Behavior Genetics, Vol. 36, No. 1, January 2006 (© 2006)
DOI: 10.1007/s10519-005-9009-8

Linkage Analyses of IQ in the Collaborative Study on the Genetics of Alcoholism (COGA) Sample

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Received 5 Aug. 2005—Final 12 Sep. 2005

Intelligence, as measured by standardized psychological tests, has been shown to be highly heritable, though identifying specific genes influencing general intelligence has proven difficult. We conducted genome-wide linkage analyses to identify chromosomal regions containing genes influencing intelligence, as measured by WAIS full-scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ). Non-parametric multipoint linkage analyses were conducted with Merlin-regress software, using a sample of 1111 genotyped and phenotyped individuals from 201 families, ascertained as part of the Collaborative Study on the Genetics of Alcoholism (COGA). The strongest evidence of linkage was obtained for FSIQ on chromosome 6 (LOD = 3.28, 12 cM) near the marker D6S1006. This region was also implicated with suggestive linkage in a recently published genome screen of IQ in Australian and Dutch twin pairs, and it has been implicated in linkage studies of developmental dyslexia. Our findings provide further support that chromosome 6p contains gene(s) affecting intelligence.

KEY WORDS: Cognitive ability; genetics; intelligence; IQ; linkage analyses.

INTRODUCTION

A substantial body of literature from twin, family, and adoption studies documents the significant heritability of human intelligence (Bouchard and McGue, 1981). Estimates range from 40–80%, and meta-analyses suggest an overall heritability of ~50%, with evidence for increasing importance of genetic effects from childhood to adulthood (Devlin *et al.*, 1997; McGue *et al.*, 1993). Intelligence is conceptualized as general cognitive ability, sometimes referred to as "g", and represents the covariance that exists across different dimensions of cognitive ability, including verbal ability, spatial ability, memory, and processing speed. The average correlation among these diverse neuropsychological abilities is approximately 0.30, and about 40% of the total phenotypic variance among the tests is accounted for by a general cognitive factor, considered to represent general intelligence (Plomin, 2003). Importantly, multivariate genetic research studies suggest that although the phenotypic correlation between diverse tests of intelligence is only ~0.30, the genetic correlations between tests are generally > 0.80, suggesting that shared genes largely contribute to the construct of general intelligence (Petrill, 2002).

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Despite considerable evidence for genetic influences on intelligence, the identification of specific genes contributing to variation in intelligence has largely been limited to single gene effects that cause profound mental disabilities (Flint, 1999). Finding genes that contribute to the variation in intelligence found in the normal range has proven more elusive. Initial efforts focused largely on candidate gene association testing. Positive reports of association have been reported for several genes, including Cathepsin D (CTSD, chromosome 11p; Payton *et al.*, 2003), the cholinergic muscarinic 2 receptor (CHRM2, chromosome 7q; Comings *et al.*, 2003), and catechol-*O*-methyltransferase (COMT, chromosome 22q; Egan *et al.*, 2001; Malhotra *et al.*, 2002). Replication is key in evaluating the significance of these genes for human intelligence, as some early reports of association with candidate genes, such as the IGF2R on chromosome 6q (Chorney *et al.*, 1998), have failed to replicate (Hill *et al.*, 2002), a common problem in the genetics of complex phenotypes.

