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Mood congruent psychotic symptoms and specific cognitive deficits in carriers of the novel schizophrenia risk variant at MIR-137

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HIGHLIGHTS

- We investigated the clinical symptom profiles of carriers of the schizophrenia mir137 risk allele.
- The sample included 821 patients with schizophrenia, schizoaffective disorder and bipolar I disorder.
- Risk allele carriers had lower scores for positive symptoms and less psychosis incongruity.
- On neurocognitive testing in a subset, there were more cognitive deficits in risk allele carriers.

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ABSTRACT

Objective: The Schizophrenia Psychiatric Genome-wide Association (GWAS) Consortium recently reported on five novel schizophrenia susceptibility loci. The most significant finding mapped to a microRNA, MIR-137, which may be involved in regulating the function of other schizophrenia and bipolar disorder susceptibility genes.
Method: We genotyped 821 patients with confirmed DSM-IV diagnoses of schizophrenia, bipolar affective disorder I and schizoaffective disorder for the risk SNP (rs1625579) and investigated the clinical profiles of risk allele carriers using a within-case design. We also assessed neurocognitive performance in a subset of cases ($n = 399$) and controls ($n = 171$).
Results: Carriers of the risk allele had lower scores for an OPCRIT-derived positive symptom factor ($p = 0.04$) and lower scores on a lifetime measure of psychosis incongruity ($p = 0.017$). Risk allele carriers also had more cognitive deficits involving episodic memory and attentional control.
Conclusion: This is the first evidence that the MIR-137 risk variant may be associated with a specific subgroup of psychosis patients. Although the effect of this single SNP was not clinically relevant, investigation of the impact of carrying multiple risk SNPs in the MIR-137 regulatory network on diagnosis and illness profile may be warranted.

1. Introduction

The Schizophrenia Psychiatric Genome-Wide Association (GWAS) Consortium recently reported on the largest molecular genetic investigation of schizophrenia to date [9]. The study, a meta-analysis of GWAS data, included 9394 cases and 12,462 controls; top loci were than evaluated in a replication sample of 8442 cases and 21,397 controls. This confirmed two previously identified risk loci and identified five novel loci, of which the most significant finding mapped to a single nucleotide polymorphism (SNP) (rs1625579; $p = 1.6 \times 10^{-11}$) within the precursor for microRNA 137 (MIR-137), a known regulator of neuronal development [9]. The odds ratio for this risk allele was found to be 1.12. The study adds to a growing list of common and rare genetic risk variants being implicated in schizophrenia susceptibility, although most of the population variance in risk is yet to be explained [22].

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A key question, which has both diagnostic and therapeutic implications, is whether schizophrenia etiology involves one or many different molecular risk mechanisms. Although the associated 'T' allele at SNP rs1625579 has a modest overall effect on schizophrenia risk (OR = 1.12), it is of interest as it may implicate a particular molecular risk mechanism. MicroRNAs (miRNAs) are small non-coding RNAs that play a regulatory role in cellular processes, including brain functioning, by regulating the function of potentially hundreds of genes through RNA interference. MIR-137 has been directly implicated in regulation of neuronal maturation [17] and adult neurogenesis [16,18]. In the Psychiatric GWAS Consortium (PGC) study [9], SNPs mapping to the 301 high-confidence predicted gene targets of MIR-137 were more likely to be associated with schizophrenia than would be expected by chance. Gene targets of MIR-137 include the bipolar disorder susceptibility gene CACNA1C, suggesting that MIR-137 mechanism may have a wider impact on psychosis risk. A small GWAS study by Potkin et al. [15] reported modest association between genetic variants in the gene network regulated by MIR-137 and reduced dorsolateral prefrontal cortex (DLPFC) activation during a working memory task. Predicted target genes of MIR-137 include 4 genes which have reached genome-wide significance in schizophrenia studies, namely CSMD1, C10orf26, CACNA1C and TCF4 [12]. There has not been evidence to date of altered MIR-137 expression in either peripheral tissue or brain tissue in individuals with schizophrenia [3].

