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Questions of intelligence

The public interest in the controversial issue of intelligence and heredity has never been greater, if the furore surrounding the recent publication of the best-selling book, *The Bell Curve*[1], is anything to go by. The 845-page tome, written by the late Richard Herrnstein and Charles Murray, has climbed to the top of the US best-seller lists in spite of a critical pounding. Throughout their book, Herrnstein and Murray refer to countless studies that estimate that hereditary factors account for 40–80% of cognitive ability. However, their notion of an emerging 'cognitive elite' blessed with high IQ (intelligence quotient) values will do little to settle the age-old 'nature versus nurture' debate. Nor does it prove the existence of the hypothetical *g* factor — the measure of general cognitive ability which the likes of Stephen Jay Gould claim is a mere statistical artefact, while others are convinced of its heritability.

At the other end of the cognitive bell curve, however, there are signs of progress in defining specific causes of low intelligence, or mental retardation. The results of a study presented by Jonathan Flint (of the Institute of Molecular Medicine in Oxford) and colleagues, on page 132 of this issue[2], seem likely to herald a much improved understanding of the causes of many previously unexplained cases of mental retardation.

As Flint and colleagues explain, about 3% of the population in developed countries have an IQ of less than 70. Yet in about half of those cases, the cause of the mental deficiency is not known. The most common congenital form of mental retardation is Down syndrome, originally termed 'Mongolism' by John Down, who first described the syndrome some 130 years ago. While the extra copy of chromosome 21 in Down syndrome, not to mention other chromosomal trisomies and translocations, affects the dosage and/or integrity of large numbers of genes and can produce severe abnormalities, there are single-gene disorders capable of causing profound mental deficiencies as well. One example is phenylketonuria, which affects only about 1 in 10,000 people, but accounted for about 1% of mentally retarded patients in institutions before the implementation of low phenylalanine diets to combat the disorder[3]. A more mysterious cause of mental retardation is the fragile-X syndrome, produced by the expansion of trinucleotide repeats in the *FMR1* gene. With an incidence of 1 in 1,250 males, fragile-X syndrome is the most common hereditary (as opposed to congenital) form of mental deficiency. In addition to a second fragile site on the X chromosome cloned in 1993, there are hundreds of other single-gene defects with varying associated degrees of intellectual impairment.

But what of the search for the cause of the unaccounted cases of mental retardation? There has long been a suspicion that subtle chromosomal abnormalities may bear some responsibility. A few years ago, David Weatherall predicted: "Since 40% of cases of mental retardation, in which the cause is known, are due to chromosomal abnormalities ... it is likely that at least some cases for which the cause is unknown will turn out to be due to more subtle chromosomal changes that are not amenable to analysis by current cytogenetic

techniques,"[4] which cannot resolve deletions less than five megabases. Weatherall was speaking partly from experience, for in 1981 he had described three unusual severe cases of α-thalassaemia (Hb H), in which the patients also suffered mental retardation, which he doubted was simply due to coincidence[5]. His group later found that some of these patients with what is now called the α-thalassaemia/mental retardation syndrome[6] harboured deletions of chromosome 16p13.3 close to the telomere, in the so-called 'subtelomeric region'.

In 1992, Weatherall offered Flint a position at Oxford to begin a search for cryptic chromosomal rearrangements potentially associated with mental retardation. Realizing that a comprehensive search of the entire genome was beyond their means, Flint and colleagues decided to concentrate on these interesting subtelomeric regions. Flint *et al.*[2] took 99 patients with varying degrees of mental retardation but no obvious chromosomal abnormalities as judged by karyotype analysis, and using three dozen highly informative VNTR (variable number tandem repeat) probes, which could distinguish both parental alleles in the vast majority of cases, surveyed 28 subtelomeric regions for signs of deletions. Somewhat surprisingly, they found three deletions among the 99 patients. In one developmentally retarded infant, there was a *de novo* deletion on the long arm of chromosome 13, detected with two VNTR probes and confirmed by fluorescence *in situ* hybridization (FISH) analysis. In two other patients, *de novo* deletions were detected on the long arm of chromosome 22, although of very different sizes (correlating with the degree of impairment).

By flow sorting and labelling the deleted chromosomes from the three patients, Flint *et al.* went on to examine the nature of the three deletions in more detail. The chromosome-13 deletion proved to involve an unbalanced translocation with the X and Y chromosomes. The more severely affected patient with a 22q deletion was revealed to have a translocation with chromosome 9q. The third patient, a mildly affected boy, appears to have suffered a specific 60-kilobase (kb) deletion on 22q as judged by pulse-field gel electrophoresis.

How significant is the presence of deletions in three out of 99 mentally retarded patients? In order to exclude the possibility that chromosomes 13 and 22 might be more prone than usual to deletions, Flint has earnestly looked for similar deletions on the long arms of these two chromosomes in more than 200 control families, as well as for trisomies in these regions in several thousand unrelated individuals. In all cases, he found nothing. If one then takes into account the facts that about 20 subtelomeric regions were not analyzed, and that the probes that were used were not completely informative or necessarily as close to the telomere (that is, within one megabase or so) as the researchers would like, Flint *et al.* suggest that the true frequency of cryptic subtelomeric deletions in mental retardation is at least 6%, and probably much higher.

The genetics of *g*: Finding many of these genes involved with mental retardation will not prove easy. But some, such as the gene on chromosome 22q mapped by Flint *et al.* to just 60 kb, or other single gene loci that are close to being discovered, should prove fascinating once characterized. Meanwhile, behavioural geneticists, such as Robert Plomin at Penn State University, are scanning the genome for signs of quantitative trait loci that may influence cognitive ability[3], reporting two recent hints on chromosomes 3 and 6 for example[7]. But these will require thorough confirmation to avoid the sad fate that has befallen other recent reports of genetic linkage in behavioural disorders. Flint views this work as being very useful and complementary to his own, in that it may identify genes in which variations are shown to influence cognitive ability. This would be in contrast to his own studies on mental retardation patients, which may uncover a number of genes essential for neurodevelopment.

The interesting discovery of cryptic rearrangements in mental retardation patients is a welcome advance for the field, but much remains to be done. If Flint *et al.*'s estimates prove to be accurate, about 1 in 500 people in the population may harbour similar defects, but that still leaves many other putative hereditary and environmental causes of mental retardation to be determined.

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3. Plomin, R., Owen, M.J. & McGuffin, P. *Science* **264**, 1733–1739 (1994).
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6. Wilkie, A.O.M. *et al. Am. J. hum. Genet.* **46**, 1112–1126 (1990).
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