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Brief Research Communication

Suggestive Linkage of Chromosome 10p to Schizophrenia Is Not Due to Transmission Ratio Distortion

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The genome scan of the European-American schizophrenia families from the Human Genetics Initiative of the National Institute of Mental Health (NIMH) reported a suggestive linkage to chromosome 10p. Subsequently, Paterson and Petronis [1999] reported evidence for transmission ratio distortion on 10p to females. They suggested that transmission ratio distortion to females might have created spurious evidence for linkage to 10p. To address this issue, we reanalyzed our 10p data using only male-male affected sibling pairs. The two chromosome 10p markers that gave the most evidence for linkage in our prior report continued to show evidence for linkage: D10S1423 (NPL Z = 3.0, P = 0.001) and its neighbor D10S582 (NPL Z = 2.9, P = 0.002). These data suggest that our prior report of suggestive linkage of schizophrenia to markers on 10p cannot be attributed to the transmission ratio distortion to females reported by Paterson and Petronis. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88:607–608, 1999.

KEY WORDS: schizophrenia; linkage; transmission ratio distortion; chromosome 10

Although a schizophrenia gene has yet to be cloned, linkage analyses have identified several regions of interest. Among these is an area on chromosome 10p that showed suggestive evidence of linkage in the European-American sample from the NIMH Genetics Initiative [Faraone et al., 1998], a series of Irish families [Straub et al., 1998], and a set of German/Israeli pedigrees [Schwab et al., 1998]. This region has also been implicated for bipolar disorder in the NIMH Genetics Initiative bipolar disorder pedigrees [Rice et al., 1997; Foroud et al., 1998].

Subsequent to these reports, Paterson and Petronis [1999] explored the possibility that transmission ratio distortion on chromosomes 10p might have created false evidence for linkage. Using 40 CEPH pedigrees and CEPH genotype data, they found evidence for linkage of female but not male sex to D10S211, a marker in the region that had been implicated for schizophrenia and bipolar disorder. Thus, they suggested that transmission ratio distortion to females might affect the interpretation of the positive linkage findings.

To address this issue, we reexamined evidence for linkage in the NIMH Genetics Initiative schizophrenia families in male-male affected sibling pairs. The Genetics Initiative was a multi-site study that created a national repository of DNA from families informative for genetic linkage studies of schizophrenia, bipolar disorder, and Alzheimer's disease. The schizophrenia families were collected at three sites: Columbia

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University, Harvard University, and Washington University.

The African-American sample had shown no evidence of linkage to chromosome 10p [Kaufmann et al., 1998] and will not be discussed in this report. The European-American sample comprises 43 nuclear families and 146 subjects [Faraone et al., 1998]. Ninety-six of the family members were considered affected by virtue of having a DSM-III-R diagnosis of schizophrenia (N = 82) or schizoaffective disorder, depressed (N = 14). The families contained a total of 50 independent affected sib-pairs (calculated as the number of affected siblings minus one). Thirty-six families had two affected sibs and seven families had three affected sibs. Methodological details of sample ascertainment are given by Cloninger et al. [1998].

To determine if our prior finding could be attributed to transmission ratio distortion to females, we reanalyzed the 22 male-male affected sib pairs using GENEHUNTER [Kruglyak et al., 1996]. In this reduced sample, the two chromosome 10p markers, which gave the most evidence for linkage in our prior report, continued to show evidence for linkage: D10S1423 (NPL Z = 3.0, P = 0.001) and its neighbor D10S582 (NPL Z = 2.9, P = 0.002). These results do not differ much from our original report: D10S1423 (NPL Z = 3.4, P = 0.0004) and its neighbor D10S582 (NPL Z = 3.2, P = 0.0006).

Notably, if female transmission ratio distortion gives spurious evidence for linkage, there should be many spurious reports of linkage of 10p for many diseases in which large-scale genome scans have been completed. That has not been the case. That observation, along with our data, suggest that our prior report of suggestive linkage of schizophrenia to markers on 10p cannot be attributed to the transmission ratio distortion to females reported by Paterson and Petronis [1999].

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