Behav Genet (2007) 37:265–272
DOI 10.1007/s10519-006-9131-2

ORIGINAL PAPER

Association of *CHRM2* with IQ: Converging Evidence for a Gene Influencing Intelligence

Danielle M. Dick · Fazil Aliev · John Kramer · Jen C. Wang · Anthony Hinrichs · Sarah Bertelsen · Sam Kuperman · Marc Schuckit · John Nurnberger Jr · Howard J. Edenberg · Bernice Porjesz · Henri Begleiter · Victor Hesselbrock · Alison Goate · Laura Bierut

Received: 12 July 2006 / Accepted: 9 November 2006 / Published online: 12 December 2006

Abstract The cholinergic neurotransmitter system is thought to be involved in many aspects of memory, attention, and higher cognition. In the Collaborative Study on the Genetics of Alcoholism (COGA) sample, we have previously reported linkage and association to the cholinergic muscarinic 2 receptor gene (*CHRM2*) on chromosome 7 with evoked EEG oscillations (Jones et al. 2004), providing evidence that this gene may be involved in human brain dynamics and cognition. In addition, a small number of genetic markers were genotyped in *CHRM2* in the Minnesota Twin and Family Study (Comings et al. 2003) and a Dutch family study (Gosso et al. 2006, in press) and both research groups found evidence that this gene may be involved in intelligence. In the COGA sample, we have extensively genotyped SNPs within and flanking the *CHRM2* gene. We find evidence of association with multiple SNPs across *CHRM2* and Performance IQ, as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R). These results remain significant after taking into account alcohol dependence and depression diagnoses in the sample.

Keywords Intelligence · IQ · *CHRM2* · Cognitive ability · Genetics · Association analyses

Edited by Danielle Posthuma

Henri Begleiter—Deceased

D. M. Dick (✉) · F. Aliev · J. C. Wang · A. Hinrichs · S. Bertelsen · A. Goate · L. Bierut
Department of Psychiatry, Washington University in St. Louis, 660 South Euclid Ave., Box 8134, St. Louis, MO 63130, USA
e-mail: dickd@psychiatry.wustl.edu

F. Aliev
Ankara University, Ankara, Turkey

J. Kramer · S. Kuperman
University of Iowa, Iowa City, IA, USA

M. Schuckit
University of California at San Diego, San Diego, CA, USA

J. Nurnberger Jr · H. J. Edenberg
Indiana University, Indianapolis, IN, USA

B. Porjesz · H. Begleiter
SUNY Health Science Center at Brooklyn, Brooklyn, NY, USA

V. Hesselbrock
University of Connecticut School of Medicine, Farmington, CT, USA

Introduction

A substantial body of literature from twin, family, and adoption studies documents significant genetic effects on human intelligence (Bouchard and McGue 1981). Heritability estimates range from 40 to 80%, and meta-analyses suggest an overall heritability of ~50% (Devlin et al. 1997; McGue et al. 1993). Although single genes have been identified that cause profound mental disabilities (Flint 1999), the identification of specific genes that contribute to the variation in intelligence across the full distribution of scores has been difficult. However, several recent publications have reported genome-wide linkage scans of IQ (Dick et al. 2006; Luciano et al. 2006; Posthuma et al. 2005), as well as related cognitive traits (Buyske et al. 2006). Importantly, some of the regions of linkage, such as on

chromosome 6p, have replicated across studies (Dick et al. 2006; Posthuma et al. 2005).

A complementary strategy that has been employed to identify genes involved in intelligence is the candidate gene approach. This strategy has a longer history in the search for genes that contribute to variation in human intelligence. Although positive reports of association have been reported for several genes, (e.g., Cathepsin D, CTSD, (Payton et al. 2003); IGF2R, (Chorney et al. 1998)), thus far, there has not been widespread success in replicating reported associations (e.g., (Hill et al. 2002)).

