

DNA Markers Associated with General and Specific Cognitive Abilities

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Multivariate quantitative genetic research suggests a hierarchical model of cognitive abilities where genetic effects are largely general, cutting across most cognitive abilities. Some genetic effects, however, are specific to certain cognitive abilities. These results lead to a hypothesis for molecular genetic research: Although most genes associated with one cognitive ability will be related to other cognitive abilities, some genes will be specific to a

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particular cognitive ability. The current research explored this hypothesis in an analysis of data on specific cognitive abilities from 86 children from 6 to 12 years of age from a larger allelic association study of general cognitive ability. Eight DNA markers were entered simultaneously in separate multiple regression analyses predicting each of four specific cognitive ability factors (Verbal, Spatial, Perceptual Speed, Memory), as well as WISC-R subtest scores. Four markers (CTGB33, EST00083, HLA, and SOD2) showed similar effects across the cognitive ability scales, suggesting that they are related to general cognitive ability (*g*). These associations became negligible when the effects of '*g*' (WISC-R IQ) were removed. Three markers (ADH5, DM, and NGFB) continued to be significantly associated with specific cognitive ability scales after the effects of '*g*' were removed. Although preliminary, these molecular genetic results support the hierarchical model predicted by quantitative genetic research.

Many genes associated with cognitive disability have been identified. Most involve rare, recessive single genes that broadly disrupt cognitive development and lead to general mental retardation. The classic example is PKU and the most important recent example is fragile-X syndrome. More than 100 relatively rare genetic disorders include mental retardation among their symptoms, most notably Duchenne muscular dystrophy and Lesch-Nyhan syndrome (Wahlstrom, 1990). Although most of these single-gene disorders lead to general mental retardation, it is thought that some effects are more specific. For example, fragile-X males often show better language skills than expected on the basis of IQ scores, especially for language comprehension as compared to language expression (Dykens, Hodapp, & Leckman, 1994). In contrast, Duchenne muscular dystrophy is thought to affect verbal abilities more severely than nonverbal abilities (Emery, 1993). Lesch-Nyhan usually results in speech and learning difficulties, but memory for recent and past events appears to be unaffected (Anderson, Ernst, & Davis, 1992). A dominant single-gene disorder, neurofibromatosis, often results in general learning difficulties, but verbal abilities tend to be higher than nonverbal abilities (Ferner, 1994). Of considerable recent interest is Williams syndrome, for which mental retardation is common, but expressive language skills appear to be spared or even enhanced (Bellugi, Wang, & Jernigan, 1994). Two genes have been identified that account for most cases of the relatively rare early-onset version of Alzheimer's disease, which begins with loss of memory and attentional problems (Hardy & Hutton, 1995).

In addition to these recognized single-gene disorders, genetic links have also been found with complex cognitive disabilities that are influenced by both multiple genes as well as environmental factors. The strongest risk factor known for the common, late-onset form of Alzheimer's disease is a particular allele of the apolipoprotein E gene, which increases risk about sixfold and accounts for about 15% of the variance in liability (Owen, Liddell, & McGuffin, 1994). New quantitative trait loci (QTL) linkage techniques were used to identify and replicate a linkage between reading disability and a QTL region on chromosome 6 (Cardon et al., 1994). Although these genetic effects appear to be specific—to the memory loss of dementia and to reading disability—it is not yet known the extent to

which their effects extend more broadly. For example, recent studies of apolipoprotein E in the elderly suggest that the gene is related to general cognitive decline (Feskens et al., 1994; Henderson et al., 1995). It is also possible that the linkage for reading disability is associated with general cognitive ability even though low-IQ individuals were excluded from the original study.

Associations between DNA markers and normal variation in general cognitive ability are also beginning to be explored. The IQ QTL Project has examined allelic associations between 100 DNA markers in or near genes of neurological relevance and general cognitive ability (Plomin et al., 1994, 1995). One DNA marker (EST00083) was significantly associated with high versus low general cognitive ability in two samples, and other markers were marginally significant. Because the samples were selected for high versus low general cognitive ability, previous reports from the IQ QTL Project did not consider specific cognitive abilities. The purpose of the report presented here is to use these data to explore associations with specific cognitive abilities. A recent report suggests that some DNA associations might involve specific cognitive abilities rather than general cognitive ability. A DNA marker for the dopamine D₂ receptor gene showed a significant association with a test of spatial ability but not with general cognitive ability (Berman & Noble, 1995). The lack of association with general cognitive ability was replicated in the IQ QTL Project (Petrill et al., in press).

