

Comparing men and women: A proposal concerning the genes vs gender issue in studies of cognitive abilities

In the ongoing genetic analysis of complex human behaviour, one contentious issue is the origin of differences between men and women in certain cognitive skills¹. For instance, there is consensus that men do better than women in certain tests of visuospatial ability^{2,3}. Among American preadolescents with very high scores in standardized tests of mathematical reasoning ability⁴, boys outnumber girls 13:1. Environmentalists argue that this difference is due to gender bias, both at home and in school, with smart boys getting more attention and support than girls. However, there are other tests of higher order cognition, such as verbal fluency and the production of rapid and fluent speech, in which women appear to do better than men^{5,6}, an observation for which plausible environmental arguments are few. The polarization of biologically-oriented and socially-oriented researchers over these and related results is a reflection of the difficulties in distinguishing between the effects of genes from those of gender and politics on quantitative measures of cognition. These difficulties have prompted some authors to assert that the genes vs gender issue will remain with us for many years. In their attempts to estimate the contribution of intrinsic factors to such complex human behaviour, geneticists have relied extensively on the analysis of twins and sib-pairs⁷. But this approach is inadequate for sorting out the effects of genes from those of gender because of the extent of underlying genetic variation between sibs and between dizygotic (DZ) twins. Here I draw attention to a rare and apparently little known⁸ condition – monozygotic (MZ) twins discordant for sex (46, XY male – 45, XO female)⁹ – which might provide better resolution of the relative contributions of genes and gender than has been possible with standard twin-pair and sib-pair comparisons.

MZ twins discordant for sex arise as a result of the simultaneous occurrence of twinning and post-zygotic loss of the Y chromosome in the first or an early cleavage division⁹. As a result, evidence of cellular mosaicism is often seen, with

XY cells being detectable in the female twin and XO cells in her male co-twin¹⁰. The incidence of MZ twin births – about the same in all populations – is less than 1:200, and that of XO new-born, 1:10000. But for reasons unknown, the simultaneous occurrence of twinning and the XO constitution is 5 to 10 times higher than that suggested by their individual probabilities¹¹. This increment appears to consist primarily of MZ twins. However, it would be necessary to exclude inappropriate cases such as those in which one or both twins exhibit unacceptable levels of sex-chromosome mosaicism and others in which, say, the XO twin shows developmental anomalies that may have their origins in twinning and are not part of classical Turner stigmata. As a result, the number of twins that may become available for study is likely to be small. Studies of complex phenotypes by the twin method generally involve numbers in excess of fifty pairs. In the present case, however, the proposed comparisons would essentially be between MZ twins and not between cohorts of MZ and DZ twins. This factor, and the tradition in neuroscience of gleaning from intensive study of a small number of cases information of general validity¹²⁻¹⁶, might allow one to work with smaller numbers. A recent example of this tradition is a study of hypotheses relating mathematical intuition to linguistic competence and visuospatial representations¹⁷. The cohort sizes in this study were less than ten. But it is likely that identification of such twins even in small numbers would require the collective efforts of a consortium of laboratories from among countries with established twin and Turner registries. A consortium approach might also help in defining criteria for case selection and in enabling longitudinal studies.

What are the limitations of this system from the standpoint of genetics? The X chromosome in XY-XO MZ twins is necessarily maternal (X^mO). As a consequence, if there are parent-of-origin effects of X-linked genes on cognition, the results may not be applicable to XO women in whom the X is

paternal in origin (X^p). MZ twins in whom one twin is an XO female and the other an XX female are known¹⁸, although they are just as rare or possibly more rare than XY-X^mO MZ twins. Since the X chromosome in the XO twin of an XX-XO MZ pair can be either paternal or maternal, comparative studies of XX-X^pO and XX-X^mO MZ twins may provide a basis for distinguishing between the effects, if any, of paternal vs maternal origin of the X chromosome on cognitive skills in Turner women. Skuse *et al.*¹⁹ compared X^pO and X^mO singletons and found that, as a group, the X^pO women in their cohort achieved better cognition and social adjustment scores than X^mO women. These observations led them to suggest that there is an X-linked gene influencing social cognition and that it is imprinted when inherited from the mother. According to some investigators, however, this evidence requires reassessment (see ref. 20).

The X chromosome forms less than 5% of the haploid (23, X) genome and contains approximately 165 megabases of DNA²¹, of which roughly 3 megabases are in the X-Y homologous pseudoautosomal regions (PARs) at the X termini (X short arm PAR = 2.6 megabases²²; X long arm PAR = 0.4–0.5 megabases²³). As a result, in spite of monozygosity, an XO twin would differ from her XY co-twin in the dosage of genes located in the PARs. Recombination between the X and Y does not normally occur outside the PARs. Nineteen of the genes located in the nonrecombining regions of the X have copies on the Y chromosome²⁴. A phenotypic trait under the control of a dose-sensitive X-Y gene pair might show dimorphism between XX females and XY males if the X copy is subject to inactivation^{25,26}, but no such genes are known. Additionally, in XO women and XY men, the effective copy number of X-specific genes not subject to X inactivation would be half that in XX individuals²⁷, but again, clear examples of such genes are not known.

XO women appear to differ from XX women in one respect relevant to this proposal. Their intelligence is usually

normal, but social competence and adjustment are frequently impaired²⁸. For this reason, it may not be possible to compare an XO twin with her XY co-twin in, for instance, 'executive' skills. In spite of these limitations, it is worth noting that, because they arise from the same zygote, the genetic variation between such twins is the smallest known between two humans of unlike sex. One theoretical possibility with less variation is an MZ pair in which one twin is an XX female and the other an XX male (with or without *SRY*, the Sex determining Region of the Y)²⁹, but no such case has been reported.

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H. SHARAT CHANDRA

Department of Microbiology and
Cell Biology,
Indian Institute of Science,
Bangalore 560 012, India;
and
Centre for Human Genetics,
Bangalore, India