Failure to Replicate a QTL Association between a DNA Marker Identified by EST00083 and IQ

STEPHEN A. PETRILL
DAVID BALL
THALIA ELEY
LINZY HILL
ROBERT PLOMIN
Social, Genetic, and Developmental Psychiatry Research Centre, Institute of Psychiatry, London

GERALD E. MCCLEARN
DEBORAH L. SMITH
The Pennsylvania State University

KAREN CHORNEY
MICHAEL CHORNEY
MILTON S. HERSHZ
The Pennsylvania State University Medical Center

DOUGLAS K. DETTERMAN
LEE A. THOMPSON
Case Western Reserve University

CAMILLA BENBOW
DAVID LUBINSKI
Iowa State University

Direct all correspondence to: Dr. Stephen A. Petrill, Judd Hall, Wesleyan University, Middletown, CT, 06459 <spetrill@wesleyan.edu>.

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JOHANNA DANIELS
MICHAEL J. OWEN
PETER MCGUFFIN
University of Wales College of Medicine

In a paper published in this journal, a possible QTL association was reported between general cognitive ability and a marker, identified by an expressed sequence tag, EST00083 (Skuder et al., 1995). In two small samples, the frequency of the common allele of this DNA marker, which was shown to be in the threonine transfer RNA gene in mitochondrial DNA, was significantly greater in a high-IQ group than in a low-IQ group. As part of the ongoing IQ QTL Project (Plomin et al., 1995), we have attempted to replicate this QTL association. First, we found that the QTL association remained significant when we compared 51 high- and 51-average IQ subjects, drawn in part from the samples used in the previous report. However, when we examined the association in new samples of 40 extremely high-IQ subjects and 50 average-IQ subjects, the association did not replicate. This underlies the need for replication in case-control studies of allelic association.

One of the most exciting directions for genetic research on complex traits such as general cognitive ability (*g*, intelligence, IQ) is to harness the power of molecular genetics to identify some of the genes responsible for genetic variation when multiple genes (quantitative trait loci, QTL) are involved (Plomin, Owen, & McGuffin, 1994). The high heritability of *g*, its high reliability and stability, its key role in cognitive neuroscience, and its importance as a predictor of educational and occupational attainment make *g* a reasonable target for such a program of research (Plomin, 1997).

As part of the ongoing IQ QTL Project, allelic associations between 100 DNA markers in or near genes of neurological relevance and IQ were examined (Plomin et al., 1995). One marker, identified by EST00083, shown to be within a mitochondrial gene coding threonine transfer RNA, yielded significant differences between high- and low-IQ groups in two small samples (Skuder et al., 1995). The authors concluded that although this could be a chance result given the large number of markers examined, further research was warranted.

The purpose of this brief paper is to report an attempt to replicate the association between EST00083 and IQ.

METHOD

Sample

Figure 1 describes the various samples employed in the current study. In review, Phase I of the IQ QTL Project focused on the comparison between high- vs. low-IQ groups in a "Phase I original" sample (n = 24 and n = 18, respectively) and an independent "Phase I replication" sample (n = 27 and n = 17, respectively), along with a small number of average-IQ participants (n = 21) for comparison (Plomin et al., 1994; Plomin et al., 1995; Skuder et al., 1995). All participants lived in the Cleveland metropolitan area and were assessed on the Wechsler Intelligence Scale for Children—Revised (WISC-R: Wechsler, 1974). Details concerning this sample can be found in Plomin et al. (1995).

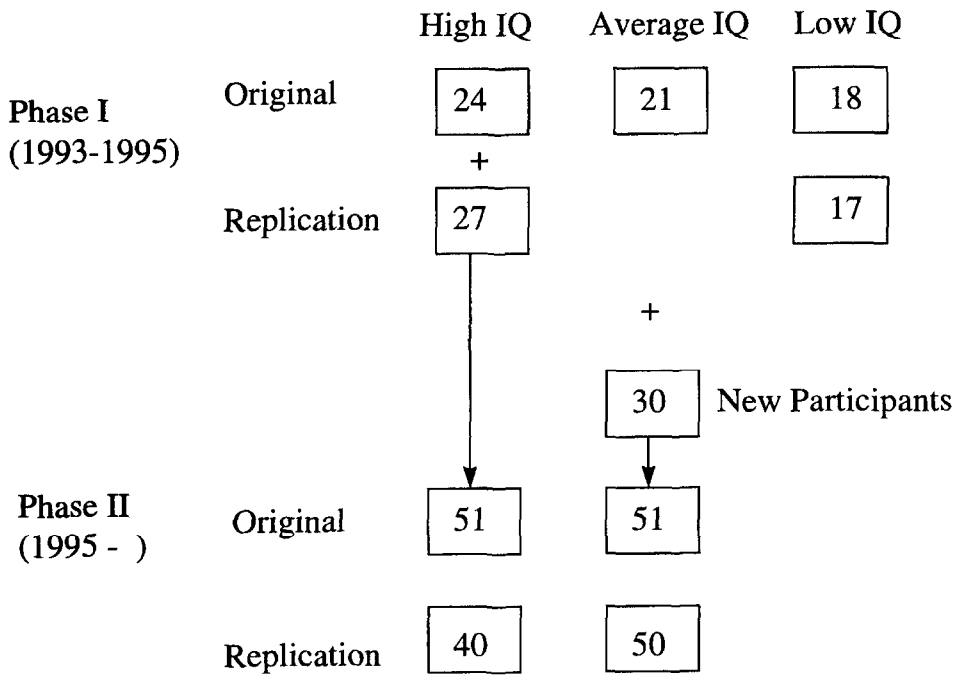

Figure 1. Sample Composition of the IQ-QTL Study

Currently in Phase II, the IQ QTL Project is examining allelic frequency differences between high- and average-IQ groups for reasons explained elsewhere (Plomin, 1997). Again, these groups were compared across two independent samples. The "Phase II original" sample was composed of 51 high- and 51 average-IQ participants. All high-IQ subjects were drawn from groups employed in Phase I (24 Phase I original + 27 Phase I replication). Average-IQ participants were composed of the 21 Phase I middle-IQ participants, plus 30 additional children recruited from the Greater Cleveland metropolitan area.

