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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