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Analysis of the *DISC1* translocation partner (11q14.3) in genetic risk of schizophrenia

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Abstract

The Disrupted-in-Schizophrenia 1 (DISC) locus on human chromosome 1 was identified as a consequence of its involvement in a balanced translocation (1;11)(q42.1;q14.3) segregating with major psychiatric disorders in a Scottish family. Recently a comprehensive meta-analysis of genome-wide association scan data found no evidence that common variants of *DISC1* (1q42.1) are associated with schizophrenia. Our aim was to test for association of variants in the 11q14.3 translocation region with schizophrenia. The 11q14.3 region was examined by meta-analysis of genome-wide scan data made available by the Genetic Association Information Network (GAIN) and other investigators (non-GAIN) through dbGap. P values were adjusted for multiple testing using the false discovery rate (FDR) approach. There were no SNPs significant ($P < 0.05$) after correction for multiple testing in the combined schizophrenia data set. However one SNP (*rs2509382*) was significantly associated in the males only analysis with $P_{\text{FDR}} = 0.024$. Whilst the relevance of the (1;11)(q42.1;q14.3) translocation to psychiatric disorders is currently specific to the Scottish family, genetic material in the chromosome 11 region may contain risk variants for psychiatric disorders in the wider population. The association found in this region does warrant follow-up analysis in further sample sets.

Introduction

Schizophrenia has a significant heritable component of approximately 80% (Sullivan *et al.* 2003). Genome-wide association scans in schizophrenia have revealed the importance of rare structural variations in disease etiology (International Schizophrenia Consortium 2008; Stefansson *et al.* 2008; Vacic *et al.* 2011; Walsh *et al.* 2008), however, these variants account for only a small proportion of cases (<5%). A genome-wide study testing common single nucleotide polymorphism (SNP) variants for a role in the causation of schizophrenia provides evidence that the majority of the heritable component resides in thousands of risk variants of very small effect (International Schizophrenia Consortium *et al.* 2009).

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Statement of interest

None to declare

The Disrupted-in-Schizophrenia (DISC) locus on human chromosome 1 was identified as a consequence of its involvement in a balanced translocation (1;11)(q42.1;q14.3) segregating with major psychiatric disorders in a large Scottish family (Millar *et al.* 2000). The DISC1 gene encodes a scaffold protein involved in a number of pathways, such as neuronal migration and formation of the hippocampus, that have been implicated in the etiology of schizophrenia (Hennah *et al.* 2006). Subsequent genetic association studies have implicated common variants of the DISC1 gene as risk factors for schizophrenia among Caucasian and Asian populations (Schumacher *et al.* 2009). However a recent comprehensive meta-analysis of genome-wide association scan (GWAS) data, combined with imputation of data from 10 candidate gene studies, that consisted of 11,626 cases and 15,237 controls found no evidence of *DISC1* are associated with schizophrenia (Mathieson *et al.* 2011).

Although a great deal of work has gone into assessing DISC1 for variants contributing to schizophrenia, genetic material in the translocation breakpoint (11q14.3, but originally described as 11q21) has been largely overlooked due to suggestions of an absence of genes in this region (Millar *et al.* 2000). However the region of chromosome 11 that is involved in the translocation identified in the Scottish family (St Clair *et al.* 1990) is near the site of another reported reciprocal translocation between chromosome 9 and 11 that co-segregates with manic-depressive illness in an independent family (Smith *et al.* 1989). Recently, evidence of a transcript at the 11q14.3 breakpoint in the Scottish family with possible fusion proteins as a result of (1;11)(q42.1;q14.3) translocation has emerged (Zhou *et al.* 2008, 2010; Eykelenbomm *et al.* 2012), leaving the chromosome 11 locus as an additional region of interest. Therefore we examined the 11q14.3 region by meta-analysis of genome-wide scan data made available by the Genetic Association Information Network (GAIN) and other investigators (non-GAIN) through dbGap (GAIN Collaborative Research Group *et al.* 2007).

Subjects and Methods

Subjects

Data for cohorts of European-American (CEU) cases and matched controls were obtained from the general research use (GRU) subsets of two sample sets publically-available through the dbGAP database (www.ncbi.nlm.nih.gov/dbgap); GAIN schizophrenia (Genome-Wide Association Study of Schizophrenia (GAIN) dbGaP Study Accession: phs000021.v3.p2; cases = 1351 and controls = 1378) and non-GAIN schizophrenia (Molecular Genetics of Schizophrenia - nonGAIN Sample (MGS_nonGAIN) dbGaP Study Accession: phs000167.v1.p1; cases = 1149 and controls = 1347). These sample sets are an initiative of the Foundation for National Institutes of Health (FNIH, <http://www.fnih.org>) and the US National Institute of Health (NIH) with support from various private partners (GAIN Collaborative Research Group *et al.* 2007). The data for both cohorts was originally obtained by a study conducted by Evanston North-Western Healthcare (Suarez *et al.* 2006) from the Molecular Genetics of Schizophrenia Collaboration dataset. Study participants were enrolled in these studies through recruitment in various medical institutions and support groups across the United States and Australia. Diagnosis was by DIGS (Diagnostic Instrument for Genetic Studies) and DSM-IV criteria for schizophrenia or schizoaffective disorder. The study was approved by the appropriate ethics committee in addition to the relevant GAIN

