A Quantitative Trait Locus Associated With Cognitive Ability in Children

M.J. Chorney, K. Chorney, N. Seese, M.J. Owen, J. Daniels, P. McGuffin, L.A. Thompson, D.K. Detterman, C. Benbow, D. Lubinski, T. Eley and R. Plomin

Psychological Science 1998 9: 159
DOI: 10.1111/1467-9280.00032

General Article

A QUANTITATIVE TRAIT LOCUS ASSOCIATED WITH COGNITIVE ABILITY IN CHILDREN

By M.J. Chorney,[1] K. Chorney,[1] N. Seese,[1] M.J. Owen,[2] J. Daniels,[2] P. McGuffin,[2] L.A. Thompson,[3] D.K. Detterman,[3] C. Benbow,[4] D. Lubinski,[4] T. Eley,[5] and R. Plomin[5]

[1]Department of Microbiology and Immunology, Milton S. Hershey Medical Center, Pennsylvania State University; [2]Department of Psychological Medicine, University of Wales College of Medicine, Cardiff, Wales, United Kingdom; [3]Department of Psychology, Case Western Reserve University; [4]Department of Psychology, Iowa State University; and [5]Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London, United Kingdom

*Quantitative trait loci (QTLs) associated with general cognitive ability (*g*) were investigated for several groups of children selected for very high or for average cognitive functioning. A DNA marker in the gene for insulin-like growth factor-2 receptor (IGF2R) on Chromosome 6 yielded a significantly greater frequency of a particular form of the gene (allele) in a high-*g *group (.303; average IQ = 136,* N = *51) than in a control group (.156; average IQ = 103,* N = *51). This association was replicated in an extremely-high-*g *group (all estimated IQs > 160,* N = *52) as compared with an independent control group (average IQ = 101,* N = *50), with allelic frequencies of .340 and .169, respectively. Moreover, a high-mathematics-ability group (*N = *62) and a high-verbal-ability group (*N = *51) yielded results that were in the same direction but only marginally significant (*p = *.06 and .08, respectively).*

Family, twin, and adoption studies consistently converge on the conclusion that general cognitive ability (*g*), often indexed by intelligence (IQ) tests, is one of the most highly heritable behavioral traits (Plomin, DeFries, McClearn, & Rutter, 1997). For example, a recent report of a 20-year longitudinal adoption study showed that adopted children become increasingly like their biological parents from childhood through adolescence and to the same degree as children and parents in nonadoptive families (Plomin, Fulker, Corley, & DeFries, 1997).

Although much remains to be learned about the nature and nurture of *g* (Plomin & Petrill, 1997), the most exciting direction for genetic research on complex traits such as *g* is to harness the power of molecular genetics to identify some of the genes responsible for this genetic influence (Plomin, Owen, & McGuffin, 1994). The high heritability of *g*, its high reliability and stability, its key role in cognitive neuroscience, and its social importance as the best predictor of educational and occupational attainment make *g* a reasonable target for such a program of research (Benbow, 1992; Brody, 1992; Gottfredson, 1997; Lubinski & Dawis, 1992). However, *g* presents three challenges for molecular genetic analysis: It is a quantitative trait with a roughly normal distribution; it is multifactorial, involving environmental as well as genetic sources of variance; and its heritability seems likely to be due to multiple genes of varying effect size rather than a few genes of major effect (Plomin, 1997). In other words, the genetic contribution to *g* is likely to involve what is known as *quantitative trait loci* (QTLs), genes that have relatively small effect size and provide probabilistic and interchangeable propensities on average in the population rather than the hard-wired effects characteristic of single genes.

The goal of our research is to identify some of the QTLs that contribute to the highest end of the distribution of *g*, not because we expect to find QTLs for high *g* per se, but rather because this may be an efficient strategy for identifying QTLs that are responsible for genetic variation throughout the distribution. We hypothesized that high *g* will develop only if an individual has most of the positive alleles and few of the negative alleles for high *g*. That is, suppose that 25 genes with an average effect size of 2% accounted for the heritability of *g*. In this case, individuals with average *g* scores would be expected to have different combinations of half of the increasing alleles and half of the decreasing alleles for these genes. In contrast, individuals with high *g* scores would be expected to have increasing alleles for many of these genes. For this reason, by selecting the highest *g* extremes, we expected to increase power to detect QTLs that account for genetic variation throughout the distribution. In contrast, at the lowest end of the distribution, idiosyncratic genetic (e.g., mutational) and environmental (e.g., prenatal) factors might disrupt normal developmental processes, making it more difficult to find QTLs that account for normal variation.

Address correspondence to Robert Plomin, Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, DeCrespigny Park, Denmark Hill, London, SE5 8AF, United Kingdom; e-mail: r.plomin@iop.bpmf.ac.uk.

Because *g* is a quantitative trait likely to be influenced by multiple genes of varying effect size as well as by multiple environmental factors, QTLs for *g* may be of small effect size in the population. For this reason, the traditional method for identifying single-gene effects is unlikely to succeed (Risch & Merikangas, 1996). The traditional method, called linkage, uses large pedigrees of several generations to trace the co-inheritance of a DNA marker and a disorder. Linkage is a violation of Mendel's second law of heredity, which states that the inheritance of one gene is not affected by the inheritance of another gene, that is, genes are inherited independently. Mendel's second law holds except when two genes reside close together on a chromosome, in which case they are inherited together. Unless genes are near each other on the same chromosome, they will recombine by a process in which chromosomes exchange parts. Recombination occurs during meiosis in the ovaries and testes, when gametes are produced. The probability of recombination between two genes on the same chromosome is a function of the distance between them.