The wealth of evidence supporting overlap of heritability across schizophrenia, bipolar disorder and schizoaffective disorder [13,19] taken with the identification of the psychiatric diagnosis as "the weak component of modern research" [1], the overlap of symptoms across diagnostic entities, and the differing clinical manifestations of each individual diagnosis throws into relief longstanding debates over the validity of Kraepelin's dichotomy [11]. A convincing argument has been made for the use of more complex models [6] in psychiatric research, to avert the problems associated with a categorical diagnostic approach, which lose information regarding symptomatic experience of illness.

The aim of this study was to investigate whether carriers of the risk allele at MIR-137 represented a specific psychosis subgroup as defined by clinical or neuropsychological features. To test this hypothesis we examined clinical profiles of psychosis patients ($n = 821$) using a within case design to determine if carriers of the MIR-137 risk allele (rs1625579) had different symptom profiles. Using a dimensional approach facilitated the inclusion of subjects with bipolar disorder and schizoaffective diagnoses, as the dimensional approach favors the capture of subtle differences in clinical manifestations both within and across diagnostic categories.

We also assessed whether carrying this allele was associated with differences in neurocognitive performance in a subset of cases ($n = 399$) and controls subjects ($n = 171$).

2. Methods

2.1. Subjects and assessment

Subjects were recruited through community and inpatient mental health facilities throughout the island of Ireland for genetic studies of psychotic disorders. The sample was a convenience sample. Treating teams nominated potential participants, who were then invited to meet researchers. Where individuals were identified in an acute phase of their illness, interview was deferred. Approximately 20% of nominated participants declined to partake. Of the 902 participants recruited by the time of this analysis, 81 were excluded from further analysis (diagnoses of delusional disorder, OCD, intellectual disability, epilepsy, bipolar affective disorder II, psychotic disorder not otherwise specified). All participants provided written informed consent and were interviewed using the Structured Clinical Interview for DSM-IV Axis 1 Diagnoses (SCID) [8]. Diagnosis of a major psychotic disorder was made by the consensus lifetime best estimate method using DSM-IV criteria with all available information – interview, the Operational Criteria Checklist for Psychotic Illness (OPCRIT) [14], family or staff report, and chart review. All cases were over 18 years of age, of Irish origin (with 4 Irish grandparents) and had been screened to exclude substance-induced psychotic disorder or psychosis due to a general medical condition. The current study included 821 patients with a DSM-IV diagnosis of schizophrenia ($N = 573$), schizoaffective disorder ($N = 123$) or bipolar affective disorder I ($N = 125$). Further demographic details on subjects have been published elsewhere [10].

The sample for neurocognitive testing consisted of 399 cases and 171 controls. Cases consisted of clinically stable patients with a DSM-IV diagnosis of SZ ($n = 329$) or schizoaffective disorder ($n = 70$) recruited from 5 sites across Ireland. Other clinical characteristics of the clinical sample are detailed elsewhere [20].

The healthy control sample was recruited on the basis of responses to local media advertisements. Control participants were only included if they were aged between 18 and 65 and satisfied, based on clinical interview, the criteria of having no history of major mental health problems, intellectual disability or acquired brain injury, and no history of substance misuse in the preceding 6 months based on self report. Control participants were also excluded from the study if they reported having a 1st degree relative with a history of psychosis.

The Bipolar Affective Disorder Dimension Scale (BADDS), developed by Craddock et al. [5] as an adjunct to conventional categorical diagnosis, was used as an additional measure of lifetime symptomatology, in order to capture a more complete description of frequency and severity affective and psychotic episodes, which can be lost in hierarchical diagnoses. The BADDS provides a measure of severity over the course of illness for manic, depressive, psychotic, incongruent dimensions. The four dimensions – mania, depression, psychosis and incongruence are each rated as an integer on a 0–100 scale. The range within which the score lies is informed by the severity of the worst episode, and within that range it is determined by the number of episodes. Anchor points are clearly defined. For example, an individual who has experienced a number of hypomanic episodes, but no manic episodes, would score between 40 and 59 in the mania dimension, depending on the number of episodes. An extra point is scored for the number of similar episodes, while half a point would be added for each less severe episode.

