Introduction: Social skill group training (SSGT) is one of the most common interventions for children and adolescents with autism spectrum disorder (ASD). Individual responses to SSGT vary and limited clinical predictors exist for the treatment.

Material and Methods: Therefore, we performed a detailed genetic characterization using genotyping, CNV calling and exome sequencing of autistic individuals from one of the largest randomized clinical trial for SSGT and analyzed the association between genetic factors and SSGT treatment outcome. Identified rare copy number variations (CNVs) were prioritized and polygenic risk score (PRS) was calculated from ASD, education attainment (EA) and attention deficit hyperactivity disorder (ADHD) based on different p-value thresholds (Pt < 0.01, 0.05, 0.1, 0.5, 1).

Results: Individuals who carried large CNVs (> 500kb) showed significant worse outcome at 12 weeks post-treatment ($\beta = 15.4$, $p = 0.017$) and 3-months follow-up ($\beta = 14.2$, $p = 0.028$). In addition, inferior outcomes were implicated for individuals with higher PRS for ASD (Pt = 0.5: $\beta = 6.5$, $p = 0.018$) and ADHD (Pt 1.0: $\beta = 6.7$, $p = 0.015$) at follow-up treatment. Currently, we are analyzing exome sequencing data from the same 205 individuals and then combining different rare and common genetic variant data carriers together.

Conclusion: Autistic individuals with higher genetic burden for the disorder, including large rare CNVs and higher load of PRS, have different benefits of SSGT compared with individuals with lower genetic risk. Our results can aid in personalized intervention modifications for ASD in the future.

D. Li: None. **I. Rabkina:** None. **S. Stamouli:** None. **H. Jiao:** None. **M. Becker:** None. **U. Jonsson:** None. **N. Choque-Olsson:** None. **S. Bölte:** Other; Modest; Huber/Hogrefe. **K. Tammimies:** None.

P09.025B
Evidence for altered calcium signaling and altered mitochondrial function in an autism case study

R. L. Nguyen, P. Flodman, M. Smith, J. J. Gargus

University of California, Irvine, Irvine, CA, United States

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by deficits in social interaction, communication, and stereotypic behaviors. While its etiology is unknown, the large assemblage of risk variants impacting calcium ion channels and signaling proteins suggest that a functional disruption of this signaling hub may be involved in ASD pathogenesis. In this study, we evaluate how such risk variants exert their deleterious effects in a unique ASD case.

We identified this subject in a previous study where we observed significant changes in the single-channel inositol triphosphate (IP3) receptor kinetics of ASD fibroblasts via "optical patch-clamp" and found that this feature could be visualized with a high-throughput Fluorometric Imaging Plate Reader (FLIPR) screening assay as a decrease in calcium release from the ER. This release was below the lower limit of controls in >75% of ASD subjects, but uniquely high in an 18-year old autistic female at a level far exceeding the upper limit of controls, nearing levels obtained with ionomycin, an ionophore.

To assess the molecular basis of this finding, we completed a transcription analysis to compare expression levels of calcium signaling-related genes in fibroblast-derived RNA from this subject to those of two controls and two typical autism cases. The subject's transcriptome showed increased expression (>5sd) of genes including the ATP2A3 calcium pump and purinergic receptors, and extremely low expression (>24sd) of VDAC2, a mitochondrial calcium uptake channel. These findings corroborate suggestions of mitochondrial dysfunction in her clinical biochemical assays and are extended with Seahorse XFp assays.

R.L. Nguyen: None. **P. Flodman:** None. **M. Smith:** None. **J.J. Gargus:** None.

P09.026A
Establishing genotype-phenotype associations for ASD

A. C. G. Ilhéu, M. Asif, F. M. Couto

LASIGE, Lisbon, Portugal

Genotypic and phenotypic heterogeneity of Autism Spectrum Disorder (ASD) has hindered the establishment of genotype-phenotype associations. Herein, we presented a novel approach that integrates semantic similarity and unsupervised machine learning methods to dissect the ASD genotypic heterogeneity and to identify phenotypic manifestations of ASD genetic variants. This approach was applied to copy number variants (N=6650), disrupting 3998 genes from 1119 ASD patients. Functional similarities among genes were computed using Resnik semantic similarity measure. Semantic similarity score, ranging from 0 to 1 represents the functional similarity between two genes, where 1 represents identical genes while score 0 reflects functionally dissimilar genes. Agglomerative hierarchical clustering of the computed gene similarity matrix identified four different clusters of functionally related genes. Silhouette analysis indicated that clusters were compact and consistent (average Silhouette value=0.31). The genes (N=519) of cluster 1 was more relevant to ASD as they were enriched for Cell adhesion molecules (CAMs) (adjusted p-value=0.00001) and Axon guidance (adjusted

p-value=0.02) pathways, which are known to be strongly associated with ASD. Cluster 1 genes were also most significantly enriched for Schizophrenia Human Phenotype Ontology (HPO) term, which is a co-occurring condition with ASD. The other three clusters were not enriched for ASD related HPO terms. The results indicated that phenotypic-genotypic associations can established for ASD by reducing its genotypic heterogeneity i.e. clustering of functionally similar genes. However, to associate these clusters with phenotype, further efforts are required to enrich HPO resource. (Grant reference: PTDC/CCI-BIO/28685/2017)

A.C.G. Ilhéu: None. **M. Asif:** None. **F.M. Couto:** None.

