Molecular Psychiatry (2009), 1–6
© 2009 Nature Publishing Group All rights reserved 1359-4184/09 $32.00
www.nature.com/mp

ORIGINAL ARTICLE

Association of *DISC1* and *TSNAX* genes and affective disorders in the depression case–control (DeCC) and bipolar affective case–control (BACCS) studies

A Schosser[1,8,9], D Gaysina[1,7,9], S Cohen-Woods[1], PC Chow[1], L Martucci[1], N Craddock[2], A Farmer[1], A Korszun[3], C Gunasinghe[1], J Gray[1], L Jones[4], F Tozzi[5,6], J Perry[5,6], P Muglia[5,6], MJ Owen[2], IW Craig[1] and P McGuffin[1]

[1]*MRC SGDP Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London, UK;* [2]*Department of Psychological Medicine, Cardiff University, School of Medicine, Heath Park, Cardiff, UK;* [3]*Centre for Psychiatry, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Charterhouse Square, London, UK;* [4]*Division of Neuroscience, Department of Psychiatry, University of Birmingham, Birmingham, UK;* [5]*Genetics Division, Drug Discovery, GlaxoSmithKline R&D, Verona, Italy;* [6]*Genetics Division, Drug Discovery, GlaxoSmithKline R&D, Greenford, Middlesex, UK;* [7]*Ufa Scientific Center, Institute of Biochemistry and Genetics, RAS, Ufa, Russia and* [8]*Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria*

The gene known as Disrupted-in-Schizophrenia-1, *DISC1*, was originally discovered in a large family, in which it also co-segregated with bipolar affective disorder (BD) and with major depressive disorder (MDD). The *TSNAX* (Translin-associated factor X) gene, located immediately upstream of *DISC1*, has also been suggested as a candidate gene in relation to psychiatric illness, as one transcript resulting from intergenic splicing encodes a novel *TSNAX–DISC1* fusion protein. We explored the *TSNAX–DISC1* gene region for an association with BD and MDD in a sample of 1984 patients (1469 MDD, 515 BD) and 1376 ethnically matched controls. Eight single nucleotide polymorphisms (SNPs) within the *TSNAX–DISC1* region (rs766288, rs3738401, rs2492367, rs6675281, rs12133766, rs1000731, rs7546310 and rs821597) were investigated using the SNPlex Genotyping System. We found a significant allelic and genotypic association of the *TSNAX–DISC1* gene region with BD, whereas a haplotypic association was found for both BD and MDD. Therefore, our results suggest an association between the *TSNAX–DISC1* region and both forms of affective disorders, and support the hypothesis that a portion of the genotypic overlap between schizophrenia and affective disorders is attributable to this gene.
Molecular Psychiatry advance online publication, 3 March 2009; doi:10.1038/mp.2009.21

Keywords: bipolar disorder; depression; association; psychosis

Introduction

Recent twin studies suggest correlations between the liabilities to unipolar or major depressive disorder (MDD) and to bipolar disorder (BD),[1] as well as between BD and schizophrenia (SZ).[2] Association studies also provide evidence for overlap in genetic susceptibility across the traditional classification categories.[3] The Disrupted-in-Schizophrenia-1 (*DISC1*) gene was initially identified at the breakpoint of a balanced translocation (1,11)(q42.1;q14.3), which segregated with major mental illnesses (SZ, schizoaffective disorder, BD, unipolar affective disorder and adolescent conduct disorder) in a large Scottish family.[4] Thus, *DISC1* is a putative susceptibility gene for psychoses, such as SZ and BP, as well as for MDD.

A number of key central nervous system proteins, thought to be highly relevant to the development of mental illness, have also been identified as interacting partners (for review, see Chubb *et al.*[5]), and several DISC1 interactors have been defined as independent genetic susceptibility factors for major mental illness.

