Letter to the Editor

A QUANTITATIVE TRAIT LOCUS NOT ASSOCIATED WITH COGNITIVE ABILITY IN CHILDREN: A FAILURE TO REPLICATE

To the Editor:

In 1998 in this journal, we reported results suggesting that a gene (insulin-like growth factor-2 receptor, IGF2R) on chromosome 6 was associated with general cognitive ability (*g*) in two independent case-control samples of children selected for very high *g* (cases) or for average *g* (controls; Chorney et al., 1998). The suggested association with the IGF2R gene was especially interesting because IGF2R had recently been shown to be active in brain regions most involved in learning and memory (Wickelgren, 1998). The IGF2R association emerged in the first step of our attempts to move in the direction of a systematic genome scan for association in which we genotyped 47 simple-sequence repeat (SSR) DNA markers on the long arm of chromosome 6 (Chorney et al., 1998). In two independent samples, we found significant associations for an SSR marker that happened to be in the IGF2R gene. The SSR marker in the IGF2R gene involved two nucleotide base pairs of DNA (TG in this case) that repeat several times; the number of repeats varies and is stably inherited. One allele (allele 5) for this TG repeat marker yielded frequencies of about 30% in the two high-*g* groups and about 15% in the two control groups of average *g*, with a *p* value of .02 in each of the two samples and a combined *p* value of .001. We also found higher than average allele 5 frequencies for two other groups of high-*g* individuals who were either especially high in mathematics ability or especially high in verbal ability, although these two additional comparisons were only marginally significant (*p*s = .06 and .08). We concluded that "our results suggest that the IGF2R gene is associated with high *g*" (Chorney et al., 1998, p. 164).

Because of the likelihood of false positive results in the quest for quantitative trait loci (QTLs) of small effect size using many DNA markers, replication is crucial (Cardon & Bell, 2001). We had hoped that other laboratories would attempt to replicate the IGF2R association with *g,* but 4 years after the original publication in this journal, we are not aware of such efforts. For this reason, we conducted our own replication analysis. The purpose of the present letter is to report results for the IGF2R gene for a new sample that is as large as the two previously reported samples combined. A more detailed description of this replication study and its implications is available on the Web at www.sgdp.org.uk.

The new sample was obtained in the same manner as in the original study (Chorney et al., 1998). The samples were restricted to non-Hispanic, Caucasian participants to reduce the likelihood that differences in marker allele frequencies between the groups would be due to ethnic stratification. For the new sample, DNA was extracted from cheek swabs (Freeman et al., 1997), yielding an average of 50 μg of DNA for each individual. Genotyping was conducted using procedures similar to those described in our earlier publication (Chorney et al., 1998).

The results we reported for the combined original and replication samples yielded an allelic frequency for allele 5 of 32% in the high-*g* group and 16% in the control group, $\chi^2(1, N = 186) = 12.41$, $p = .0004$. In the present sample, the frequency of allele 5 was 19% in the high-*g* group and 24% in the control group, $\chi^2(1, N = 188) = 1.54$, $p = .22$. Tests of other alleles and genotypic comparisons also failed to replicate our previous results.

After publishing our article using the TG repeat marker in the IGF2R gene, we discovered that there is another polymorphism within the sequence of 100 base pairs that we had amplified (Hol, Geurds, Hamel, & Mariman, 1992). This polymorphism, which involves the insertion or deletion of a sequence of 4 base pairs (ACAA), is within the forward primer itself and would complicate analysis of our original marker because DNA strands with the ACAA deletion would not be amplified (Hill, Craig, Chorney, Chorney, & Plomin, 1999). To address this problem, we genotyped the samples again using a different set of primers (Hol et al., 1992) with a forward primer upstream from the original primer. The new primer set thus encompassed both the ACAA insertion/deletion polymorphism and the TG repeat marker. Analyses taking into account both the TG repeat marker and the ACAA insertion/deletion polymorphism yielded similar results in that the significant results found in our previous study were not replicated in the present sample. (For details, see Hill, 2002.)

The present sample was as large as our original and replication samples combined and provided 98% power to detect a QTL association with an effect size as small as 1%. Thus, we conclude that the TG repeat polymorphism in IGF2R is not associated with high *g*. This finding joins a long list of reported associations that have failed to be replicated (Cardon & Bell, 2001), and those associations that have shown some replication, such as dopamine gene associations with hyperactivity (Thapar, 2003), have not done so consistently. The most likely reason is that the ubiquitous heritability of complex traits such as cognitive abilities and disabilities is due to many QTLs, each of very small effect size, which means that substantially greater power is needed to identify and especially to replicate QTLs (Cardon & Bell, 2001). It has been recommended that QTL association studies be designed to break the 1% QTL barrier, which no behavioral study has yet done (Plomin, DeFries, Craig, & McGuffin, 2003).

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REFERENCES

Cardon, L.R., & Bell, J. (2001). Association study designs for complex diseases. *Nature Genetics*, *2*, 91–99.

Chorney, M.J., Chorney, K., Seese, N., Owen, M.J., Daniels, J., McGuffin, P., Thompson, L.A., Detterman, D.K., Benbow, C., Lubinski, D., Eley, T., & Plomin, R. (1998). A quantitative trait locus associated with cognitive ability in children. *Psychological Science*, *9*, 159–166.

Freeman, B., Powell, J., Ball, D.M., Hill, L., Craig, I.W., & Plomin, R. (1997). DNA by mail: An inexpensive and non-invasive method for collecting DNA samples from widely dispersed populations. *Behavior Genetics*, *27*, 251–257.

Hill, L. (2002). *Molecular genetic strategies for quantitative trait analysis of complex traits: Association-based studies of general cognitive ability.* Unpublished manuscript, Institute of Psychiatry, King's College London, London, United Kingdom.

Hill, L., Craig, I.W., Chorney, M.J., Chorney, K., & Plomin, R. (1999). IGF2R and cognitive ability in children. *Molecular Psychiatry*, *4*(Suppl. 1), S108.

Hol, F.A., Geurds, M.P., Hamel, B.C., & Mariman, E.C. (1992). Improving the polymorphism content of the 3' UTR of the human IGF2R gene. *Human Molecular Genetics*, *1*, 347.

Plomin, R., DeFries, J.C., Craig, I.W., & McGuffin, P. (Eds.). (2003). *Behavioral genetics in the postgenomic era.* Washington, DC: American Psychological Association.

Thapar, A. (2003). Attention Deficit Hyperactivity Disorder: New genetic findings, new directions. In R. Plomin, J.C. DeFries, I.W. Craig, & P. McGuffin (Eds.), *Behavioral genetics in the postgenomic era* (pp. 445–462). Washington, DC: American Psychological Association.

Wickelgren, I. (1998). Tracking insulin to the mind. *Science*, *280*, 517–519.

Cognitive Ability and a Failure to Replicate

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