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18 novel subtype-dependent genetic variants for autism spectrum disorders revealed

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By dividing individuals with autism spectrum disorders (ASD) into four subtypes according to similarity of symptoms and reanalyzing existing genome-wide genetic data on these individuals vs. controls, researchers at the George Washington University School of Medicine and Health Sciences have identified 18 novel and highly significant genetic markers for ASD.

In addition, ten of the variants were associated with more than one ASD subtype, providing partial replication of these genetic markers. This study thus identifies candidate genes for ASD and potential subtype-dependent genetic markers for diagnostic screening. These findings, published in the April 27 edition of the journal PLoS ONE, demonstrate the increased statistical power to identify significant genetic variants when the heterogeneity of the samples tested is reduced by subtyping and further begin to associate genotype with phenotype.

"By working to tease apart the heterogeneity associated with varying severity of autistic symptoms exhibited by individuals with ASD and examining the resulting subtypes of ASD, we believe that we will continue to make strides in figuring out the genetic contributions to autism," said Valerie Hu, Ph.D., professor of Biochemistry and Molecular Biology at GW's School of Medicine and Health Sciences. "The goal of our research is to identify SNPs associated with a subtype of ASD that rise above the 'noise' of the hundreds of thousands of other SNPs when compared against controls, with the hope that we can identify genetic biomarkers for these disorders as well as clues to the

biology of autism."

The researchers first identified genetic variants or single nucleotide polymorphisms (SNPs) that are associated with the degree of severity of various different autistic traits, and then they performed case-control genetic association analyses using these variants and subgroups of autistic individuals who share similar symptoms. This helped the researchers to identify the 18 genetic markers that are associated with four subtypes of ASD, ten of which were associated with more than one ASD subtype. They then examined the minor allele frequencies of the shared SNPs in the respective ASD subtypes and found that the odds ratio is different for each shared SNP, further suggesting genetic heterogeneity among the subtypes. The study also found that all of the novel variants were located in nonexonic DNA regions that do not code for protein and further identified two SNPs that are associated with differentially expressed genes from an earlier study by Dr. Hu's laboratory, suggesting a possible functional relationship between the SNPs and gene expression levels. Based on these findings, the researchers hypothesized that perhaps the newly identified genetic variants are affecting gene regulatory processes, rather than causing a change in protein structure.

More information: Hu VW, Addington A, Hyman A (2011) Novel Autism Subtype-Dependent Genetic Variants Are Revealed by Quantitative Trait and Subphenotype Association Analyses of Published GWAS Data. PLoS ONE 6(4): e19067. doi:10.1371/journal.pone.0019067

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