence of regions with specialized functions and connectivity that are important for cognition and compromised in mental disorders. Variation in functional specialization and connectivity across the neocortex arises in part from variation in neocortical composition. My work using the Allen Institute's human brain transcriptional atlas indicates that genes enriched in the upper layers of the human neocortex distinguish major cortical subtypes (sensory/motor, paralimbic, associational). Further, spatial expression of these genes is associated with large-scale brain network organization as measured by functional connectivity MRI. Expression of other genes, including sets from curated gene ontologies (Broad Institute Molecular Signatures Database) and genes linked to connectivity in rodents, do not consistently associate with human cortical network organization. Molecular modifications of upper cortical layers may be an important component in the evolution of long-range corticocortical projections. These results raise further questions about the extent to which cortical transcriptional phenotypes in humans are phylogenetically conserved, as well as which cell types underlie transcriptional variation observed at the aggregate level from bulk tissue. Answers to these questions can help us build a system for understanding the molecular basis of neocortical specializations in primate evolution.

Speaker 4: Alex Pollen
Presentation Title: Evolution and development of human neural stem cells.
Presentation Content: The dramatic expansion of the cerebral cortex over the last six million years is one of the most conspicuous features of human evolution. Across mammals, radial glia along the ventricular zone act as neural stem cells to regulate brain size. In humans, a second population of radial glia in the outer subventricular zone termed basal or outer radial glia generates the majority of cortical neurons, but their molecular features remain elusive. Here we use single cell approaches to establish an integrative definition of outer radial glia cells based on position, morphology, cell behavior, developmental potential, and gene expression. By analyzing gene expression across single cells, we find that outer radial glia cells preferentially express genes related to extracellular matrix formation, migration, and stemness, including TNC, PTPRZ1, FAM107A, HOPX, and LIFR, and we relate these genes to the position, morphology, and behaviors previously used to classify these cells. Many of these genes are involved in growth factor signaling and self-renewal pathways, suggesting that outer radial glia cells establish a self-sustaining proliferative niche in the outer subventricular zone that may contribute to developmental brain expansion. By comparing gene expression across human, primate and rodent cortical development, we find that the outer radial glia signature is conserved in primates, but identify species- specific changes in radial glia gene expression that may contribute to specialized aspects of human brain development. Together, these results will help to link human-specific mutations with developmental cell behaviors that contribute to changes in human brain anatomy.