One proposed candidate gene is the cholinergic muscarinic 2 receptor gene (*CHRM2*). Muscarinic acetylcholine receptors (mAchRs) belong to a family of G-protein coupled receptors that activate a multitude of signaling pathways important for modulating neuronal excitability, synaptic plasticity and feedback regulation of acetylcholine release (Volpicelli and Levey 2004). These receptors are expressed in the central and peripheral nervous system (among other places, including muscles and glands). Importantly, there is evidence that muscarinic receptors are involved in many brain functions, such as learning and memory. In the Collaborative Study on the Genetics of Alcoholism sample (COGA), we have found evidence of both linkage and association with *CHRM2* and evoked brain oscillations elicited using the visual oddball paradigm (Jones et al. 2004). In this task, subjects are presented with three types of visual stimuli: target (the letter X), non-target (squares), and novel (a different colored geometric figure on each trial). Subjects are asked to respond to the target stimulus by pressing a button. Interestingly, the association with *CHRM2* was only observed with oscillations evoked in response to target, but not non-target, stimuli, suggesting that *CHRM2* may be involved in higher cognitive processing (Jones et al. 2004).

CHRM2 was also associated with IQ, as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R), in a preliminary report using data from the parents of twins from the Minnesota Twin and Family Study (Comings et al. 2003). A single SNP was genotyped in the 3′ UTR region of *CHRM2*, and a significant linear increase in IQ was observed across the three genotypes. Recently, Posthuma and colleagues have extended this association by genotyping three tagging SNPs across *CHRM2* in a sample of Dutch families (Gosso et al. 2006, in press). Using family-based methods, significant association was observed with IQ, with the strongest evidence of association with rs324650 and Performance IQ.

In the Collaborative Study of the Genetics of Alcoholism sample, we have conducted extensive genotyping across *CHRM2* (Wang et al., under review). Here, we report family-based association analyses of *CHRM2* and Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) as measured by the Wechsler Adult Intelligence Scale-Revised. To our knowledge, this study represents the most thorough investigation of the relationship between *CHRM2* and different components of IQ to date.

Methods

Sample

Families were identified through probands at local inpatient and outpatient alcohol dependence treatment centers at six sites across the United States: Indiana University, State University of New York Health Science Center, University of Connecticut, University of Iowa, University of California/San Diego, and Washington University, St. Louis. The institutional review boards of all participating institutions approved the study. Probands were invited to participate if they had a sufficiently large family (usually sibships >3 with parents available) with two or more members in any of the COGA catchment areas (Reich 1996). Families that had at least two affected first degree relatives in addition to the proband (excluding probands who were the offspring of two affected parents) were invited to participate in the genetic study. In these families, all first degree relatives of affected individuals and connecting family members were assessed, along with their mates if the union had produced offspring. Second and third degree relatives in the families were assessed when they were considered to be informative for genetic linkage studies. All individuals were administered the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview (Bucholz et al. 1994; Hesselbrock et al. 1999). Psychiatric diagnoses (used as a covariate in some analyses, as detailed below) were determined using computerized algorithms of SSAGA interview responses. Alcohol dependence was defined by the presence of a DSMIII-R diagnosis and Feighner definite criteria. Lifetime depression was assessed using DSMIIIR criteria.

A subset of the COGA participants completed the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The WAIS (Wechsler 1981, 1997) is a traditional intelligence test with high test-retest reliability, stability across different age spans, concurrent and predictive validity, and substantial heritability (Bouchard and McGue 1981). Due to time restrictions, not all subtests of the WAIS were administered; rather, we selected