The BADDS is a particularly useful instrument as it is able to accommodate sub-clinical features, discriminates between illness severity within disease category and show similarities in course of illness in individuals within different disease categories. The initial validation study included subjects with schizophrenia [5], and a further reliability study has been completed in schizoaffective disorder [21].

The Operational Criteria Checklist for Psychotic Illness (OPCRIT) was developed, by McGuffin and Farmer [14], as a computer suite of programmes to facilitate a polydiagnostic approach. It involves a 90 item checklist. 30 items relate to background information, while 60 items apply to the presence or otherwise of clinical features or symptoms. Scoring is typically between 0 and 2, with 1 typically indicating a symptom having been present for no more than a few days.

Neuropsychological assessment focused on the domains of (1) general cognitive ability (IQ) as measured by an abbreviated version of the Wechsler Adult Intelligence Scale (WAIS-III); (2) verbal episodic and working memory as measured by the Logical

Table 1
RS1625579 SNP genotype groups and demographic variables.

	GG (n = 26) Mean (SD)	TG (n = 231) Mean (SD)	TT (n = 547) Mean (SD)	F/X^2 value	p value
Age at onset	21.17 (7.069)	24.23 (8.297)	24.03 (8.476)	1.388	.250
Duration of illness (years)	14.9148 (15.43135)	19.9946 (12.26666)	19.9617 (12.30284)	1.850	.158
Chlorpromazine equivalent (mg)	412 (412.838)	506.86 (449.29)	468.86 (411.856)	.730	.483
Gender (% male)	84.0%	62.67%	66.16%	4.683	0.096

Memory (LM), Letter Number Sequencing (LNS), and digit span sub-tests from the Wechsler Memory Scales (WMS-III); (3) spatial episodic and working memory as assessed using the CANTAB paired associate learning task and the Spatial Working Memory task; and (4) attentional control as assessed using the CPT-IP. Further details on the neuropsychological assessment are reported elsewhere by Walters et al. [20].

2.2. Genotyping

The SNP rs1625579, was genotyped using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems). The call rate for 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) were genotyped for quality control purposes. All genotypes were found to be concordant with available online HapMap data.

2.3. Statistical analysis

The risk 'T' allele is common, but because there is insufficient basis to test a specific genetic model (e.g. dominant or recessive) our primary analysis was based on all three genotype groups TT ($n = 547$), TG ($n = 231$) and GG ($n = 26$). Where significant differences were detected these were further explored in a two-group analysis of homozygous 'T' risk allele carriers versus carriers of 1 or 0 risk alleles.

We investigated for association between rs1625579, and demographic variables which could potentially have relationships with lifetime dimension scores, using Chi-squared tests and ANOVAs. ANOVAs were performed examining for interactions between each genotype group and each of the four BADDS dimension scores for manic, depressive, psychotic and incongruent symptoms. For the factor analysis, we selected the 60 signs and symptoms within the Operational Criteria Checklist for Psychotic Illness (OPCRIT) to enter into exploratory factor analysis with VARIMAX rotation, using SPSS 16.0. Variables not directly associated with phenomenology (e.g. source of rating, duration of illness) were excluded. We used the scree plot, displayed in Supplementary Fig. 1 to determine the number of factors that best accounted for the covariance among these items. We selected items with loadings of 0.4 or greater to create factor-derived scales, yielding 44 items. A five factor solution gave an interpretable pattern of factors, namely manic, depressive, positive, disorganized and negative factors. These five factors accounted for 47.58% of the total variance. The Kaiser–Meyer–Olkin Measure of Sampling Adequacy was 0.856, sufficient for a satisfactory factor analysis to proceed. Bartlett's test of sphericity was 14,958.995, $p < 0.0001$. Factor score coefficients were then calculated in SPSS 16.0 using the regression method. Having derived the factor scores, we then performed MANOVAs looking for an association between SNP rs1625579 status and each of the five identified factors.