The translin-associated factor X (*TSNAX*) gene is located immediately upstream of *DISC1*, and intergenic splicing (splicing together of exons from separate genes) between the *DISC1* and the gene encoding *TSNAX* was shown by Millar *et al.*[6] One transcript resulting from intergenic splicing encodes a novel *TSNAX–DISC1* fusion protein, and *TSNAX* has been suggested to be considered as a candidate gene in relation to psychiatric illness as well. Evidence for an association between BD and SZ and the

Correspondence: Dr A Schosser, MRC SGDP Centre, Institute of Psychiatry, King's College London, Box P080, De Crespigny Park, London SE5 8AF, UK.
E-mail: alexandra.schosser@iop.kcl.ac.uk
[9]These two authors contributed equally to this work.
Received 1 December 2008; accepted 14 January 2009

TSNAX–DISC1 region was shown in the general Scottish population.[7] Recently, Palo *et al*.[8] examined the association of allelic variants of the *TSNAX–DISC1* gene cluster in 723 members of the 179 Finnish BD families. One haplotype at the 5′-end of *DISC1* was over-transmitted to males with psychotic disorder, which was consistent with an earlier finding in Finnish SZ.[9] Haplotypes at the 3′-end of *DISC1* were associated with bipolar spectrum disorder, similar to a two-single nucleotide polymorphism (SNP) haplotype at the 5′-end of *TSNAX*.

Although there were a number of patients with MDD among the family members of the reported chromosomal translocation in the large Scottish family, a possible association of the *DISC1* gene with MDD has so far only been investigated by Hashimoto *et al*.[10] They reported on an association of the genetic variations of *DISC1* and MDD, showing that the Cys704 allele frequency of Ser704Cys (rs821616) was significantly higher in patients than in controls. They further reported on weak evidence for an association with the marker rs6541281.

The aim of this study is to explore the *DISC1–TSNAX* gene region for an association with BD and MDD in a large depression case–control (DeCC) and in a bipolar affective disorder case–control study (BACCS) sample from the United Kingdom.

Materials and methods

Samples

Our sample of 1469 patients with a diagnosis of recurrent MDD (446 men, 1023 women; mean age ± s.d.: 47.39 ± 12.33) and 515 patients with a diagnosis of BD (176 men, 339 women; mean age ± s.d.: 47.99 ± 11.40), as defined by the DSM-IV (Diagnostic and Statistical Manual Fourth edition) operational criteria and by the ICD10 (International Classification of Diseases Tenth edition) operational criteria, was recruited from London (UK) in the case of BD, and from London, Cardiff and Birmingham (UK) in the case of MDD. Participants were identified from psychiatric clinics, hospitals and general medical practices and from volunteers responding to media advertisements. Only participants of white European parentage were included. All participants were interviewed using SCAN (Schedules for Clinical Assessment in Neuropsychiatry).[11]

The clinical methodology used in the DeCC collection is described in detail in the study by Farmer *et al*.[12] Participants were excluded if they, or a first-degree relative, ever fulfilled the criteria for mania, hypomania or SZ. Moreover, the participants were also excluded, if they experienced psychotic symptoms that were mood incongruent or present when there was no evidence of a mood disturbance. Other exclusion criteria were intravenous drug use with a lifetime diagnosis of dependency; depression occurring solely in relation to alcohol or substance abuse; depression only secondary to medical illness or medication; and a clear diagnosis of BD, SZ, schizoaffective disorder or acute, or transient psychotic disorders in first- or second-degree relatives.

A total of 1376 control participants (579 men, 797 women; mean age ± s.d.: 41.70 ± 13.16), screened for a lifetime absence of psychiatric disorders using a modified version of the Past History Schedule,[13] were recruited. Participants were excluded if they, or a first-degree relative, ever fulfilled the criteria for major depression, BD or SZ. Moreover, the participants were also excluded, if they scored 10 or above on the Beck Depression Inventory,[14] did not return consent or failed to return cheek swabs. The study was approved by the Local Ethical Committees at the three centres, and informed written consent was obtained from all the participants.