Only recently have there been more systematic efforts to identify genes contributing to intelligence. Plomin and colleagues (2001b) undertook a genome-wide scan for allelic association, testing 1842 simple sequence repeat (SSR) markers using a case–control pooling design. Cases were selected to represent individuals with very high IQs, with a mean IQ of 136 in one sample, and IQs >160 in a second sample. A five-stage sampling design was employed, whereby markers that were nominally significant in the first case–control sample were replicated in a second case–control sample; markers that remained significant were individually genotyped in the first and subsequently in the second case–control samples. Finally, remaining markers of interest were genotyped in a sample of parent–offspring trios. No markers survived all stages of testing, although several markers of interest emerged and are being further investigated. Data from the HapMap now suggests that the number of markers typed in the study is too sparse to adequately encompass the genetic variation that exists across the genome. Nonetheless, the study represents an important early step in systematically attempting to identify genes contributing to intelligence. More recently, a genome-wide linkage scan of IQ has been reported in a sample consisting of sibling pairs from Australian and Dutch families (Posthuma *et al.*, 2005). One region, on chromosome 2q, yielded significant evidence of linkage (LOD score = 4.42) to Performance IQ. A second region, on chromosome 6p, met criteria for suggestive evidence of linkage (LOD score = 3.2) to Full Scale IQ.

This paper contributes to the growing effort to systematically identify genes influencing intelligence by reporting results from a genome-wide scan of IQ in a sample of 1111 genotyped and phenotyped individuals from 201 families who completed the Wechsler Adult Intelligence Scale (WAIS) as part of the Collaborative Study on the Genetics of Alcoholism (COGA) study.

METHODS

Sample

Families were identified through probands in 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). DSMIV alcohol dependence diagnoses (used as a covariate in some analyses, as detailed below) were assessed using the SSAGA interview. A subset of the COGA participants completed the Wechsler Adult Intelligence Scale – Revised (WAIS–R). The WAIS (Wechsler, 1981, 1997) is a traditional neuropsychological intelligence test with high predictive validity, stability across different age spans 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). The resulting prorated scaled scores for Full Scale IQ (FSIQ), VIQ, and PIQ were analyzed.

Although the WAIS–R was part of the original COGA assessment battery, it was found that 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 battery. The data included here represent those subjects who were tested and whose test batteries were appropriately supervised. A total of 201 families, containing 1928 individuals ($n = 954$ females, 974 males), had members with phenotype data and were included in the analysis files. Of these 1928 individuals, 1512 had genotype data, 1144 had phenotype data, and 1111 had both genotype and phenotype data. Of the 201 families, the majority (50%) consisted of 6–10 members; 17% had 3–5 members, 26% had 11–15 members, and 7% had 16 or more members (range 16–37).

Genotyping and Analysis

Genotyping was carried out in laboratories at Indiana University and Washington University in St. Louis using radioactive and fluorescence-based detection systems, as described previously (Reich *et al*., 1998). The current analyses are based on a map of 315 autosomal microsatellite markers with an average intermarker distance of 11.5 cM. Pedigrees were checked for non-Mendelian inheritance using the GeneMaster database and the programs CRIMAP (Green, 1990) and USERM13 (Boehnke, 1991). Recombination-based marker maps were generated from the sample using CRIMAP. Maximum likelihood estimates of marker allele frequencies were computed from the data using USERM13. Multipoint linkage analyses were carried out using Merlin-regress software (Abecasis *et al*., 2000). This regression-based approach to quantitative trait linkage, based on the work of Sham and colleagues (Sham *et al*., 2002), can handle non-randomly ascertained samples and deviations from multivariate normality of the observed data, but retains the statistical power of variance components linkage methods (Sham *et al*., 2002). The complexity of several large, multigenerational COGA families required family structures to be simplified to make data analysis feasible and time-efficient with available hardware; seven families were divided into separate branches, making every effort to maximize the genetic information retained. The average family size in the analysis data file was nine members, and the average number of generations per family was 2.8 (ranging from two to five). There were 1061 sib-pairs, 92 half-sib pairs, 1708 parent–child, 454 grandparent–grandchild, 543 avuncular pairs, and 152 cousin pairs used in analyses. 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 97.1 (Var = 178.3), 97.9 (Var = 193.6) and 96.6 (Var = 209.9) for FSIQ, PIQ and VIQ, respectively, which may reflect the ascertainment strategy employed in COGA. Since overall sample mean values for our quantitative traits were less than mean values for founders, we used as input estimated mean values and variances for Merlin-regress from the literature. The mean value used for all IQ scales was 100 with standard deviation 15. The sibling correlations for FSIQ, PIQ, and VIQ were 0.51, 0.39, and 0.48 in our sample, comparable to published values (Plomin *et al*., 2001a). We used a heritability estimate of 80% in our analyses, based on existing twin literature of the heritability of IQ in adults (e.g., McGue *et al*., 1993). Multipoint lod scores were estimated at the markers; the steps = 3 option was used on chromosome 6 for additional estimation between markers.

