Exon Sequencing within Runs of Homozygosity in Patients with Schizophrenia

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Introduction

Background. Around 1.8% of the human population have schizophrenia, a severe mental disorder (Sklar, 2006). Those diagnosed with schizophrenia experience paranoia, hallucinations, and an overall loss of contact with reality. Studies of this psychiatric disease in families suggest that the disease has a strong genetic basis (O’Dushlaine et al., 2003; ISC, 2008). One reason for this is that the two genes being sequenced, Neurogranin (NRGN) and FEZ1, are involved in the development of neuropsychiatric disease. FEZ1 has an effect on the dendritic spines of neurons. Bundling and elongation within axon bundles, while NRGN is known to have a role in the development of neuropsychiatric disease. FEZ1 has an effect on the dendritic spines of neurons.

Materials and Methods

Before the FEZ1 and NRGN regions of the 8 schizophrenia samples could be sequenced, the isolated genes were amplified from the genomic DNA. After the genomic DNA derived from the Biological Samples Platform, it underwent purification, sequencing, and analysis.

Results and Conclusions

All 8 exomes of FEZ1 and NRGN were successfully sequenced.

- 7 SNPs were detected, 4 in FEZ1 and 3 in NRGN.
- All SNPs found in FEZ1 have been previously reported in dbsNP, while one SNV was found in NRGN.

Future 2: SNP location on FEZ1

In addition to the 7 SNPs in FEZ1, we find 3 other SNPs located on the chromosome 5 of our samples (Figure 3). However, these SNPs are not transmitted and their minor allele frequencies do not significantly differ from a CEPH control population (Figure 4).

Significant Findings

- SNPs rs2867457, a coding SNP, was observed by Yamada (2008) in a screen of a Japanese population, to have a frequency of 2% in schizophrenia cases, but 0.001% in control populations. In our study, the rare allele was found at a strikingly high frequency of 0.1875 in schizophrenia samples. Interestingly, the rare allele of rs2867457 will result in a change from the amino acid Aspartic Acid to Glutamic Acid (GAT-GAA) during translation.

- In conclusion, we were successful in identifying a rare variation that had a striking association with schizophrenia. Our results validate a novel strategy for detecting rare variations through targeted sequencing that is informed by GWAS results. We have deployed a novel strategy for detecting rare variations through targeted sequencing that is informed by GWAS results. Our approach was highly successful at identifying individual and locus enrichment for variation implicated in the etiology of schizophrenia and paving the way for the discovery of additional candidate loci.

Acknowledgments

Mary thanks to: Nick Sanchez, Tim Chamber, and Colm O’Dushlaine for their generosity; Megan Nichols, Rachel Woodside, and Alfonso Martinez for making the experience possible.

Oldham KG, Votava KH, and Shae Purcell for designing the experiment used in analysis.

Table 1. Summary of Detected SNPs

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Population</th>
<th>Region</th>
<th>Genotype frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEZ1</td>
<td>rs2867457</td>
<td>Non-Coding</td>
<td>FEZ1</td>
<td>0.1875</td>
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<td>rs597570</td>
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<td>NRGN</td>
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<td>0.0041</td>
</tr>
</tbody>
</table>

For more information, please contact the authors at the corresponding email addresses.

Figure 3: Summary of Detected SNPs

Figure 4: Minor Allele Frequencies

Figure 5: Minor Allele by sample

Additional resources:

- NM_033176.2, A7R5C, D07S1480, chr11:124,599,829-1
- NM_020822, A7R5C, D07S1480, chr11:125,305,648-1

For a detailed discussion on the significance of these findings, please refer to the authors’ original publications.

Future Directions

Further investigation:

- Genetic testing: A cost-effective, rapid follow-up genetic testing using dbSNP
- Data storage in a genome database
- Use of any protein variations caused by our SNPs

Long-term Application

- To understand genetic factors that confer a higher risk for developing schizophrenia
- To apply knowledge to discover new medicine to treat genetic diseases

Figure 2: SNP location on FEZ1

Figure 3: SNP location on NRGN

Figure 4: Minor Allele by sample

Figure 5: Minor Allele Frequencies