The Phase II replication sample was composed of 40 extremely high-IQ individuals and 50 average-IQ individuals. These high-IQ individuals were recruited from the Study of Mathematically Precocious Youth (SMPY: Benbow, 1992) and had IQ-equivalents at least four standard deviations above the population mean. The average-IQ replication group was recruited from the Cleveland metropolitan area and possessed IQ's within .5 SD of the population mean. Thus, the sample examined in the current study is composed of a Phase II original sample (51 high-IQ versus 51 average-IQ) and a Phase II replication sample (40 high- versus 50 average-IQ). Table 1 presents IQ data, as well as age and gender information for these groups.

All subjects were white to attenuate the possibility of association caused by ethnic stratification. Permanent cell lines have been established for all subjects in order to create a permanent DNA resource for molecular genetic analysis of general cognitive ability.

Table 1. Sample Characteristics: Phase II IQ-QTL Sample

							Gender	
Group	*Mean IQ*	*SD*	*Min*	*Max*	*Age*	*SD*	*Male*	*Female*
Original								
Mid	103.0	5.6	91	110	12.3	2.7	25	26
High	136.0	9.3	117	156	9.9	1.7	34	17
Replication								
Mid	101.4	7.2	85	116	13.7	1.9	27	23
High*	198.2	6.6	184	207	10.0	0.7	31	9

Note: *IQ scores for the replication high group are estimated scores based upon SAT-Verbal and SAT-Math Scores.

Table 2. Allelic Frequencies of EST00083 in High-IQ and Average-IQ groups: Phase II Original and Replication Samples

Sample	*High-IQ*	*Average-IQ*	*Chi-Square*
Original	.98	.80	16.51*
Replication	.85	.86	0.07

Note: *$p<.0$

EST00083

EST00083 (GenBank M6027) is a 550 base pair (bp) brain-expressed tag site (BESTS) sequenced from clone from a hippocampus cDNA library. The clone was found to be a chimera between genomic DNA on chromosome 6 and mitochondrial DNA (mtDNA). The EST00083 polymorphism association with IQ was from the mtDNA part of the clone and shown to be in a mtDNA gene that codes for threonine transfer RNA (Skuder et al., 1995) DNA extraction and genotyping procedures were identical to those used in Phase I of the IQ/QTL project (Skuder et al., 1995).

RESULTS

Allelic frequencies for the high-IQ and average-IQ groups for Phase II original and replication samples are presented in Table 2. As noted, the high-IQ group is composed of the same high-IQ individuals examined in Phase I and thus, the allelic frequency is the same as in our previous report (Plomin et al, 1995). The difference is that, in Phase II, this high-IQ group is compared to an average-IQ group rather than a low-IQ group. The first row of Table 2 shows that the allelic frequency of EST00083 is significantly different when the Phase II original high- IQ group is compared to the Phase II original average-IQ group.

In contrast, the Phase II replication sample does not yield a significant allelic frequency difference between high versus average IQ. In this sample, the allelic frequency of the high-IQ group is similar in magnitude to the allelic frequency of both Phase II average-IQ groups.

DISCUSSION

We attempted to replicate the significant allelic frequency association between EST00083 and high- and low-IQ groups found in Phase I of the IQ QTL study. Although the results of this study suggest that the Phase I high-IQ groups are significantly different from average- as well as low-IQ groups, this association was not replicated in a completely independent sample of high- and average-IQ subjects in Phase II.

Phase II represents an extension as well as a replication of Phase I. That is, the high-IQ replication group in Phase II is composed of extremely high-IQ individuals selected from the highest-performing SMPY participants with IQ-equivalent scores exceeding 160 (4 SD above the population mean). In contrast, the high-IQ participants in Phase I had IQ scores above 130 (2 SD above the population mean). The rationale for this extension in Phase II was to increase power to detect associations by selecting individuals with the highest possible IQ's. However, because Phase II is not simply a replication of Phase I, it is possible that EST00083 is associated with high IQ in the normal range (that is +2 SD IQ's vs. average IQ) but not at the +4 SD extreme. This reliance on an even more extreme IQ group in our replication study may explain why EST00083 fails to replicate when a 4SD IQ group is used but is, nevertheless, associated with IQ when 2SD IQ groups are employed (Plomin et al, 1995; as well as the "original" sample in our current study). However, one would expect a greater probability of unique genetic effects in groups possessing extremely high IQ scores as opposed to groups of high, but unexceptional intelligence. For this reason, we accept the simpler conclusion that the present study fails to replicate the association between EST00083 and IQ.

These results reinforce the importance of replication in association studies. Selecting for the extremes of a quantitative trait as in the IQ QTL Project greatly increases statistical power relative to genotyping effort. For example, an unselected sample of several thousand subjects would need to be genotyped to attain comparable power to detect a QTL like EST00083. Nonetheless, QTL association analyses with extreme selection do not escape false positive results when multiple markers are examined. For this reason, Phase II of the IQ QTL Project will include not only the extremely high-IQ replication sample described in this report, but also two other high-IQ SMPY samples, one sample especially high in mathematics and the other sample especially high in verbal ability

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