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Evidence for genetic susceptibility to the alcohol dependence syndrome from the thiamine transporter 2 gene solute carrier *SLC19A3*

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The risk for developing the alcohol dependence syndrome (ADS) has a substantial genetic component. The human thiamine transporter protein 2 (hTHTR2) is encoded by the *SLC19A3* gene, which is on chromosome 2q37. hTHTR2 is responsible for the cellular uptake of thiamine (B_1), a water-soluble essential vitamin that plays a fundamental and ubiquitous role in carbohydrate metabolism. This gene was also found to be associated with biotin-responsive basal ganglia disease, an autosomal recessive metabolic disorder characterized by encephalopathy and ophthalmoplegia (Ozand *et al.*, 1998; Zeng *et al.*, 2005). Homozygous or compound heterozygous mutations in *SLC19A3* cause two distinct clinical phenotypes: biotin-responsive basal ganglia disease and Wernicke's-like encephalopathy. Biotin and/or thiamine are effective therapies for both diseases (Yamada *et al.*, 2010). A missense mutation in exon 5 of the *SLC19A3* was found in 18 cases of biotin/thiamine-responsive basal ganglion disease presenting with subacute encephalopathy and extrapyramidal signs (Alfadhel *et al.*, 2013). Kono *et al.* (2009) described two Japanese brothers, who were both compound heterozygotes for the K44E and E320Q mutations in *SLC19A3*, who developed a syndrome of thiamine-responsive diplopia, ophthalmoplegia and ataxia, similar to Wernicke's encephalopathy, despite normal serum thiamine levels (Kono *et al.*, 2009). Yamada *et al.* (2010) reported a pathogenic homozygous mutation (c.958G > C, [p.E320Q]) in *SLC19A3* in four patients from a single family. They report a wide variety of neurological signs in *SLC19A3* mutation carriers. Our previous unpublished research found that four markers in the *SLC19A3* gene showed significant allelic association with Wernicke–Korsakoff syndrome (WKS) in a sample of 120 cases when compared with normal controls. In the present study, the entire *SLC19A3* gene was screened for DNA variation in a WKS subset ($n = 120$) of a UK ADS case–control sample comprised of 1032 alcohol-dependent cases and 1022 controls. High resolution melting curve analysis, which is based on the melting characteristic of double-stranded DNA, was carried out using a LightCycler 480 Real-Time PCR System (Roche, Burgess Hill, UK). Genetic variation was validated with Sanger DNA sequencing. Thirteen single nucleotide variants were identified through high resolution melting analysis. Two exon 3 variants that were predicted to cause amino acid substitutions, 2:228563818T/C and rs148144444, were selected for genotyping in the entire ADS case–control sample using an allele-specific fluorescent PCR method (KasPar; LGC Genomics, Hoddesdon, UK). Statistical analysis was carried out on the previously unreported 2:228563818T/C change of a T to C substitution at position 228 563 818 on chromosome 2. This variant causes an R250G amino acid substitution in the largest cytoplasmic domain of the protein and it is, therefore, likely to affect post-translational function. rs148144444

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causes the amino acid change G141S which is likely to exert an effect on protein phosphorylation and conformation because of the introduction of the aliphatic chain of serine. Neither the cases nor the controls in the present study had the *SLC19A3* disease susceptibility variants that have been reported previously (Zeng *et al.*, 2005; Kono *et al.*, 2009). The minor allele of 2:228563818T/C was detected in five ADS cases, but was absent in the control samples ($P = 0.033$). The minor allele of rs148144444 was detected in five ADS cases and in four controls and was not associated with ADS. Neither of these variants was present in the 120 WKS cases in our ADS sample. Our data suggest that genetic variation in the *SLC19A3* thiamine transporter at 2:228563818T/C may make a modest contribution towards the genetic susceptibility to ADS.

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Conflicts of interest

There are no conflicts of interest.

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