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No Major Schizophrenia Locus Detected on Chromosome 1q in a Large Multicenter Sample

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Reports of substantial evidence for genetic linkage of schizophrenia to chromosome 1q were evaluated by genotyping 16 DNA markers across 107 centimorgans of this chromosome in a multicenter sample of 779 informative schizophrenia pedigrees. No significant evidence was observed for such linkage, nor for heterogeneity in allele sharing among the eight individual samples. Separate analyses of European-origin families, recessive models of inheritance, and families with larger numbers of affected cases also failed to produce significant evidence for linkage. If schizophrenia susceptibility genes are present on chromosome 1q, their population-wide genetic effects are likely to be small.

Schizophrenia causes severe morbidity in 0.2 to 1% of the world's population, with a heritability of 0.70 to 0.85 attributable to complex inheritance (*1*). No specific genetic variation has been convincingly associated with susceptibility. Some genome-wide scans have produced significant evidence for linkage, but no result has been consistently replicable (*2*). In small genome scans of complex disorders, the largest estimated genetic effects often reflect a substantial upward bias, requiring evaluation in independent, larger samples (*3*). The present multicenter pedigree sample was assembled to determine the degree of support for schizophrenia candidate regions (*4, 5*).

Several recent reports have suggested schizophrenia susceptibility loci of major effect on chromosome 1q. Brzustowicz *et al.* (*6*) reported a significant multipoint lod score (logarithm of the odds ratio for linkage) of 6.50 between markers D1S1653 and D1S1679 [162 to 163 cM from the p terminus (*7*)] in 22 Canadian-Celtic families. Nearby, Gurling *et al.* (*8*) reported a multipoint lod score of 3.2 (176.6 cM) in 13 British and Icelandic pedigrees. More distally, Ekelund *et al.* (*9*) reported lod scores of 3.2 (240.4 cM) in 168 Finnish nuclear families, and of 2.30 (222 cM) in 53 families from an isolated subpopulation. Finally, the Disrupted in Schizophrenia (DISC) genes *DISC-1* and *DISC-2* (*10*) (238.5 cM) are disrupted by a balanced (1;11) (q42.1;q14.3) translocation that segregates with schizophrenia and mood disorders in a Scottish pedigree (*11*).

To evaluate these findings, we genotyped 16 microsatellite markers (*12*) on chromosome 1q in 779 informative pedigrees containing 984 affected sibling pairs (ASPs) and 1918 genotyped individuals with schizophrenia or schizoaffective disorder, from eight independently collected samples (*13*) [Web tables 1 and 2 (*14*)]. The chromosome 1q findings were reported after formation of the multicenter sample (i.e., there was no selection bias). Primary statistical analyses included multipoint ASP (*15*) and nonparametric linkage (NPL) analyses (*16*) and logistic regression analysis (*17*) to test for intersample heterogeneity of sharing in ASPs and for linkage while taking intersample heterogeneity into account (*18*). Results are shown in Fig. 1 [for details, see Web table 3 (*14*)]. Only one of the individual samples [National Institute of Mental Health (NIMH)] produced a nominally significant result ($P = 0.049$) near the Finnish isolate peak (*9*). We observed no other significant results in individual samples or in the combined sample.

There are several possible explanations for the absence of support for linkage in this large sample, aside from the possibility of undetected genotyping errors or differences in diagnostic practice. Ethnicity could be a factor (*19*). However, many families in the University of Wales College of Medicine (Cardiff) and Virginia Commonwealth University (VCU)/Ireland samples had ethnic backgrounds (Scottish,

