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INVITED EDITORIAL
Finding Genes on the X Chromosome by Which *Homo* May Have Become *Sapiens*

Gillian Turner

Hunter Genetics and The University of Newcastle, Waratah, New South Wales

The map of the X chromosome is now littered, from one telomere to the other, with genes for mental handicap, alone or in combination with other features. In this issue of the *Journal,* Lindsay et al. (1996) report such an entity from the Scottish Highlands, which they give the catchy title of "PPM-X syndrome," denoting the association of pyramidal tract signs, psychosis, and macroorchidism with mental handicap (XLMR). They have localized this to Xq28 and discuss other genes in the same area, which include L1CAM (associated with MASA [mental retardation, aphasia, shuffling gait, and adducted thumbs] and X-linked hydrocephalus) and two genes for nonspecific XLMR—MRX3 and MRX25. It is also the localization of the gene for G6PD deficiency, which, in earlier studies, had demonstrated linkage to bipolar affective disorders, although this has been questioned in more recent studies. There may well be other families with this pattern of abnormalities who have remained undescribed because depression is so often not diagnosed in those with moderate mental handicap. The occurrence, in this family, of mental handicap with a bipolar disorder may be the chance association of two common disorders, or it may a significant association—at this stage, one cannot judge.

Moderate and mild mental handicap are common, with a prevalence of 3–4/1,000 in the former and 10/1,000 in the latter. It has been known for the past 100 years that mental handicap is more prevalent in males, the excess being on the order of 25%–50% (Lehrke 1974; Turner and Turner 1974; Herbst and Miller 1980). This excess is due to genes on the X chromosome, which account for at least a quarter of all handicap in males and, possibly, for 10% of mild handicap in females (because of heterozygous expression). The original interest generated by the clinical recognition of the fragile X syndrome, followed by the identification of the underlying mechanism as a triplet repeat, brought into the limelight the major importance of X-linked mental retardation. There have now been seven bi-yearly international workshops with published proceedings. Over these 14 years the emphasis at these meetings has changed from the fragile X syndrome to the problem of other causes of XLMR in general.

The commonest and most interesting category of X-linked mental retardation has been given the uninspiring name of "nonspecific XLMR" (Kerr et al. 1991). It is three times more common than the fragile X syndrome. However, it usually fails to be diagnosed, since there are no phenotypic distinguishing features and the only problem is reduced learning capacity; but this latter is—or should be—the diagnostic clue. With the fragmentation of families and smaller family size it becomes harder to establish the supportive evidence derived from an X-linked family history, and clinicians are unwilling to make the clinical diagnosis without added evidence of this kind. It is even harder to do linkage studies when three-generation pedigrees and extensive DNA collections are required. It takes considerable energy and collaboration between genetic units to achieve this. Nevertheless, 35 such pedigrees with nonspecific XLMR have now been mapped. These include at least eight discreet gene localizations, with more being likely as the localizations are narrowed (Gedeon et al., in press). It is of great interest that there is no recognized entity of nonspecific mental retardation inherited as an autosomal dominant or autosomal recessive trait; all such genes are on the X chromosome.

Mutations in these genes involve only learning capacity. Surely they are misnamed. It is more realistic to acknowledge that these are the genes associated with the development of abstract thought, planning, and complex verbal communication; in other words, they are the genes for higher intelligence (Lehrke 1972).

It is interesting to speculate how the genes for intelligence developed so successfully on the X chromosome. Higher intelligence, as a selected characteristic in evolution, has only occurred in mammals, with very rapid more recent developments in the primates. Successful

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Address for correspondence and reprints: Prof. Gillian Turner, Hunter Genetics, P.O. Box 84, Waratah, New South Wales 2298, Australia.

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gene changes on the X chromosome could be spread very rapidly through a single dominant male. The X chromosome has been recognized to be conserved in mammals (Ohno's law). Only the genes on one X chromosome function; the second X chromosome is inactivated. Ohno (1970, p. 1) writes: "Had evolution been entirely dependent upon natural selection, from a bacterium only numerous forms of bacteria would have emerged. The creation of metazoans, vertebrates and finally mammals from unicellular organisms would have been quite impossible, for such big leaps in evolution required the creation of new gene loci with previously nonexistent functions. Only the cistron which became redundant was able to escape from the relentless pressure of natural selection, and by escaping, it accumulated formerly *forbidden* mutations to emerge as a new gene locus."

X inactivation may be one successful method of hiding *forbidden* mutations. One X chromosome spends its lifetime inactivated, with only the brief period of being exposed to natural selection during the development of the gonads. Some may spend two or three lifetimes in almost complete inactivation. Maybe it is X inactivation, a mechanism unique to the X chromosome, that has allowed the hidden mutations underlying the development of women's intelligence to have evolved and been passed down to man.

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