We also performed sensitivity analysis to see if LOD scores changed as a function of varying the input estimated values for means and standard deviations of IQ. Changes of those parameters across a reasonable range did not significantly alter LOD scores. In addition, we performed linkage with residuals of the regression of each of the IQ scale scores with DSMIV alcohol dependence and gender. The magnitude and position of linkage peaks were very similar using the residual scores, suggesting that the results were not heavily influenced by the nature of the ascertained COGA sample. Alcohol dependence and gender were not consistently significantly related to each of the IQ scale scores, and these variables accounted for <1% of the total variance across all IQ scores. Accordingly, we present here results for the original standard IQ scale scores.

Merlin was also used to conduct simulation analyses to estimate empirical significance levels for our primary finding on chromosome 6. The method

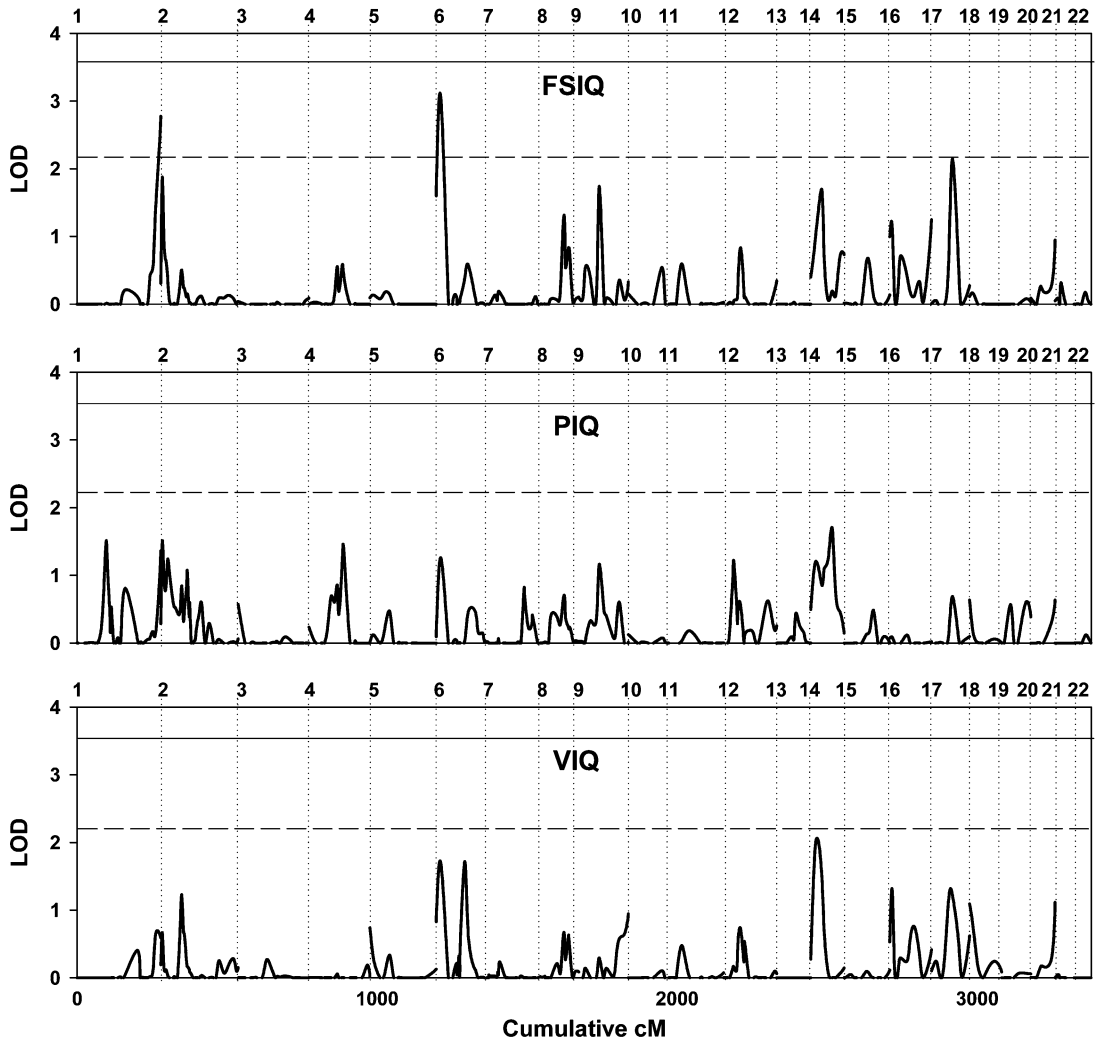

Fig. 1. Genome-wide linkage analysis results for Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ). Chromosomes are denoted at the top of the graph, with dotted vertical lines differentiating each chromosome. Horizontal solid lines denote genome-wide significance thresholds, and horizontal dashed lines represent genome-wide suggestive thresholds, as simulated by Lander and Kruglyak (1995).

employed performs gene dropping simulations that replace input data with simulated chromosomes conditional on the family structure, marker spacing, allele frequencies, and missing data patterns of the study's original input files. One thousand simulations were performed on the chromosome 6 data. These simulations indicated that a lod score of 2.48 for FSIQ, 2.60 for PIQ, and 2.70 for VIQ, corresponded to a significance level of 0.01 in our sample. Genome-wide simulations proved impractical due to the computationally intensive nature of the extended COGA pedigrees and practical time limitations. Other linkage results are discussed in relation to published guidelines for interpreting genome-wide significance (Lander and Kruglyak, 1995).