These facts have been used to "map" genes on chromosomes using linkage methods. Linkage has been used to locate genes for many single-gene disorders, but it cannot detect genes of smaller effect size, which is the case if many genes affect a trait. A new type of linkage method, called *QTL linkage*, may be able to detect genes that account for as little as 10% of the variance in quantitative traits (Fulker, Cherny, & Cardon, 1995; Kruglyak & Lander, 1995; Risch & Zhang, 1995). QTL linkage was first used in human behavioral studies to identify a linkage for reading disability (Cardon et al., 1994) that has received support from another linkage study (Grigorenko et al., 1997). Although such QTL linkage studies will be important for determining whether any QTLs account for 10% or more of the variance in quantitative traits, QTLs for *g* may be of smaller effect size.

Allelic association is an increasingly used alternative strategy. Despite some potential limitations, it can provide the statistical power to detect QTLs of small effect size (Owen, Holmans, & McGuffin, 1997; Risch & Merikangas, 1996). In contrast to linkage, allelic association (Edwards, 1991) refers to a correlation in the population between a particular allele of a DNA marker and a trait. For example, a particular allele (Allele 4) of a gene that codes for apolipoprotein E on Chromosome 19 is associated with Alzheimer's disease. The frequency of Allele 4 of this gene is about 40% for people with late-onset Alzheimer's disease, as compared with about 15% in control samples. This association would not have been found unless apolipoprotein E itself or a gene very close to it directly affects Alzheimer's disease because recombination in the population would break up such associations unless two genes are very close together on a chromosome (Morton, 1982). (Linkage analysis within families might still detect a linkage if two genes were far apart on a chromosome because within families, there is relatively little recombination.)

Although linkage is not powerful in detecting QTLs of small effect size, it is systematic in that linkage can scan the entire genome with just a few hundred markers. In contrast, allelic association is powerful in that it can detect QTLs of small effect size, but it has not been used in a systematic manner because allelic association requires that a DNA marker be so close to the effective QTL that the marker and the gene are not separated by recombination. For this reason, allelic association has largely been limited to studies of a few "candidate" genes, that is, known genes whose function is expected to affect a trait. Linkage cannot be made much more powerful with realistic sample sizes, but association can be made more systematic by using a dense map of markers, for example, at intervals of roughly 1 million base pairs of DNA, which means that any QTL will be within half a million base pairs from a marker. Although such a systematic search of the genome would require genotyping 3,500 markers, we embarked on a pilot search on the long arm of Chromosome 6 (called 6q). We began our search on Chromosome 6 in part because it is likely to be the first large chromosome whose DNA sequence will be completely determined as part of the Human Genome Project, which will greatly facilitate attempts to identify specific genes and their functions once associations with DNA markers are found.

We used an allelic association design with 37 markers on 6q to compare multiple groups of high ability with control groups of average ability. We used a multistage process of replication, with a lenient *p* value in the initial stage, in order to strike a balance between false positive and false negative findings for QTLs of small effect size. In the first stage, which compared a high-*g* group and an average-*g* group, a *p* value of .027 was used as a criterion for "suggestive" association in that this criterion would permit one false positive result when testing 37 markers. Suggestive associations were tested in the second stage using independent samples of super-high-*g* and average-*g* individuals. In addition, two other high-*g* groups were used for further replication and for extending the research to consider two specific cognitive abilities, high verbal ability and high mathematical ability.

Our hypothesis was that this multistage approach using multiple samples selected for extreme *g* and a dense map of DNA markers would be able to detect allelic association with *g* for QTLs of small effect size.

METHODS

Subjects and Measures

All participants were Caucasian in order to attenuate possible problems due to population stratification, that is, allelic associations that occur because groups with different allelic frequencies are mixed. DNA was extracted from permanent cell lines established from blood. The original high-*g* sample included 51 children (mean IQ = 136, *SD* = 9.3) who were compared with a control group of 51 children of average ability (mean IQ = 103, *SD* = 5.6). The children ranged in age from 6 to 15 at the time of testing. All participants lived in a six-county area around Cleveland, Ohio. IQ was assessed using the Wech-

sler Intelligence Scale for Children—Revised (Wechsler, 1974). The high-*g* group combined children from two smaller samples from an earlier phase of our project that focused on comparisons between high and low *g* using a candidate-gene approach that investigated known genes but did not identify any replicated associations (Plomin et al., 1995). The present control group included 21 individuals from this earlier phase of the project plus 30 new participants recruited to the present study.