Data Access Committees and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their written informed consent prior to their inclusion in the study.

SNP Selection and Quality Control

The two datasets were genotyped using the Affymetrix 6.0 platform (GAIN Collaborative Research Group *et al.* 2007) and merged for combined analysis. The region surrounding the breakpoint on chromosome 11, the region q14.3 (position 88760352 to 92460352 according to NCBI37) containing 1038 SNPs that had been genotyped in both GAIN and nonGAIN data sets was analysed. Analysis only included SNPs within the defined region that had a minor allele frequency of >0.01 and a Hardy-Weinberg Equilibrium P -value of >0.001 , leaving 878 SNPs in the combined dataset. SNPs that contained more than two distinct alleles were excluded from the combined dataset in an effort to remove errors arising from coding alleles on different strands, leaving 874 SNPs. All SNPs in the Table were checked for possible stranding issues by comparing the combined dataset allele frequencies to those in the two individual datasets. This process was also applied to the sex-specific data sets (see below) leaving 845 SNPs in the combined male dataset and 831 in the combined female dataset. A list of the genotyped SNPs used in this analysis can be found in Supplementary Table 1. SNPs with experiment-wide significant association were visually inspected for genotyping integrity using the genotype cluster plots available through dbGAP or, in the case of the non-GAIN schizophrenia dataset cluster plots were constructed using Affymetrix Genotyping Console software. Individuals were filtered also, only those with a missing genotype proportion <0.2 were included in the analysis, resulting in a total 1123 cases (228 removed) and 1097 controls (281 removed) in the GAIN schizophrenia data set, while all individuals in the non-GAIN data set had missing genotype proportions of <0.2 . The individuals from the GAIN and nonGAIN datasets were each split into male only and female only data subsets. For the GAIN dataset this gave a female subset of 329 cases and 570 controls and a male subset of 794 cases and 527 controls. Similarly for the nonGAIN data the female subset comprised 346 cases and 678 controls, while the male subset contained 803 cases and 669 controls.

Statistical analysis

Region-wide association analysis was undertaken using PLINK (Purcell *et al.* 2007) in which both basic allelic association analysis and Cochran-Armitage Trend analysis was conducted. Imputation of the region was carried out using IMPUTE2 (Howie *et al.* 2009). The HapMap phase III, plus the 1000 genomes data (June 2012, NCBI build 36) were used as reference. P values from the allelic association analyses were adjusted for the multiple testing inherent in the analysis of the 874 SNPs in the 11q14.3 region using the false discovery rate (FDR) approach (Benjamini and Hochberg, 1995). Power calculations (Supplementary Figure 1) were performed as previously described (Johnson *et al.* 2001).

Results

Analysis of the 11q14.3 region revealed the most associated SNP in the combined analysis to be *rs7124944* ($P_{\text{UNCORRECTED}} = 2.3 \times 10^{-4}$), however it was not significant after

correction for multiple testing by the FDR method ($P_{\text{FDR}} > 0.05$) (Table 1). Data were split by sex due to previously reported sex-specific effects at *DISC1* in various mental illnesses including schizophrenia (Chen *et al.* 2007; Hennah *et al.* 2003, 2008; Schumacher *et al.* 2009). One SNP (*rs2509382*) was significantly associated in the males only analysis with $P_{\text{FDR}} = 0.024$ ($P_{\text{UNCORRECTED}} = 4.8 \times 10^{-5}$), with nominally significant association observed in each of the GAIN and nonGAIN datasets (Supplemental Table 2; OR (95% CI) = 1.25 (1.01-1.56), $P = 0.043$ in GAIN and 1.46 (1.20-1.77), $P = 1.7 \times 10^{-4}$ in nonGAIN). Significance was retained after correction for the sex analysis ($P = 0.048$). SNP *rs2509382* was in strong LD ($r^2 = 0.90$) with the other 4 nominally significant SNPs in the male only analysis (Table 1). SNP *rs2509382* maps 131kb upstream of the identified gene (*DISC1* fusion partner (*DISC1FP*)) in this region, with the remaining 4 SNPs mapping between *rs2509382* and the beginning of *DISC1FP* (84-8kb upstream). No SNPs in the female only analysis were significantly associated after correction for multiple testing.

