Additive genetic risk for schizophrenia predicts widespread changes in brain structure

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Introduction

- The genetic variation in complex traits consists of many components due to additive, dominance, and interaction effects of genes.
- There is growing theoretical and empirical evidence that additive genetic variation accounts for the majority of genetic variance in complex traits (1).
- Here, we have examined the accrued genetic risk for schizophrenia among five risk markers for association with cortical thickness and white matter fractional anisotropy.
- All of the markers are downstream of the MECP2 pathway. MIR137, CACNA1C, and ZNF804A are strongly implicated in genome-wide association studies of schizophrenia (2,3). Furthermore, GAD1 and BNDF have been associated with cortical morphology within schizophrenia, and lower concentrations of the gene products have been observed in cortical and hippocampal regions of patients with schizophrenia (4-6).

Methods

Participants for Genetic Investigation of Neuroimaging Phenotypes:
- 89 patients with a diagnosis of schizophrenia or schizoaffective disorder and 109 healthy control subjects completed all imaging, and genetics protocols. (Table 1)

Table 1. Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Control (N=109)</th>
<th>Schizophrenia (N=89)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (M)</td>
<td>56.90%</td>
<td>50.50%</td>
<td>0.04</td>
</tr>
<tr>
<td>Females (F)</td>
<td>43.10%</td>
<td>49.50%</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA0 (years)</td>
<td>25.15</td>
<td>25.95</td>
<td>0.02</td>
</tr>
<tr>
<td>AIMS</td>
<td>0.99</td>
<td>2.38</td>
<td></td>
</tr>
<tr>
<td>PANSS</td>
<td>53.9</td>
<td>15.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Positive</td>
<td>14.01</td>
<td>5.70</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>85.99</td>
<td>94.30</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>25.45</td>
<td>6.78</td>
<td></td>
</tr>
</tbody>
</table>

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- There were no significant differences in the frequencies for any of the five markers between patients and healthy controls.
- No significant deviation from Hardy-Weinberg equilibrium in either group (p>0.05).

Disease Genetics

- There was no significant difference in the frequencies for any of the five markers between patients and healthy controls.

Results

- No significant deviation from Hardy-Weinberg equilibrium in either group (p>0.05).

Figure 1. Additive genetic risk predicts poorer white matter fractional anisotropy
- Greater additive risk score predicted reduced fractional anisotropy across multiple brain regions, and the effect was larger within schizophrenia patients. Areas coloured from red to yellow correspond to p-values ranging from 0.05 and lower following FDR correction for multiple comparisons at q=0.05.

Figure 2. Significant additive risk by diagnosis interaction for vertex-wide cortical thickness
- Schizophrenia subjects with greater additive risk have reduced cortical thickness. Areas coloured from blue to yellow correspond to p-values ranging from 0.05 and lower following FDR correction for multiple comparisons at q=0.05.

Conclusions

- Our study is the first to show that schizophrenia risk variants have an additive effect on white matter structure and cortical thickness.
- These findings suggest that our additive genetic risk model can predict a large effects on brain structure.
- Since we observed a significant risk by diagnosis interaction, we will follow up on our findings within schizophrenia patients.
- Next steps will be to investigate subphenotypes within schizophrenia such as cognitive functioning to test if these structural variants impact on clinical outcomes.

Literature