

## Foetal origins of schizophrenia: testable hypotheses of genetic and environmental influences

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Although four-fifths of the variance in schizophrenia is attributable to genes, the locus of genetic defect remains elusive. Moreover, genetic investigation provides little detail, beyond suggesting that the contribution of genes is complex, probably polygenic and unlikely to be sufficient in most cases to allow expression of the syndrome (Vincente & Kennedy, 1997). Some apparently genetic effects also need explanation in a more complex model. Population studies show that schizophrenia is more likely to be inherited from an affected mother than from an affected father (Byrne *et al*, 2002), and increasing paternal age confers increased risk (Malaspina *et al*, 2001). Other effects are difficult to explain in conventional genetic terms: season of birth, urbanicity and migration are consistently reported to affect rates of schizophrenia in adulthood (Mortensen *et al*, 1999; Cantor-Graae *et al*, 2003), as is prenatal exposure to famine (Susser & Lin, 1992). Hypotheses of schizophrenia must be able to account for this interplay of genetic and environmental risk factors.

### FOETAL GROWTH AND SCHIZOPHRENIA

Abnormalities of foetal growth (especially extremes of deviant growth) are consistently related to risk of neurodevelopmental disorder and schizophrenia. Restricted foetal growth, rather than postnatal growth, may be particularly associated with male early-onset illness (Gunnell *et al*, 2003). Wahlbeck *et al* (2001) proposed a linear increase in the risk of schizophrenia with decreasing birth weight, decreasing crown-rump length at birth and decreasing placental weight. Low birth weight is also associated with cerebral palsy, developmental delay, cognitive and motor deficits and, in later life, short stature and syndrome X (hypertension, coronary artery

disease, insulin resistance and type 2 diabetes mellitus). Parents of low-birth-weight offspring have an increased risk of type 2 diabetes (fathers more than mothers), as do people with schizophrenia and their unaffected relatives (Hattersley & Tooke, 1999; Ryan *et al*, 2003). It has been proposed that low birth weight, insulin resistance, glucose intolerance and hypertension may all be phenotypes of the same insulin-resistance genotype, such that insulin-related foetal growth reflects not only maternal glycaemia but also foetal genetic factors that regulate insulin secretion (Hattersley & Tooke, 1999). If this were the case, birth-weight variation could largely be explained by foetal genetic control of glucose metabolism or insulin resistance, which shows most variation in the normal population and has been clearly associated with low birth weight (Hattersley & Tooke, 1999). The determinants of low birth weight in a population are complex and various, but mechanisms that control both foetal growth and insulin sensitivity may be involved in the causes of schizophrenia.

### GENOMIC IMPRINTING AND PARENTAL CONFLICT

Genomic imprinting is a mammalian form of gene regulation dependent on parent of origin – and a notable exception to Mendelian laws of inheritance – which may hold important clues to the causes of schizophrenia. Imprinting marks a subset of mammalian genes for allelic preference or (less commonly in humans) for monoallelic expression, and is responsible for the non-equivalent contributions of maternal and paternal genomes in mammals. Most imprinted genes occur in clusters (e.g. on chromosomes 7, 11 and 15) and most have a critical role in foetal growth, central nervous system growth, social cognition, behavioural development

and cancer susceptibility (Reik *et al*, 2003). Imprinting evolved with the advent of mammalian (placentally dependent) live birth and coincided with increasing brain size (Killian *et al*, 2001). Insulin-like growth factor (IGF) genes were the first imprinted genes to be identified and are now known to be crucial for placental development. One of these, IGF-2, is a major modulator of placental growth and its gene is expressed only paternally in most tissues, including foetus and placenta (Constancia *et al*, 2002). In general, paternally expressed imprinted genes enhance foetal growth (possibly by influencing extraction of maternal nutrients from placenta), whereas maternally expressed genes restrict it (Reik *et al*, 2003).

The genetic conflict hypothesis predicts an evolutionary selective advantage for paternal genes, which extract more resources from the placenta, whereas maternal genes are selected to restrain foetal growth in order to conserve resources for future offspring (Moore & Haig, 1991). Mouse knockouts have provided some support for the genetic conflict theory. Deletion of paternally expressed IGF-2, Peg1/Mest, Peg3 or Ins1/Ins2 genes results in intrauterine growth restriction (Lefebvre *et al*, 1998), whereas knockout of maternally expressed IGF-2 or H19 genes or overexpression of paternal IGF-2 result in foetal overgrowth (Reik *et al*, 2003). Recently, Constancia *et al* (2002) reported that IGF-2 – and possibly other imprinted genes, such as Peg1 (Lefebvre *et al*, 1998) – appear to control both the placental supply of, and the genetic demand for, maternal nutrients to the mammalian foetus. In the IGF-2-null knockout mice placental and foetal size deficits arise at a similar stage in development, soon after mid-gestation. Reik *et al* (2003) propose that levels of circulating IGF-2 may be correlated with the regulation of nutrient supply from placenta to foetus and that paternally expressed IGF-2 acts in the placenta to channel maternal resources to the foetus. In humans, the risk of low birth weight in babies at term (in a particular population) varies with circulating concentrations of a maternal placental protein, pregnancy-associated plasma protein A (PAPP-A) in the first 10 weeks of gestation (Smith *et al*, 2002). This protein acts as a protease on IGF-binding proteins; it may thus increase the known stimulatory effects of placental IGFs and be responsible for their activation.