P09.027B

Resolving effects of *CASK* mutations in children with neurodevelopmental disorders

M. Becker[1], F. Mastropasqua[1], J. P. Reising[2], I. Rabkina[1], L. Ballenberger[1], M. Kele[3], C. Willfors[1], E. Herlenius[2], S. Bölte[1], B. M. Anderlid[4], A. Falk[3], K. Tammimies[1]

[1]Center of Neurodevelopmental Disorders (KIND), Department of Women's and Children's Health, Karolinska Institutet, Solna, Sweden, [2]Department of Women's and Children's Health, Karolinska Institutet, Solna, Sweden, [3]Department of Neuroscience, Karolinska Institutet, Solna, Sweden, [4]Department of Molecular Medicine and Surgery, Solna, Sweden

Introduction: Mutations in the *CASK* gene cause a range of childhood neurodevelopmental disorders such as microcephaly with pontine and cerebellar hypoplasia (MICPCH), epilepsy, developmental delay and autism. *CASK*, located on Xp11.4, plays a role in neuronal differentiation and synapse function. The molecular consequences of *CASK* mutations have not been studied in human neurons. Our project aims to elucidate the downstream effects of different *CASK* mutations using patient-derived induced pluripotent stem cells (iPSCs).

Materials and Methods: Skin cells from two patients, one female with severe MICPCH and one male with autism, with different CASK mutations were programmed to iPSCs and further differentiated to functional neurons. Bulk and single-cell RNA-sequencing was performed to identify molecular phenotypes and guide morphological and functional assessment of neuronal pathology in comparison with control iPSCs.

Results: A splice-site mutation in the ASD patient decreases wild-type CASK mRNA and a tandem duplication of two *CASK* exons is expressed in the MICPCH patient. The mutations reduce CASK protein levels in differentiating neurons. Transcriptome analysis revealed dysregulation of genes involved in the synaptic vesicle cycle and single-cell RNA-sequencing indicated an imbalance in excitatory-inhibitory neuronal populations. Consequently, we study synapse morphology and spontaneous firing rates of excitatory and inhibitory neurons. Moreover, we observed neuron subtype-specific upregulation of WNT signaling pathway components.

Conclusions: We provide strong evidence that *CASK* mutations lead to perturbed neurotransmission through dysregulation of synapse vesicle trafficking and differential distribution of neuronal populations. Our results can guide drug development and aid in understanding the pathological spectrum of *CASK* mutations.

M. Becker: None. **F. Mastropasqua:** None. **J.P. Reising:** None. **I. Rabkina:** None. **L. Ballenberger:** None. **M. Kele:** None. **C. Willfors:** None. **E. Herlenius:** None. **S. Bölte:** None. **B.M. Anderlid:** None. **A. Falk:** None. **K. Tammimies:** None.

P09.029D

Implicating genetic risk variants for circadian rhythm and sleep trait difficulties in individuals with autism spectrum disorder

Z. Schmilovich[1,2], R. Tesfaye[1,2], G. Huguet[3,4], A. Dionne-Laporte[1], O. Diallo[1], B. Chaumette[2,5,6], S. Jacquemont[3,4], M. Elsabbagh[1,2], P. A. Dion[1,2], G. A. Rouleau[1,2]

[1]McGill University, Montreal, QC, Canada, [2]Montreal Neurological Institute and Hospital, Montreal, QC, Canada, [3]CHU Sainte-Justine, Montreal, QC, Canada, [4]Université de Montréal, Montreal, QC, Canada, [5]Université Paris Descartes; Bio Sorbonne Paris Cité; INSERM, Laboratoire de Physiopathologie des Maladies Psychiatriques, Centre de Psychiatrie et Neurosciences, UMR 894, GDR3557-Institut de Psychiatrie, Paris, France, [6]Centre Hospitalier Sainte-Anne, Service hospitalo-universitaire, GHU Paris Psychiatrie et Neurosciences, Paris, France

Introduction: Autism spectrum disorder (ASD) is a largely hereditary neurodevelopmental disorder characterized by difficulties in social interaction and communication, and restricted and repetitive behaviour. Sleep is disturbed in up to 80% of affected youths with ASD. Genes underlying the circadian rhythm are proposed to elucidate sleep and other timing problems in individuals with ASD. Our first aim investigates whether copy-number variants (CNVs) encompassing core circadian clock genes, circadian pathway genes, and sleep trait candidate genes, detected from previous large genome-wide association studies, are