

The functional GRM3 Kozak sequence variant rs148754219 affects the risk of schizophrenia and alcohol dependence as well as bipolar disorder

Niamh L. O'Brien^{a,*}, Michael J. Way^{a,b,*}, Radhika Kandaswamy^{a,*}, Alessia Fiorentino^a, Sally I. Sharp^a, Giorgia Quadri^a, Jarram Alex^a, Adebayo Anjorin^a, David Ball^c, Raquin Cherian^d, Karim Dar^d, Aynur Gormez^e, Irene Guerrini^{c,f}, Mathis Heydtmann^g, Audrey Hillman^h, Sudheer Lankappaⁱ, Greg Lydall^a, Aideen O'Kane^k, Shamir Patel^d, Digby Quested^e, Iain Smithⁱ, Allan D. Thomson^a, Nicholas J. Bass^a, Marsha Y. Morgan^b, David Curtis^a and Andrew McQuillin^a

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^aMolecular Psychiatry Laboratory, Division of Psychiatry, UCL, London, ^bUCL Institute for Liver & Digestive Health, University College London, ^cNational Addiction Centre and Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, London, ^dGatehouse Alcohol Clinic and Max Glatt Unit, Central and North West London NHS Foundation Trust, St Bernards Hospital, Middlesex, ^eOxford Health NHS Foundation Trust, Warneford Hospital, Headington, Oxford, ^fBexley Substance Misuse Services, South London & Maudsley NHS Trust, Erith Health Centre, Kent, ^gRoyal Alexandra Hospital, ^hCathcart Centre, ⁱGartnavel Royal Hospital, NHS Greater Glasgow & Clyde,

Glasgow, ^jQueens Medical Centre, Nottingham and ^kNewcastle and North Tyneside Addictions Service, Plummer Court, Newcastle upon Tyne, UK

Correspondence to David Curtis, MD, PhD, Molecular Psychiatry Laboratory, UCL, Rockefeller Building, 21 University Street, London, WC1E 6JJ
Tel: +020 7679 6564; fax: +020 3108 2194; e-mail: d.curtis@ucl.ac.uk

*Niamh L. O'Brien, Michael J. Way and Radhika Kandaswamy contributed equally to the writing of this article and are joint first authors.

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We previously reported that a Kozak sequence variant in the metabotropic glutamate receptor 3 gene (*GRM3*), rs148754219, is associated with bipolar disorder (BP) and affects gene transcription and translation (Kandaswamy *et al.*, 2013). A marker near *GRM3*, rs12704290, is one of the top hits and reached genome-wide significance in a recently reported genome-wide association study of schizophrenia (SZ) (Ripke *et al.*, 2014), and markers for *GRM3* have also been reported to demonstrate association with alcohol dependence syndrome (ADS) (Levey *et al.*, 2014). In our original sample, considering patients successfully genotyped for rs148754219, 19 out of 1062 BP cases and only four out of 932 controls were heterozygous [odds ratio (OR)=4.2 (1.4–12.3), $P=0.005$]. We have genotyped this variant in additional controls and cases diagnosed with BP, SZ and ADS with the same ancestry. Patients were assessed by trained clinicians as described previously (Kandaswamy *et al.*, 2013; Way *et al.*, 2014). Allele counts were compared and significance was tested using Fisher's exact test. Thirteen out of 934 additional BP cases and three out of 377 additional controls were heterozygous [OR=1.8 (0.49–6.2), P =not significant]. Combined with the originally reported results (Kandaswamy *et al.*, 2013), 32 out of 1964 BP cases and seven out of 1309 controls were heterozygous [OR=3.0 (1.3–6.8), $P=0.003$]. Out of 1235 SZ cases 16 were heterozygous and were compared with the total control sample [OR=2.4 (0.99–5.8), $P=0.03$]. Out of 1514 ADS cases 18 were heterozygous and one was

homozygous for the variant allele [OR=2.5 (1.0–5.9), $P=0.03$]. If all case cohorts (BP, SZ and ADS) are combined together, there would be one homozygote and 66 heterozygotes out of 4971 cases compared with the seven heterozygotes out of 1309 controls [OR=2.7 (1.2–5.8), $P=0.004$]. Previous work has supported the view that some genetic risk factors may be common to different psychiatric diagnoses (Lydall *et al.*, 2011; Lee *et al.*, 2013). Although the individual results are of questionable significance, the magnitude and direction of effect are consistent across all the cohorts and thus suggest the possibility that this rare variant may have a direct, functional effect on the risk of developing any of these three disorders. Because of its rarity, large sample sizes would be needed to confirm these results. Doing this would be worthwhile because if this finding is confirmed it could provide molecular insight into a mechanism involving *GRM3* leading to increased risk of mental disorders and could provide a basis for further functional and therapeutic studies.

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Conflicts of interest

There are no conflicts of interest.

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