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Modifiers of severity in autism spectrum disorder

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Autism spectrum disorder (ASD) comprises a complex of neuro developmental disorders primarily characterized by deficits in verbal communication, impaired social interaction and repetitive behaviors. The complex genetic architecture of ASD encompasses profound clinical heterogeneity, which poses huge challenges in understanding its pathophysiology. We conducted a large scale association analysis of the MSSNG whole genome sequencing data to elucidate potential modifiers of ASD severity. Using linear regression, we have directly tested the association between 6,198,166 SNPs and Vineland Adaptive Behavior Scale scores, a standardized metric for measuring severity across multiple ASD spectra. The most significant variants direct us to a significant haplostretch chr3p21 (pval 3.68e-12) of SNPs, n=132) containing variants on chromosome three including a highly interesting non-synonymous SNV rs11539148 within the *QARS* gene (NM_001272073:c.A821G:p.N274S MAF=0.0391) a glutaminyl-tRNA synthetase coding gene crucial in brain development. Furthermore, we analyzed eQTLs for *QARS* and found decreased expression across several datasets, a result consistent with the observed effect. The effect further potentially explains differences in significant changes in head circumference. To leverage the size of the region, we conducted a pathway enrichment analysis of the set of highly significant loci. The most significant categories include brain development and structural component of the myelin sheath. Genes categorized as neurological, developmental and immune-related constitute 65% of all the genes contributing to these pathways. Our analysis has detected a region that may be a hallmark of severity in ASD. As the genetic predisposition may be different for almost every ASD individual, understanding the common mechanisms for endo phenotypes may help elucidate ASD causal mechanisms.

Biography

Sandra P Smieszek is leading several genetic disorders in the CNS domain and other rare complex phenotypes. She just completed her Postdoctoral training in the Department of Epidemiology and Biostatistics working for Dr. William Bush and Dr. Jonathan Haines. She completed her PhD at the Centre for Systems and Synthetic Biology at Royal Holloway, University of London under the supervision of Dr. Paul Devlin. Her research focuses on translating biomedical big data with the aim of elucidating the human genotype-phenotype associations. Specifically her research focuses on delineating the genetic underpinnings of complex traits and disorders with emphasis on Alzheimer's disease, HIV associated phenotype and autism spectrum disorders among others. Her particular interests include application of concepts within the domains of translational bioinformatics, machine learning, systems biology and network inference to elucidate the complex interactions giving rise to observed phenotypes. Her previous research was in the domain of the circadian clock working on various types of omics time series data. She is a Member of the International Society for Computational Biology, American Society of Human Genetics and Royal Society of Biology with avid interest in synthetic genomics, genetic engineering and science policy.

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