The miR-137 Schizophrenia Susceptibility Variant rs1625579 does not Predict Variability in Brain Volume in a Sample of Schizophrenic Patients and Healthy Individuals

Emma J. Rose,[1,2] Derek W. Morris,[1] Ciara Fahey,[1] Dara Cannon,[3] Colm McDonald,[3] Cathy Scanlon,[3] Sinead Kelly,[1,2] Michael Gill,[1,2] Aiden Corvin,[1,2] and Gary Donohoe[1,2,3]*

[1]Neuropsychiatric Genetics Group & Department of Psychiatry, Institute of Molecular Medicine, Trinity College Dublin, St. James Hospital, Dublin 8, Ireland

[2]Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland

[3]Clinical Neuroimaging Laboratory, Departments of Psychiatry, Anatomy & Psychology, National University of Ireland Galway, Galway, Ireland

The micro RNA 137 (miR-137) variant rs1625579 has been identified as a genome-wide significant risk variant for schizophrenia. miR-137 has an established role in neurodevelopment and may mediate cognitive dysfunction in schizophrenia. This role of miR-137 may be related to changes in brain morphology for risk-related genotypes; however this has not yet been delineated. Here we considered whether rs1625579 genotype was predictive of indices of brain structure in patients with schizophrenia and healthy controls. Structural magnetic resonance imaging (sMRI) data (i.e. 3T T1-TFE or 1.5T T1-MPRAGE) were acquired from 150 healthy controls and 163 schizophrenic patients. Two volumetric analyses that considered the impact of miR-137/rs1625579 genotype were carried out on sMRI data. In the first analysis, voxel based morphometry was employed to consider genotype-related variability in local grey and white matter across the entire brain volume. Our secondary analysis utilized the FIRST protocol in FSL to consider the volume of subcortical structures (i.e. bilateral accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus). Several brain regions in both analyses demonstrated the expected main effect of participant group (i.e. schizophrenics < controls), yet there were no regions where we observed an impact of rs1635579 genotype on brain volume. Our analyses suggest that the mechanism by which miR-137 confers risk for schizophrenia and impacts upon cognitive function may not be mediated by changes in local brain volume. However, it remains to be determined whether or not alternative measures of brain structure are related to these functions of miR-137.

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INTRODUCTION

A single nucleotide polymorphism (SNP), rs1625579 (G/T), within the microRNA 137 (miR-137) gene was identified as a risk variant

Emma J. Rose's present address is: is Center for Translational Research on Adversity, Neurodevelopment and Substance abuse (C-TRANS), Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

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*Corresponding Author: Gary Donohoe Professor of Psychology Millennium Arts Building National University of Ireland Galway Galway, Ireland
E-mail: gary.donohoe@tcd.ie

for schizophrenia in a genome-wide association study (GWAS) of more than 50,000 individuals [Schizophrenia Psychiatric Genome-Wide Association Study, 2011]. This variant, located on chromosome 1p21.3, was found to be the strongest predictor of schizophrenia risk in this GWAS analysis. MicroRNAs are small, noncoding RNA molecules that are involved in the expression of mRNAs. They are believed to play an important role in brain development and maturation, and miR-137 has been implicated in adult neurogenesis [Smrt et al., 2010].