Genotyping

Blood samples were obtained from all patients and either blood or buccal mucosa swabs were obtained from controls. Genomic DNA was extracted using an in-house-validated procedure from blood and cheek swabs as described earlier.[15,16]

We examined seven SNPs of the *DISC1* gene: rs3738401 (exon 2), rs2492367 (exon 6), rs6675281 (exon 9), rs12133766 (exon 9), rs1000731 (intron 9), rs7546310 (intron 9) and rs821597 (intron 9), and one SNP located in intron 4 of the *TSNAX* gene, rs766288. Genotyping of the eight SNPs of the *TSNAX–DISC1* locus was performed applying the SNPlex Genotyping System (Applied Biosystems, Foster City, CA, USA). The system uses oligonucleotide ligation, polymerase chain reaction and capillary electrophoresis to analyse bi-allelic SNPs. Genotyping was performed blind with regard to all phenotypic information, including affection status, and 2616 samples were successfully genotyped. Analysing the raw data was performed using the GeneMapper Software v3.7 and Microsoft Office Excel 2003. As an internal control, 2 plates (176 samples) were re-genotyped, resulting in a 100% consistence in all the SNPs. The following quality control criteria were applied: SNPs were omitted from analysis, if poor genotype clustering prevented the GeneMapper from making calls. Individual genotypes were omitted if their peak heights were $<20\%$ of the average for that genotypic group, across the entire sample to avoid a false heterozygosity assignment because of background noise in poor-quality samples. As low call rates may indicate inaccurate genotyping, markers were omitted if the call rate after the earlier exclusions was $<80\%$.

Statistics

To test for deviation from the Hardy–Weinberg Equilibrium (HWE), the computer program FINETTI (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was used to perform exact statistics, and cases and controls were considered separately.

Genotype and allele frequencies were assessed for an association with BD and MDD using standard contingency table analyses incorporating the

chi-squared test of independence, producing a χ^2-statistic with one or two degrees of freedom depending on the number of parameters and corresponding *P*-values for the allele and genotype distributions, respectively.

The UNPHASED program[17] was applied using two-, and three-marker slide windows to test for haplotypic association. Maximum likelihood haplotype frequencies were estimated with the Expectation-Maximisation (EM) algorithm and a rare haplotype frequency threshold was taken as 0.01 (both in cases and in controls). The program, UNPHASED, uses unconditional logistic regression to perform likelihood ratio tests under a log-linear model of the probability that an allele or haplotype belongs to the case rather than to the control group. The global null hypothesis is that the odds ratios (ORs) of all haplotypes are equal between cases and controls. Individual haplotypes were also tested for association by grouping the frequencies of all the other haplotypes together.

The Haploview 4.0 program[18] was used to perform linkage disequilibrium analysis of all SNPs in our BACCS and DeCC samples. The measure of linkage disequilibrium, denoted as D' and r^2, was calculated from the haplotype frequency using the EM algorithm. Individuals with call rates <80% were excluded from analysis.

To calculate the power of our case–control sample, we used the Power and Sample Size Calculations (PS) program.[19] In this program, the method of Schlesselman[20] is used for independent case and control groups, applying an uncorrected chi-squared test. When the case and control sample sizes were unequal, PS uses the generalization of Casagrande's method proposed by Fleiss.[21] The alternative hypothesis is specified in terms of ORs.

All the reported *P*-values are two tailed. The problem of multiple testing was addressed by the false discovery rate (FDR) method.[22] In the case of single-marker analyses, it was assumed that eight independent tests were performed. Haplotype analyses were corrected for the number of sliding windows that were used.