RESULTS

Figure 1 shows genome-wide linkage plots for each of the IQ measures. In Table I, we have highlighted regions yielding lod scores >1.5 for any of the three IQ measures. If any one IQ measure yielded a lod score >1.5, the corresponding lod scores for the other measures in that region are also shown. Across all three phenotypes of intelligence analyzed, the strongest evidence of linkage was for FSIQ on chromosome 6

Table I. Chromosomal Regions with LOD scores >1.5 for Anyone of the IQ Scores

Chromosome	Position	LOD Scores			Marker
		FSIQ	PIQ	VIQ	
1	97.4	0.01	1.51	0.00	D1S198
1	279.2	2.82	1.36	0.59	D1S547
2	4.9	1.88	1.50	0.67	D2S1329
6	15.9	3.03	1.26	1.68	D6S1006
6	95.3	0.38	0.03	1.72	D6S1021
9	68.1	1.74	1.16	0.29	D9S301
14	16.7	1.03	1.21	2.02	D14S597
14	36.5	1.70	0.86	1.52	D14S583
14	71.2	0.19	1.70	0.00	D14S59
17	69.8	2.15	0.68	1.22	D17S250

(LOD = 3.03 at the marker D6S1006). A maximum LOD score of 3.28 was obtained at 12 cM between the markers D6S477 and D6S1006 when the steps option was employed. Figure 2 shows the lod score graph for chromosome 6 using the steps option. LOD scores >3.0 extend from 7–22 cM in the region. The peak LOD score for VIQ was 1.77, and for PIQ was 1.26 in the region. On chromosome 1q, the LOD score for FSIQ was 2.82 at the end of the chromosome, located at 279 cM near the marker D1S547 (Fig. 3). Since there is some concern of false positive results at markers at the end of chromosomes due to the extrapolation employed in multipoint analyses, we reran the analyses on chromosome 1 using the 'single-point' option. As expected, the LOD score decreased somewhat (LOD = 2.04), but it did not disappear altogether, suggesting that the result was not purely an artifact. Figure 4 shows the lod score graph for chromosome 17, which yielded a peak lod score of 2.15 with FSIQ at 70 cM.