It has been suggested that miR-137 is important in the neurodevelopmental trajectory in neuropsychiatric conditions such as schizophrenia [Perkins et al., 2007] and recent reports implicated miR-137 in aspects of behavior and brain function that may be important in the schizophrenia disease phenotype. For example, microdeletions on 1p21.3 comprising miR-137 may be associated with intellectual disability [Willemsen et al., 2011]. Similarly, the rs1625579 SNP seems to predict variability in schizophrenia phenotypes, such that carrying the risk allele (i.e. 'T') is associated with a subtype of schizophrenia marked by cognitive impairment [Green et al., 2012]. A recent study by our group further suggests that in patients diagnosed with schizophrenia, schizoaffective disorder, or bipolar affective disorder I, miR-137 is associated with mood congruent psychotic symptoms and may predict memory deficits in risk carriers [Cummings et al., 2013]. The rs1625579 SNP has also been linked to brain function in individuals at high risk of developing schizophrenia (i.e. the unaffected family members of individuals with schizophrenia, who are more likely to carry genetic variants that predict disease risk) [Whalley et al., 2012]. Whalley and colleagues found that during performance of a sentence completion paradigm there was a main effect of genotype on function in the medial frontal gyrus (i.e. risk (TT) < nonrisk (GG/GT). They also observed that individuals who were homozygous for the risk variant *and* were at high genetic risk for schizophrenia exhibited lower activations in the amygdala and pre/postcentral gyrus compared to non-risk controls.

These initial studies of rs1625579 suggest that this variant has an impact on cognition, behavior and brain functions that are relevant for schizophrenia. Yet to-date there has been little consideration of the impact of miR-137 on brain structure. Brain structure is related to function and behavior and is an excellent candidate intermediate phenotype for schizophrenia since it has been shown to be heritable [Glahn et al., 2007; Peper et al., 2007; Thompson et al., 2001], and is known to be altered in schizophrenia and related disorders [e.g., bipoloar disorder; Goldman et al., 2009; Goldman et al., 2008; Honea et al., 2008; McDonald et al., 2006]. Brain structure is also known to segregate with schizophrenia in families (McDonald et al., 2006; Moran et al., 2013) and there is overlap between genetic factors that are related to both schizophrenia and brain volume (van Haren et al., 2012). In addition, since miR-137 is postulated to play a role in neurodevelopment, variability in brain structure is potentially a key intermediate phenotype for the role of miR-137 variants that confer risk for schizophrenia. In other words, structural variability may constitute part of the pathway by which miR-137 influences brain function, behavior and disease risk. Here we considered whether rs1625579 was associated with brain morphology in patients with schizophrenia *and* healthy individuals. It was hypothesized that miR-137 risk status would be associated with variability (i.e., statistically significant increases and/or decreases) in regional gray (GM) and white matter (WM) volume. We also tentatively hypothesized that SNP-related structural variability would be seen in brain regions related to the function and behavioral consequences of rs1625579 (e.g. medial frontal gyrus, amygdala, hippocampus).

METHODS

Participants

Participants were right-handed, Irish (i.e. Irish paternal *and* maternal grandparents) adults who were recruited from the general population at two sites in Ireland (Galway and Dublin) though outpatient clinics (for patients) and local media advertising (for healthy participants). Participants were screened for MRI safety criteria, as well as scientific and ethical criteria for inclusion in neuroimaging. Healthy participant sampling at the Dublin site included individuals involved in the Trinity College Biobank project [as described elsewhere; Rose et al., 2012]. Participants provided written, informed consent in accordance with local ethics committee guidelines. The experimental sample consisted of 150 healthy individuals (mean age (years) = 33.49; 84 male) and 163 schizophrenia patients (mean age (years) = 38.51; 55 male). All patients were chronic, but stable, medicated outpatients, with a confirmed diagnosis. Individuals in both groups were included based upon the quality of T1 structural data and successful genotyping of the rs1625579 SNP. There were similar numbers of individuals included from each imaging site (i.e. Dublin: N = 159; Galway: N = 154), although a greater percentage of the control sample were imaged in Dublin (i.e. ≈80%), while the majority of patients underwent imaging in Galway (i.e. ≈74%).

