589W

Copy number aberrations affecting adhesion genes involved in the development of the cerebellar vermis are associated with autism spectrum disorders. *S. Hochreiter[1], D.-A. Clevert[1,2].* 1) Institute of Bioinformatics, Johannes Kepler University Linz, Linz, Austria; 2) Charité University Medicine, Berlin, Germany.

Motivation: We investigated neurodevelopmental dysfunctions in autism spectrum disorders (ASD) by a integrative analysis including the two largest genome-wide studies on associations between copy number aberrations (CNA) and ASD, the BioGPS tissue atlas, the Allen brain atlas, and *in situ* hybridization histochemistry data from the developing mouse brain. In contrast to the original association studies, we considered "ASD candidate genes" each of which is the only CNA-impaired gene in an ASD case, therefore, presumably causing ASD. For extracting ASD candidate genes, we developed an analysis pipeline for rare and small CNAs. Rare CNAs are supposed to be more disease-specific, because CNAs that cause ASD with high probability are assumed to be *de novo* and quickly vanish in the population due to their low reproductive fitness. Small CNAs affect only few genes and, therefore, are very specific concerning the genes they are impairing. **Results:** ASD candidate genes that are indentified independently in both CNA studies include the neurexins *CNTNAP2* and *NRXN1*, the catenin *CTNNA3*, the cadherin *CDH13*, and the contactins *CNTN5* and *CNTN6*. Gene set enrichment analysis of ASD candidate genes showed that significant biological processes are all related to cell and synaptic adhesion the postsynaptic density, membrane and synapse. At data from the BioGPS, the Cancer Genome Anatomy Project, and the Allen brain atlas, ASD candidate genes have significantly different variations in their expression values in cerebellum compared to other genes, where at the Allen brain atlas cerebellar vermis lobes I-II, III, VI, and VIII where most significant. *In situ* hybridization histochemistry data indicate that ASD candidate genes are primarily expressed in the developing mouse cerebellum. **Discussion:** Our results which hint at the cerebellar vermis as the location of ASD's pathogenesis are consistent with pathological studies of ASD cases, where, in over 90% of the examined brains, well-defined cerebellar abnormalities were found. Also studies on children with vermal lesions showed phenotypes like speech disorders and behavioral disturbances similar to autism. The high percentage, 60-80%, of ASD cases showing motoric deficits again hints at the cerebellum. We explain 4:1 male to female ratio in ASD by the regulatory influence of estrogen on the development of the cerebellum. The human estrogen 17β-estradiol enhances in the cerebellum synaptic connectivity.

590W

High coverage of copy number variants (CNVs) in Finnish patients with autism spectrum disorders using Nimblegen 2.1M array. *K. Kantojärvi[1], R. Vanhala[2], T. Lepistö[2], R. Alen[3], I. Järvelä[1], L. Muthuswamy[4].* 1) Department of Medical Genetics, University of Helsinki, Helsinki, Finland; 2) Hospital for Children and Adolescents, University of Helsinki, Finland; 3) Department of Pediatrics, Jyväskylä Central Hospital, Jyväskylä, Finland; 4) The Ontario Institute for Cancer Research, Toronto, Canada.

Autism spectrum disorders (ASD) are neuropsychiatric disorders characterized by restricted repetitive behavior and abnormalities in communication and social interaction. The model of inheritance of ASD seems to be very complex and probably involves multiple interacting genes. Several studies have shown that de novo copy number variants (CNV) contribute to autism risk in 5-15% of cases in families with one affected individual. We performed array comparative genomic hybridization (aCGH) utilizing Nimblegen 2.1M oligonucleotide array on 21 Finnish families with autism spectrum disorders (ASD). The findings were confirmed using quantitative PCR. We detected five copy-number variations that most likely are causative of autism, because they either arose de novo and/or overlapped with known microdeletions. One of the deletions was de novo NRXN1 previously shown in neuropsychiatric conditions.

591W

Familial occurrence of Asperger Syndrome associated with a 1Mb Duplication on Xq including the MCT8-Gene. *P.M. Kroisel[1], K. Wagner[1], M. Mach[1], E. Vallant[1], M. Brunner-Hantsch[2], M.R. Speicher[1], K.M. Roetzer[1].* 1) Human Genetics, Medical University of Graz, Graz, Styria, Austria; 2) Psychiatric consultant, Graz, Austria.