LOD scores >1.5 were also detected on chromosome 2 (LOD for FSIQ = 1.88, LOD for PIQ = 1.50, both at the 5 cM region, at the marker D2S1329), chromosome 9 (LOD for FSIQ = 1.74, 68 cM region, at the marker D9S301), and broadly across chromosome 14q with FSIQ and the component tests (peak LOD for VIQ = 2.02, 17 cM at the marker D14S597; peak LOD for FSIQ = 1.70, 37 cM, at the marker D14S583; peak LOD score for PIQ = 1.70, 71 cM, at the marker D14S59).

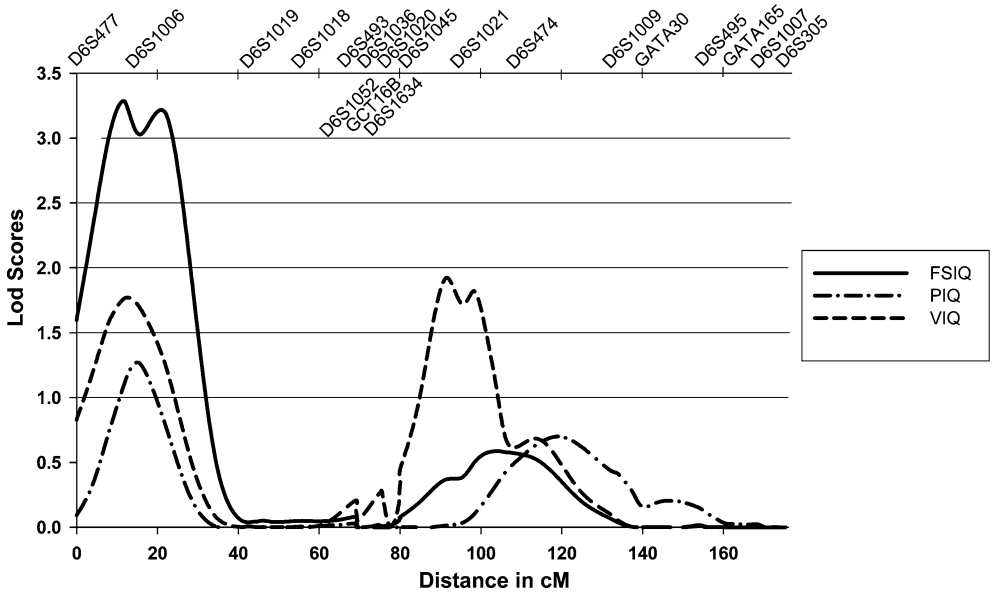

Fig. 2. Linkage analysis results on chromosome 6.

