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Genetic research on cognitive ability

I would like to comment on the article regarding genetic locus associations with cognitive ability (Plomin & Craig, 2001). The use of *g* as a measure of 'intelligence' or 'cognitive function' is controversial and far from universally accepted. Significant criticisms of *g* have been put forth (Gould, 1996) and *g* has been used to promote some rather objectionable eugenic views in the past (Hernstein & Murray, 1994). Admittedly, that still leaves the task of explaining the alleged positive correlation between a high *g* score and some genetic loci.

First, I would hope that any common racial/cultural prevalence found in the 'high' *g* group compared with the 'average' *g* group has been controlled for, as this would otherwise tend to produce a number of false positives simply due to genetic homogeneity.

Second, despite the claim that the expected number of chance false positives in such a DNA pooling study were exceeded, I challenge the authors to use a real-world control rather than a mathematical calculation to prove this assertion. This could be calculated quite simply by randomising the initial sample without regard to *g* scores and determining the number of positive linkages found. The same randomisation could then be performed for the second sample and a replication attempted. Presumably, any replicated linkages would be false positives unless you wanted to track down the study subjects and find something that they had in common (e.g. finding raisins to be tasty or some such thing). This could be repeated several times to give a true expected false positive rate. I suspect that, on average, the randomised groups will have as many positive linkages as those found in the initial study.

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Authors' reply: Although *g* may be controversial in the media, it is no longer controversial among scientists or science journalists (Neisser *et al*, 1996), as seen for example in the reaction to a recent report linking individual differences in grey matter density in the frontal cortex with *g* (Thompson *et al*, 2002). Such research shows that *g* has a biological basis. As mentioned in our review, more genetic research has been amassed about *g* than any other trait in the biological or behavioural sciences and all of that research converges on the conclusion that individual differences in *g* are substantially heritable.

The evidence for a substantial genetic basis to *g* is so overwhelming that there is no longer any need for studies that merely demonstrate yet again the heritability of *g*. One direction for future research is to identify the specific environmental influences on *g*. Genetic research on complex traits provides the best available evidence for the importance of environmental influences and helps to identify specific environmental factors using genetically sensitive designs that can disentangle the effects of nature and nurture. Another direction for research is to attempt to identify some of the specific genes responsible for the substantial heritability of *g*. As part of our review, we reported our work in progress along these lines.

Pittelli hopes that our cases and controls do not differ. The second sentence of our method section states that all subjects were of European descent and non-Hispanic so that differences in marker allele frequencies between the groups were less likely to be due to ethnic differences. We also included a paragraph about ethnic stratification in our Conclusion, in which we note that we are adding a within-family component (parent–child trios) to our design in order to control for any remaining effects of stratification. In addition, we have subsequently applied the genomic control method (Pritchard & Rosenberg, 1999) to pooled DNA and found no evidence for stratification in our samples (Plomin *et al*, 2002*a*). Pittelli proposed randomising subjects to provide an empirical false positive rate. We cannot do this because our genotyping data are based on pooled DNA for the groups. However, genomic control analyses are relevant to establishing an empirical false positive rate. Contrary to Pittelli's prediction, we do not find more than the expected chance number of results using the genome control method (Plomin *et al* 2002*a*).

It is now generally recognised that progress has been slow in identifying specific genes associated with most complex dimensions and disorders, probably because the effect sizes of individual genes is smaller than expected (Plomin *et al*, 2002*b*). Research on *g* is no exception. The in-progress research described in our review has led to a genome scan using nearly 2000 markers in which we find no associations with *g* that cleanly replicate in two case–control samples (each twice as large as the samples described in our review) as well as in a parent–child trio sample (Plomin *et al* 2002*a*). Although the many hurdles that we set for acceptance of a quantitative trait locus association may have been too high, it is important to be conservative in light of reports of associations with complex traits that do not replicate (Plomin *et al*, 2002*b*). None the less, we are following up several promising leads, as well as applying new approaches that capitalise on methodological and substantive advances from the Human Genome Project.

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