Letter to the Editors

Clinical symptomatology and the psychosis risk gene *ZNF804A*

Dear Editors,

The single nucleotide polymorphism (SNP) rs1344706, mapping to the gene *ZNF804A*, has been implicated in schizophrenia susceptibility (O'Donovan et al. 2008; International Schizophrenia Consortium, 2009; Stefansson et al. 2009; Steinberg et al. 2010). The original study reported stronger association when the phenotype was broadened to include bipolar disorder ($p = 9.96 \times 10^{-9}$) (O'Donovan et al. 2008), but the variant is likely to have a modest effect on disease risk (OR = 1.12). Understanding the function of psychosis risk genes is a key step towards understanding disease biology. Little is currently known about the encoding protein, zinc finger protein 804A, except that it is brain-expressed and predicted to be involved in regulation of gene expression. Two recent studies suggest that the *ZNF804A* risk allele is likely to influence brain function, both with respect to connectivity within and between the dorsolateral prefrontal cortex and hippocampus (Esslinger et al. 2009) and on episodic and working memory (Walters et al. in press).

An unanswered question is whether this gene has an effect at the level of clinical symptomatology within patient populations. Specifically, does this risk variant delineate a specific form of illness on the mood-psychosis spectrum (Craddock et al. 2006). For this study we investigated clinical symptom factors in a large sample ($n = 820$) of Irish psychotic patients. The study included 820 patients with a DSM-IV diagnosis of schizophrenia ($N = 568$), schizoaffective disorder ($N = 127$) or bipolar affective disorder ($N = 125$). Because clinical symptoms can vary over time we analyzed two measures of clinical symptomatology based on lifetime severity (BADDS) and presence of specific symptoms (Operational Criteria Checklist for Psychotic Illness, OPCRIT) (McGuffin et al. 1991).

SNP rs1344706 was genotyped using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems) ($n = 529$) and the Sequenom iPLEX Gold system ($n = 291$) (detailed in Walters et al. in press). The call rate for both genotyping platforms was >95%. Both case/control samples were in Hardy–Weinberg Equilibrium (HWE; $p > 0.05$). A number of HapMap CEU DNA samples ($n = 90$: www.hapmap.org) and duplicates ($n = 60$) were genotyped across platforms for quality control purposes.

All genotypes were found to be concordant with either the available online HapMap data or each other for this SNP.

An exploratory factor analysis using the 60 items relating to clinical signs and symptoms from the Operational Criteria Checklist for Psychotic Illness yielded 44 items with loadings of 0.4 or more. A five factor solution gave an interpretable pattern of factors, namely manic, depressive, positive, disorganized and negative factors (Supplementary Fig. 1, Supplementary Table 1). Factor score coefficients were then calculated in SPSS 16.0 using the regression method. There were no significant differences observed between the *ZNF804A* genotype groups with respect to current age, age at onset, gender, diagnosis, medication and course of disorder (Supplementary Table 2).

A MANOVA looking at the relationship between *ZNF804A* status and BADDS Scores showed a significant association between *ZNF804A* status and the BADDS score for mania ($p = 0.014$). Carriers of the previously identified risk allele had higher BADDS mania scores. Partial eta squared was 0.011, which suggested that *ZNF804A* genotype was responsible for 1.1% of variance of this score (Table 1).

ZNF804A genotype status was not associated with higher Manic Factor scores derived from the OPCRIT factor analysis ($p = 0.169$), (Supplementary Table 3). Examining the individual symptom items there was nominal evidence for association between the risk allele and 'reduced need for sleep' ($p = 0.014$) and having 'racing thoughts' ($p = 0.048$). Neither finding would withstand correction for the number of symptoms examined, but in both instances, carriers of the risk allele experienced more symptoms.

This study suggests modest evidence that carriers of the rs1344706 risk allele score higher on a measure which weights for the number and severity of lifetime manic episodes. This did not translate into association with a derived factor score based on a lifetime history of having specific manic symptoms, but there was modest support for an increase in 'racing thoughts' and 'reduced need for sleep'.

We attempted to address the difficulties inherent in measuring symptoms which fluctuate over time by using two different validated lifetime measures to capture information on illness episodes and illness factors based on discrete symptoms. Within a broad psychosis population we may have undersampled patients with manic symptomatology and the study may be underpowered. Further data, for example, using serial assessments in larger samples may be required to address these possibilities. This would assume that the effect was driven exclusively by the subset of

Table 1
Multivariate analysis of variance of *ZNF804A* genotype groups (CC vs AC vs AA) with BADDS dimension scores.