Association between MIR-137 rs1625579 and the phenotypes of general cognitive function, episodic memory, working memory and attentional control were tested using a general factorial design in the same statistical package. Our analysis was based on a comparison of the three genotype groups (TT versus TG versus GG) and diagnosis (cases versus controls), both of which were entered as fixed effects. In a series of ANCOVAs scores for each neuropsychological subtest were entered as the dependent variables, with age and gender included as covariates where appropriate.

3. Results

The final clinical analysis included 803 cases who passed genotyping QC. Demographic and clinical characteristics by rs1625579 genotype (TT, GT, and GG) appear in Table 1. There was no association between the risk SNP and diagnosis (schizophrenia, schizoaffective disorder or bipolar disorder), current age, gender, or medication dosage in chlorpromazine equivalents (Supplementary Table 1). The risk allele for SNP rs1625579 was associated with lower BADDS incongruence dimension scores ($p = 0.017$) as well as lower OPCRIT-derived positive symptom scores ($p = 0.041$). When analyses of the relationship between the BADDS incongruence groups were restricted to diagnostic groups, the signal

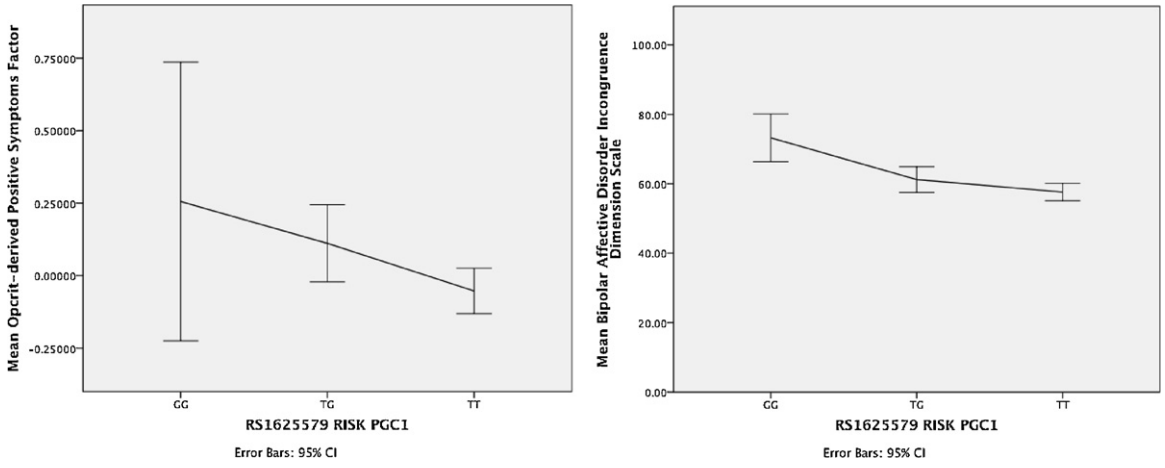

Fig. 1. Relationships between genotype groups and Opcrit-derived positive symptom factor score, Bipolar Affective Disorder Incongruence Dimension Score.

Table 2
RS1625579 (PGC1) stats results table (2 groups).