Multivariate genetic research on general and specific cognitive abilities suggests a hypothesis for molecular genetic research in this area. Phenotypically, most researchers accept a hierarchical factor solution in which specific cognitive abilities such as verbal and spatial ability intercorrelate to yield a factor of general cognitive ability, 'g' (Carroll, 1993). Multivariate genetic research suggests that this hierarchical factor model is mirrored in genetics. That is, although independent genetic variance exists for specific cognitive abilities, most of the genetic variance loads on a genetic 'g' factor (Cardon, Fulker, De Fries, & Plomin, 1992; Luo, Petrill, & Thompson, 1994). These findings lead to the hypothesis that although some genes associated with cognitive ability will be specific to a particular cognitive ability, most associations will be general, yielding correlations across most cognitive abilities.

Our research explores this hypothesis in association analyses between eight DNA markers and specific cognitive abilities for 86 children from the IQ QTL Project for whom complete DNA and specific cognitive ability data are available.

METHOD

Participants

The IQ QTL Project includes two independent samples. The original sample was drawn from 278 twin pairs who participated in the Western Reserve Twin Project (Thompson, Detterman, & Plomin, 1991). High-IQ ($n = 24$) and low-IQ ($n = 18$) participants were selected to provide extreme IQ groups with IQs ± 2 SD

above or below the mean. A middle-IQ group ($n = 21$) was selected to provide a comparison group with IQs near the mean. A second, independent replication sample of singletons was also obtained that included an additional 27 high-IQ and 17 low-IQ participants selected for IQ scores ± 3 SD above or below the population mean. Thus, taken together, data from 107 individuals were collected across the original and replication samples. All were white and lived in a six-county area surrounding Greater Cleveland, Ohio, U.S. Participants were screened for major gene disorders and environmental trauma. Blood was drawn and DNA cell lines established for all participants. Details about the sample are available elsewhere (Plomin et al., 1994, 1995; Skuder et al., 1995).

From the 107 participants included in our previous studies (Plomin et al., 1994, 1995), 86 possessed complete DNA and specific cognitive ability data. This combined sample consisted of 46 high-, 17 middle-, and 23 low-IQ individuals.

Tests

All participants were administered a battery of cognitive tests. The Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974) was administered to provide an index of general cognitive ability. The Colorado Specific Cognitive Abilities battery (CSCA; Plomin, DeFries, & Fulker, 1988) was also administered; it yields verbal, spatial, perceptual speed, and memory scales. For the current study, WISC-R Full Scale IQ was employed as a measure of general cognitive ability, and the CSCA scales and WISC-R subtests were used as measures of specific cognitive abilities. Unlike the WISC-R, the CSCA does not provide age-standardized scales. Thus, age was regressed out of the CSCA using a multiple regression procedure.

DNA Markers

One hundred DNA markers, described previously in this journal (Plomin et al., 1995), were genotyped for all high- and low-IQ participants in the original sample. Markers significant in the original sample were also genotyped in the replication sample and in the middle-IQ group. For this analysis, we selected the eight markers that showed (1) significant allelic frequency differences between the high- and low-IQ groups in the original sample, and (2) at least 10% allelic frequency differences between high- and low-IQ groups in the combined samples. Of these eight markers, only one (EST00083) was also significant in the replication sample. Table 1 provides a description of the location and phenotypic expression of the eight selected markers.