BADDS dimension score	Mean (SD) CC	Mean (SD) AC	Mean (SD) AA	Type III sum of squares	df	Mean square	F(CC vs AC vs AA)	Sig.	Partial eta squared
Mania	24.07 (28.81)	31.69 (31.26)	32.89 (31.25)	8209.327	2	4104.663	4.301	.014	.010
Depression	44.23 (40.65)	39.49 (40.6)	41.17 (41.75)	1533.638	2	766.819	.452	.636	.001
Psychotic	40.33 (28.39)	38.50 (40.60)	39.73 (28.22)	396.802	2	198.401	.248	.781	.001
Incongruence	56.50 (32.01)	58.69 (30.73)	60.80 (29.20)	1578.198	2	789.099	.929	.395	.002

patients in the study with a diagnosis of bipolar disorder ($n = 125$) or schizoaffective disorder ($n = 127$). However, when we restrict the analysis to patients with schizophrenia only ($n = 568$) the association between genotype and BADDS mania score remains significant ($p = 0.05$). A secondary question is whether this association is independent of, or related to, the previous observation of relatively spared cognitive performance in patient carriers of the risk allele. We have insufficient cognitive data available on bipolar patients (or patients who score highly on BADDS mania) within our sample to address this question as part of the current work.

Contributors

Dr Elizabeth Cummings and Dr Aiden Corvin conducted data analyses and drafted the manuscript. Dr Gary Donohoe, contributed to the data analysis and writing of the paper. Dr. Aiden Corvin, Professor Michael Gill and Dr Derek Morris conceived the study. Dr Derek Morris conducted the genotyping. Professors McDonald, Dinan, Murphy, Waddington, O'Neill and O'Callaghan were involved in the study design and recruitment of participants. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2010.05.022.

References

Craddock, N., O'Donovan, M.C., Owen, M.J., 2006. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. Schizophr. Bull. 32 (1), 9–16.

Esslinger, C., Walter, H., Kirsch, P., Erk, S., Schnell, K., Arnold, C., Haddad, L., Mier, D., Opitz von Boberfeld, C., Raab, K., Witt, S.H., Rietschel, M., Cichon, S., Meyer-Lindenberg, A., 2009. Neural mechanisms of a genome-wide supported psychosis variant. Science 324 (5927), 605.

International Schizophrenia Consortium, 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460 (7256), 748–752.

McGuffin, P., Farmer, A., Harvey, I., 1991. A polydiagnostic application of operational criteria in psychotic illness: development and reliability of the OPCRIT system. Arch. Gen. Psychiatry 48 (8), 764–770.

O'Donovan, M.C., Craddock, N., Norton, N., Williams, H., Peirce, T., Moskvina, V., Nikolov, I., Hamshere, M., Carroll, L., Georgieva, L., et al., 2008. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat. Genet. 40 (9), 1053–1055.

Stefansson, H., Ophoff, R.A., Steinberg, S., et al., 2009. Common variants conferring risk of schizophrenia. Nature 460 (7256), 744–747.

Steinberg, S., Mors, O., Børglum, A.D., Gustafsson, O., Werge, T., Mortensen, P.B., et al., 2010. Expanding the range of *ZNF804A* variants conferring risk of psychosis. Mol. Psychiatry. doi:10.1038/mp.2009.149 Electronic publication ahead of print January 5.

Walters J.T.R., Corvin A., Williams H., Dragovic M., Quinn E.M., et al. In Press. The psychosis susceptibility gene *ZNF804A* is associated with less impaired cognitive performance in schizophrenia. Archives of General psychiatry.

E. Cummings
Neuropsychiatric Genetics Research Group,
Department of Psychiatry and Institute of Molecular Medicine,
Trinity College Dublin, Ireland

G. Donohoe
Neuropsychiatric Genetics Research Group,
Department of Psychiatry and Institute of Molecular Medicine,
Trinity College Dublin, Ireland
Trinity Institute of Neuroscience, Trinity College, Dublin, Ireland

C. McDonald
Department of Psychiatry,
National University of Ireland Galway, Galway, Ireland

T.G. Dinan
Department of Psychiatry , University College Cork,
Cork, Ireland

F.A. O'Neill
The Department of Psychiatry, The Queens University, Belfast,
Northern Ireland

E. O'Callaghan
Cluain Mhuire Family Centre and Department of Psychiatry,
University College Dublin, Dublin, Ireland

J.L. Waddington
Molecular & Cellular Therapeutics, Royal College of Surgeons in
Ireland, Dublin, Ireland
Cavan-Monaghan Mental Health Service, St. Davnet's Hospital,
Monaghan, Ireland

K.C. Murphy

Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland
The Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin, Ireland

M. Gill
D.W. Morris
A. Corvin*

Neuropsychiatric Genetics Research Group, Department of Psychiatry and Institute of Molecular Medicine, Trinity College Dublin, Ireland

Trinity Institute of Neuroscience, Trinity College, Dublin, Ireland
*Corresponding author. Trinity Centre for Health Sciences, St James's Hospital, Dublin 8, Ireland. Tel.: +353 1 8962468; fax: +353 1 8963405.
E-mail address:* acorvin@tcd.ie (A. Corvin).

11 February 2010
Available online xxxx