Population stratification was assessed using EIGENSTRAT (Li and Yu, 2008), with a genomic inflation factor of 1.15 in the combined males and females analysis and 1.11 in the males-only analysis. Given that these factors are close to that typically expected from GWAS (< 1.1 ; Yang *et al.* 2011) and that the minor allele frequency of *rs2509382* is very similar in diverse populations (EUR=0.161, AFR=0.152, ASN=0.124) it unlikely that population stratification is playing a significant role in our data.

Given that the variants genotyped on the Affymetrix 6.0 array capture, on average, 83% of the common variation in the Caucasian genome (Li *et al.* 2008) we imputed the combined males only and combined females only data sets. In the males only data set an additional 19 SNPs were found nominally associated with schizophrenia that were in strong LD with *rs2509382* ($r^2 > 0.86$; $1.29 < \text{OR} < 1.35$; $8.1 \times 10^{-4} < P < 4.8 \times 10^{-5}$). The 24 SNPs formed a clear haplotype block and All mapped between 131kb and 1kb upstream of *DISC1FP1*. Of these SNPs *rs2509382* at the extreme downstream end of the block was the strongest associated (+131kb), with the third strongest associated (*rs34339130*: OR=1.43, $P = 5.1 \times 10^{-5}$, r^2 with *rs2509382* of 0.86) at the extreme upstream end of the block (+1kb). No significant associations were observed in the imputed females only data set.

Discussion

According to the genomic fusion sequence described in the original paper (St Clair *et al.* 1990) the region of 11q14.3 containing the proposed *DISC1FP* transcript spans 89984400-90648220bp (NCBI37) with the break occurring between bases 90361098 and 90361099. There are two possible fusion transcripts created by *DISC1FP* and *DISC1* in the Scottish family, the first of which is a fusion of exons 1-3 of the *DISC1FP* with exons 9-13 of *DISC1* and the second is a fusion of *DISC1* exons 1-8 with exons 4-7 of *DISC1FP* (Zhou *et al.* 2008). Given the structure of the fusion proteins, the nominally associated SNPs reported here are outside of the actual gene region. This does not, however, preclude a possible role for these SNPs in common schizophrenia – SNPs that influence gene expression and are causative for common disease have been reported in intergenic regions (Cunnington *et al.* 2010; Carvajal-Carmona *et al.* 2011). Of course, whilst the relevance of this fusion to psychiatric disorders is, at this stage, specific to the Scottish family, the fusion

implicates genetic material in the chromosome 11 region as a candidate for harboring risk variants for psychiatric disorders in the wider population. The association found in this region can be regarded as potentially genuine and does warrant follow-up analysis in further sample sets.

Concerning a possible role for DISC1FP1 in schizophrenia, Zhou and colleagues (2010) identify that within the human brain there is novel expression of a single exon of DISC1FP1 that is not present in lymphoblastoid cells, additionally there are several splice variations of the gene present in human thalamus. There is some suggestion that this gene may have an inhibitory interaction with the brain expressed CHORDC1 gene, which has been implicated in stress response. Zhou *et al.* (2010) found that the DISC1- DISC1FP1 fusion protein is insoluble, in contrast to the DISC1FP1 -DISC1 fusion protein. Insoluble DISC1 proteins have been found to aggregate in the brains of patients with schizophrenia and it is suggested that this limits the ability of DISC1 to interact with necessary binding partners (Leliveld *et al.* 2008). The DISC1-DISC1FP1 proteins cluster in the mitochondria where they destroy membrane potential (Eykelboom *et al.* 2012).

Despite the amount of data analysed in this study (>800 genotyped SNPs in a total of 2272 schizophrenia cases and 2444 controls), two questions remain that can only be addressed by analysis of larger sample sets with more genetic variants. Firstly, in the case of common risk variants, we were underpowered to detect weak effects of OR < 1.3 in the combined and males only analyses and power was very low in the females only analysis (Supplementary Figure 1). However, we are confident that we have excluded the possibility of the existence of a schizophrenia variant with modest effect (OR > 1.3) in the analysed region. Secondly, our study could not address the possible contribution of rare variants in the region to schizophrenia. Although variants were tested to a level of MAF 0.01, our power was minimal at this frequency (Supplementary Figure 1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1

Markers (top 5) with strongest evidence for association in combined GAIN and non-GAIN schizophrenia and separate male and female analyses.

