Handedness, language lateralisation and anatomical asymmetry: relevance of protocadherin XY to hominid speciation and the aetiology of psychosis

Point of view

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Sommer *et al* (2001) used meta-analyses to review the literature on handedness, dichotic listening and anatomical asymmetry in schizophrenia and concluded that there was strong evidence for decreased cerebral lateralisation. As they point out, the implication is that finding the locus of the gene for cerebral dominance could unravel the genetic predisposition to schizophrenia. Procopio (2001) raises a number of points relevant to the findings of Sommer *et al* and concludes that both genetic and environmental factors have to be accounted for – 'the right shift is still only a hypothesis'. Procopio's comments focus on handedness and it is important to remind ourselves, as Sommer *et al*'s review makes clear, that handedness is no more than an indirect and developmentally labile index of anatomical asymmetry and language lateralisation; it is this last variable and its genetic determination (Crow, 1998*a*,*b*) that is of greatest relevance.

GENETIC AND ENVIRONMENTAL INFLUENCES

Procopio (2001) rightly draws attention to the study by Steinmetz *et al* (1995) of asymmetry of the planum temporale in monozygotic twins concordant and discordant for handedness. Twins discordant for handedness were more likely to be discordant for planum temporale asymmetry (Fig. 1). Handedness and asymmetry are thus related, but if the underlying determinant is genetic why should monozygotic twins be discordant, as they often are, for either? Procopio proposes that an environmental influence is relevant but the nature of such an influence is obscure (see below). The alternative is to assume that there are unaccounted for (random or epigenetic) variations in development. The importance of the study of Steinmetz *et al* is that it demonstrates that such presently intangible variation is large in relation to the component that, according to a simple view, can be attributed to sequence variation (i.e. that common to identical twins), as has always been implicit in Annett's (1999) right-shift theory.

What environmental factor might influence the development of cerebral asymmetry? Procopio points to the finding of Salvesen *et al* (1993) that children who had been screened by ultrasonography *in utero* were more likely to be non-right-handed than those who had not. However, the difference was small (odds ratio 1.32%; 95% CI 1.02–1.71). As Salvesen *et al* emphasise, non-right-handedness was one of six initial hypotheses, and no association with impaired neurological development was found. An effect of ultrasound on cerebral dominance is a concern but the evidence is modest.

NATURE AND LOCATION OF THE ASYMMETRY FACTOR

The key question is the nature of the asymmetry factor itself. Unless this can be identified as more than a hypothetical gene, not much progress can be expected. That it is the key to understanding disorders of development was suggested by Orton (1937) in relation to reading disability, and Annett (1985) in relation to cognitive development in general. Orton predicted deficits at the point of equal hand skill and Annett, on the basis of heterozygote advantage formulation, at the extremes of the hand skill continuum (see Annett, 1999). Our findings in the National Child Development Study cohort (Crow *et al*, 1996, 1998; see also Leask & Crow, 2001), including that reading disability is a precursor of psychosis (Crow *et al*, 1995), support Orton more strongly than Annett, but the important point is that the dimension of lateralisation is a determinant of the human ability to handle symbols. Recent evidence reinforces the conclusion that directional asymmetry on a population basis is a human (or at least hominid) characteristic (Fig. 2). What this evidence suggests is that at some point in hominid evolution there was a discrete genetic change (a saltation), and that this change was associated with cerebral lateralisation and played a role in the evolution of language. This hypothesis can be related

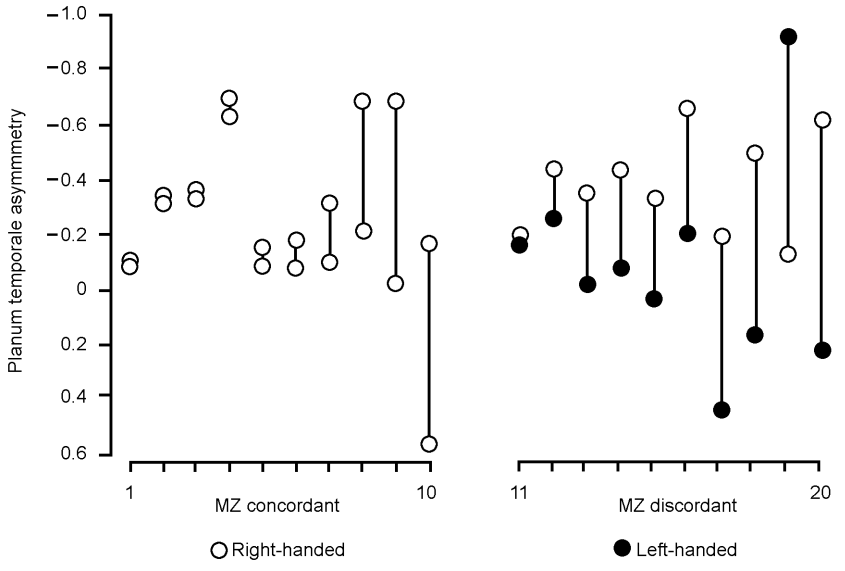

Fig. 1 Distribution of direction and degree of planum temporale asymmetry in 20 pairs of monozygotic (MZ) twins. MZ concordant: twin pairs 1–10 concordant for handedness; MZ discordant: twin pairs 11–20 discordant for handedness (X-axis). Y-axis: negative values indicate left-ward, positive values right-ward planum temporale asymmetry (adapted from Steinmetz *et al*, 1995).