Procedure

Genotyping. Genetics analysis was carried out using DNA obtained from blood samples or saliva samples that were collected using Oragene DNA self-collection kits (DNA Genotek). The rs1625579 SNP was genotyped using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems). The call rate for the Taqman genotyping was >95% and the samples were in Hardy-Weinberg Equilibrium ($P > 0.05$). In addition a small number of HapMap CEU DNA samples (www.hapmap.org) were genotyped for rs1625579 for quality control purposes and were all found to be concordant with available online HapMap data for this SNP. In the healthy participant sample there were 4 homozygous, non-risk ('GG') carriers, 41 heterozygous ('GT') carriers and 105 homozygous, risk ('TT') carriers. The genotype distribution was similar in schizophrenia patients, where the genotype distribution was: 2 'GG', 49 'GT' and 112 'TT'.

Magnetic resonance imaging (MRI). For participants imaged at the Dublin site, structural MRI sequences were acquired on a Philips Intera Achieva 3T MR system, with whole-brain imaging consisting of a T1-weighted image utilizing a TFE gradient echo pulse sequence (TE (ms) = 3.8; TR (ms) = 8.4; Flip angle (°) = 8; FOV = 230; Matrix = 256 × 256; 180 slices; slice thickness (mm) = 0.9; Voxel-size (mm^3) = 0.9 × 0.9 × 0.9). Participants who were scanned at the Galway site underwent imaging in a 1.5T Siemens Magnetom scanner, which involved acquisition of a T1-weighted MPRAGE structural image (TE (ms) = 4.38; TR (ms) = 1140; Flip

angle (°) = 15; FOV = 230; Matrix = 512 × 512 (k-space interpolation from 256 × 256); 160 slices; slice thickness (mm) = 0.9; Voxel-size (mm^3) = 0.45 × 0.45 × 0.9).

Data analysis

Voxel Based Morphometry (VBM) [Ashburner and Friston 2000]. VBM analysis was performed within SPM5 (http://www.fil.ion.ucl.ac.uk/spm) running under Matlab (v7.8; The MathWorks) and utilizing the VBM toolbox (v5.1; http://dbm.neuro.uni-hen.de/vbm). Individual volumes were visually inspected for scanner artifacts and gross anatomical abnormalities. Volumes that passed initial data quality control, were segmented into GM, WM and cerebrospinal fluid, without tissue priors and using a Hidden Markov Random Field weighting of 0.15. Segmented images were normalized using the DARTEL toolbox [Ashburner, 2007] in which GM and WM templates were created using standard parameters. Jacobian scaled ('modulated') warped tissue classes were subsequently created for both GM and WM for each subject. The resultant images were smoothed with an 8mm3 Gaussian kernel. Since the participant groups were not well matched for mean age (healthy participants < patients; $P < 0.001$) or gender distribution ($P < 0.001$) and to account for normal structural variation, age, gender and total GM or WM volume were included as co-variates in VBM analyses. For these analyses, we included subject data as normalized to native space (i.e. the DARTEL template) rather than a standard template, such as MNI. Subjects for sMRI included individuals in a range of developmental stages, including young, middle, and late adulthood, making normalization to a standard template inappropriate. All outcomes were corrected for multiple comparisons, and significance was defined as the voxel-wise threshold for family wise error (FWE) at $p_{CORRECTED} < 0.05$. Since non-uniform smoothness of VBM data can influence interpretation of these types of analysis [Ashburner and Friston, 2000; Worsley et al., 1999], determination of significance included a non-stationarity cluster extent correction, which utilized the random field theory version of cluster inference under non-stationarity [Hayasaka et al., 2004] and was implemented using the NS toolbox (http://fmri.wfubmc.edu/cms/NS-General).