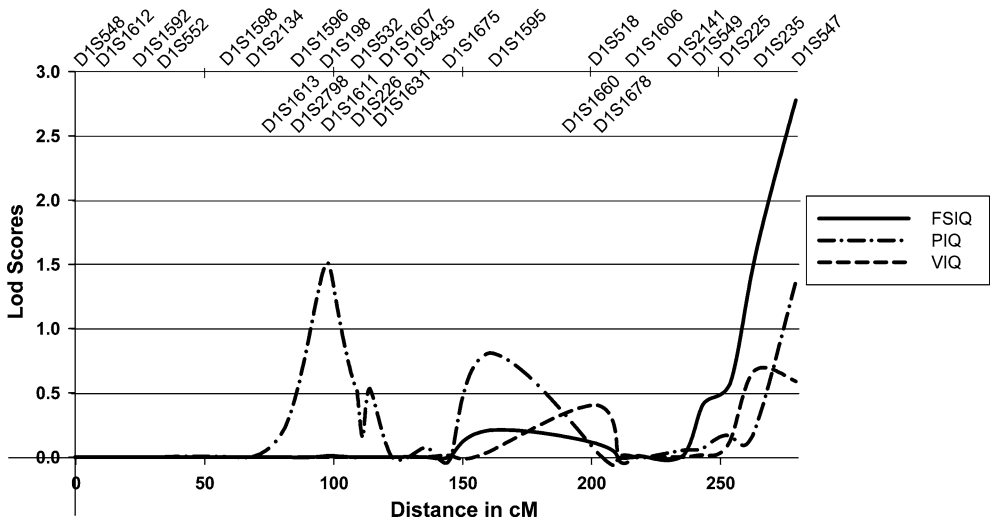

Fig. 3. Linkage analysis results on chromosome 1.

DISCUSSION

This study represents an effort to systematically screen the genome for genes related to intelligence. We found evidence of significant linkage, based on our empirically simulated values, to full scale IQ on chromosome 6p (maximum lod score = 3.28). Although this value does not meet published thresholds for significance (Lander and Kruglyak, 1995), these thresholds are conservative (Wiltshire *et al.*, 2002). There was suggestive evidence of linkage based on the published guidelines (Lander and Kruglyak, 1995) on chromosomes 1 and 17.

Our finding on chromosome 6 is of particular interest, as this region yielded the second highest lod score (LOD = 3.2 for FSIQ) in a recently published genome-screen for intelligence in Dutch and Australian siblings (Posthuma *et al.*, 2005). Their peak on 6p was found at the marker D6S2434 in the region between markers D6S942 and D6S422, which is approximately 1.7 cM from our linkage peak. In addition, there is a wealth of previous studies

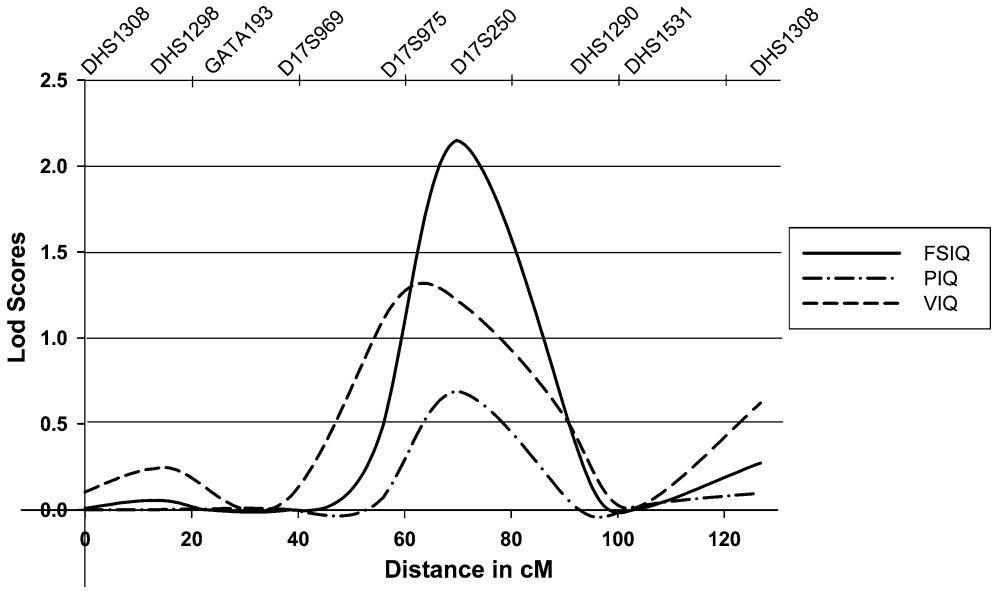

Fig. 4. Linkage analysis results on chromosome 17.