those subtests that would provide a good approximation of Verbal IQ (VIQ) and Performance IQ (PIQ). Thus, our battery consisted of five Verbal subtests (Information, Similarities, Vocabulary, Comprehension and Digit Span) and four Performance subtests (Picture Completion, Block Design, Object Assembly and Digit Symbol). Although the WAIS-R was part of the original COGA assessment battery, not all COGA sites were able to provide appropriate training and supervision of the planned neuropsychological (including intelligence) testing. Further, many subjects could not be tested due to the time requirements for other parts of the COGA assessment battery. The data included here represent those subjects who were tested and whose test batteries were appropriately supervised. A subset of scores were flagged for further review based on a considerable difference in VIQ and PIQ scores (22 or more points (Iverson et al. 2001; Matarazzo and Herman 1984)) and/or a FSIQ score that was outside of the range defined by that individual's VIQ and PIQ scale scores. The raw data was reviewed in these cases, and the scores were corrected or, in some cases, excluded ($N = 38$) where further review provided indication that external factors may have unduly influenced their test performance (e.g., head injury with loss of consciousness, extremely heavy, long-term alcohol or drug use, marked vision, motor, or hearing problems).

For the association analyses reported here, a total of 200 families, containing 2,158 individuals ($N = 1062$ females, 1,096 males) were available for analysis. Of the 200 families, 168 were European-American, 26 were African-American, 2 were Pacific Islanders, and 4 were of mixed ethnicity. Of the 2,158 individuals, 1,708 had genotype data, 1,124 had phenotype data, and 1,113 had both genotype and phenotype data. The mean IQ among founders in the sample was 100 for all scales, comparable to national general population norms. The means in the full sample were 97.19 (sd = 12.98), 98.49 (sd = 12.90) and 96.88 (sd = 13.58) for FSIQ, PIQ and VIQ, respectively. The correlation between FSIQ and PIQ was 0.85, between FSIQ and VIQ, 0.93, and between the VIQ and PIQ subscales, 0.62. This pattern of correlations roughly approximates the respective correlations reported in the WAIS-R standardization sample (WAIS-R Manual, p. 46), 0.91, 0.95, and 0.74, and in the more recent, revised WAIS-III/WMS-III Manual (2002, p. 78), 0.92, 0.95, and 0.75.

Genotyping and analysis

Publicly available databases, dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) and HapMap (http://www.hapmap.org), were used to identify SNPs within and flanking the *CHRM2* gene. In addition, a number of novel SNPs were identified by sequencing (Wang et al. under review). We genotyped 27 SNPs within and flanking *CHRM2*; Fig. 1 shows the location of the SNPs in the gene. SNPs were selected to cover the single coding exon, as well as all five exons in the promoter region and a region in intron 3 that is conserved across multiple species. The minor allele frequency was >0.10 in all cases (average = 0.45). Genotyping was done with a modified single nucleotide extension reaction, with allele detection by mass spectroscopy [Sequenom MassArray system; Sequenom, San Diego, CA]. All genotypic data were checked for Mendelian inheritance of marker alleles with the USERM13 (Boehnke 1991) option of the MENDEL linkage computer programs, which was then used to estimate marker allele frequencies. Trio data from Caucasian individuals genotyped in the COGA dataset was entered into the program Haploview (Barrett et al. 2005) to examine the linkage disequilibrium structure of the genotyped SNPs. Six LD blocks were identified in our dataset, with several SNPs located in interblock regions. Information about the LD block structure of the SNPs is included in Table 1. Additional details about the genotyping and LD structure across the gene are presented in (Wang et al. under review).

Association was evaluated with the Quantitative Pedigree Disequilibrium Test (QPDT) using the QPDTPHASE program contained in the UNPH-

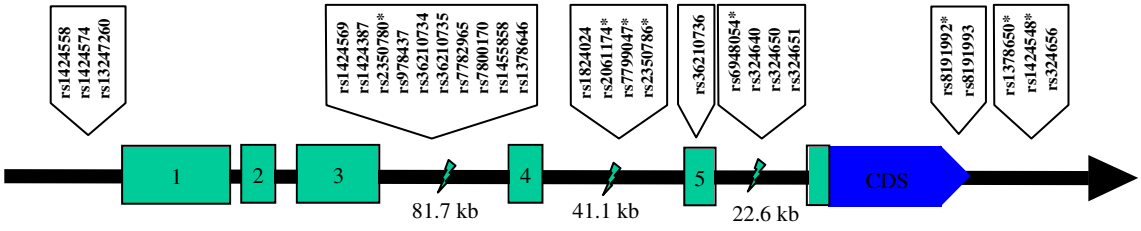

Fig. 1 Location of genotyped SNPs within and flanking the *CHRM2* gene. SNPs yielding *P*-values <0.05 with PIQ indicated with an asterisk (*). Green boxes indicate exons. Blue box indicates the coding region of *CHRM2*