Cognitive function	Test or subscale	Sample	*n*	Mean (SD) GG/GT	Mean (SD) TT	$F_{\text{Case versus Controls}}$	*p*	$F_{\text{Main effect}}$	*p*	$F_{\text{Interaction effect}}$	*p*
IQ	Abbreviated Full Scale IQ	Patients	275	93.31 (17.82)	90.63 (17.19)	293.1	<.0001	2.384	.123	.410	.522
		Controls	133	124.33 (12.2)	121.82 (15.4)						
	WTAR (adult reading test)	Patients	275	96.45 (11.93)	97.32 (11.32)	.012	<.0001	.012	.461	0	.985
		Controls	133	110.06 (3.73)	109.55 (5.34)						
	Verbal IQ	Patients	275	94.06 (16.02)	93.03 (17.51)	282.1	<.0001	.817	.367	.079	.778
		Controls	133	125.79 (13.8)	123.7 (14.99)						
	Performance IQ	Patients	275	93.75 (20.8)	89.71 (18.59)	173.4	<.0001	3.04	.051	.099	.753
		Controls	133	119.33 (13.5)	116.03 (19.3)						
Working memory	LN sequence	Patients	370	8.162 (3.548)	7.51 (3.24)	.014	.924	1940	.014	.005	.956
		Controls	167	13.38 (2.91)	12.78 (3.34)						
	CANTAB SWM (between error)	Patients	366	−.80 (1.32)	−1.02 (1.3)	96.98	<.0001	.628	.149	1.186	.277
		Controls	159	.237 (.716)	.281 (.823)						
Episodic memory	Logical Memory Immediate	Patients	379	7.01 (3.52)	6.18 (3.31)	346.2	<.0001	1.535	.023	1.72	.19
		Controls	167	12.75 (2.54)	12.72 (2.95)						
	Logical Memory Delayed	Patients	379	7.46 (3.19)	7.21 (3.21)	369.1	<.0001	.035	.244	.354	.552
		Controls	167	13.29 (2.4)	13.34 (2.65)						
	CANTAB PAL (adjusted standard score)	Patients	291	−2.65 (3.84)	−2.77 (3.77)	53.89	<.0001	.001	.297	.092	.762
		Controls	123	.1592 (1.2)	.2654 (1.08)						
	Faces 1	Patients	355	8.69 (2.83	8.76 (2.77)	85.1	<.0001	.221	.639	.031	.861
		Controls	168	11.14 (2.64)	11.54 (2.88)						
	Faces2	Patients	355	9.2 (2.86)	9.34 (2.93)	46.5	<.0001	2.054	.152	.845	.358
		Controls	168	11 (2.46)	11.63 (2.84)						
Vigilant attention	CPT_IP (3 letters)	Patients	74	1.85 (1.01)	2.02 (.973)	–	–	1.457	.229	–	–
		Controls	0								
	IDED (8 shapes adjusted)	Patients	322	10.85 (10.65)	12.93 (10.97)	17.85	<.0001	5.16	.047	.042	.838
		Controls	157	7.05 (7.95)	9.39 (10.15)						
	IDED (6 shapes adjusted)	Patients	322	1.05 (2.85)	.812 (1.49)	2.53	.112	.204	.652	2.738	.099
		Controls	157	.381 (.652)	.814 (2.3)						

was strongest amongst those with a diagnosis of bipolar disorder ($p = 0.024$, partial eta squared = 0.060). These findings were confirmed in a two-group analysis, where having two copies of the risk allele was associated with significantly lower incongruence dimension ($p = 0.019$) and positive symptom factor ($p = 0.015$) scores, compared with having one or no copies of the risk allele in this psychosis sample. Partial eta squared for both scores is 0.007. The relationship between genotype and the scores for these measures (shown in Fig. 1) suggests an allele dosage effect.

Mean scores for each of the four cognitive domains (IQ, working memory, episodic memory and attention) by MIR-137 genotype group for cases and controls are presented in Table 2. As expected, patients performed below controls on all cognitive tests administered ($p < 0.0001$). MIR-137 genotype was not associated with differences in IQ, either as a main effect or as an interaction effect with case–control status. Analysis of the three allele groups (TT, GT, and GG) identified association between groups carrying 'T' risk allele and verbal episodic memory (Logical Memory, Immediate; $F = 1.16$, $p = 0.048$) and extradimensional set shifting (as measured by the IDED-ED scores) (attentional control phenotypes; $F = 3.23$, $p = 0.04$). In each case carrying the risk allele was associated with worse performance; there was no interaction effect with case/control status. Given the small number of homozygous risk carriers, these were repeated in a two-group analysis comparing the homozygous carriers of the 'T' risk allele with all other patients; both findings were confirmed.