## IMPRINTING AND NEURODEVELOPMENT

If genomic imprinting (and placentation of mammals) evolved alongside increasing brain size and the development of neocortex, abnormalities of imprinting might result in defects specific to neocortical development. In people with schizophrenia, ratios of ventricular to brain volumes are normally distributed. In addition, the neuropathological abnormalities 'characteristic' of the disorder show marked overlap with normal brain structural heterogeneity in the general population (Harrison, 1999). These features imply involvement of a process that controls normal growth and is polymorphically expressed, such as imprinting. Interestingly, ratios of birth weight to placental weight are greater in male than in female infants, and greatest in growth-restricted males (Edwards *et al*, 2000). With a relatively smaller placenta, factors reducing placental function further may have greater impact on male brain growth and in part explain the greater incidence of developmental disorder and neurodevelopmental schizophrenia in males. Reduction in neuronal size is anatomically specific in schizophrenia and not found in, say, visual cortex or motor cortex (Harrison, 1999), which suggests that whatever is responsible for the neurodevelopmental abnormality has some specificity. Neocortical areas such as prefrontal cortex are the last to mature, and therefore may be more vulnerable to growth abnormalities. In the neurogenetic disorder Angelman's syndrome, which is thought to be associated with inappropriate imprinting of chromosome 15q11–13, anomalies of cortical growth occur, including cortical atrophy, microencephaly and ventricular dilatation: see Davies *et al* (2001) for review.

Abnormalities of imprinting have also been described in disorders of abnormal growth control, i.e. tumours. Lack of imprinting or overexpression of (paternal) IGF-2 have been described in gigantism associated with Wilms' tumours. If schizophrenia were associated with an imprinting defect, for example underexpression of paternal or overexpression of maternal (?IGF-2) genes, one might expect the opposite effect: reduced foetal growth (with or without reduced placental function) and less tumorigenesis. There is some evidence that this is the case. Relatives of people with schizophrenia are less likely than the

general population to develop cancer, whereas in people with schizophrenia both higher and lower rates of cancer have been reported, although these data tend to be confounded by socio-economic factors and increased rates of smoking in people with schizophrenia (Jablensky & Lawrence, 2001). Deletion of paternally expressed IGF-2 is known to result in reduced foetal growth and insulin resistance in later life (Ozanne & Hales, 1999), both of which are features of schizophrenic phenotypes.

Abnormal imprinting is also consistent with the greater maternal inheritance and paternal age effects in schizophrenia. Maternal schizophrenia may be associated with inherited abnormalities of imprinting (e.g. loci of imprinted genes may be adjacent to loci relevant to schizophrenia) or with environmental factors (reduced maternal resources or increased maternal stressors) that promote changes in imprinting, such as reduction of paternally expressed IGF-2. Abnormalities of paternally expressed IGF-2 may also be likely to occur with greater parental age. Other epigenetic phenomena, such as unstable trinucleotide repeat sequences, can also account for paternal age effects, although evidence to date suggests that that this is not the case in schizophrenia (Vincent *et al*, 2000).

## IMPRINTING AND ENVIRONMENT

Environmental factors may be better explained by epigenetic effects such as imprinting than by conventional DNA sequence genetics. Season of birth effects in schizophrenia may occur through seasonal alterations in IGF expression and placental development. In sheep, lambs born in autumn or winter have substantially lower birth weights than those born in spring, and this seasonal variation is secondary to reductions in levels of maternal circulating IGF-1 and placental size (Jenkinson *et al*, 1995). In humans, seasonal variation in birth weight is consistently reported, although the mean change appears small in populations where extremes of resource availability do not occur seasonally. Migration, urbanicity and famine could also alter resource availability and affect foetal–placental maternal nutrient supply by influencing IGF expression. This is likely to be an archaic adaptation that would allow a variation in

placental flow of nutrients to the foetus in anticipation of reduced environmental resources during the winter months (perhaps signalled by light period) or during famine. It is interesting that in some species in which male foetuses may 'cost mothers more', fewer males are born as population density increases (Kruuk *et al*, 1999).

The hypothesis that schizophrenia in part stems from abnormal foetal growth control derived from environmental and other influences on imprinted genes is eminently testable. Using population databases, birth-weight distributions in healthy and ill populations can be described and the interaction between sex (of parent and/or offspring) and environment can be explored. Animal genetic knockout models can be used to study the links between imprinting and placental and cerebral development. Longitudinal human imaging studies can explore the effect of sex and foetal size on brain development, and markers of placental function can be examined during pregnancy in women at risk.

## DECLARATION OF INTEREST

None.

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