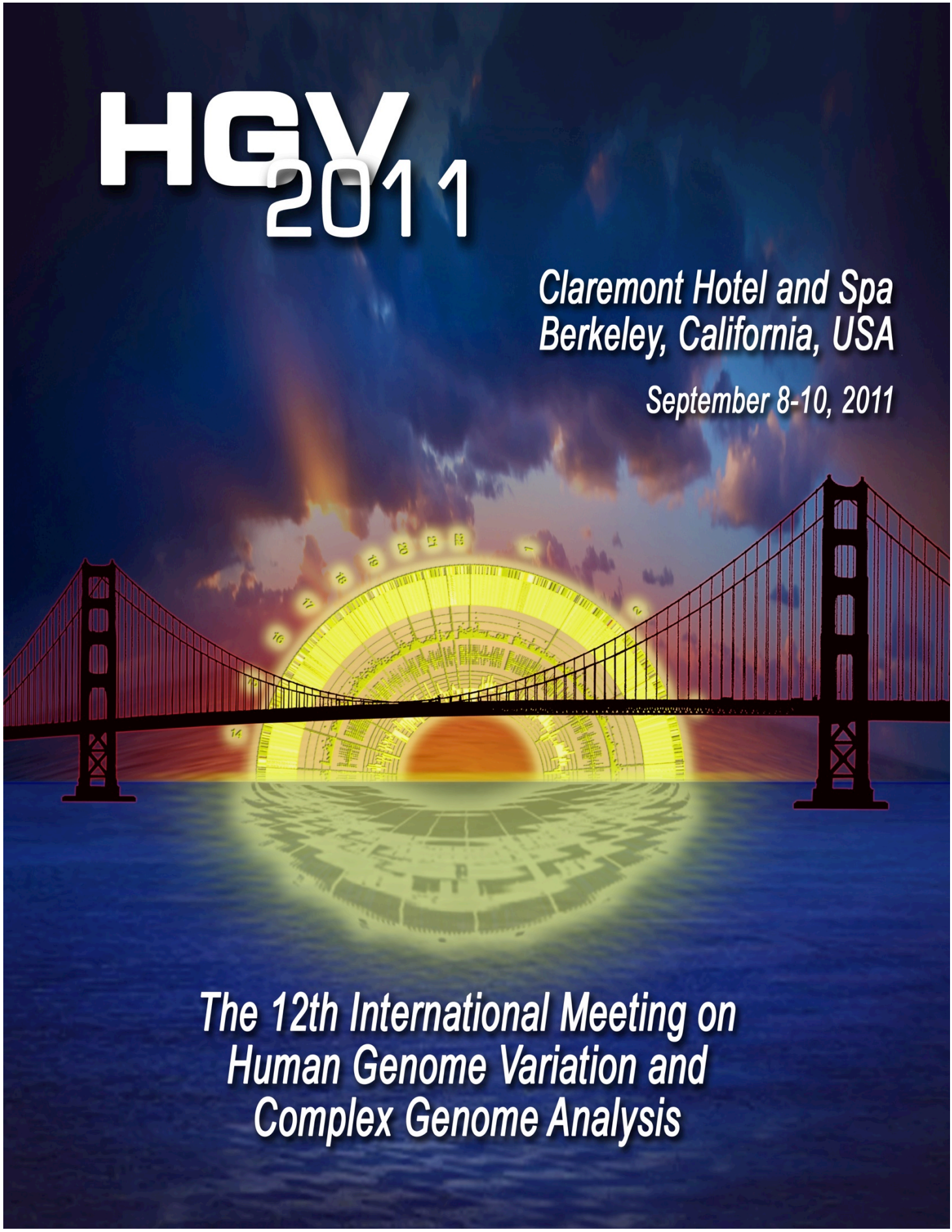
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Copy Number Aberrations Affecting the Developing Cerebellar Vermis are Associated with Autism Spectrum Disorders

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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: 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.

Gene set enrichment analysis of ASD candidate genes showed that significant biological processes are all related to cell and synaptic adhesion and significant cellular components are postsynaptic density, membrane and synapse. 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.

Discussion: Our results which hint at the cerebellar vermis as the location of ASD’s pathogenesis are consistent with pathological studies, where, in over 90% of the examined ASD 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. In patients with the Dandy-Walker malformation, vermal abnormalities were found to delay the acquirement of cognitive skills.

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 binds enhances in the cerebellum synaptic connectivity and density between parallel fibers and Purkinje cells.

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