Subcortical segmentation: FMRIB's Integrated Registration and Segmentation Tool (FIRST) [Patenaude et al., 2011]

As a complimentary analysis to the whole brain voxel-by-voxel analysis of VBM we also considered comparisons between genotypes on more gross anatomical segmentations, which had the advantage of significantly reducing the number of comparisons between groups. For this analysis we utilized the FIRST protocol in FSL. The procedure used for the FIRST segmentation of subcortical structures has already been described in detail [Patenaude et al., 2011]. In brief, the FIRST algorithm models the subcortical structures of interest as a surface mesh, using a Bayesian model that incorporates a training set of multiple images (i.e. 336 from a range of subject populations). Using the run_first_all routine in FIRST, the following bilateral areas were segmented: lateral ventricles, thalamus, caudate, putamen, accumbens, pallidum, hippocampus, and amygdala. Although the routine does involve segmentation of the brain stem, these segmentations were not reliably reproduced across subjects and so were excluded from analysis. The individual volume of each segmented region was then extracted using the fslstats function within FSL [Smith et al., 2004]. Regional volume estimates were used as the dependent variable in full factorial analysis modeling group (patients vs. controls) and miR-137 risk (GG/GT vs. TT) as fixed factors and age and gender as co-variates. These analyses were carried out in SPSS (version 21) and the results were corrected for multiple comparisons using a Bonferroni correction based upon the number of regions considered (i.e. 16 total).

RESULTS

Participant Demographics

Control participants were significantly younger than schizophrenia patients (i.e. $t_{(312)} = -3.85$, $P < 0.001$) and the control sample consisted of a great proportion of male participants (i.e. $\chi^2 = 17.81$, df = 1, $P < 0.001$; 56% vs. 32%). However, the groups did not differ with regards to rs1625579 genotype distributions ($P > 0.05$). Due to the relatively small number of homozygous 'G' individuals, imaging analysis focused on the comparison of individuals who carried either one or two copies of the non-risk 'G' allele (i.e. GG/GT) and those who were homozygous for the risk allele ('T'). There was no genotype-related variability in age or gender ($P > 0.05$).

VBM

There were schizophrenia-related reductions in brain volume in both GM and WM in a wide range of brain areas ($p_{CORRECTED} < 0.05$; see Supplementary Results for details). However, there were no areas in VBM analysis in which regional GM or WM varied as a function of miR-137/rs1625579 genotype. Similarly, genotype had no significant effect on total GM or WM or indices of total brain or intracranial volume.

Subcortical Segmentation/FIRST

Compared to healthy individuals there were schizophrenia-related reductions in volume bilaterally in the putamen (i.e. left: $F_{(1,312)} = 14.47$ & right: $F_{(1,312)} = 15.03$, $P < 0.001$) and accumbens (left: $F_{(1,312)} = 18.04$, $P < 0.001$ & right: $F_{(1,312)} = 9.47$, $P < 0.002$), and also in left hippocampus ($F_{(1,312)} = 11.42$, $P < 0.001$) and right caudate ($F_{(1,312)} = 11.86$, $P < 0.001$). Conversely, there were no subcortical regions where volume differed according to miR-137/rs1625579 genotype.

DISCUSSION

Here we sought to determine whether the recently identified schizophrenia-risk variant rs1625579 on the miR-137 gene was predictive of variability in brain volume. We considered both regional variations in GM and WM volume using VBM and the volume of a range of subcortical structures using the FIRST segmentation paradigm. While we found evidence to support well-established volumetric differences in brain structure between patients with schizophrenia and healthy individuals, we failed to find any regions where brain volume was predicted by miR-137/

rs1625579 genotype. This was true of both VBM and subcortical volume analyses. This suggests that the mechanism by which rs1652279 confers risk for schizophrenia is unlikely to be mediated by volumetric changes in brain structure.

Intriguingly, our results appear to contradict those of a recently published study by Lett and colleagues (Lett et al., 2013), which considered the impact of the rs16245579 variant on brain volume. This study suggested effects of the risk variant on hippocampal and ventricle volume that were patient-specific. While the studies both included schizophrenic patients and healthy individuals and were concerned with the impact of rs1625579 on brain volume, there are key methodological differences between the studies that may have contributed to this discrepancy. Firstly, our sample included a greater number of both controls and patients (i.e., patients: 92 vs. 163 and controls: 121 vs. 150). Secondly, the analysis in the Lett et al., study was limited to hippocampal and ventricle volumes, rather than the whole brain VBM and multiple segmentation approaches that we adopted; both of which required stricter corrections for multiple comparisons. Taking these factors into account there are two potential explanations for the between-study differences. On one hand the reduced participant numbers in the Lett et al study may have reduced power and resulted in a false positive outcome. Alternatively, the greater number of comparisons in our study may have been overly restrictive once we corrected for multiple comparisons, resulting in a false negative outcome. Further replication of both approaches in larger samples is warranted to clarify the nature of this discrepancy.