Five of the eight markers showed significant associations in the combined original and replication samples (see Table 2). Thus, the markers selected are not a random sample of DNA markers in the IQ QTL Project, but rather those that showed an association with general cognitive ability, at least in the original sample. This was necessary because the middle-IQ group and the replication sample

TABLE 1
Description of DNA Markers Employed in This Study

Marker Name	Location	Description
ADH5	4q21-q23	Alcohol Dehydrogenase 5: Only brain-expressed alcohol dehydrogenase
CTGB33	3	Brain-expressed triplet repeat
DM	19q13.3	Dystrophia Myotonica: Associated with peripheral nervous system disorder as well as general neurological malaise
ESR	6q24-q27	Estrogen Receptor
EST00083	15925MtDNA	Mitochondrial DNA segment: Located in threonine gene which is associated with various rare neurological disorders
HLA	6p21.3	Major Histocompatibility Complex
NGFB	1p13	Nerve Growth Factor, beta polypeptide: Regulation and differentiation of sympathetic and sensory neurons
SOD2	6q21	Superoxide Dismutase: Required for normal biological functioning of tissues; maintains functioning of mitochondrial enzymes susceptible to inactivation by superoxide

were genotyped only for these markers, and these additional participants were needed for the analyses presented here. Nonetheless, it is reasonable to ask whether associations that appeared for general cognitive ability are general to all specific cognitive abilities and whether any associations with specific cognitive abilities remain after the effects of general cognitive ability are removed.

TABLE 2
Allelic Frequency and Chi-Square Analyses Examining Allelic Associations Between Combined High vs Low IQ Groups: Previous IQ QTL Results

Marker	High	Low	Chi-square
Plomin et al. (1994)			
CTGB33	.34	.56	7.5*
ESR	.45	.57	2.5
DM	.10	.22	4.0*
HLA	.79	.60	7.7*
SOD2	.62	.77	4.5*
Plomin et al. (1995)			
ADH5	.48	.64	1.9
EST00083	.98	.77	4.4*
NGFB	.77	.65	1.7

Note. All markers significant in the original IQ QTL sample.
 * $p < .05$ in the combined sample.

Statistical Procedures

Because WISC-R IQ was used to select both the sample and the markers employed in the IQ QTL study, we examined these possible selection effects on the WISC-R and CSCA measures.

The major goal of this study is to examine the association between the DNA markers and specific cognitive abilities. In all cases allelic information was analyzed. A correlation matrix was calculated that included the 8 DNA markers, the 4 CSCA scales, 11 WISC-R subtests (excluding Mazes), and WISC-R Full Scale IQ to provide an overall picture of the relationship between DNA markers and cognitive ability scores. Despite the utility of correlation as an indicator of bivariate relationships among the DNA markers and specific cognitive abilities, multivariate procedures were necessary to control for potential intercorrelations among the DNA markers introduced by their shared association with WISC-R IQ. More importantly, the central question is whether the relationships between DNA markers and specific cognitive abilities are independent of general cognitive ability.

Thus, we examined the extent to which WISC-R IQ accounts for associations between DNA markers and CSCA scales. Multiple regression was selected as the principal analytic method. The 4 CSCA scales (Verbal, Spatial, Perceptual Speed, and Memory) and 11 WISC-R subtests served as dependent variables in two separate analyses. In Analysis I, allelic data for the eight DNA markers (ADH5, CTGB33, DM, ESR, EST00083, HLA, NGFB, and SOD2) were entered simultaneously as independent variables. Significant associations in this first step of the multiple regression analyses indicate which DNA markers are independently associated with individual cognitive ability scores. In Analysis II, the eight DNA markers were entered simultaneously along with WISC-R Full Scale IQ. If the variance in CSCA scales explained by DNA markers becomes nonsignificant when WISC-R IQ is entered, we can conclude that these DNA markers are associated with general cognitive ability rather than specific cognitive abilities. If DNA markers remain significant predictors of CSCA scales and WISC-R subtests after WISC-R IQ is entered, we can conclude that these markers are associated with the specific cognitive abilities independent of general cognitive ability.

RESULTS

Descriptive statistics are presented in Table 3. The WISC-R IQ mean for our sample is above the population mean, as expected because the IQ QTL sample included more participants in the high-IQ group than the low-IQ group. The standard deviation is double the usual IQ standard deviation because the IQ QTL sample was selected for low and high IQ plus individuals selected for IQs near 100. This also explains why the IQ distribution is negatively skewed and platykurtic. However, stem-leaf plots indicate that the IQ distribution is unimodal and quantitatively distributed, as shown in Figure 1. Descriptive statistics for the CSCA specific cognitive abilities are similar.