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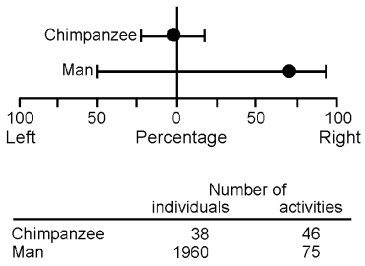

	Number of individuals	activities
Chimpanzee	38	46
Man	1960	75

Fig. 2 Direction of hand preference for a range of daily activities in a population of *Homo sapiens* (data from Provins *et al*, 1982) and *Pan troglodytes* in the Gombe National Park (data from Marchant & McGrew, 1996). Each individual is assigned a point on the 100% left to 100% right scale. Medians and boundary values (horizontal bars) for 95% of the populations have been calculated from data on graphs in the original publications.

to the argument (e.g. Bickerton, 1995) that language is a relatively recent and abrupt acquisition in the hominid lineage and to evidence (e.g. Mellars, 1998) from the archaeological records that the ability to represent in symbols goes back no more than 90 000 years. These general views are consistent with the concept (Stringer & McKie, 1996) that the capacity for language is the characteristic that defines modern *Homo sapiens* as a species with an origin somewhere in East Africa around 100 000 years ago. The question is unresolved regarding whether lateralisation was introduced at this time, or whether it was present earlier, for example in *Homo erectus* (Steele, 1998) and was modified by a subsequent genetic change. The implication of this evolutionary perspective is that the genetic changes that led to the evolution of language were relatively simple and small in number.

I have argued (Crow, 1993, 1994) that the pattern of verbal and spatial deficits associated with the sex chromosome aneuploidies indicates that the genetic determinant of asymmetry is in a region of homology between the X and the Y chromosomes. The evolutionary history of the sex chromosomes provides a pointer to its location (Lambson *et al*, 1992; Sargent *et al*, 1996, 2001; Schwartz *et al*, 1998): after the separation of the lineages that led to the chimpanzee and *H. sapiens* a translocation occurred from Xq21.3 to the Y chromosome short arm, and the translocated block was split by a subsequent paracentric inversion (Fig. 3).

Gene sequences within this block are present on the X and Y chromosomes in humans but only on the X in other primates. Within this region of homology a gene – protocadherinXY – has recently been described (Blanco *et al*, 2000) that is a member of a class of cell adhesion molecules expressed in the brain that have a role in axonal guidance. It is therefore a candidate for *H. sapiens*-specific characteristics such as cerebral asymmetry (Crow, 2001). In that there are sequence differences between the X and Y copies, this gene can account for gender differences such as those observed in age of onset of psychosis, lateralisation and the development of verbal ability. According to the X–Y theory of cerebral asymmetry, the chromosomal re-arrangements that led to protocadherinX being represented on the Y as well as the X chromosome were speciation events in hominid evolution (Crow, 2000).

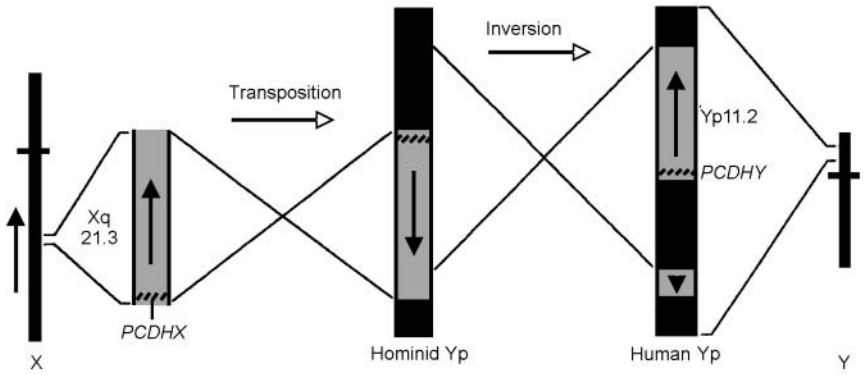

Fig. 3 The transposition from Xq21.3 and subsequent paracentric inversion on Yp, that generated the Xq21.3/Yp11 block of homology and its orientation in modern *Homo sapiens*. Vertical arrows indicate the orientation of the gene sequence. Yp, Y chromosome short arm; cross-bars on the X and Y chromosome icons indicate centromeres. *PCDHX*, protocadherinX; *PCDHY*, protocadherinY. (Adapted from Schwartz *et al*, 1998.)

EPIGENETICS OF ASYMMETRY

The particular interest of an X–Y homologous gene subject to recent evolutionary change is its status with respect to X inactivation – the epigenetic process by which the expression of most genes on one X chromosome in females is inhibited (Lyon, 1974, 1999). Genes with a copy on the Y chromosome are protected from this process, although the mechanism of this protection is obscure. It presumably applies to protocadherinXY. Genes that have recently translocated from the X to the Y are in a new environment; the Y copy escapes from X inactivation and there must be a process whereby the state of inactivation of the gene on the X chromosome changes (see Jegalian & Page, 1998). One possibility is that the protected sequences are those that are able to pair in male meiosis with similar sequences on the Y (Burgoyne, 1982; Crow, 1991; but also see Burgoyne & McLaren, 1985). Determining the mechanism and rules that govern this process could be a necessary prelude to an understanding of the variability that is intrinsic to the species.

CONCLUSIONS

ProtocadherinXY in the Xq21.3/Yp region of homology is a candidate determinant of cerebral asymmetry and therefore of the human capacity for language. If the X–Y hypothesis is correct, a component of the variation with respect to this recent and species-specific evolutionary development is epigenetic rather than sequence-based, and it is this, rather than unidentified environmental factors, that accounts for variability of transmission of handedness and psychosis.

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