Results

Genotyping results for each SNP are shown in Table 1. Marker rs3738401 was excluded from further analyses, as the controls were out of the HWE and the percentage of missing data was >10%. All the other SNPs had missing data between 0.5 and 2.7%, and the genotype frequencies of the controls were in HWE. The distributions of genotype frequencies of rs2492367 and rs7546310 polymorphisms within the BD group were significantly out of HWE ($P=0.001$ and $P=0.007$, respectively), even after multiple testing correction (FDR $P=0.008$ and FDR $P=0.028$, respectively). The genotype distributions of all the other SNPs were in the HWE within the BD group, as well as within the MDD group.

Single-marker association analyses showed significant genotypic ($P<0.001$) and allelic ($P=0.022$) associations of BD with the rs2492367 polymorphism

Table 1 Results of single-marker association analyses (genotypic/allelic) of the *TSNAX–DISC1* genes in MDD and BD (*P*-values <0.05 are in bold).

	SNP ID	*Location*	*Position (chr 1)*[a]	*Alleles*[b]	*MD %*	*Control*		*MDD*		*BD*	
						N	*MAF*	N	P-*value (MAF)*	*N*	P-*value (MAF)*
1	rs766288	*TSNAX* intron 4	229 760 311	A/C	1	954	0.39	1188	0.27/0.15 (0.37)	448	0.15/0.06 (0.35)
2	rs3738401	*DISC1* exon 2	229 896 918	A/G	12	773	0.34	1100	0.77/0.59 (0.33)	428	0.25/0.49 (0.33)
3	rs2492367	*DISC1* exon 6	229 973 212	C/T	0.5	952	0.11	1202	0.31/0.97 (0.11)	449	**<0.001/0.022** (0.14)
4	rs6675281	*DISC1* exon 9	230 020 724	C/T	1.8	934	0.13	1190	0.47/0.23 (0.15)	446	0.40/0.49 (0.14)
5	rs12133766	*DISC1* exon 9	230 020 768	A/G	2.7	952	0.07	1145	0.69/0.60 (0.06)	448	0.89/0.88 (0.06)
6	rs1000731	*DISC1* intron 9	230 030 114	A/G	1.6	955	0.24	1172	0.84/0.57 (0.24)	449	0.28/0.13 (0.22)
7	rs7546310	*DISC1* intron 9	230 128 443	A/C	1.3	948	0.40	1187	0.13/0.066 (0.43)	447	**0.008/0.012** (0.45)
8	rs821597	*DISC1* intron 9	230 168 887	C/T	0.6	955	0.36	1196	0.40/0.28 (0.37)	449	0.87/0.94 (0.36)

Abbreviations: BD, bipolar disorder; chr, chromosome; *DISC1*, Disrupted-in-Schizophrenia-1; MAF, minor allele frequency; MD, missing data; MDD, major depressive disorder; *N*: sample size; SNP, single nucleotide polymorphism; *TSNAX*, Translin-associated factor X.

[a]Position according to the HapMap database 2007 (http://www.hapmap.org).

[b]Minor alleles are underlined.

Table 2 LD between *TSNAX–DISC1* SNPs in controls, MDD and BD

		Control		*MDD*		*BD*	
Marker 1	*Marker 2*	*D′*	*r^2*	*D′*	*r^2*	*D′*	*r^2*
rs766288	rs2492367	0.081	0.001	0.043	0	0.196	0.011
rs766288	rs6675281	0.114	0.001	0.028	0	0.201	0.004
rs766288	rs12133766	0.435	0.008	0.351	0.005	0.482	0.008
rs766288	rs1000731	0.141	0.01	0.01	0	0.194	0.019
rs766288	rs7546310	0.125	0.007	0.113	0.005	0.088	0.005
rs766288	rs821597	0.034	0.001	0.028	0.001	0.031	0
rs2492367	rs6675281	0.071	0.004	0.041	0	0.034	0.001
rs2492367	rs12133766	0.655	0.004	0.313	0.001	0.226	0.001
rs2492367	rs1000731	0.046	0	0.046	0.001	0.196	0.022
rs2492367	rs7546310	0.087	0.001	0.126	0.003	0.063	0.001
rs2492367	rs821597	0.174	0.002	0.077	0.001	0.17	0.003
rs6675281	rs12133766	1	0.011	1	0.011	1	0.011
rs6675281	rs1000731	1	0.048	1	0.052	1	0.045
rs6675281	rs7546310	0.197	0.009	0.209	0.01	0.141	0.004
rs6675281	rs821597	0.178	0.003	0.023	0	0.138	0.002
rs12133766	rs1000731	1	0.022	1	0.02	1	0.018
rs12133766	rs7546310	0.12	0.002	0.079	0	0.071	0
rs12133766	rs821597	0.118	0.001	0.347	0.005	0.452	0.008
rs1000731	rs7546310	0.239	0.012	0.194	0.009	0.05	0.001
rs1000731	rs821597	0.115	0.008	0.089	0.004	0.114	0.007
rs7546310	rs821597	0.135	0.007	0.003	0	0.015	0