4. Discussion

A common genetic variant at MIR-137 has recently emerged as a risk factor for schizophrenia. We investigated the role of the MIR-137 risk SNP (rs1625579) on psychosis symptom factors and dimensional measures of lifetime symptomatology. We identified association between the 'T' risk allele and lower scores for an OPCRIT-derived psychotic symptom factor. Carriers of the risk allele also scored lower on a lifetime measure of psychosis-symptom incongruity. This finding suggests that carriers of the MIR-137 risk allele are more likely to represent a subgroup of psychotic patients with fewer psychotic symptoms, where these symptoms are mood-congruent. There was no converse finding of an increased burden of negative symptoms, and there was no evidence that the variant influenced mood symptomatology directly within our cohort. One possible explanation is that this group represents patients defined by a particular molecular aetiology. Alternatively, the risk variant may have a modifying effect which increases risk of mood congruent psychotic symptoms among psychosis-spectrum patients, where psychotic symptoms are experienced.

While cognitive deficits are less prominent in bipolar disorder than in schizophrenia, where both global and specific cognitive deficits are described, a range of abnormalities have been reported including deficits in episodic and working memory, processing speed and sustained attention [2,4]. The cognitive deficits associated with MIR-137 in this study affected domains reported to be impaired in both disorders. Specifically, risk allele carriers did not show deficits in global function as measured by IQ, but did show subtle deficits in both episodic memory and attentional control. In both cases, the deficits were more prominent in a 2-groups comparison of homozygous risk carriers versus the other genotype groups combined. Previous work by our group suggested that deficits in attentional control disassociate from more general cognitive deficits within the schizophrenia population [7]. Whether the subtlety of these effects reflects this risk variant's particular association with an affective form of psychosis in which cognitive deficits are less pronounced, or simply reflect the modest cognitive effects of this variant remains to be elucidated. Further studies, incorporating functional MRI may be helpful in establishing the true strength of this effect.

Multiple statistical tests were performed in this study and the findings could reflect Type 1 errors. However, although a relatively large clinical sample ($n = 831$), our study was significantly underpowered to detect subtle clinical effects compared to large GWAS samples such as the PGC. We tried to control for the temporal instability of clinical symptomatology by using two different measures of psychopathology in a cohort of psychosis patients with generally well-established illness (mean duration of illness 19 years, SD 12 years). One measure captured the life-time presence of different symptoms (OPCRIT), while the other measured severity and frequency of illness episodes over time. Our psychosis sample was over-represented for schizophrenia cases ($n = 573$) and the life-time measure employed (BADDSs) was developed and validated for use in bipolar disorder subjects. Further studies using serial assessment of clinical symptoms and neurocognitive performance are warranted.

It is important to note that MIR-137 genotype was responsible for <1% of the variance in scores (based on the associated partial eta squared values) on the incongruity dimension and psychosis factor. This indicates that the common risk variant at MIR-137 does not have a clinically meaningful effect on either symptom profile or cognitive performance. In the Psychiatric GWAS Consortium (PGC) study, SNPs mapping to the 301 high-confidence predicted gene targets of MIR-137 were enriched for association signals with schizophrenia, compared with other genes of similar size or genetic marker density in the genome. Excluding the gene itself and the major histocompatibility complex region (MHC), 4 of 9 associated loci in a combined meta-analysis of schizophrenia and bipolar GWAS data had predicted MIR-137 target sites, i.e. TCF4, CACNA1C, CSMD1, and C10orf26 [9]. Further questions raised by this study, are whether having a greater burden of common risk variants from this gene network is associated with increased illness risk, the extent of this risk, and whether this maps a molecular subtype of psychosis characterized by less psychotic or incongruent psychotic symptomatology and subtle cognitive deficits.

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Disclosure

Professor Dinan has performed consultancy work for Alimentary Health. Other authors report no financial relationships with commercial interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2012.08.065.

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