M14. SPECIFIC ASD PHENOTYPES ARE MODULATED BY DISTINCT GENETIC VARIANTS CONVERGING AT NETWORK LEVEL
Andreas G. Chiocchetti¹, Regina Waltes¹, Denise Haslinger¹, Silvia Lindlar¹, Sabine Klauck¹, Eftichia Duketis¹, Michael Sachse¹, Anette Voran², Monica Biscaldi³, Martin Schulte-Rüther⁴, Stephan Kupferschmid³, Sven Cichon⁶, Markus Nöthen⁷, Jörg Ackermann⁸, Ina Koch⁸, Christine M. Freitag¹
¹Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Goethe University Frankfurt, Frankfurt am Main, ²Department of Child and Adolescent Psychiatry, Saarland University, Homburg, ³Department of Child and Adolescent Psychiatry, University Hospital Freiburg, ⁴Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, University Hospital RWTH Aachen, ⁵University Hospital of Child and Adolescent Psychiatry, University of Bern, Bern, ⁶Division of Medical Genetics, University of Basel, Basel, ⁷Institute of Human Genetics, University of Bonn, Bonn, ⁸Molecular Bioinformatics, Institute of Computer Science, Goethe University Frankfurt, Frankfurt am Main

Background Autism spectrum disorders (ASD) are a group of genetically and phenotypically heterogeneous neurodevelopmental disorders. Common genetic variants are currently estimated to account for over 50% of ASD liability, and are also suggested to contribute to phenotypic variability. Only few studies have reported association of genetic variants with quantitative ASD phenotypes and it is unclear if different phenotypic aspects of the disorder have a distinct etiology. Here, we aim at discovering associations of common variants with ASD related phenotypes. To interpret the findings in their biological context we mapped significant variants to their genes and tested for enriched pathways and networks implicated in brain development.

Methods We investigated phenotype and genotype data of 637 German trios with ASD and of the Autism Genome Project cohort (2004 families). Both cohorts were harmonized and quality checked at phenotypic (Autism Diagnostic Interview Revised, ADI-R items) and genotypic (Illumina Microarrays) level. We performed factor analysis of 28 single items of the ADI-R used in the diagnostic algorithm. To increase genetic resolution and the number of overlapping variants between the two datasets we imputed common variants with a MAF>0.05 using the “1000 Genomes” data as reference. SNPs significantly associated with the phenotype were identified using regression models corrected for ancestry, gender and IQ. Significant variants identified in both, the German and the AGP cohort, were subjected to GO-term, KEGG, and pathway enrichment analysis. Gene-regulatory modules implicated in brain development were defined by weighted gene co-expression analysis using publicly available transcriptome data of the developing human brain (brainspan.org) and tested for enrichment with the associated gene sets.

Results We extracted 5 factors of the ADI-R items labeled as joint attention, social interaction and communication, non-verbal communication, repetitive sensory-motor behavior and compulsion and restricted interests. Of the 7.5M variants with a MAF > 0.05 available after imputation and quality check over 500 were associated nominally significant and replicated with each factor respectively. Analysis of the underlying genes showed that the associated GO-terms were specific for each factor and reflected directly linked biological processes such “sensory processing” for repetitive sensory-motor behavior. Finally, we present developmental time-frames specifically enriched for associated gene-sets.
Discussion Our findings suggest that each ASD related phenotype is underlying a specific genetic etiology. The identification of critical periods during development further allows understanding the effects of genetic variants at specific brain-developmental and brain-regional networks. These findings thus provided a deeper insight into the complex genetic architecture of ASD and increased our understanding of mechanisms modulating ASD phenotypes.

Disclosure: Nothing to Disclose.