No Evidence for a Parent-of-Origin Effect Detected in the Pattern of Inheritance of Schizophrenia

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Background: Schizophrenia is a complex genetic disorder with no clear pattern of inheritance. Epigenetic modification of genes may thus play a role in its transmission.

Methods: In our study, 439 families with at least two ill siblings with schizophrenia (208 with unilineal transmission) were examined for evidence of a parent-of-origin effect (e.g., evidence of parental imprinting on the familial transmission of schizophrenia).

Results: No significant difference in the prevalence of maternal compared with paternal transmission was found. In addition, affected male subjects did not differ from affected female subjects in the proportion of their offspring diagnosed with schizophrenia.

Conclusions: Although the transmission of schizophrenia may be influenced by epigenetic events, our study fails to find evidence that one epigenetic mechanism, a parent-of-origin imprinting effect, determines whether an individual expresses the illness.

Key Words: Schizophrenia, genetic disorder, imprinting, epigenetics

Introduction

Although a genetic predisposition for schizophrenia is evident, its pattern of inheritance is not simply Mendelian (reviewed by Kendler and Diehl 1993). Because discordance for illness among monozygotic twins is relatively high (approximately 50%) and the risk to secondary relatives is less than that which would be expected for a “genetic” disorder, it is generally thought that environmental or epigenetic mechanisms must contribute to the eventual expression (Gottesman and Shields 1982).

Recently, epigenetic mechanisms, defined as nonenvironmental modifications of gene expression, have gained some attention (Petronis et al 1999). One such mechanism, “anticipation,” an increase in severity from parental to offspring generation, has been observed in several neurodegenerative disorders (reviewed in Petronis et al 1995; Wells and Warren 1998) and in some (Bassett and Honer 1994; Bassett and Husted 1997; Beckmann et al 1996; Chotai et al 1995; Gorwood et al 1996, 1997; Heiden et al 1999; Imamura et al 1998; Johnson et al 1997; McInnis et al 1999; Ohara et al 1997; Penrose 1991; Thibaut et al 1995; Valero et al 1996; Yaw et al 1996), but not all (Asherson et al 1994) studies of schizophrenia. Although it is difficult to separate true age-of-onset differences from family collection bias, anticipation is now known, at least in some diseases, to be due to expanding lengths of triplet repeats in coding regions of a gene (reviewed in Brannan and Bartolomei 1999; Ross et al 1993).

Another epigenetic mechanism, “imprinting,” has been less studied in psychiatric disorders but is known to be responsible for differential expression of some other genetic disorders. The classic example is Prader–Willi and Angelman syndromes (reviewed in Jablonka and Lamb 1995). Thus, a mutation in the same gene is expressed in different ways depending on whether the defect is transmitted maternally or paternally, and this in turn depends on whether there is differential parental methylation of the gene.

Imprinting as a determinant of schizophrenia has been examined in only a few studies, and all but one in relation to its effect on age of onset, rather than development of the disorder itself. No imprinting effect has generally been found (Asherson et al 1994; Gorwood et al 1996; Imamura et al 1998; Thibaut et al 1995; Valero et al 1998). Two studies (Husted et al 1998; Ohara et al 1997) found anticipation (as measured by younger age of onset in offspring of ill parents) to be greater from paternal than maternal inheritance, with a nonsignificant trend observed in another study (Stober et al 1998). Yaw et al (1996), on the other hand, found the reverse and McInnis et al (1999) found anticipation in aunt:niece/nephew, but not in uncle:

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of schizophrenia among the offspring of men and women with schizophrenia was not significantly different ($\chi^2 = 0.10, p = .75$). There was no difference in age at the time of evaluation between the offspring of male compared with female probands.

**Discussion**

Our investigation was an attempt to determine whether differential imprinting of a gene could account for the pattern of inheritance of schizophrenia within families. This hypothesis was based in part on previous literature, which has shown that risks of illness to first-, second-, and third-degree relatives of probands with schizophrenia are less than would be predicted by Mendelian inheritance. Some other genetic disorders depend on the parental origin of the defect—for example, the Prader–Willi defect on chromosome 15q (Hall 1990) and Turner’s (XO) syndrome. For the latter, some behavioral and cognitive deficits are evident when the sole X in the affected individual is maternal, but not paternal (Skuse et al 1997).

Imprinting is also of interest in neuropsychiatric disorders since normal development is largely dependent on the timing of imprinting of genes involved in migration and differentiation of neurons (Jablonka and Lamb 1995; Keverne et al 1996). It is conceivable that a deviation in this process could be responsible for the development of neuronal pathways that lead to psychosis susceptibility.

Focusing on the notion that imprinting of a gene depends on the parent of origin (Keverne et al 1996), we hypothesized that there would then be a significant maternal versus paternal difference in inheritance of schizophrenia. Age-of-onset and fertility effects introduce a potential
bias, however. Because women tend to have later onset of schizophrenia than men, they will be more likely to have offspring before becoming ill, leading to an apparently higher frequency of unilineal maternal than paternal families. However, when we examined this relationship after restricting the analysis to those families in which there was unilineal transmission and the transmitting parent was well, no difference in risk was observed. We also focused on a later generation and examined only those probands with schizophrenia who had offspring. In this analysis, again, we found no difference in rates of schizophrenia in offspring of men with schizophrenia compared with offspring of women with schizophrenia. These data are preliminary, given that this is the youngest generation and still within the age of risk for future development of schizophrenia. Because the number of offspring was small, we also did not examine whether a later age of onset in female compared with male offspring could have contributed to these negative results. Our previous findings in a subsample of this population (McInnis et al 1999) indicate that age of onset, as evidence of anticipation, interacts with gender, and thus this should be taken into account. Nonetheless, taken together, both sets of analyses in our present study show a lack of evidence for differential parental imprinting to be operating on a gene that leads to schizophrenia.

Future studies might consider that a broader phenotype, such as that which includes affective and anxiety disorders, may contribute to the pattern of genetic transmission within families. These diagnoses are less reliably established and are less closely related to schizophrenia in family studies, however, and thus have not been included in the analyses presented here.

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References


