Abstract/Session Information for Program Number 2374T

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Session Information

Session Title: Psychiatric Genetics, Neurogenetics and Neurodegeneration **Session Type:** Poster

Session Location: Exhibit Hall, Lower Level South, Moscone Center **Session Time:** Thu 7:00AM-4:30PM

Abstract Information

Program Number: 2374T **Presentation Time:** Thu, Nov 8, 2012, 3:15PM-4:15PM

Keywords: Psychiatric Genetics, Neurogenetics and Neurodegeneration, KW011 - brain/nervous system, KW034 - copy number/structural variation, KW122 - neurodegeneration

Abstract Content

An integrative analysis pinpoints the pathogenesis of autism in the cerebellar vermis. *D.-A. Clevert, S. Hochreiter* Institute of Bioinformatics, Johannes Kepler University Linz, Austria.

Motivation: We investigated neurodevelopmental dysfunctions in autism spectrum disorders (ASD) by an integrative analysis including the three 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 all 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, IV, VI, VII, 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, that locate the pathogenesis of ASD in the cerebellar vermis, 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.

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