Intelligence and the X chromosome

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T-shirts that read: "Xq28—Thanks for the genes, Mom!" were produced in the homosexual community in San Francisco when linkage studies first suggested that the gay gene might be at that location. A T-shirt with a wider application might be one that gives thanks to mothers from their children for her X chromosomes for their major contribution to their intelligence.

Intelligence has been defined "as the ability to deal adaptively with the changing environment, to benefit from past experience, to proceed in goal-directed fashion, to pursue productive avenues of problem solving, and to perceive common properties in otherwise separate domains of experience".[1] The inheritance of intelligence is reported to be mutifactorial, with continuing controversy over the importance of the nature-nurture components. Several studies of monozygotic twins reared apart show a correlation in adult intelligence quotient (IQ) values of about 0·7 "indicating that about 70% of the observed variation in IQ . . . can be attributed to genetic variation".[2] The distribution of IQ scores measuring some aspect of intelligence is bell-shaped, with both sexes having the same mean scores but with wider variability in the male. There are significant differences in scoring between the sexes, with male individuals having better mathematical and musical abilities, and female better verbal abilities.

Lehrke[3,4] was the first to suggest that the genes for coding intellectual function might be on the X chromosome. He based his argument on the known excess of males with mental handicap, the different distributions of IQ in male and female individuals, and from a personal study of ten families in which non-specific mental retardation was segregating in an X-linked pattern. This suggestion was regarded as so unorthodox that Lehrke's first published paper was followed by two invited commentaries,[5,6] both of which were highly critical but offered no evidence to refute his conclusions.[7] In 1992 with Partington,[8] I restated Lehrke's hypothesis, suggesting that there was now molecular evidence to support his proposal. Morton[9] gently replied, stating that on theoretical grounds the evidence presented was not strong enough. The epidemiological and molecular evidence has continued to grow such that there is need for reappraisal.

At the time of the Lehrke controversy our group[10] was studying the epidemiology of mental handicap in New South Wales. We documented the expected excess of males with moderate handicap as 32%. We also found many more families with two affected sons than two affected daughters, which was supportive evidence that genes on the X chromosome were contributing substantially to the male excess. Herbst and Miller[11] recorded the same male and brother pair excess in British Colombia, their data including the mildly handicapped. They suggested that there might be nine to 17 single genes on X that were involved with mental handicap.

Since then at least 154 entities have been described with mental retardation and X-linked inheritance.[12] In some of these, the intellectual handicap is clearly a secondary feature, and one would not suspect that these genes were directly concerned with intelligence. For example, we can reasonably suppose that in X-linked hydrocephalus the mental retardation is secondary to the structural abnormality of the brain and that in the Lesch-Nyhan syndrome it is secondary to the inborn error of purine metabolism. However, there is an increasing number of other conditions in which loss of intelligence (mental retardation or intellectual handicap) is equally clearly the primary or only event.

In primary or non-specific X-linked mental retardation (XLMR) affected males have no phenotypical, neurological, or biochemical features in common apart from mental retardation. The prevalence of XLMR is three times that of the fragile X syndrome (2·5 per 10 000[13]) in the moderately handicapped and may be even more common in the mildly handicapped. There are now 32 extended pedigrees in which linkage studies have localised the genes to areas on the X chromosome. In many the limits of the locations overlap, but eight discrete localisations have emerged, which define the lowest limit of the number of genes involved. They extend over the short and long arm of the X chromosome.[14] The genes themselves are not sequenced and their individual functions are unknown.

Morton's counterargument was that there were a calculated 325 recessively inherited genes associated with mental retardation. Therefore by calculating total DNA content of all the chromosomes the contribution of the X chromosome should be 17 genes. Theoretically there may be 308 genes on the autosomes that contribute to mental retardation. Indeed there are many recessive or dominantly inherited conditions that are associated with mental retardation but no families listed in the McKusick catalogue in which the single and only feature is mental handicap. The total number of genes on X relating to mental handicap is now at least 154 plus these eight locations for XLMR, which greatly exceeds the theoretical 17 suggested from Morton's calculations.

The conclusion seems inescapable that the genes now localised in families with XLMR indicate mutations in genes coding for aspects of intelligence. These genes are distributed along the whole length of the X chromosome and, presumably, code for various anatomical or functional parts of the neural substratum of intelligence. The female is a mosaic of two X chromosomes, one of which is methylated and inactivated randomly early in embryogenesis. The male with his single X chromosome is, therefore, likely to be more affected by either advantageous genes on the X chromosome or by

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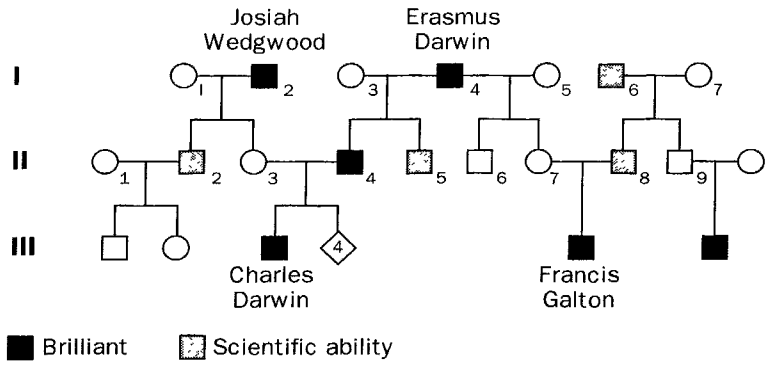

Figure: **Abridged pedigree of the Wedgwood, Darwin, Galton family tree**[15]

deleterious mutational events, which may explain the difference in distribution of IQ between the sexes. The variation in patterns of ability between the sexes could result from greater diversity in the female, she being mosaic reflecting the functioning of genes on both her X chromosomes.

A second approach to identifying genes for intelligence would be through linkage studies in families in which high intelligence is segregating. The classic family is that of Charles Darwin (figure). His grandfather was the founder of Wedgwood Pottery and his cousin, Galton, was a prolific writer and the founder of the Eugenic movement. The pedigree shown in the figure was said, at the beginning of the century, to indicate that genius is a Y-linked dominant, but it could equally well be explained by X linkage. Charles Darwin received Joshua Wedgwood's X chromosome and therefore his intelligence through his mother (II-3), and Erasmus Darwin's brilliance having reappeared in Francis Galton via his mother (II-7), rather than his father. Mary Howard (I-3), was also related to the Galtons.

If the genes coding for intelligence have evolved on the X chromosome this has evolutional advantage. The X or Y system is the mechanism in mammals of sex determination. The X is conserved throughout mammalian evolution.[16] The more intelligent male would be the better provider and may father more children, allowing for rapid propagation of any advantageous change.

In day-to-day practical evolutionary terms for our new millennium the male needs to remember that his primitive urges in mate selection are coded in his genome, and that they target current ideals of sexual attractiveness and youth. His frontal cortex should interpose reminding him that his sons' intelligence, if that is important to him, is solely dependent on his partner, and that is mirrored in both her parents. The female has more freedom of choice; she may be driven to mate by her partners physique but the brightness of her children lies mainly within her. His daughters are helped by the paternal contribution but it is her potential mother-in-law, not her father-in-law, who needs checking out.

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