Table 1 *P*-values associated with family-based association tests for Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), and residual scores of PIQ after regressing on alcohol dependence and depression

SNP	Gene Location	LD Block Location*	NCBI Position	FSIQ	VIQ	PIQ	PIQ-residual
rs1424558		Block 1	135988926	0.238	0.259	0.417	0.462
rs1424574		Block 1	136006288	0.212	0.359	0.368	0.460
rs13247260	upstream of exon 1		136010518	0.481	0.761	0.331	0.500
rs1424569			136026671	0.254	0.403	0.407	0.599
rs1424387		Block 2	136046865	0.988	0.619	0.526	0.263
rs2350780		Block 2	136050224	0.100	0.493	**0.016**	**0.016**
rs978437			136071433	0.569	0.348	0.748	0.393
rs36210734		Block 3	136080468	0.725	0.753	0.527	0.775
rs36210735		Block 3	136080901	0.217	0.478	0.092	0.100
rs7782965		Block 3	136081388	0.802	0.570	0.126	0.123
rs7800170		Block 3	136081575	0.363	0.594	0.174	0.121
rs1455858		Block 3	136088958	0.785	0.548	0.115	0.133
rs1378646	intron 3–4	Block 3	136092256	0.944	0.471	0.236	0.213
rs1824024		Block 3	136100949	0.644	0.707	0.077	0.071
rs2061174		Block 4	136118655	0.311	0.829	**0.016**	**0.017**
rs7799047		Block 4	136128813	0.431	0.772	**0.023**	**0.027**
rs2350786	intron 4–5	Block 4	136133825	0.317	0.731	**0.016**	**0.025**
rs36210736	exon 5	Block 5	136134189	0.129	0.079	0.969	0.603
rs6948054		Block 5	136138056	0.498	0.751	**0.041**	**0.043**
rs324640			136146251	0.642	0.924	0.272	0.238
rs324650		Block 6	136150916	0.785	0.967	0.454	0.409
rs324651	intron 5–6	Block 6	136156516	0.854	0.637	0.851	0.635
rs8191992			136158563	0.158	0.512	**0.036**	**0.042**
rs8191993	3′UTR		136158818	0.284	0.650	0.186	0.250
rs1378650			136162406	0.148	0.473	**0.028**	0.052
rs1424548			136167015	0.169	0.465	**0.037**	**0.035**
rs324656	downsteam of exon 6		136171367	0.355	0.556	0.275	0.380

Note: *P*-values < 0.05 are indicated in bold

* SNPs without a block number listed were located between blocks (Wang et al. under review)

ASED software suite (Dudbridge 2003). QPDT-PHASE implements the quantitative trait PDT described in Monks & Kaplan (Monks and Kaplan 2000), with extensions to deal with haplotypes and missing data. The null hypothesis is no linkage or no association, under which the trait and genotypes are uncorrelated. The covariance is estimated within each family and the estimates combined across the dataset by the central limit theorem. We tested for association with each of the SNPs genotyped in *CHRM2* and FSIQ, PIQ, and VIQ.