TABLE 3
Descriptive Statistics for WISC-R Full Scale IQ, CSCA Verbal, Spatial, Perceptual Speed, and Memory Scales

Variable	<i>M</i>	<i>SD</i>	<i>Skew</i>	<i>Kurtosis</i>	<i>Min</i>	<i>Max</i>
WISC-R IQ	112.88	28.34	-0.58	-0.75	40	151
CSCA						
Verbal	0.54	2.72	-0.52	-0.72	-5.71	4.82
Spatial	0.23	2.53	-0.67	-0.52	-5.67	4.24
Speed	0.05	2.79	-0.55	1.13	-9.63	6.28
Memory	0.15	2.00	-0.14	-0.34	-5.19	4.39

Note. CSCA *SDs* > 1 because CSCA scales are composite variables composed of age-corrected subtests.

The intercorrelations among the 8 DNA markers, the 4 CSCA scales, 11 WISC-R subtests, and WISC-R IQ are presented in Table 4. Examining the correlation between DNA markers and the cognitive scales, it appears that some markers show a general effect. EST00083 is significantly correlated with all cognitive tests. CTGB33 and HLA also correlate significantly with most of the cognitive tests. SOD2 is correlated with CSCA Verbal, Spatial, and Speed scales, as well as four WISC-R subtests. In contrast, other markers appear to show more specific effects. ADH5 is correlated with nonverbal tasks such as CSCA Spatial, Speed, and Memory, as well as WISC-R Block Design. DM appears to show specificity toward verbal scores such as CSCA Verbal and WISC-R Vocabulary and Comprehension, but is also correlated with WISC-R Coding. NGFB, al-

Values	Frequency
15 1	1
14 00122345555577888	17
13 03444455577999	14
12 01133356666789	14
11 007	3
10 012224445778	12
9 237	3
8 01123778	8
7 0144568	7
6 33569	5
5	0
4 05	2

Figure 1. Stem-leaf plot: WISC-R Full Scale IQ.

TABLE 4
Intercorrelations Among DNA markers, CSCA Subtests, WISC-R Subtests,
and WISC-R Full Scale IQ

Variable										
ADH5										
CTGB33	.02									
DM	.16*	.25**								
ESR	.15*	-.08	-.13							
EST083	-.13	-.15	-.20**	.10						
HLA	-.29**	-.00	-.20**	-.19*	-.02					
NGFB	.24**	-.16*	-.03	.33**	.05	-.15*				
SOD2	.26**	.03	.06	.21**	-.00	-.22**	.22**			
VERBAL	-.12	-.24**	-.23**	.06	.33**	.17*	.09	-.15*		
SPACE	-.18*	-.20**	-.08	.00	.27**	.19*	.13	-.20*	.78**	
SPEED	-.15*	-.21**	-.12	.01	.21**	.16*	.06	-.17*	.77**	.79**
MEMORY	-.16*	-.21**	-.08	.03	.28**	.11	.12	-.11	.71**	.72**
Info	-.10	-.17*	-.15	.11	.31**	.16*	.06	-.11	.83**	.69**
Vocab	-.07	-.22**	-.16*	.03	.29**	.18*	.06	-.15*	.90**	.75**
Simil	-.05	-.11	-.14	.08	.19**	.20**	.03	-.08	.78**	.67**
Comp	-.05	-.19*	-.17*	.05	.26**	.16*	.05	-.12	.86**	.75**
Arith	-.04	-.14	-.14	.08	.28**	.18*	.05	-.12	.84**	.75**
Block	-.18*	-.12	-.06	.03	.22**	.19*	.04	-.17*	.71**	.82**
Object	-.07	-.19*	-.07	.04	.18*	.16*	.12	-.21**	.65**	.73**
PicComp	-.07	-.19*	-.09	-.02	.19*	.23**	.14	-.15	.67**	.71**
PicArr	-.07	-.18*	-.14	.05	.24**	.14	.06	-.13	.67**	.72**
Coding	-.11	-.24**	-.16*	.06	.36**	.12	.12	-.15	.74**	.83**
Digit	-.07	-.14	-.13	-.02	.24**	.13	.06	-.21**	.78**	.73**
FullIQ	-.09	-.20**	-.15	.07	.30**	.20*	.08	-.16*	.89**	.86**

