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Commentary

Is Psychosis a Disorder of XY Epigenetics?

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Psychosis genetics has ploughed an unyielding furrow. The time for predictions that with sufficient markers the three prototypical conditions (schizophrenia, bipolar or manic-depressive disorder and unipolar depression) will each be found associated with specific chromosomal loci is long past. Linkage strategies failed to give simple or even consistent solutions. Genome Wide Association studies (GWAs) have done better but the answer – that many (108 at a recent count) autosomal genes each of very small effect are involved – is puzzling. Some researchers point to the anatomical correlates (deficits in grey matter in the insula, cingulate and para-hippocampal gyri) that follow relatively simple rules, perhaps reflecting rates of brain growth, in probands and their first degree relatives. It is now apparent that anatomical variation in the same brain regions is a characteristic also of anxiety states, obsessive–compulsive disorder, and even substance abuse (Goodkind et al., 2015). A major source of genetic variation has yet to be uncovered.

In the psychosis spectrum we are dealing with variation in form and incidence that crosses populations. Moreover the spectrum is associated with a biological disadvantage – fecundity is decreased – more in males than in females (Power et al., 2013). What balancing advantage keeps these gene(s) in the population?

One answer is that it is the feature that defines the species — the capacity for language (Crow, 2008). Much is unknown about speciation but a part of what we do know is incorporated in Haldane's rule – when in a hybrid cross one sex is inviable or infertile – it is the hetero-gametic sex – that holds across phyla. The generally accepted explanation is that the homo-gametic chromosome – in mammals the X – is involved.

The neural correlate of the capacity for language is cerebral asymmetry — in all populations most individuals are right-handed, but some are left-handed, and the proportions are genetically influenced. Genes with lateralized expression have been sought and not found (Pletikos et al., 2014). The solution comes from a different direction as Ji et al. (2015) have appreciated – individuals with sex chromosome aneuploidies have deviations in verbal and spatial abilities consistent with relative hemispheric dominance – deficits in spatial ability in Turner's (XO) syndrome are opposed to difficulties with words and language delays in Klinefelter's (XXY) and XXX syndromes. Such deficits point to a gene in the XY homologous class (Crow, 1994), and a number of imaging studies document that the sex chromosome aneuploidies are associated with consistent deviations in the cerebral torque, the bias from right frontal to left occipital that is characteristic of the human brain (Rezaie et al., 2009; Lin et al., 2015).

XY homologous genes "escape" X-inactivation, a process usually explained as necessary for dosage compensation between males and females. But could "escape" have a more fundamental role as the pattern that identifies the species? If the pattern includes genes that differentiate a new from an existing species, as Haldane's rule suggests, and, as the observations of Ji et al. indicate, that such genes are expressed in relation to disorders of the sapiens-specific ability to create and communicate in symbols, this possibility deserves consideration.

But what about the males? Any deviation of expression is strikingly absent from the male lines that Ji et al. have examined. The genes of particular interest in males are the homologues in the non-recombining region of the Y chromosome. One would like to know more of what is happening to KDM5D, the homologue of KDM5C on the Y. By the differences between X and Y homologues such gene pairs can account for sexual dimorphisms, as in the case of cerebral dominance and age of onset of psychosis. Such differences are relevant to Paterson's specific mate recognition theory of speciation incorporating Kaneshiro's concept that the first change seen in speciation is a feature in males that can be recognized and selected by females. The gene that codes for this feature might be on the Y chromosome.

The themes of speciation, cerebral dominance, and XY epigenetics are inter-woven in a recent meta-analysis of VBM (voxel-based morphometry) studies in psychosis (Bora et al., 2012). Inclusion of all studies yielded an excess of males with early onset schizophrenia, and deficits of grey matter in insula and cingulate gyrus on both sides. Selecting studies for a balanced sex ratio gave greater resolution — deficits were seen in schizophrenia in the insula on the left and the cingulate gyrus on the right, and in bipolar disorder in the insula on the right and cingulate gyrus on the left. Thus the two major syndromes are inter-related as points on a sex-dependent continuum of hemispheric dominance.

Ji et al. draw attention to XIST as the initiator of the inactivation process and to the KDM5C gene, as normally escaping its influence. Two other members of this select class of 36 XY homologous non-recombining gene pairs are already held to be relevant to psychiatric disorders. The NLGN4 gene has been associated with autism, and the Protocadherin11XY gene-pair that lies within the Xq21.3/Yp11.2 region of homology created by a duplication from Xq to Yp at 6MYA (Williams et al., 2006) is proposed as a candidate in relation to psychosis. It may be that others of the genes in the XY non-recombining regions of homology are relevant. If so Ji et al. will prove to have opened up a new field of investigation in psychosis genetics.

Disclosure

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