Abbreviations: BD, bipolar disorder; *DISC1*, Disrupted-in-Schizophrenia-1; LD, linkage disequilibrium; MDD, major depressive disorder; SNP, single nucleotide polymorphism; *TSNAX*, Translin-associated factor X.

in exon 6 and with the rs7546310 polymorphism in intron 9 of *DISC1* (genotypic $P=0.008$ and allelic $P=0.012$; see Table 1). The FDR genotypic *P*-values were 0.008 and 0.032, respectively. No significant genotypic or allelic association was observed with any of the investigated SNPs and MDD.

The linkage disequilibrium pattern between the SNPs in controls, MDD and BD is shown in Table 2. The strongest linkage disequilibrium is observed within a region of exon 9–intron 9 of the *DISC1* gene. We analysed two- and three- marker haplotypes. The results of haplotype analyses in MDD and BD are shown in Table 3. Two-marker haplotype analyses across the *TSNAX–DISC1* gene cluster showed an association for one two-marker combination (rs7546310–rs821597) with both MDD ($P=0.034$, FDR $P=0.102$) and BD ($P=0.05$, FDR $P=0.043$). Individual haplotype analyses showed that this A–T haplotype was over-represented in MDD (16%, $P=0.003$, FDR $P=0.018$) and in BD (16%, $P=0.03$, FDR $P=0.03$). In the BD group, analyses revealed two other global haplotype associations: rs766288–rs2492367 ($P=0.019$, FDR $P=0.03$) and 1000731–rs7546310, ($P=0.02$, FDR $P=0.03$). Individual haplotype analyses showed that the A–C haplotypes of these two-marker combinations were under-represented in BD ($P=0.004$ in both cases, FDR $P=0.012$). Additional significant individual two- and three-marker haplotypes are shown in Table 3.

Discussion

We have performed a large case–control study to investigate whether the *TSNAX–DISC1* locus is involved in genetic vulnerability to the DSM-IV and/or to the ICD-10 diagnosis of both recurrent unipolar depression (MDD) and bipolar disorder (BD). *TSNAX* is located immediately upstream of *DISC1* and intergenic splicing (that is, splicing together of exons from separate genes) between *DISC1* and *TSNAX* results in a transcript encoding a novel *TSNAX–DISC1* fusion protein.[6] The regions of *DISC1* and *TSNAX* bind and interact with each other or with multiple proteins,[5,23,24] thus, being an interesting candidate region for major psychiatric diseases, such as BD and MDD. The results of single-marker analyses of eight SNPs showed significant allelic and genotypic associations of rs2492367 and rs7546310 with BD, and the genotypic *P*-values withstood correction for multiple testing applying the FDR. There was no association of any of the investigated SNPs with MDD.

Although several studies investigated an association between the *DISC1–TSNAX* locus and BD,[7,8,25–27] to date only one study has focused on MDD,[10] showing a significant association of the Cys704 allele of the functional SNP rs821616 (Ser704Cys) with MDD.