Results

Table 1 presents results from association analyses between all genotyped SNPs across *CHRM2* and each of the three IQ scores. Eight SNPs across *CHRM2* yielded evidence of association with PIQ at $P < 0.05$. We have previously observed association between *CHRM2* and alcohol dependence and depression in the COGA sample (Wang et al. 2004). Accordingly, there was some concern that the association between *CHRM2* and PIQ might be influenced by the association between *CHRM2* and these two psychiatric disorders in the COGA sample. PIQ is significantly associated with alcohol dependence in the sample ($r = -0.08$, $P = 0.01$), although the magnitude of the correlation is small. Nevertheless, for PIQ, we conducted association tests on residuals, after regressing on the alcohol dependence and depression phenotypes that also yielded evidence of association in the region (Wang et al. 2004). The association with PIQ remained significant (Table 1). We note that the correlation was not significant between the other IQ scales and alcohol dependence ($r = -0.05$, $P = 0.08$ for FSIQ; and $r = -0.01$, $P = 0.79$ for VIQ), and none of the IQ scales were significantly associated with depression ($r = 0.006$, $P = 0.85$ for FSIQ; $r = -0.01$, $P = 0.64$ for PIQ; and $r = 0.02$, $P = 0.45$ for VIQ). No SNPs in *CHRM2* were associated with FSIQ or VIQ.

For each of the SNPs significant at $P < 0.05$ with PIQ, Table 2 reports the absolute mean difference in PIQ for individuals carrying each allele and for individuals with each genotype. The nucleotides encoded by allele 1 and 2 are also shown. Allelic mean differences in PIQ ranged from 0.98 to 2.26 points; genotypic mean differences (i.e., the difference

Table 2 Absolute mean difference in Performance IQ score by allele and by genotype for each of the SNPs showing evidence of association at $P < 0.05$

SNP	Alleles (1/2)	1	2	Mean Allelic Difference	1-1	1-2	2-2	Mean Genotypic Difference
Rs2350780	A/G	97.05	98.85	1.79	96.59	98.02	100.15	3.56
Rs2061174	C/T	96.88	98.13	1.25	96.19	97.34	98.49	2.29
Rs7799047	C/G	98.30	96.57	1.73	98.67	97.41	95.42	3.24
Rs2350786	A/G	96.25	98.26	2.01	95.62	96.63	98.84	3.22
Rs6948054	A/G	97.05	98.03	0.98	96.73	97.27	98.36	1.63
Rs8191992	A/T	99.03	96.77	2.26	101.35	97.31	96.43	4.92
Rs1378650	C/T	97.29	98.29	1.00	97.05	97.68	99.08	2.03
Rs1424548	A/G	98.36	97.25	1.11	97.90	98.65	96.42	1.48

between individuals homozygous for each allele, 1/1 compared to 2/2) ranged from 1.48 to 4.92 PIQ points.

The SNPs that show evidence of association span several haplotype blocks in the gene. For haplotype analysis, we selected 3 SNPs based on the SNPs showing evidence of association and the pattern of LD across the gene. We included in the haplotype: rs2350780, the sole associated SNP in intron 3–4, located in LD block 2; rs2061174 (the associated SNP in intron 4–5, LD block 4, which was also genotyped in the Posthuma study); and rs8191992, the SNP yielding the strongest genotypic effect, located in the 3′ UTR, that was also genotyped in the Comings et al study. The results of this haplotype analysis are presented in Table 3. The global p-value was not significant ($P = 0.17$); however, we note that this test had limited power because, by chance, the haplotype comprised of the 3 alleles that are associated with decreased PIQ at the three SNPs and the haplotype comprised of the 3 alleles associated with increased PIQ at the three SNPs each have a low frequency (0.06 and 0.02, respectively). However, we note that the mean PIQ associated with these haplotypes is in the direction predicted. Though these results should be interpreted cautiously due to the small sample size, the mean PIQ associated with the haplotype comprised of the three decreaser alleles was 85, and the mean PIQ associated with the haplotype comprised of the three increaser alleles was 103. All other haplotypes were associated with mean PIQ scores in the range of 96.4–100.6.