For the present study, 50 additional control individuals (mean IQ = 101, *SD* = 7.2) were selected in the same manner to form a replication control group. A replication high-ability group was obtained from the Study of Mathematically Precocious Youth (SMPY; Lubinski & Benbow, 1994). Although SMPY began as a study of mathematical talent, beginning in the late 1970s, the study has put as much emphasis on verbal as mathematical talent. SMPY participants qualify for longitudinal tracking through earning exceptional verbal or math scores on the Scholastic Assessment Test (SAT). Each year, the top 3% of individuals are selected from the more than 1 million seventh and eighth graders on the basis of a standardized test administered in their schools and are invited to take the SAT college entrance exam 4 years early, before the age of 13.

Fifty-two of the highest scoring individuals selected for the SMPY over the years were targeted for our high-*g* replication sample. These participants earned both verbal and math SAT scores of at least 630 or a verbal SAT score of at least 550 plus a math SAT score of at least 700. They were required to have "flat" SAT profiles in the sense that their verbal and math scores were required to be within 1 standard deviation of each other. These participants represent a selection intensity of about 1 in 30,000, as indicated by IQ scores greater than 160 estimated from their composite (verbal + math) SAT scores (Lubinski & Benbow, 1994). It should be noted that this is a constructive replication, the most stringent type of replication (Lykken, 1968), in that the investigators, sampling frame, and procedures involved in selecting the high-*g* subjects differed in the original sample and replication sample.

In addition, the SMPY sample was used to select a group high in verbal ability and a group high in mathematics ability. Individuals in both groups were in the top 1 in 10,000 in either verbal or mathematical reasoning ability (i.e., verbal SAT ≥ 630 or math SAT ≥ 700), but their lower SAT scale differed from their dominant SAT scale by more than 1 standard deviation. In other words, they are said to have "tilted" SAT profiles in the sense that they are much more exceptional in one of the SAT measures than the other. We refer to these two groups as the high-verbal group (N = 51) and the high-math group (N = 62), and we compare their results with those of the combined control group of 101 individuals.

Genotyping

Primers for the DNA markers were purchased from Research Genetics. The primers detect dinucleotide repeat markers in which two base pairs of DNA repeat several times; the number of repeats is stably inherited and used as a DNA marker in the sense that the polymorphism is in DNA itself. Standard conditions were used to genotype individuals for the 37 DNA markers. Radioactive bands were separated on a 6% acrylamide gel under denaturing conditions.

RESULTS

The original high-*g* (N = 51) and control (N = 51) groups were genotyped for 37 6q markers. Figure 1 shows the order and approximate locations of these markers. Table 1 shows the frequency of the most common allele for each of the 37 markers for these two groups. One marker, insulin-like growth factor-2 receptor (IGF2R) at 6q26, reached significance when the most common allele was compared with all other alleles for the two groups. The most common allele of IGF2R (Allele 4) yielded a frequency of .660 in the high-*g* group (N = 94 alleles) and .809 in the control group (N = 94 alleles), $\chi^2(1) = 5.34$, $p = .021$.

IGF2R refers to a dinucleotide repeat DNA marker in the IGF2R gene. The forward primer purchased from Research Genetics for this marker contains the following sequence of 20 DNA bases: TTTTCTCTGACACCTCAACT; the reverse primer that brackets the DNA to be amplified by polymerase chain reaction is CTGGTGAATTCAAACAACCT. The forward primer is at base pairs 8,482 through 8,501 of the messenger RNA for the IGF2R protein, which contains a total of 9,090 base pairs; the reverse primer is 80 base pairs away, at base pairs 8,402 through 8,421. These primers were used to amplify DNA using polymerase chain reaction at 60 ˚C with 27 cycles (Hol, 1992).

IGF2R was then genotyped in the replication high-*g* group (N = 52) and replication control group (N = 50). The results for the replication sample were similar to those for the original sample. The frequency of Allele 4 was .633 in the replication high-*g* group (N = 98 alleles) and .784 in the replication control group (N = 88 alleles), $\chi^2(1) = 5.11$, $p = .024$.

Table 2 shows the results of further analyses of IGF2R. IGF2R yielded the following seven alleles in our samples (frequencies shown in parentheses): Alleles 1 (.005), 2 (.003), 3 (.003), 4 (.721), 5 (.232), 6 (.025), and 9 (.002). Because Alleles 4 and 5 accounted for more than 95% of the alleles, we focused on the comparison of Alleles 4 and 5, but we also compared Allele 4 and Allele 5 with all other alleles for the two groups. In comparisons between Alleles 4 and 5 (first panel in Table 2) in the original samples, the frequency of Allele 5 was .303 in the high-*g* group (N = 89 Alleles 4 and 5) and .156 in the control group (N = 88 Alleles 4 and 5), $\chi^2(1) = 5.54$, $p = .019$. In the replication sample, the frequency of Allele 5 was also twice as high in the high-*g* group (N = 94 Alleles 4 and 5) as in the control group (N = 83 Alleles 4 and 5), $\chi^2(1) = 6.76$, $p = .009$. Similar allelic frequency results were obtained when Allele 4 and Allele 5 were compared with all other alleles, as shown in the second and third panels of Table 2.