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Welsh, Irish, Anglo-Saxon) similar to the Celtic Canadian sample. Although the peak Cardiff NPL score (0.92, 160 cM) was near the Canadian peak, any genetic effect would be small; in this sample, the estimate of 53% identical-by-descent (IBD) allele sharing, with 22.7% of ASPs sharing 0 alleles by descent, predicts a locus-specific relative risk to siblings of 1.1. The only nominally significant result observed here was on distal 1q, in the ethnically diverse NIMH sample. We then analyzed 679 European-origin and 58 African-origin families separately [Web table 4 (*14*)] (*20*). For European-origin families, maximum values were Z_{all} = 0.08 (222 cM) and maximum lod score (MLS) = 0.48 (222 cM, 51% IBD sharing). Three samples produced NPL scores of >1.0 [NIMH, 2.35, 222 cM, P = 0.015; Johns Hopkins University (JHU), 1.52, 258.1 cM, P = 0.09; Australia/U.S. (AU/US), 1.33, 213.9 cM, P = 0.126); only the NIMH sample produced an MLS value of >1.0 (1.32, 222 cM, 60% IBD sharing, P = 0.032). At the Canadian peak location, no single sample produced an MLS value of >0.16 or an NPL score of >0.91. For African-origin families, maximum values were NPL = 1.25 (193.3 cM, P = 0.18) and MLS = 0.55 (193.3 cM, 56% sharing, P = 0.18). Note that genetic distances among Europeans are small compared with other world populations, although Finns and Icelanders are outliers (*21*). Our sample does not include comparable families to evaluate the possibility of linkage specifically in Finnish families on distal 1q (*9*) or in Icelandic families on proximal 1q (*8*).