Discussion

This paper reports a comprehensive analysis of the *CHRM2* gene as it is related to IQ scores measured by the WAIS-R. We find evidence for association between multiple SNPs in *CHRM2* and PIQ, providing further support for the previous reports of association between variants in *CHRM2* and IQ in the Minnesotan sample (Comings et al. 2003) and Dutch sample (Gosso et al. 2006, in press). The SNPs genotyped in those previous reports were included among the more extensive SNP panel genotyped in our sample. Interestingly, the one SNP genotyped by Comings and colleagues (rs8191992) was one of the SNPs that yielded evidence of association in our sample as well, with this SNP associated with the largest mean difference in PIQ scores (4.92 points across genotypes) in our sample. All three SNPs genotyped by Posthuma and colleagues (rs2061174, rs324640, and rs324650) yielded evidence of association in the Dutch family-based sample, with

Table 3 Haplotype analyses for three SNPs showing association with PIQ, and spanning different LD blocks across CHRM2: rs235780, rs2061174, rs8191992

Haplotype	Z	*P*-value	Gametes	Frequency	Mean PIQ
1-1-1	–1.27	0.20	63	0.04	97.52
1-1-2[a]	–0.12	0.90	97	0.06	84.98
1-2-1	0.58	0.56	229	0.13	97.66
1-2-2	–2.17	0.03	864	0.50	97.66
2-1-1	1.43	0.15	257	0.15	100.60
2-1-2	1.62	0.10	59	0.03	96.42
2-2-1[b]	0.66	0.51	38	0.02	103.00
2-2-2	0.26	0.80	121	0.07	99.00

Global test: chi-square = 10.34, $P = 0.17$

[a] haplotype comprised of decreaser alleles across the 3 SNPs

[b] haplotype comprised of increaser alleles across the 3 SNPs

the strongest association observed with rs324650 in that study. The SNP rs2061174 also yielded evidence of association with PIQ in our sample; however, the other two SNPs were not significantly associated. These findings are consistent with the actual functional variant being in LD with the associated SNPs in these studies, with LD structure varying across the populations. It is also possible that there are multiple variants in *CHRM2* that contribute to variation in IQ. The associated SNPs in the Posthuma study were located in intron 4–5 and intron 5–6. Consistent with these findings, we also observe significance with SNPs in both of these regions. However, the SNP yielding significance in the Comings study, and which also yields evidence of association in the COGA sample, is located in the 3′ UTR of the gene. In addition, we find evidence of association with SNPs located in introns 3–4 and downstream of intron 6 with the more extensive genotyping conducted across this region in the COGA sample. Thus, the association does not appear to be limited to a single genomic region. Additionally, the associated SNPs span several haplotype blocks in the gene. To attempt to further understand the association, we conducted a haplotype analysis comprised of associated SNPs located in different genomic regions and LD blocks across *CHRM2*. The haplotypes comprised of the three decreaser alleles and the three increaser alleles, respectively, showed the most extreme spread in PIQ scores, ranging from 85 to 103 at either extreme. We believe these results are consistent with the possibility that there are multiple variants in *CHRM2* that influence PIQ. If the different associated SNPs were simply all tagging a single mutation within the *CHRM2* gene impacting PIQ, we would have expected a haplotypic difference in PIQ scores that more closely paralleled the difference observed with the individual SNPs.

It is also of note that the SNPs yielding evidence of association with alcohol dependence, depression, and IQ in the COGA sample are not entirely overlapping. These findings are of particular interest as the muscarinic receptor genes appear to show complex transcriptional regulation and alternative splicing patterns. In a paper examining the transcriptional regulation of the *CHRM2* gene in human tissue culture (from airway smooth muscle), *CHRM2* exhibited considerable variability, with eight different mRNA transcripts observed and multiple transcription start sites identified (Fenech et al. 2004). In addition, there is suggestion based on work done in chicks that transcripts derived from different cells may exhibit different upstream arrangements (Rosoff et al. 1996). Currently it is unknown to what extent this alternative splicing is present in human brain tissue, but the studies that have been conducted in other species and other human tissues suggest that transcriptional regulation is likely. The functional implications of the alternatively spliced transcripts are unclear. However, the considerable variability observed in the *CHRM2* gene, and the association findings observed across different parts of the gene with different phenotypes suggests that alternative splicing of this gene may be differentially involved in various outcomes, ranging from psychiatric problems to general variation in cognition.

