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Family-based association testing of glutamate transporter genes in autism

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SUMMARY

Glutamate transporters are critical for signaling and excitotoxicity because they regulate extracellular glutamate in the synapse. Four glutamate transporter genes, *SLC1A1*, *SLC1A2*, *SLC1A3*, and *SLC1A6*, are positional and functional candidates for autism. Studies have implicated *SLC1A1* in obsessive compulsive disorder (Arnold et al. 2006) and autism spectrum disorder (ASD) (Brune et al. 2008). Up-regulation of *SLC1A2* and *SLC1A3* has been reported in brains of individuals with autism (Purcell et al. 2001). *SLC1A2* is under the highest linkage peak in the Autism Genome Project scan (Szatmari et al. 2007). Both *SLC1A3* and *SLC1A6* are most abundantly expressed in cerebellum (Bridges and Esslinger 2005) where structural and functional deficits occur in autism. Based on these lines of evidence, we hypothesized that variations in these four glutamate transporter genes confer risk for autism susceptibility.

Previously we tested the association between autism and *SLC1A1* in a strictly defined sample (N=85) and found a nominally significant association with a *SLC1A1* SNP (rs301979) (Brune et al. 2008). Subsequently, we recruited additional families (N= 68) with either “strict autism” (N=39) or “broad ASD” (N=29). “Strict” autism was defined as a proband with Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) autism plus a best estimate diagnosis of autism by a clinical psychologist and/or child psychiatrist. The “broad ASD” probands had a best estimate diagnosis of any ASD (autism, Asperger’s disorder or PDD-NOS) plus combinations of ADI-R/ADOS criteria of Autism/ASD, ASD/Autism, or ASD/ASD. Altogether, 14 SNPs were genotyped in 153 trio families using TaqMan[®] SNP genotyping assay, including four *SLC1A1* SNPs (rs301430, rs301979, rs301434, rs301443), three *SLC1A2* SNPs (rs3088168,

rs911562, rs1923291), three *SLC1A3* SNPs (rs13173144, rs2269271, rs2301066), three *SLC1A6* SNPs (rs10414225, rs873599, rs2285980), and one *C9ORF68* (gene overlapping *SLC1A1*) SNP (rs384535).

We dropped rs13173144 (*SLC1A3*, $p=0.014$) and rs384535 (*C9ORF68*, $p=0.024$) due to deviation from Hardy-Weinberg Equilibrium in founders; dropped four trio families because of Mendelian errors in remaining SNPs. Family-Based Association Test (FBAT) was performed on the new sample ($N=68$), strict combined sample ($N=124$) and overall combined sample ($N=153$) for both additive and recessive models. Only $p < 0.05$ uncorrected for multiple testing are reported. Association between rs301979 (*SLC1A1*) and autism was observed in the new samples (recessive model, $Z=-2.778$, $p=0.005$) as well as in the overall combined samples (additive, $Z=-2.137$, $p=0.033$; recessive, $Z=-2.424$, $p=0.015$). One *SLC1A2* SNP (rs3088168) was nominally significant in the new sample under a recessive model ($Z=-2.178$, $p=0.029$), but not in the overall combined sample. Exploratory haplotype analyses revealed nominally significant associations between five SNP pairs including rs301979-rs301434 ($p=0.04$), rs301979-rs1923291 ($p=0.02$), rs1923291-rs911562 ($p=0.03$), rs911562-rs10414225 ($p=0.01$), rs301443-rs2285980 ($p=0.01$) under a recessive model.

In summary, this study supported the previous association between *SLC1A1* and autism, but failed to provide additional evidence for associations with three other glutamate transporter genes. However, given the small sample size and power, these genes require further investigation with denser markers and exploration of copy number variations in a larger sample set.

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