In a sample from the Scottish population,[7] a three-marker haplotype C–G–T (rs2492367–rs2812393–

Table 3 A two- and three-marker sliding approach was used for haplotypic analyses within the *TSNAX–DISC1* region, and results in unipolar depression (MDD) and BD, are shown

SNPs	*Haplotype*	*Control freq*	*Global* P-*values*		*Individual* P-*values*[a]	
			MDD	*BD*	*MDD (frequency)*	*BD (frequency)*
1–3	A–C	0.34	0.54	**0.019**		**0.004** (0.29)
3–4	T–C	0.08	0.77	0.14		**0.03** (0.12)
5–6	G–A	0.24	0.81	0.25		0.10 (0.22)
6–7	A–C	0.17	0.32	**0.02**		**0.004** (0.12)
7–8	A–T	0.12	**0.034**	**0.05**	**0.003** (0.16)	**0.03** (0.16)
1–3–4	A–C–C	0.31	0.24	0.19	**0.04** (0.28)	**0.007** (0.26)
3–4–5	T–C–G	0.9	0.84	0.3		**0.05** (0.11)
4–5–6	C–G–A	0.24	0.74	0.39		0.09 (0.21)
5–6–7	G–A–C	0.17	0.36	0.06		**0.004** (0.12)
	G–G–A	0.30			0.07 (0.32)	
6–7–8	A–C–C	0.09	0.29	0.11		**0.02** (0.06)
	G–A–T	0.09			**0.006** (0.13)	

Abbreviations: BD, bipolar disorder; *DISC1*, Disrupted-in-Schizophrenia-1; MDD, major depressive disorder; SNP, single nucleotide polymorphism; *TSNAX*, Translin-associated factor X.
[a]Haplotypes with *P*-values < 0.10 are presented, *P*-values < 0.05 are in bold.
SNP 1 = rs766288, SNP 3 = rs2492367, SNP 4 = rs6675281, SNP 5 = rs12133766, SNP 6 = rs1000731, SNP 7 = rs7546310 and SNP 8 = rs821597.

rs1322784), containing the C-allele of rs2492367, showed a higher frequency in BD (31%) than in controls (22%, $P = 0.0063$), whereas in our sample, we observed an over-representation of the minor T-allele of rs2492367 in BD. Maeda *et al*.[26] investigated two common haplotypes which differed in two alleles only, and found that one haplotype including the G-allele of rs1000731 (HP1) was over-transmitted to the BD phenotype ($P = 0.01$), whereas a second haplotype (HP2) including the A-allele of rs1000731 was under-transmitted. Interestingly, within the current study, the A–C haplotype of rs1000731–rs7546310 was underrepresented in BD (global $P = 0.02$, FDR $P = 0.03$; individual $P = 0.004$, FDR $P = 0.012$). Palo *et al*.[8] showed that the C–G haplotype of rs6675281–rs1000731 was over-transmitted in a psychotic disorder group, and that a haplotype within the *TSNAX–DISC1* gene cluster at the 5′-end of *DISC1* (T–A of rs751229 and rs3738401) was over-transmitted in males with a psychotic disorder (and an extended haplotype to both genders). In SZ, this common two-SNP haplotype, assigned to as HEP3, has been earlier reported to be over-transmitted to affected males, when the population frequency was taken into account.[27,28] Within the study of Palo *et al*.,[8] the psychotic group consisted of patients suffering from BD type I with intermitted psychotic features, psychotic depression, SZ, schizoaffective disorder and psychosis NOS (not otherwise specified). In the current study, as the controls were out of the HWE and the percentage of missing data was >10%, SNP rs3738401 was excluded from haplotype analyses.