There are a number of factors that may have potentially contributed to the pattern of results in our study. Firstly, given the relatively small effect size corresponding to variants that increase risk for schizophrenia (i.e. rs1625579 OR = 1.12 (95% CI)) there remains the possibility that our study was not sufficiently powered to detect genotype-related differences in brain structure. We carried out a *post hoc* sensitivity analysis, which suggested that with 313 participants we would have total capability to detect moderate effects (e.g. Cohen's d >0.27); although our ability to detect small effects with this sample was somewhat more limited (e.g. 30% chance of detecting effects of d < 0.1). However, at more than 300 individuals, our sample was larger than many similar imaging genetics investigations and was in fact larger than some studies that have found genotype-related variability in brain structure for variants of similar risk magnitude [see Rose and Donohoe, 2012 for review]. Moreover, our sample size was larger than both the Lett et al. [2013] study and a recent fMRI investigation [Whalley et al., 2012] of this risk variant that did find evidence of an effect of miR-137/rs1652279 genotype on neuroimging intermediate phenotypes, suggesting that sample size/power may not have been the key mitigating factor in the negative outcome here.

Another consideration is the indices of brain structure that we employed here. It is possible that alternative measures of brain structure may have facilitated elucidation of the mechanisms by which miR-137 is associated with disease risk. For example, it has been suggested that cortical thickness measures may serve as a more genetically sensitive with greater power to determine the effects of risk variants for neuropsychiatric conditions [Winkler et al., 2010]. miR-137/rs1625579 may exert more subtle effects on brain structure than were detectable in our analysis; these may have been observable with a structural measure based on cortical thickness. While miR-137 is believed to be involved in neuronal development, what is less well established is the trajectory of potentially small genotypic effects and their interactions or associations with other genetic *and* environmental factors that are important in the development of the disease phenotype. Perhaps the impact of this variant may be more apparent in younger cohorts or those with a less complex phenotypic profile (e.g. less exposure to stressful life events, medications or other age-related comorbidities that likely impact brain structure). Alternatively, the effect of miR-137 on neural development may be so subtle that its effects are not apparent in the more gross volumetric anatomical measures employed here and instead may be more obvious in more refined indices of neuroanatomy, e.g. such as postmortem histological measures. It is also possible that non-volumetric measures of brain structure hold the key to understanding to role of mir-137/rs1625579 in disease risk. The observations of previous investigations of this variant suggest that its role in schizophrenia risk may reside in its impact on brain function, rather than structure, and related cognitive and behavioral processes. If so, alternative measures that relate more closely to functional alterations, e.g. measures of brain connectivity such as diffusion tensor imaging, may prove to be more relevant for delineating the mechanisms by which miR-137/rs1625579 confers risk for schizophrenia.

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TABLE 1. Demographic summary

	Healthy individuals (N = 150)	Schizophrenic Patients (N = 163)
Age /years[mean (s.d.)]	33.49 (13.07)	38.51 (10.84)
Gender (male: female)	84: 66	55: 111
rs1625579 genotype (GG: GT: TT)	4: 41: 105	2: 49: 112
Imaging site (Dublin: Galway)	121: 29	121: 38
Age of illness onset /years (mean)	n/a	Dublin: 23 Galway: 24
Duration of illness /years (mean)	n/a	Dublin: 20.32 Galway: 10

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SUPPORTING INFORMATION

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