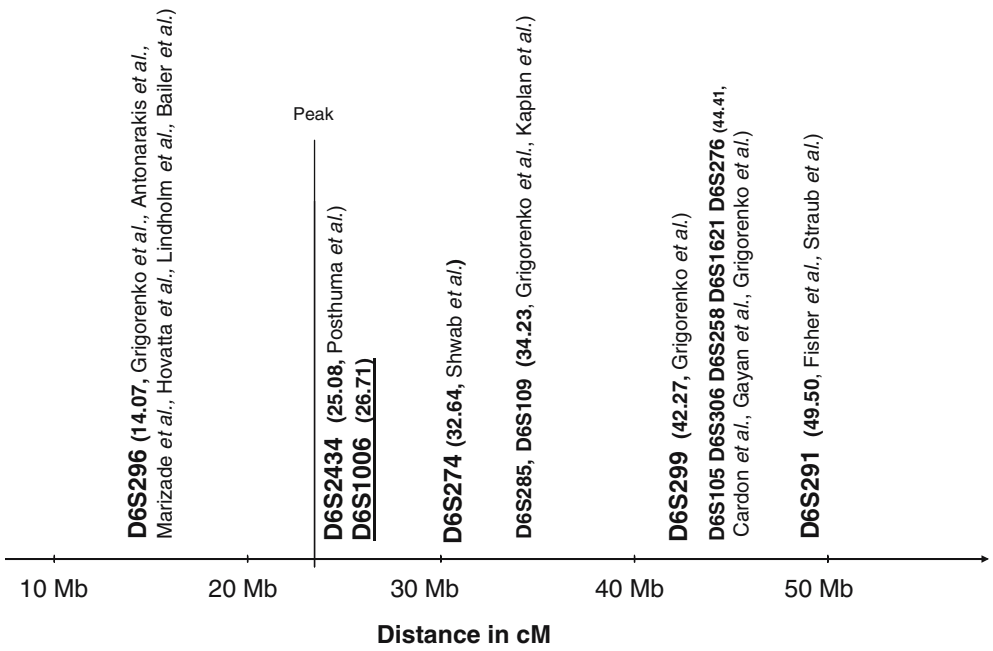

Fig. 5. Location and distribution of the markers with reported linkage near D6S1006, the marker nearest to our peak lod score on chromosome 6. Italicized markers are related to schizophrenia; all others have been related to developmental dyslexia.

demonstrating linkage in this region of 6p to developmental dyslexia. Evidence for linkage to dyslexia stretches from marker D6S109 at 34.2 cM (Grigorenko *et al*., 1997) to marker D6S291 at 49.5 cM (Fisher *et al*., 1999), and numerous studies have demonstrated linkage within this region (Cardon *et al*., 1994, 1995; Cope *et al*., 2005; Gayan *et al*., 1999; Grigorenko *et al*., 1997, 2000, 2003). This region also has been linked to schizophrenia (Antonarakis *et al*., 1995; Bailer *et al*., 2000; Hovatta *et al*., 1998; Lindholm *et al*., 1999; Maziade *et al*., 2001; Schwab *et al*., 2000; Straub *et al*., 2002). This is of interest, as there is a substantial literature demonstrating impaired cognitive abilities in schizophrenics and in their unaffected first degree relatives, suggesting that impaired cognition may be related to the genetic liability toward schizophrenia and represent an endophenotype for the disorder (McIntosh *et al*., 2005; Paunio *et al*., 2004). Figure 5 attempts to synthesize this literature of previous linkage findings to related phenotypes in the region; it illustrates the relationship between the marker yielding our peak lod score for FSIQ and the locations of peak lod scores from other studies finding linkage to this region. Marker distances in Figure 5 are reported from the Marshfield Database in an effort to place all findings on a similar map and eliminate chromosomal position differences that may result from the use of different maps; thus, the distances may differ from those mentioned in the original published studies.