Hodgkinson *et al*.[25] reported a strong association of both BD and schizoaffective disorder with the T-allele of rs6675281. Palo *et al*.[8] could not replicate a single-marker association of rs6675281; however, the C–G haplotype of rs6675281–rs100731 was over-transmitted in their psychotic disorder group. In the current study, we failed to replicate a single-marker association of SNP rs6675281 with BD as well; however, the common A–C–C combination of haplotypes rs766288–rs2492636–r6675281 showed significantly lower frequencies in both MDD ($P = 0.04$) and in BD ($P = 0.007$) when compared with controls. We also showed a significantly lower frequency of a haplotype including allele A of the *TSNAX* polymorphism rs766288, namely A–C of rs766288–rs2492367, within the BD group ($P = 0.004$). Thus, we conclude that this might be a protective haplotype for BD.

The associations that we have identified are unlikely to have arisen as a result of any admixture within our investigated groups, in part, because the genotype and allele frequencies of all the analysed SNPs are congruent with the data for Centre d'Etude du Polymorphisme Humain (CEPH) population and for the studies published earlier; in addition, all our participants are of white European parentage, which also reduces this possibility.

The power of our sample to detect the allelic association of a SNP with a minor allele frequency of 0.39 (as in the case of rs766288) with a nominally significant *P*-value ($P = 0.05$) and OR = 1.5, is 99.6% in DeCC and 93.9% in BACCS; however, the power decreases to 53.9 and 34.9% in a case of smaller effect size with OR = 1.2. Power decreases for the SNPs with a very rare allele, similar to the case of rs12133766, to 73 and 52% for OR equal to 1.5 and 1.2 in the DeCC sample, and to 20 and 14% in the BACCS sample.

In conclusion, by investigating a large sample of BD and MDD patients and comparing them with healthy controls, we found a significant allelic and genotypic

association of the *TSNAX–DISC1* gene region with BD, but not with MDD. A haplotypic association was found with both BD and MDD. Therefore, our results suggest an association between the *TSNAX–DISC1* region and both forms of affective disorders, and support the hypothesis that a portion of the genetic overlap between SZ and affective disorders is attributable to this gene.

Acknowledgments

Dr Schosser was supported by an Erwin-Schrödinger Fellowship (Ref. No. J2647) of the Austrian Science Funds. Dr Gaysina was supported by the INTAS Postdoctoral Fellowship (Ref. No. 04-83-3802) and by the Russian Science Support Foundation. Dr Cohen-Woods was supported by a Medical Research Council (MRC) UK PhD studentship. The depression case–control collection (DeCC) was funded by the MRC UK and the bipolar affective disorder case–control study (BACCS) collection was supported by GlaxoSmithKline, Research and Development.