By array CGH using a 60k Agilent oligonucleotide array we were able to identify a maternally inherited microduplication of about 1Mb at Xq12.3-q13.3 that affects at least 5 genes in a patient with Asperger-syndrome. One of the genes involved in this microduplication is the MCT8-(monocarboxylate transporter-8)-gene, already known to cause Allan-Herndon-Dudly-syndrome(AHDS), which follows an X-linked pattern of inheritance and leads to a severe form of mental retardation combined with distinct dysmorphic features in males whereas females show a mild phenotype with no neurologic anomalities. Since different and occasionally reciprocal phenotypic features can be observed in patients with microdeletions versus microduplications of particular genomic regions or loci like the Williams-Beuren- or DiGeorge-syndrome critical region or the PMP22-gene, a different phenotype to AHDS is not unexpected in the patient described here with the identified Xq microduplication. The affected male patient as well as his maternal uncle shows a much milder phenotype compared to AHDS patients with just a few characteristic facial anomalies like smaller ears however a pronounced form of Asperger-syndrome and a general reduction of mental capacity with remarkable strength in fine coordination and spatial orientation is present. Potential additional effects related to an increased gene dosage of the KIAA2022-gene and the ZDHHC15-gene with regard to mental impairment can not be ruled out at the current state of this investigation. Because just a few similar microduplications are currently listed in databases like Decipher a comparison with these patients is difficult. From our findings we would propose that at least in this familial setting a genetic explanation for the development of Asperger-syndrome was found and gain of function mutations of the MCT8-gene might be a more common reason for this syndrome than the identified specific microduplication or mutations of the linked neuroligin-3(NLGN3)-gene.

592W

Genome-wide investigation of rare CNVs in a newly characterized Canadian autism cohort. *A.C. Lionel[1,2], B. Thiruvahindrapuram[1], D. Merico[1], J.L. Howe[1], Z. Wang[1], J. Wei[1], L. Zwaigenbaum[3], B.A. Fernandez[4], W. Roberts[5], P. Szatmari[6], C.R. Marshall[1], S.W. Scherer[1,2].* 1) The Centre for Applied Genomics and Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada; 2) McLaughlin Centre and Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada; 3) Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; 4) Disciplines of Genetics and Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada; 5) Autism Research Unit, The Hospital for Sick Children and Bloorview Kids Rehabilitation, University of Toronto, Toronto, Ontario, Canada; 6) The Offord Centre for Child Studies, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada.

Autism spectrum disorder (ASD), a common neurodevelopmental disorder with an estimated prevalence rate of nearly 1% of children, is characterized by impairment in reciprocal social interaction, communication deficits and a repetitive pattern of behavior. In recent years, several studies have highlighted the role of rare copy number variants (CNVs) in the genetic etiology of ASD. The study of these rare deletions and duplications in the genomes of ASD patients has proven to be a powerful tool for the identification of novel candidate genetic loci for further investigation by targeted gene sequencing and functional studies. We conducted, and present here for the first time, a genome-wide CNV scan of more than 700 unrelated, newly characterized Canadian ASD patients using two high resolution SNP genotyping platforms: the Affymetrix SNP 6.0 and the Illumina Omni2.5M-Quad. A multi-algorithm approach incorporating Birdsuite, Affymetrix Genotyping Console and iPattern (for Affymetrix data) and iPattern, PennCNV and CNVPartition (for Illumina data) was utilized for CNV detection. High confidence CNVs detected by this approach in the ASD cases were compared with CNVs found in array data from more than 2,000 ancestry-matched population based controls. We detected and confirmed validated rare exonic CNVs in the ASD cases that were absent in controls and overlapped previously implicated ASD loci (e.g. *NRXN1*, *SHANK3*, *PTCHD1*, 16p11.2), or identified new candidate susceptibility loci for ASD (e.g. *NRXN3*). We are currently collecting samples from the parents and extended family of the ASD cases in order to study the inheritance patterns of the CNVs of interest and their potential segregation with elements of phenotype. We will also test for gene interaction sub-networks enriched for rare CNVs in ASD cases compared to controls. Our results provide support for the role of rare CNVs in risk for ASD and identify new candidate genetic loci for further investigation.