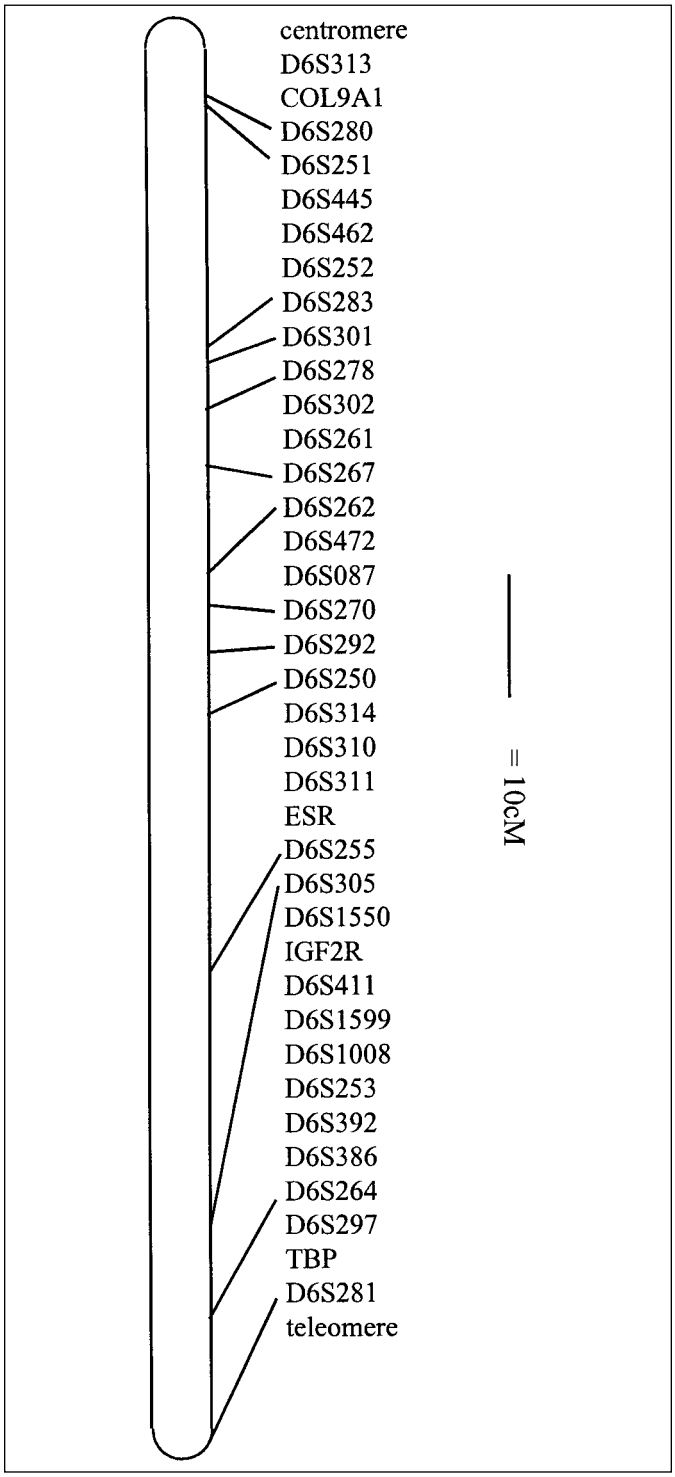

Fig. 1. Order and approximate locations of 37 DNA markers on 6q. The centromere is where this long arm of Chromosome 6 is attached to the short arm. The teleomere is the end of the chromosome. The lines connecting certain markers to the chromosome indicate the approximate locations of "anchor" markers, whose locations on the chromosome are well established. Marker order is from World Wide Web site http://cedar.genetics.soton.ac.uk/pub, and genetic distances are from http://www.chlc.org/ChlcIntegratedMaps.html.

Table 1. *Allelic frequencies for 37 6q markers and χ^2 results comparing the most common allele with all other alleles for the original high-*g *and control groups*

Marker	High-*g* group (*N* = 51)	Control group (*N* = 51)	χ^2	*p*
D6S313	.448	.411	0.26	.608
COL9A1	.225	.324	2.46	.117
D6S280	.340	.353	0.04	.847
D6S251	.350	.392	0.38	.535
D6S445	.541	.529	0.03	.872
D6S462	.532	.459	1.02	.314
D6S252	.530	.598	0.95	.330
D6S283	.350	.314	0.30	.584
D6S301	.390	.353	0.30	.586
D6S278	.430	.441	0.03	.873
D6S302	.340	.353	0.04	.847
D6S261	.398	.390	0.01	.909
D6S267	.430	.382	0.48	.491
D6S262	.240	.245	0.01	.933
D6S472	.602	.569	0.23	.632
D6S087	.490	.549	0.71	.401
D6S270	.410	.451	0.35	.556
D6S292	.250	.343	2.10	.148
D6S250	.250	.216	0.33	.564
D6S314	.330	.373	0.40	.527
D6S310	.235	.275	0.42	.518
D6S311	.130	.167	0.54	.464
ESR	.330	.275	0.74	.390
D6S255	.370	.422	0.56	.454
D6S305	.260	.216	0.55	.459
D6S1550	.560	.500	0.71	.398
IGF2R	.660	.809	5.34	.021
D6S411	.770	.663	2.78	.095
D6S1599	.480	.439	0.32	.566
D6S1008	.348	.439	1.64	.200
D6S253	.520	.551	0.19	.662
D6S392	.194	.122	1.87	.171
D6S386	.300	.398	2.09	.148
D6S264	.490	.411	1.25	.264
D6S297	.550	.667	2.89	.089
TBP	.323	.441	2.92	.087
D6S281	.560	.451	2.40	.121