Previous genome-scans of intelligence (Luciano *et al*., this issue; Posthuma *et al*., 2005) found significant evidence of linkage on chromosome 2q with PIQ; this region has also been implicated as playing a role in general academic achievement (Wainwright *et al*., this issue). However, there was no evidence of linkage to this region in our sample. In contrast, the other regions with suggestive linkage in our study, on chromosomes 1 and 17, yielded no evidence of linkage in these other reports. Our region on chromosome 14, with lod scores >1.5 with FSIQ and PIQ also yielded suggestion of linkage in the Luciano *et al*. report (this issue), with a lod score of 2.2 with the verbal subtest, Arithmetic, in their sample of adolescents ranging in age from 15.7 to 22.2 years. In addition, analyses of the individual neuropsychological tests that comprise the WAIS−R in the COGA sample reported a peak lod of 6.01 with the Digit Symbol test to the same region of chromosome 14q (Buyske *et al*., this issue).

The findings of this study should be interpreted with several limitations in mind. The sample analyzed was not a random population sample collected with the primary goal of analyzing IQ; rather, it was a sample of multiplex alcoholic families ascertained through alcohol dependent probands in treatment

centers. Nevertheless, we believe our findings are not largely influenced by the ascertainment of the sample for several reasons: (1) the linkage results were very similar after regressing out alcohol dependence status, (2) our results on chromosome 6p replicate the finding for FSIQ recently reported in Posthuma *et al.* (2005) using an unselected sample, and (3) the mean and standard deviation for IQ among the COGA sample, and the sibling correlation for the IQ measures, do not deviate considerably from published reports on unselected samples. Another limitation is that we used abbreviated measures of IQ; not all subscales were administered. We did not administer all subtests of the WAIS−R because of testing time limitations and concerns about subject burden due to the lengthy assessment protocol of the COGA study. Nevertheless, it is encouraging that our results on chromosome 6p replicate those reported by Posthuma *et al.* (2005), since they used slightly different IQ test measures (the Multidimensional Aptitude Battery in Australian subjects, and the WAIS-IIIR in Dutch subjects), suggesting that the results are robust to slight variations in the measurement of IQ. Finally, the marker map used, with an intermarker distance of 11.5 cM, is not as dense as has been used in more recent genome scans.

In conclusion, these analyses provide further support for a gene or genes on chromosome 6p that influence general cognitive ability, in addition to developmental dyslexia. There is also some suggestion of linkage on chromosomes 1 and 17 for general intelligence, although these findings await replication in another sample. The convergence of studies with linkage findings on chromosome 14 also suggest that a gene or genes in this region may play a role in cognitive ability. Indeed, in light of the difficulty in replicating linkage findings for complex phenotypes (Suarez *et al.*, 1994), it is encouraging to see convergence for a number of regions from the limited number of studies of cognitive ability that are emerging. Integrating literature on genetic contributions to general intelligence, specific aspects of cognitive ability, and disorders associated with cognitive impairment promises to advance our understanding of genetic contributions to cognitive ability and its component processes.

ACKNOWLEDGMENTS

The Collaborative Study on the Genetics of Alcoholism (COGA) (Principal Investigator: H. Begleiter; Co-Principal Investigators: L. Bierut, H. Edenberg, V. Hesselbrock, B. Porjesz) 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. Edenberg, J. Nurnberger Jr., P.M. Conneally, T. Foroud); University of Iowa (S. Kuperman, R. Crowe); SUNY HSCB (B. Porjesz, H. Begleiter); 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 U10AA08401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA). Partial support was also provided by NCRR Grant M01-RR06192 to the University of Connecticut School of Medicine GCRC.

In memory of Theodore Reich, M.D., Co-Principal Investigator of COGA since its inception and one of the founders of modern psychiatric genetics, we acknowledge his immeasurable and fundamental scientific contributions to COGA and the field.

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Edited by Danielle Posthuma