SNP	11	12	22	Minor allele [†]	OR [95% CI]	P _{UNCORRECTED}	P _{FDR}
Combined							
<i>Rs7124944</i>	Case Control	1700 (0.748) 1936 (0.792)	531 (0.234) 478 (0.196)	41 (0.018) 30 (0.012)	613 (0.135) 538 (0.110)	1.26 [1.11- 1.43]	2.3 × 10 ⁻⁴ 0.097
<i>Rs1458326</i>	Case Control	1127 (0.496) 1100 (0.450)	921 (0.406) 1067 (0.437)	222 (0.098) 277 (0.113)	1365 (0.301) 1621 (0.332)	0.87 [0.79- 0.95]	1.2 × 10 ⁻³ 0.15
<i>Rs1674086</i>	Case Control	1080 (0.481) 1033 (0.431)	936 (0.417) 1091 (0.455)	227 (0.101) 272 (0.114)	1390 (0.310) 1635 (0.341)	0.87 [0.79- 0.95]	1.3 × 10 ⁻³ 0.15
<i>Rs12791202</i>	Case Control	1469 (0.648) 1674 (0.687)	707 (0.312) 695 (0.285)	90 (0.040) 68 (0.028)	887 (0.196) 831 (0.171)	1.18 [1.07- 1.32]	1.6 × 10 ⁻³ 0.15
<i>Rs1792361</i>	Case Control	1097 (0.483) 1065 (0.436)	940 (0.414) 1092 (0.447)	235 (0.103) 287 (0.117)	1410 (0.310) 1666 (0.341)	0.87 [0.80- 0.95]	1.6 × 10 ⁻³ 0.15
Male							
<i>Rs2509382</i> ²	Case Control	1074 (0.673) 886 (0.741)	466 (0.292) 283 (0.237)	57 (0.036) 27 (0.023)	580 (0.182) 337 (0.141)	1.35 [1.17- 1.57]	4.8 × 10 ⁻⁵ 0.024
<i>Rs35003084</i>	Case Control	1050 (0.662) 862 (0.729)	485 (0.306) 296 (0.250)	52 (0.033) 24 (0.020)	589 (0.186) 344 (0.146)	1.34 [1.16- 1.55]	8.2 × 10 ⁻⁵ 0.024
<i>Rs1278172</i>	Case Control	1055 (0.661) 867 (0.725)	483 (0.302) 302 (0.253)	59 (0.037) 27 (0.023)	601 (0.188) 356 (0.149)	1.33 [1.15- 1.53]	1.1 × 10 ⁻⁴ 0.024
<i>Rs1404531</i>	Case Control	1048 (0.657) 863 (0.723)	490 (0.307) 301 (0.252)	58 (0.036) 30 (0.025)	606 (0.190) 361 (0.151)	1.32 [1.14- 1.52]	1.6 × 10 ⁻⁴ 0.027
<i>Rs11019229</i>	Case Control	1052 (0.666) 858 (0.726)	467 (0.296) 295 (0.250)	61 (0.039) 29 (0.025)	589 (0.186) 355 (0.149)	1.31 [1.13- 1.51]	2.9 × 10 ⁻⁴ 0.040
Female							
<i>Rs16916137</i>	Case Control	298 (0.884) 628 (0.939)	38 (0.113) 40 (0.060)	1 (0.003) 1 (0.001)	40 (0.059) 42 (0.031)	1.95 [1.25- 3.03]	2.8 × 10 ⁻³ 0.998
<i>Rs56287704</i>	Case Control	544 (0.806) 1069 (0.857)	125 (0.185) 172 (0.138)	6 (0.009) 7 (0.006)	137 (0.102) 186 (0.075)	1.40 [1.11- 1.77]	4.0 × 10 ⁻³ 0.998
<i>Rs1531249</i>	Case Control	174 (0.258) 394 (0.316)	347 (0.514) 610 (0.489)	154 (0.228) 244 (0.196)	655 (0.485) 1098 (0.440)	1.20 [1.05- 1.37]	7.1 × 10 ⁻³ 0.998
<i>Rs7103426</i>	Case Control	646 (0.957) 1222 (0.979)	29 (0.043) 25 (0.020)	0 (0.000) 1 (0.001)	29 (0.021) 27 (0.011)	2.00 [1.18- 3.41]	8.4 × 10 ⁻³ 0.998
<i>Rs10501718</i>	Case Control	643 (0.957) 1213 (0.979)	29 (0.043) 25 (0.020)	0 (0.000) 1 (0.001)	29 (0.022) 27 (0.011)	2.00 [1.18- 3.40]	8.7 × 10 ⁻³ 0.998

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I_2 = minor allele, 1 = major allele
Genotype integrity was verified using the genotype cluster plots available through dbGAP or, in the case of the non-GAIN schizophrenia dataset, cluster plots were constructed using Affymetrix Genotyping Console software