When the original and replication samples were combined (*N* = 188 Alleles 4 and 5 and *N* = 173 Alleles 4 and 5 for the high-*g* and control groups, respectively), the frequency of Allele 5 was .322 in the combined high-*g* group and .162 in the combined control group, $\chi^2(1) = 12.4$, $p = .0004$. This *p* value remained significant ($p = .015$) when a Bonferroni correction was applied for testing 37 markers. Moreover, combining subjects from two independent studies and recalculating chi-squared is too conservative because it does not take into account the replicative nature of the two studies. Using Cochran's (1954) method as recommended by Everitt (1992) yielded a *p* value of .00024 for the combined high-*g* and control samples. A Bonferroni correction for 37 tests yielded a *p* value of .009.

Table 2. *Allelic and genotypic frequencies for a polymorphism of the insulin-like growth factor-2 receptor in the original, replication, and combined high-*g *and control groups*

A. Allele 4 versus Allele 5

	Allelic frequency (*N*)				Genotypic frequency (*N*)				
Comparison	Allele 4	Allele 5	$\chi^2(1)$	*p*	4/4	4/5	5/5	$\chi^2(2)$	*p*
Original									
High *g*	.697 (62)	.303 (27)	5.54	.019	.548 (23)	.286 (12)	.167 (7)	4.90	.086
Control	.844 (76)	.156 (14)			.773 (34)	.136 (6)	.091 (4)		
Replication									
High *g*	.660 (62)	.340 (32)	6.76	.009	.511 (23)	.311 (14)	.178 (8)	4.32	.115
Control	.831 (69)	.169 (14)			.725 (29)	.200 (8)	.075 (3)		
Combined (original + replication)									
High *g*	.678 (124)	.322 (59)	12.41	.0004	.529 (46)	.299 (26)	.172 (15)	9.11	.011
Control	.838 (145)	.162 (28)			.750 (63)	.167 (14)	.083 (7)		

B. Allele 4 versus all other alleles (O)

	Allelic frequency (*N*)				Genotypic frequency (*N*)				
Comparison	Allele 4	O	$\chi^2(1)$	*p*	4/4	4/O	O/O	$\chi^2(2)$	*p*
Original									
High *g*	.660 (62)	.340 (32)	5.34	.021	.489 (23)	.340 (16)	.170 (8)	5.48	.065
Control	.809 (76)	.192 (18)			.723 (34)	.170 (8)	.106 (5)		
Replication									
High *g*	.633 (62)	.367 (36)	5.11	.024	.469 (23)	.327 (16)	.204 (10)	3.93	.140
Control	.784 (69)	.216 (19)			.659 (29)	.250 (11)	.091 (4)		
Combined (original + replication)									
High *g*	.646 (124)	.354 (68)	10.53	.001	.479 (46)	.333 (32)	.188 (18)	8.84	.012
Control	.800 (145)	.203 (37)			.692 (63)	.209 (19)	.099 (9)		

C. Allele 5 versus all other alleles (O)

	Allelic frequency (*N*)				Genotypic frequency (*N*)				
Comparison	Allele 5	O	$\chi^2(1)$	*p*	5/5	5/O	O/O	$\chi^2(2)$	*p*
Original									
High *g*	.287 (27)	.713 (67)	5.27	.022	.149 (7)	.277 (13)	.575 (27)	4.96	.084
Control	.149 (14)	.851 (80)			.085 (4)	.128 (6)	.787 (37)		
Replication									
High *g*	.327 (32)	.674 (66)	6.98	.008	.163 (8)	.327 (16)	.510 (25)	5.79	.055
Control	.159 (14)	.841 (74)			.068 (3)	.182 (8)	.750 (33)		
Combined (original + replication)									
High *g*	.307 (59)	.693 (133)	12.32	<.001	.156 (15)	.302 (29)	.542 (52)	10.67	.005
Control	.154 (28)	.846 (154)			.077 (7)	.154 (14)	.769 (70)		

Note. Sample sizes are 51 for the original high-*g* group, 51 for the original control group, 52 for the replication high-*g* group, and 50 for the replication control group. Although the analysis focused on Alleles 4 and 5 because the total frequency of the other alleles (1, 2, 3, 6, 9) was less than 5%, the table also compares Allele 4 and Allele 5 with all other alleles. In comparisons between Alleles 4 and 5, *N* is less than total *N* in part because the other alleles were excluded; in addition, for all comparisons, genotyping of this polymorphism was not successful for some subjects in each group. Each chi-square test compared the relative allelic or genotypic frequencies for the high-*g* group versus the control group.

Analyses of genotypes rather than alleles yielded similar results, but because the sample size is considerably reduced in genotypic analyses, the results did not reach statistical significance in the original and replication groups. Nonetheless, when the original and replication groups were combined, genotypic differences were significant for all comparisons (see Table 2).