though not correlated significantly with any of the CSCA or WISC-R subtests, its correlations nearly reach significance with CSCA Spatial and Memory ability, as well as WISC-R Object Assembly, Picture Completion, and Coding. Finally, ESR is uncorrelated with any of the CSCA or WISC-R scales.

Although not in linkage disequilibrium in unselected populations, the DNA markers in the current study are not statistically independent from one another because the markers were selected on the basis that they all correlated with IQ. (As explained earlier, the reason for this is that in the IQ QTL project only these markers were genotyped for the middle-IQ and replication samples, which were required to make these analyses possible.) Furthermore, as Table 4 also indicates, there are large intercorrelations among the individual cognitive tests scores, yielding high 'g' loadings for the individual cognitive tests. Consequently, multiple regression analyses were conducted to examine the independent prediction of DNA markers upon specific cognitive abilities before and after controlling for the effects of 'g.'

Table 5 presents standardized regression coefficients and significance levels for the CSCA scales and WISC-R subtests as predicted by the eight DNA markers. Mirroring the correlation results, some markers show general effects, whereas others demonstrate more specific effects. EST00083 significantly predicts all

TABLE 5
Multiple Regression Analyses Predicting CSCA and WISC-R Scores From DNA Markers:
Standardized Beta Weights and Significance Levels

Variable	ADH5	CTBG33	DM	ESR	EST083	HLA	NGFB	SOD2
CSCA								
Verbal	-0.01	-0.16*	-0.08	0.03	0.29**	0.15*	0.09	-0.14+
Spatial	-0.10	-0.14+	0.07	0.00	0.24**	0.17*	0.18*	-0.17*
Speed	-0.08	-0.17*	0.01	0.02	0.17*	0.13+	0.09	-0.14+
Memory	-0.11	-0.16*	0.06	0.01	0.24**	0.10	0.15+	-0.09
WISC-R								
Info	-0.00	-0.10	-0.01	0.11	0.28**	0.17*	0.04	-0.11
Vocab	0.05	-0.16*	-0.03	0.03	0.26**	0.17*	0.06	-0.14+
Simil	0.04	-0.06	-0.04	0.10	0.17*	0.21*	0.02	-0.07
Comp	0.05	-0.13+	-0.05	0.04	0.23**	0.16*	0.05	-0.11
Arith	0.06	-0.08	-0.02	0.08	0.26**	0.20*	0.04	-0.11
Block	-0.10	-0.09	0.07	0.07	0.20*	0.17*	0.07	-0.14+
Object	0.01	-0.15+	0.05	0.05	0.16*	0.16*	0.14+	-0.22**
PicComp	0.02	-0.15+	0.03	-0.04	0.17*	0.23**	0.18*	-0.13+
PicArr	0.02	-0.13	-0.03	0.04	0.22**	0.14+	0.05	-0.12
Coding	-0.03	-0.17*	-0.01	0.03	0.33**	0.10	0.12	-0.14+
Digit	0.02	-0.09	-0.05	-0.03	0.23**	0.09	0.10	-0.20*

+*p* ≤ .10. **p* ≤ .05. ***p* ≤ .01.

