Association between the CHRM2 gene and Intelligence in a sample of 304 Dutch families

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I: INTRODUCTION

The muscarinic cholinergic receptor type 2 (CHRM2) gene is known to be involved in neuronal excitability, synaptic plasticity and feedback regulation of acetylcholine release, and has previously been implicated in higher cognitive processing. The gene encoding mAChR2 (CHRM2) on 7q31-35, appears to be predominantly expressed on presynaptic terminals of Ach containing neurons. Pharmacological and electrophysiological studies suggest these receptors serve as autoreceptors, playing a fundamental role in Ach (negative) release regulation.

II: AIM OF THE STUDY

We conducted a family-based association study combining tagging SNPs within the CHRM2 gene and cognition phenotypes in order to search for genetic variants that might play a role in cognitive phenotypic variation.

III: METHOD

Young Cohort | Adult Cohort
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Mean (SD) | 12.2 (0.16) | 37.3 (12.5)
M/ZM pairs | 41 | 20
D/ZM Trinucleotides | 28 | 11 (1)
D/MZ pairs | 56 | 14
D/ZF pairs | 25 | 22
DOS pairs | 27 | 17
Sib (Male/Females) | 20/37 | 2323
Incomplete Twin Pairs | 28/41 |
Total | 419 | 284

SUBJECTS - All twins and their siblings were part of two larger cognitive studies and were recruited from the Netherlands Twin Registry (NTR), which ensures population based sampling.

SAMPLING

Buccal swabs were obtained from 391 children. Blood samples were obtained from 276 adults. Cognitive ability was assessed with the Dutch adaptation of the WISC-R (Wechsler, 1986), and consisted of four verbal subtests (VIQ: similarities, vocabulary, arithmetic, and digit span) and two performance subtests (PIQ: block design, and object assembly). The Dutch adaptation of the WAISIII-R (Wechsler, 1997) was used to assessed IQ in the adult cohort (VIQ: information, similarities, vocabulary, and arithmetic; PIQ: picture completion, block design, matrix reasoning, and digit-symbol substitution).

IV: RESULTS

<table>
<thead>
<tr>
<th>N</th>
<th>rs2061174</th>
<th>97(AG-AA), 64(GG-AG), 15(GG-AA)</th>
<th>rs324640</th>
<th>64(GG-AG), 15(GG-AA)</th>
<th>rs324650</th>
<th>64(GG-AG), 15(GG-AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIQ</td>
<td>175</td>
<td>3.3 (p&lt;.05)</td>
<td>3.7 (G)</td>
<td>0.2 (G)</td>
<td>3.7 (G)</td>
<td>0.2 (G)</td>
</tr>
<tr>
<td>VIQ</td>
<td>175</td>
<td>0.4</td>
<td>1.2 (G)</td>
<td>0.0</td>
<td>1.2 (G)</td>
<td>0.0</td>
</tr>
<tr>
<td>FSIQ</td>
<td>174</td>
<td>2.4</td>
<td>2.3 (G)</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>rs324640</td>
<td>PIQ</td>
<td>209</td>
<td>7.7 (p&lt;0.01)*</td>
<td>3.7 (G)</td>
<td>5.2 (p&lt;0.18)</td>
<td>1.8 (G)</td>
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<tr>
<td>VIQ</td>
<td>209</td>
<td>1.9</td>
<td>2.5 (G)</td>
<td>1.2</td>
<td>1.2 (G)</td>
<td>1.1 (G)</td>
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<tr>
<td>FSIQ</td>
<td>209</td>
<td>4.8 (p&lt;0.01)*</td>
<td>3.1 (G)</td>
<td>2.9</td>
<td>2.9</td>
<td>1.4 (G)</td>
</tr>
<tr>
<td>rs324650</td>
<td>PIQ</td>
<td>193</td>
<td>12.1 (p&lt;0.001)*</td>
<td>4.6 (T)</td>
<td>6.0 (p&lt;0.05)</td>
<td>1.9 (T)</td>
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<tr>
<td>VIQ</td>
<td>193</td>
<td>3.9 (p&lt;0.06)</td>
<td>3.6 (T)</td>
<td>1.8</td>
<td>1.8</td>
<td>1.4 (T)</td>
</tr>
<tr>
<td>FSIQ</td>
<td>191</td>
<td>8.0 (p&lt;0.01)*</td>
<td>4.1 (T)</td>
<td>4.0 (p&lt;0.05)</td>
<td>1.7 (T)</td>
<td></td>
</tr>
</tbody>
</table>

* statistically significant based on 1000 Monte-Carlo Permutations

Table 1 - N denotes the number of individuals. For the within-family association test it denotes the number of individuals informative for the within-family association, i.e. those individuals who have siblings with different genotypes.

Figure 1 – Observed mean difference in IQ scores between siblings (i.e. within family pairs) with different genotypes for those SNPs in the CHRM2 gene that show a significant association.

VI: FUTURE PLANS

Functional studies, in combination with animal knock-out/in models, might provide more insight into the complex interplay among functional non-coding variants and cognitive ability.