Analysis of Alleles 4 and 5 in the groups selected to explore specific cognitive abilities (high verbal, high math) produced

results in the same direction. Allele 5 frequency was .257 in the high-math group (N = 118 alleles), as compared with .162 in the combined control group (N = 182 alleles), $\chi^2(1) = 3.85$, $p = .05$. The high-verbal group (N = 94 alleles) showed a similar trend, with an Allele 5 frequency of .247, $\chi^2(1) = 2.77$, $p = .096$. Using Cochran's method to combine the results for these two groups with the results for the original and replication groups yields a p value less than .00003. However, the comparisons for the high-verbal group and the high-math group are not completely independent because these comparisons used "recycled" control groups.

DISCUSSION

The present study serves as an example of a QTL study of ability rather than disability, the use of a selected-extremes association design, and a more systematic approach to allelic association involving a dense map of markers. Our results suggest that the IGF2R gene is associated with high *g*. As discussed later, this association accounts for only a small portion of genetic influence on *g*; it is not *the* gene for *g* but may be one of many genes responsible for the high heritability of *g*. Moreover, IGF2R does not even have this small effect on each individual; the association with IGF2R refers only to an average effect in the population. It should be noted that only 46% of the high-*g* individuals had at least one IGF2R Allele 5. Although this is twice as great as the frequency of 23% for individuals in the control group, it means that most of the high-*g* individuals did not happen to have this particular *g*-increasing allele; presumably these individuals have *g*-increasing alleles for other QTLs that contribute to their high *g* scores.

As we examine other associations using our approach, we hope to be able to identify some of the other relevant genes, but we do not expect that we will ever identify all of the genes involved, if for no other reason than that the effects of some genes will be so small that they cannot be detected. As indicated earlier, the essence of the QTL perspective is that multiple genes of varying but relatively small effect size are responsible for the genetic contribution to normally distributed quantitative traits like *g*. As discussed later, IGF2R on the long arm of Chromosome 6 accounts for 2% of the variance of *g*. If other QTLs for *g* have similar effect sizes, it is possible that one association of this magnitude could be found on each of the other 22 chromosomes, given that about 50% of the variance in *g* is due to genetic influence (Plomin & Petrill, 1997).

IGF2R is a gene that codes for a receptor for IGF-II, which is a hormone with structural homologies to insulin, although its function in vivo is not known. The receptor for IGF-II is also the receptor for mannose 6-phosphate (MacDonald et al., 1988), binding mannose 6-phosphate residues on lysosomal enzymes and transporting them into lysosomes (Kornfeld & Mellman, 1989). The IGF2R gene is identical to another human gene known as MPRI (mannose 6-phosphase receptor, cation-independent). This gene is also the same as a gene on Chromosome 17 in mice (Laureys, Barton, Ullrich, & Francke, 1988). The mouse gene is maternally imprinted, which means that the maternal allele is expressed (Barlow, Stoger, Herrmann, Saito, & Schweifer, 1991; Wutz et al., 1997), but in humans, there is little evidence for imprinting (Kalscheuer, Mariman, Schepens, Rehder, & Ropers, 1993).

The polymorphism that we genotyped (Hol, 1992) is at one end of the gene, called the 3' end, which is not translated and is thus unlikely to be functional. Thus, rather than being the QTL that affects *g*, the IGF2R marker used in this study might be close to another QTL that is functional with respect to *g*. We are currently attempting to identify other DNA differences (polymorphisms) near our IGF2R marker by sequencing the DNA of 20 individuals. We are also looking for new polymorphisms in coding regions of IGF2R because a polymorphism is much more likely to be functional if it is in a coding region. Moreover, it can be determined whether a polymorphism in a coding region results in an amino acid change in the gene product, which provides additional evidence for the polymorphism's functionality. Finally, further evidence for a polymorphism's functionality would be provided by finding that the polymorphism shows a stronger association with *g* than other polymorphisms in the gene. However, it will be difficult to establish definitively whether a particular polymorphism is in fact the functional polymorphism responsible for the QTL effect on a complex trait like *g*. Even more challenging is the task of understanding how the gene works to have its effect on behavior. Charting the biological and experiential pathways between genotype and phenotype is a long and arduous process that has not yet been completed for any complex trait. The hope is that QTLs will provide discrete windows through which to view neurophysiological pathways between genes and behavior. However, finding a QTL association marks the beginning, not the end, of this program of research.

It should be emphasized that the effect size of the association is small. The relative "risk" for the combined high-*g* groups as compared with the combined control groups is only 1.57, even though the high-*g* group scored more than 4 standard deviations above the control group on average. The QTL model predicts that such associations operate continuously throughout the distribution. That is, such QTLs are not genes for genius; moreover, genius involves much more than genes (Eysenck, 1995). If the QTL indexed by IGF2R operates continuously throughout the distribution, the average effect of the allele would be an increase of about 4 IQ points, about 1.5% of the variance. One implication is that an unselected sample would have to be larger than 500 individuals to have 80% power ($p < .05$, one-tailed) to detect an association of the expected magnitude between IGF2R and *g*. Because our high-*g* and control groups are highly selected and relatively small, they are not appropriate for correlating individual differences within groups for IGF2R and *g*. As expected, when we calculated these correlations using an additive genotypic model in which 4/4 geno-

types were coded as 0, 4/5 genotypes as 1, and 5/5 genotypes as 2, the within-group correlations with IQ were negligible: –.03 in the combined high-*g* groups and –.07 in the combined control groups.