TABLE 6
Multiple Regression Analyses Predicting CSCA and WISC-R Scores From DNA Markers and WISC-R
Full Scale IQ: Standardized Beta Weights and Significance Levels

Variable	WISC-R	ADH5	CTGB33	DM	ESR	EST083	HLA	NGFB	SOD2
CSCA									
Verbal	0.85**	-0.02	-0.04	-0.08*	-0.02	0.05	-0.02	0.03	-0.01
Spatial	0.83**	-0.11*	-0.03	0.07	-0.06	0.01	0.01	0.12**	-0.05
Speed	0.77**	-0.09	-0.06	0.01	-0.04	-0.04	-0.02	0.03	-0.03
Memory	0.66*	-0.12*	-0.07	0.06	-0.04	0.06	-0.03	0.10	0.01
WISC-R									
Info	0.90**	-0.01	0.02	-0.01	0.05	0.04	-0.01	-0.03	0.03
Vocab	0.93**	0.04	-0.03	-0.03	-0.04	0.01	-0.01	-0.02	-0.01
Simil	0.92**	0.03	0.07+	-0.04	0.03	-0.08*	0.03	-0.05	0.07
Comp	0.90**	0.04	-0.01	-0.05	-0.02	-0.02	-0.02	-0.02	0.02
Arith	0.92**	0.05	0.04	-0.02	0.02	0.01	0.01	-0.04	0.02
Block	0.88**	-0.11*	0.03	0.07+	0.01	-0.04	0.00	0.00	-0.01
Object	0.77**	0.00	-0.04	0.05	-0.00	-0.05	0.01	0.08	-0.11*
PicComp	0.78**	0.01	-0.04	0.03	-0.09+	-0.04	0.08+	0.12*	-0.02
PicArr	0.85**	0.01	-0.01	-0.03	-0.02	-0.01	-0.03	-0.01	0.00
Coding	0.73**	-0.04	-0.07	-0.01	-0.02	0.13*	-0.04	0.06	-0.04
Digit	0.81**	0.02	0.03	-0.05	-0.10*	0.02	-0.08	0.03	-0.07

+*p* ≤ .10. **p* ≤ .05. ***p* ≤ .01.

all or a majority of the cognitive scales (CTGB33, EST00083, HLA, and SOD2) were almost completely accounted for by WISC-R IQ. Of the 34 significant associations across these four markers, only three significant associations remained after controlling for the effects of WISC-R IQ, suggesting that these DNA markers are associated with general cognitive ability.

In contrast, correcting for general cognitive ability in this way suggested possible associations between other markers and specific cognitive abilities (see Table 6). For example, significant associations in Table 5 between NGFB and CSCA Spatial Ability and WISC-R Picture Completion remain significant in Table 6 after WISC-R IQ is removed. Moreover, ADH5, the marker that showed trends toward associations with CSCA Spatial and Memory as well as WISC-R Block Design in Table 5 show significant associations in Table 6 with WISC-R IQ removed.

DISCUSSION

Although very preliminary, this is the first report to explore relationships between DNA markers, specific cognitive abilities, and general cognitive ability. The main limitation involves two types of selection. First, the sample was selected for high, middle, and low IQ, which resulted in a doubling of the standard deviation for IQ. A more serious limitation is that markers were selected based upon their association with IQ. Only these markers were genotyped for the middle-IQ and replication samples needed for our analysis. For these reasons, intercorrelations among DNA markers and cognitive scales are somewhat higher than would be expected in a random sample. These effects, in fact, make it more difficult to show associations with specific cognitive abilities independent of general cognitive ability. This also makes such findings more noteworthy, as in the case of the significant associations independent of WISC-R IQ between NGFB and CSCA Spatial and WISC-R Picture Completion, and between ADH5 and CSCA Spatial and Memory and WISC-R Block Design. What is especially interesting about ADH5 and NGFB is that they predict analogous nonverbal cognitive abilities across both the CSCA and the WISC-R. For the same reasons, it is not surprising that the four markers (CTGB33, EST00083, HLA, and SOD2) that were associated across all four CSCA specific cognitive abilities were almost completely accounted for by WISC-R IQ.

Despite its limitations, the study presented here provides preliminary support for the hierarchical model of cognitive abilities in terms of molecular genetics. The hierarchical model predicts that most genes associated with one cognitive ability will be associated with other cognitive abilities—that is, the association will be the result of general cognitive ability—although some genes will be specifically associated with a particular cognitive ability. Although this hierarchical model is only a hypothesis, it will surely be useful for molecular genetic research to examine specific cognitive abilities as well as general cognitive abilities using a multivariate perspective.

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