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 electro-physiological 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
Mean (SD)	12.2 (0.16)	37.3 (12.5)
MZM pairs	41	20
DZM (DM Triplet) pairs	28	11(1)
MZF pairs	56	14
DZF pairs	25	22
DOS pairs	27	17
Sibs (Males/Females)	28/27	23/23
Incomplete Twin Pairs (Males/Females)		18/41
Total	409	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).

V: CONCLUSION

Identifying genes for variation in the range of normal intelligence could provide important clues to the genetic etiology of disturbed cognition in e.g. autism, reading disorder, and ADHD.
Cholinergic neurotransmission of muscarinic acetylcholine receptor genes (*CHRM*) has been implicated in higher brain cognitive functions such as attention, learning and memory.
After testing 47 extra tag-SNPs within the CHRM2 gene, the T allele of a non-coding variant (rs324650) was associated with an increase of 4.6 PIQ points, remaining significant at *p< .001* level after correction for multiple testing. Genetic variance of this particular polymorphism explains 2% of the cognitive phenotypic variance.
Genetic effect sizes based on the within family effects were 1.5 to 2.5 times as large as the population-based effect sizes, suggesting that population stratification resulted in an underestimation of the genuine allelic effect

IV: RESULTS

		N	χ^2 (nominal p-value)	Genotypic effect (increaser allele)	N	χ^2 (nominal p-value)	Genotypic effect (increaser allele)
rs2061174	PIQ	175	7.3 (*p*<.01)	3.7 (G)	648	9.0 (*p*<.01)	2.4 (G)
	VIQ	175	0,4	1.2 (G)	648	0.0	0.2 (G)
	FSIQ	174	2,4	2.3 (G)	644	2.3	1.4 (G)
rs324640	PIQ	209	7.7 (*p* <.0.1)*	3.7 (G)	640	5.2 (*p*<.05)	1.8 (G)
	VIQ	209	1,9	2.5 (G)	640	1.2	1.1 (G)
	FSIQ	207	4.6 (*p*<.01)	3.1 (G)	636	2.9	1.4 (G)
rs324650	PIQ	193	12.1 (*p*<.001)*	4.6 (T)	629	6.0 (*p*<.05)	1.9 (T)
	VIQ	193	3.9 (p<.05)	3.6 (T)	629	1.8	1.4 (T)
	FSIQ	191	8.0 (p<.01)*	4.1 (T)	625	4.0 (*p*<.05	1.7 (T)

* 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.

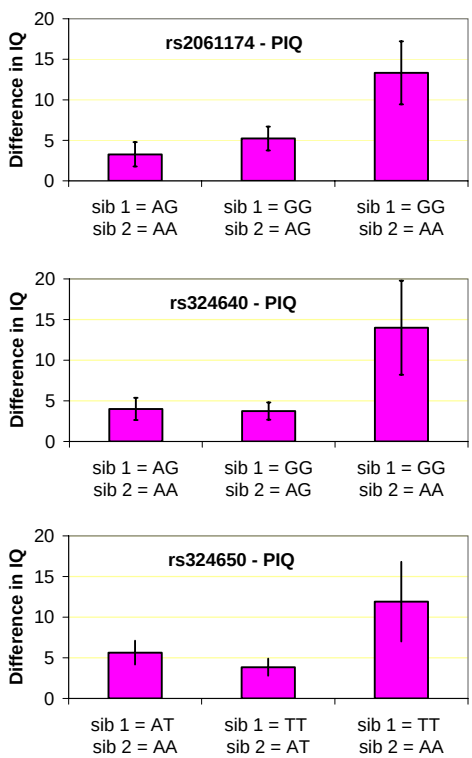

Figure 1 – Observed mean difference in IQ scores between siblings (i.e. within family pairs) with different genotypes for those SNPs in the CHRM2 gene that show a significant association.

Note: Sibling pairs include DZ pairs and non-twin sibling pairs. The number of pairs on which the difference scores are based is: rs2061174: 97(AG-AA), 64(GG-AG), 15(GG-AA); rs324640: 87(AG-AA), 97(GG-AG), 9(GG-AA); rs324650: 75(AG-AA), 98(GG-AG), 11(GG-AA).

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.