Another caveat concerns ethnic stratification, the possibility that IGF2R allelic frequencies happen to differ for certain ethnic groups who differ in *g*. It is for this reason that we restricted our samples to Caucasians. Nonetheless, ethnic stratification within the Caucasian group could be responsible for the IGF2R association if there was, within the Caucasian group, a group with a very different allelic frequency and a very different average *g*. Although we think this possibility is unlikely, we are currently obtaining DNA from parents of the high-*g* individuals to test for ethnic stratification. The transmission disequilibrium test (Ewens & Spielman, 1995) uses parental genotypes to test whether the target allele is indeed transmitted from parent to offspring more than the other alleles. Finding an association within families using this test would eliminate the possibility of ethnic stratification because family members are of the same ethnic group.

The association between IGF2R and *g*, and other DNA associations with *g* that are likely to follow, provides a new tool to address questions about development, multivariate relations, and gene-environment interplay through the use of measured genotypes rather than indirect inferences about heritable influence based on familial resemblance (Plomin & Rutter, in press). Regarding development, the present study assessed cognitive ability when the participants were in middle childhood or early adolescence. Quantitative genetic studies suggest that genetic effects on cognitive ability increase in magnitude from childhood to adulthood (Plomin & Petrill, 1997), which leads to the prediction that IGF2R may be more strongly associated with cognitive ability in adulthood. Multivariate research might explore whether IGF2R is also associated with information-processing or brain-imaging measures. Another multivariate question is whether IGF2R is associated with variation in cognitive ability throughout the range of ability, as the QTL model predicts. A question involving gene-environment interplay is whether IGF2R interacts with or correlates with experiences relevant to cognitive development. Identifying replicable QTLs associated with *g* will revolutionize genetic research on cognition, as the discovery of the apolipoprotein-E association has done for research on cognitive decline and dementia in gerontology.

Despite the exciting opportunities that QTLs offer for research, such new findings also raise new concerns, for example, concerns about genetic determinism, genetic screening, and other misuses of genetic information (e.g., Rutter & Plomin, 1997; Sherman et al., 1997). The small effect size of IGF2R should help to allay concerns about possible misuse of such information because predictions are weak and probabilistic at an individual level. That is, because IGF2R accounts for less than 2% of the variance in *g*, it would not be reasonable to use IGF2R for genetic testing for the purpose of making predictions about a specific individual even though it might be useful for analyses on large samples, as outlined earlier. Such concerns are much more immediate and dramatic in the hundreds of cases in which a single gene is necessary and sufficient to develop a disorder. These single-gene disorders have led to concerns about discrimination in insurance and employment, and several bodies, such as the Institute of Medicine in the United States and the Nuffield Council on Bioethics in the United Kingdom, are addressing these concerns. As decisions are reached for the simple and more pressing case of single-gene disorders, these decisions should provide guidance for the more complex case of QTLs. Despite the new problems created by new findings, it would be a mistake, and futile as well, to try to cut off the flow of knowledge and its benefits in order to avoid having to confront new problems.

Acknowledgments—This research was supported by the National Institute of Child Health and Human Development (Grant HD27694) of the National Institutes of Health. We also thank Melissa Holden, who assisted with the organization of the SMPY data.

REFERENCES

Barlow, D.P., Stoger, R., Herrmann, B.G., Saito, K., & Schweifer, N. (1991). The mouse insulin-like growth factor type-2 receptor is imprinted and closely linked to the Tme locus. *Nature, 349,* 84–87.

Benbow, C.P. (1992). Academic achievement in mathematics and science between ages 13 and 23: Are there differences among students in the top one percent of mathematical ability? *Journal of Educational Psychology, 84,* 51–61.

Brody, N. (1992). *Intelligence* (2nd ed.). New York: Academic Press.

Cardon, L.R., Smith, S.D., Fulker, D.W., Kimberling, W.J., Pennington, B.R., & DeFries, J.C. (1994). Quantitative trait locus for reading disability on chromosome 6. *Science, 266,* 276–279.

Cochran, W.G. (1954). Some methods for strengthening the common χ^2 tests. *Biometrics, 10,* 417–451.

Edwards, J.H. (1991). The formal problems of linkage. In P. McGuffin & R. Murray (Eds.), *The new genetics of mental illness* (pp. 58–70). Oxford, England: Butterworth Heinemann.

Everitt, B.S. (1992). *The analysis of contingency tables* (2nd ed.). London: Chapman & Hall.

Ewens, W.J., & Spielman, R.S. (1995). The transmission/disequilibrium test: History, subdivision and admixture. *American Journal of Human Genetics, 55,* 402–409.

Eysenck, H.J. (1995). *Genius: The natural history of creativity.* Cambridge, England: Cambridge University Press.

Fulker, D.W., Cherny, S.S., & Cardon, L.R. (1995). Multipoint interval mapping of quantitative trait loci using sib pairs. *American Journal of Human Genetics, 56,* 1224–1233.

Gottfredson, L.S. (1997). Why g matters: The complexity of everyday life. *Intelligence, 24,* 79–132.