Finally, we note that these results should be interpreted cautiously, as the association findings are only marginally significant, given multiple testing. Our confidence in the results is bolstered by the multiple SNPs associated, and consistency with the previous studies, in terms of the SNPs yielding association, the specificity of the association with PIQ (consistent with the Gosso report), and the magnitude of the associated effect size. In addition, the consistency between the individual SNP results and the haplotype results further supports the idea that *CHRM2* is involved in performance IQ in this sample. Nevertheless, these results should be interpreted in the context of the aforementioned limitation.

In conclusion, these analyses provide further support for a role of *CHRM2* in aspects of cognition and intelligence. The genetics of intelligence has been a widely studied and hotly debated area of research; after much work and early difficulties with replication (Plomin et al. 2001), there is now consistent evidence from three independent studies that variants in *CHRM2* appear to be involved in normal variation in human intelligence, as measured by IQ scores. To our knowledge, this is the first gene yielding consistent evidence of association with IQ across multiple studies conducted by independent research groups. The results from individual SNP analyses are consistent with this being a gene of small effect influencing intelligence, a finding that is further corroborated by the failure to detect significant linkage in this region in either of the genome scans of IQ (Dick et al. 2006; Posthuma et al. 2005), although there was some suggestion of linkage in the region in the Dutch sample. The greatest increase in PIQ was 4.92 points in the COGA sample, observed with rs8191992. This is strikingly similar to the Minnesotan sample, where there was a spread of 4.06 IQ points across the three genotypes associated with rs8191992. This finding also closely parallels the Dutch report, in which the most significant SNP was associated with an increase of 4.6 IQ points. We note that this effect size is remarkably consistent, despite the overall mean differences in IQ

observed between the COGA sample and the Dutch and Minnesotan samples (with a small reduction in mean IQ scores in the COGA sample, likely due to ascertainment based on dense alcohol dependence in the families). However, results from our haplotype analysis, which incorporated information across multiple associated SNPs in the gene, suggested that multiple variants in *CHRM2* may contribute to variation in IQ. This possibility will need to be explored further in independent studies that genotype multiple variants across *CHRM2*. In addition, future work should be directed at understanding the component processes by which *CHRM2* is involved in cognition and intelligence, as the data from the Dutch and COGA samples (which show association limited to PIQ; no information on the IQ subscales was given in the Comings paper) suggest that the gene may be more closely involved with visual-motor processes than with cognition that is more verbal in nature.

Acknowledgments The Collaborative Study on the Genetics of Alcoholism (COGA), Co-Principal Investigators B. Porjesz, V. Hesselbrock, H. Edenberg, L. Bierut, includes nine different centers where data collection, analysis, and storage take place. The nine sites and Principal Investigators and Co-Investigators are: University of Connecticut (V. Hesselbrock); Indiana University (H.J. Edenberg, J. Nurnberger Jr., P.M. Conneally, T. Foroud); University of Iowa (S. Kuperman, R. Crowe); SUNY Downstate (B. Porjesz); Washington University in St. Louis (L. Bierut, A. Goate, J. Rice); University of California at San Diego (M. Schuckit); Howard University (R. Taylor); Rutgers University (J. Tischfield); Southwest Foundation (L. Almasy). Zhaoxia Ren serves as the NIAAA Staff Collaborator. This national collaborative study is supported by the NIH Grant U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA).

In memory of Henri Begleiter and Theodore Reich, Principal and Co-Principal Investigators of COGA since its inception; we are indebted to their leadership in the establishment and nurturing of COGA, and acknowledge with great admiration their seminal scientific contributions to the field.

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