References

1 McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 2003; **60**: 497–502.
2 Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P. A twin study of genetic relationships between psychotic symptoms. *Am J Psychiatry* 2002; **159**: 539–545.
3 Craddock N, Forty L. Genetics of affective (mood) disorders. *Eur J Hum Genet* 2006; **14**: 660–668. Review.
4 Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CAM *et al.* Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Hum Mol Genet* 2000a; **9**: 1415–1423.
5 Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. *Mol Psychiatry* 2008; **13**: 36–64.
6 Millar JK, Christie S, Semple CAM, Porteous DJ. Chromosomal location and genomic structure of the human translin-associated factor X gene (TRAX; TSNAX) revealed by intergenic splicing to DISC1, a gene disrupted by a translocation segregating with schizophrenia. *Genomics* 2000b; **67**: 69–77.
7 Thomson PA, Wray NR, Millar JK, Evans KL, Le Hellard S, Condie A *et al.* Association between the TRAX/DISC locus and both bipolar disorder and schizophrenia in the Scottish population. *Mol Psychiatry* 2005; **10**: 657–668.
8 Palo OM, Antila M, Silander K, Hennah W, Kilpinen H, Soronen P *et al.* Association of distinct allelic haplotypes of DISC1 with psychotic and bipolar spectrum disorders and with underlying cognitive impairments. *Hum Mol Genet* 2007; **16**: 2517–2528.
9 Kockelkorn T, Arai M, Matsumoto H, Fukuda N, Yamada K, Minabe Y *et al.* Association study of polymorphisms in the 5′ upstream region of human DISC1 gene with schizophrenia. *Neurosci Lett* 2004; **368**: 41–45.
10 Hashimoto R, Numakawa T, Ohnishi T, Kumamaru E, Yagasaki Y, Ishimoto T *et al.* Impact of the DISC1 Ser704Cys polymorphism on risk for major depression, brain morphology and ERK signaling. *Hum Mol Genet* 2006; **15**: 3024–3033.
11 Wing J. SCAN–schedules for clinical assessment in neuropsychiatry. *Psychiatry: a World Perspective* 1990; **900**: 85–90.
12 Farmer A, Breen G, Brewster S, Craddock N, Gill M, Korszun A *et al.* The Depression Network (DeNT) Study: methodology and sociodemographic characteristics of the first 470 affected sibling pairs from a large multi-site linkage genetic study. *BMC Psychiatry* 2004; **4**: 42.
13 McGuffin P, Katz R, Aldrich J. Past and present state examination–the assessment of lifetime ever psychopathology. *Psychol Med* 1986; **16**: 461–465.
14 Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. *J Clin Psychol* 1984; **40**: 1365–1367.
15 Freeman B, Powell J, Ball D, Hill L, Craig I, Plomin R. DNA by mail: an inexpensive and noninvasive method for collecting DNA samples from widely dispersed populations. *Behav Genet* 1997; **27**: 251–257.
16 Freeman B, Smith N, Curtis C, Huckett L, Mill J, Craig IW. DNA from buccal swabs recruited by mail: evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. *Behav Genet* 2003; **33**: 67–72.
17 Dudbridge F. Pedigree disequilibrium tests for multilocus haplotypes. *Genet Epidemiol* 2003; **25**: 115–121.
18 Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005; **21**: 263–265.
19 Dupont WD, Plummer WD. Power and sample-size calculations–a review and computer program. *Control Clin Trials* 1990; **11**: 116–128.
20 Schlesselman JJ. Case-control Studies: Design, Conduct, Analysis. 1982.
21 Fleiss JL. Statistical Methods for Rates and Proportions. 2nd edn. John Wiley & Sons, New York, 1981.
22 Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I. Controlling the false discovery rate in behavior genetics research. *Behav Brain Res* 2001; **125**: 279–284.
23 Morris JA, Kandpal G, Ma L, Austin CP. DISC1 (Disrupted-In-Schizophrenia 1) is a centrosome-associated protein that interacts with MAP1A, MIPT3, ATF4/5 and NUDEL: regulation and loss of interaction with mutation. *Hum Mol Genet* 2003; **12**: 1591–1608.
24 Kamiya A, Tomoda T, Chang J, Takaki M, Zhan CX, Morita M *et al.* DISC1-NDEL1/NUDEL protein interaction, an essential component for neurite outgrowth, is modulated by genetic variations of DISC1. *HumMol Genet* 2006; **15**: 3313–3323.
25 Hodgkinson CA, Goldman D, Jaeger J, Persaud S, Kane JM, Lipsky RH *et al.* Disrupted in Schizophrenia 1 (DISC1): association with schizophrenia, schizoaffective disorder, and bipolar disorder. *Am J Hum Genet* 2004; **75**: 862–872.
26 Maeda K, Nwulia E, Chang J, Balkissoon R, Ishizuka K, Chen HM *et al.* Differential expression of Disrupted-In-Schizophrenia (DISC1) in bipolar disorder. *Biol Psychiatry* 2006; **60**: 929–935.
27 Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T *et al.* A haplotype within the DISC1 gene is associated with visual memory functions in families with a high density of schizophrenia. *Mol Psychiatry* 2005; **10**: 1097–1103.
28 Hennah W, Varilo T, Kestila M, Paunio T, Arajarvi R, Haukka J *et al.* Haplotype transmission analysis provides evidence of association for DISC1 to schizophrenia and suggests sex-dependent effects. *Hum Mol Genet* 2003; **12**: 3151–3159.