Grigorenko, E.L., Wood, F.B., Meyer, M.S., Hart, L.A., Speed, W.C., Schuster, A., & Pauls, D.L. (1997). Susceptibility loci for distinct components of dyslexia on chromosomes 6 and 15. *American Journal of Human Genetics, 60,* 27–39.

Hol, F.A. (1992). Improving the polymorphism content of the 3' UTR of the human IGF2R gene. *Human Molecular Genetics, 1,* 347.

Kalscheuer, V.M., Mariman, E.C., Schepens, M.T., Rehder, H., & Ropers, H.-H. (1993). The insulin-like growth factor type-2 receptor gene is imprinted in the mouse but not in humans. *Nature Genetics, 5,* 74–78.

Kornfeld, S., & Mellman, I. (1989). The biogenesis of lysosomes. *Annual Review of Cell Biology, 5,* 483–525.

Kruglyak, L., & Lander, E.S. (1995). Complete multipoint sib-pair analysis of quantitative traits. *American Journal of Human Genetics, 57,* 439–454.

Laureys, G., Barton, D.E., Ullrich, A., & Francke, U. (1988). Chromosomal mapping of the gene for type II insulin-like growth factor receptor/cation-independent mannose 6-phosphate receptor in man and mouse. *Genomics, 3,* 224–229.

Lubinski, D., & Benbow, C.P. (1994). The Study of Mathematically Precocious Youth (SMPY): The first three decades of a planned 50-year study of intellectual talent. In R. Subotnik & K. Arnold (Eds.), *Beyond Terman: Longitudinal studies in contemporary gifted education* (pp. 255–281). Norwood, NJ: Ablex.

Lubinski, D., & Dawis, R.V. (1992). Aptitudes, skills, and proficiencies. In M.D. Dunnette & L.M. Hough (Eds.), *The handbook of industrial/organizational psychology* (2nd ed., pp. 1–59). Palo Alto, CA: Consulting Psychologists Press.

Lykken, D.T. (1968). Statistical significance in psychological research. *Psychological Bulletin, 70,* 151–159.

MacDonald, R.G., Pfeffer, S.R., Coussens, L., Tepper, M.A., Brocklebank, C.M., Mole, J.E., & Anderson, J.K. (1988). A single receptor binds both insulin-like growth factor II and mannose-6-phosphate. *Science, 239,* 1134–1137.

Morton, N. (1982). *Outline of genetic epidemiology.* Basel, Switzerland: Karger.

Owen, M.J., Holmans, P., & McGuffin, P. (1997). Association studies in psychiatric genetics. *Molecular Psychiatry, 2,* 270–273.

Plomin, R. (1997). Identifying genes for cognitive abilities and disabilities. In R.J. Sternberg & E.L. Grigorenko (Eds.), *Intelligence: Heredity and environment* (pp. 89–104). New York: Cambridge University Press.

Plomin, R., DeFries, J.C., McClearn, G.E., & Rutter, M. (1997). *Behavioral genetics* (3rd ed.). New York: W.H. Freeman.

Plomin, R., Fulker, D.W., Corley, R., & DeFries, J.C. (1997). Nature, nurture, and cognitive development from 1 to 16 years: A parent-offspring adoption study. *Psychological Science, 8,* 442–447.

Plomin, R., McClearn, G.E., Smith, D.L., Skuder, P., Vignetti, S., Chorney, M.J., Chorney, K., Kasarda, S., Thompson, L.A., Detterman, D.K., Petrill, S.A., Daniels, J., Owen, M.J., & McGuffin, P. (1995). Allelic associations between 100 DNA markers and high versus low IQ. *Intelligence, 21,* 31–48.

Plomin, R., Owen, M.J., & McGuffin, P. (1994). The genetic basis of complex human behaviors. *Science, 264,* 1733–1739.

Plomin, R., & Petrill, S.A. (1997). Genetics and intelligence: What's new? *Intelligence, 24,* 53–77.

Plomin, R., & Rutter, M. (in press). Child development, molecular genetics, and what to do with genes once they are found. *Child Development.*

Risch, N., & Merikangas, K. (1996). The future of genetic studies of complex human diseases. *Science, 273,* 1516–1517.

Risch, N., & Zhang, H. (1995). Extreme discordant sib pairs for mapping quantitative trait loci in humans. *Science, 268,* 1584–1589.

Rutter, M., & Plomin, R. (1997). Opportunities for psychiatry from genetic findings. *British Journal of Psychiatry, 171,* 209–219.

Sherman, S.L., DeFries, J.C., Gottesman, I.I., Loehlin, J.C., Meyer, J.M., Pelias, M.Z., Rice, J., & Waldman, I. (1997). Behavioral Genetics '97: ASHG Statement. Recent developments in human behavioral genetics: Past accomplishments and future directions. *American Journal of Human Genetics, 60,* 1265–1275.

Wechsler, D. (1974). *Wechsler Intelligence Scale for Children—Revised.* New York: Psychological Corp.

Wutz, S., Smrzta, O.W., Schweifer, N., Schellander, K., Wagner, E.F., & Barlow, D.P. (1997). Imprinted expression of the IGF2R gene depends on an intronic CpG island. *Nature, 389,* 745–749.

(RECEIVED 11/30/97; REVISION ACCEPTED 12/2/97)