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

Giorgia Quadri^a, Andrew McQuillin^a, Irene Guerrini^{c,e}, Allan D. Thomson^a, Raquin Cherian^f, Jit Saini^b, Kush Ruparelia^b, Greg J. Lydall^a, David Ball^c, Iain Smith^g, Michael Way^a, Katherine Kasiakogia-Worlley^{a,g}, Shamir Patel^f, Girija Kottalgi^f, Priyanthi Gunawardena^f, Harish Rao^d, Audrey Hillmanⁱ, Ewen Douglas^g, Sherzhad Y. Qureshi^g, Gerry Reynolds^h, Sameer Jauhar^g, Aideen O'Kaneⁱ, Sally Sharp^a, Radhika Kandaswamy^a, Karim Dar^f, David Curtis^{a,d}, Marsha Y. Morgan^b and Hugh M.D. Gurling^{a,*}

Psychiatric Genetics 2014, 24:122-123

^aMolecular Psychiatry Laboratory, Division of Psychiatry, Faculty of Brain Sciences, University College London, ^bUCL Institute for Liver & Digestive Health, Royal Free Campus, University College London, ^cNational Addiction Centre and Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, ^dCity and Hackney Centre for Mental Health, East London NHS Foundation Trust, Homerton Row, London, ^cBexley Substance Misuse Services, South London & Maudsley NHS Trust, Erith Health Centre, Kent, ^cGatehouse Alcohol Clinic and Max Glatt Unit, Central and North West London NHS Foundation Trust, St Bernards Hospital, ^hIhomeless Addictions

Team, NHS Greater Glasgow and Clyde, Glasgow and Newcastle and North Tyneside Addictions Service, Plummer Court, Newcastle upon Tyne, UK

Correspondence to Andrew McQuillin, PhD, Molecular Psychiatry Laboratory, Division of Psychiatry, Faculty of Brain Sciences, University College London, Gower Street, London WC1E 6BT, UK Tel: +44 20 3108 2188; fax: +44 20 3108 2194; e-mail: a.mcquillin@ucl.ac.uk

Received 22 November 2013 Revised 4 December 2013 Accepted 28 January 2014

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 (B₁), a water-soluble essential vitamin that plays a fundamental and ubiquitous role in carbohydrate metabolism. This gene was also found to be associated with biotinresponsive 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: biotinresponsive 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 ence-

phalopathy, despite normal serum thiamine levels (Kono et al., 2009). Yamada et al. (2010) reported a pathogenic homozygous mutation (c.958G > C, [p.E320O]) 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 alcoholdependent 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 substitutions, 2:228563818T/C 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

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 3.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially. *Deceased.

0955-8829 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

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.

Acknowledgements

This work was funded by the Brain Damage Research Trust. We would like to thank the NIHR (National Institute for Health Research) funded Mental Health Research Network for their help with ADS and healthy control sample ascertainment and collection.

Conflicts of interest

There are no conflicts of interest.

References

- Alfadhel M, Almuntashri M, Jadah RH, Bashiri FA, Al Rifai MT, Al Shalaan H, et al. (2013). Biotin-responsive basal ganglia disease should be renamed biotin-thiamine-responsive basal ganglia disease: a retrospective review of the clinical, radiological and molecular findings of 18 new cases. Orphanet J Rare Dis 8:83.
- Kono S, Miyajima H, Yoshida K, Togawa A, Shirakawa K, Suzuki H (2009). Mutations in a thiamine-transporter gene and Wernicke's-like encephalopathy. N Engl J Med 360:1792-1794.
- Ozand PT. Gascon GG. Al Essa M. Joshi S. Al Jishi E. Bakheet S. et al. (1998). Biotin-responsive basal ganglia disease: a novel entity. Brain 121 (Pt 7):1267-1279.
- Yamada K, Miura K, Hara K, Suzuki M, Nakanishi K, Kumagai T, et al. (2010). A wide spectrum of clinical and brain MRI findings in patients with SLC19A3 mutations. BMC Med Genet 11:171.
- Zeng WQ, Al-Yamani E, Acierno JS Jr, Slaugenhaupt S, Gillis T, MacDonald ME, et al. (2005). Biotin-responsive basal ganglia disease maps to 2q36.3 and is due to mutations in SLC19A3. Am J Hum Genet 77:16-26.