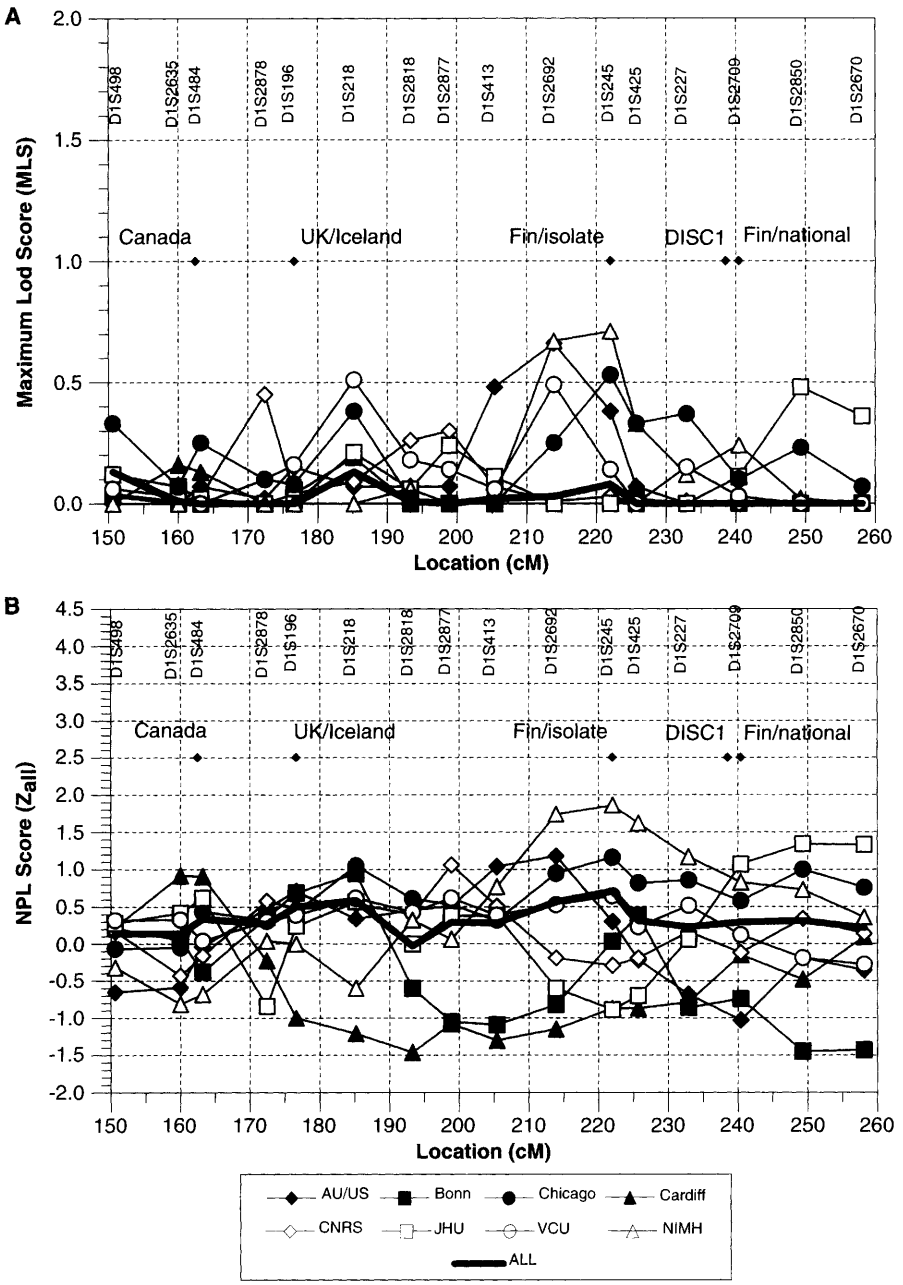

Fig. 1. Results of ASP analysis (**A**) and NPL analysis (**B**). Shown are multipoint MLS (A) and NPL scores (B) for each sample and for all families combined. Applied Biosystems map locations (*7*) are shown. Locations of reported linkage peaks were extrapolated from markers common to the Marshfield (*7*) and Applied Biosystems maps—for example, for the Canadian data set (*6*), the peak at about 168.8 (Marshfield) is shown at 162.5 cM (2 cM proximal to D1S1679); for U.K./Iceland (*9*) at D1S196 (genotyped here; 176.6 cM); for the Finnish national data set (*9*) at D1S2709 (240.4 cM); for the Finnish isolate (*9*) at D1S245 (222.0 cM); and for *DISC-1* (*10*) near D1S251 [245.05 (Marshfield) shown at 238.52 cM].

There were more affected individuals per family in the Canadian sample (mean = 3.6) than in the present data set (mean = 2.5). Analysis of 209 families with three or more affected cases produced MLS = 0.21 (222.0 cM, 52% IBD sharing) and Z_{all} = 0.87 (222.0 cM). The 52 families with four or more cases produced MLS = 0.04 (193.3 cM, 51% IBD sharing) and Z_{all} = 0.46 (258.1 cM). Thus, larger families did not produce evidence for linkage [Web table 5 (*14*)]. Finally, the MLS in the Canadian study was observed for a parametric analysis under a recessive genetic model. We reanalyzed our data under several recessive genetic models by two-point and multipoint analyses [Web table 6 (*14*)] (*22*). The largest heterogeneity lod score (Z_{max}) for the entire sample was 0.31 (multipoint, unaffecteds coded as unknown diagnosis; 185.2 cM), and the largest Z_{max} in an individual sample was 0.65 (multipoint, affecteds only; 210.5 cM, in the VCU/Ireland sample). Our sample would be expected to have 100% power to detect a large genetic effect under the reported recessive model, and to have good power for λ_{sibs} (relative risk to siblings) values of 1.30 or greater (*23*). Thus, our failure to find evidence for a major schizophrenia susceptibility locus on proximal 1q could not be explained by ethnicity, statistical approach, or pedigree size. The most parsimonious explanation is that the genetic effect reported in the Canadian data set was due to the upward bias caused by maximizing scores across the genome (*3*), particularly for small data sets and for loci of small effect, because the underlying genetic parameters are being maximized along with the evidence for linkage: "If one assumes that a published locus-specific effect-size estimate . . . is accurate . . . , one most likely overestimates the power to replicate, perhaps greatly so. . . . A corollary is that failure of replication does not imply that a reported finding is false, even though . . . the locus-specific effect-size estimate from the initial study is likely an overestimate" (*3*). We cannot determine whether the Canadian finding is a false-positive or a true-positive result whose genetic effect is smaller than reported.

In this large multicenter sample, we were unable to detect a schizophrenia susceptibility locus of major effect on chromosome 1q. It remains possible that the genes identified as disrupted in the Scottish translocation finding (*10, 11*), or genes in the regions supported by the Finnish (*9*) and/or Canadian (*6*) samples, will be shown to have small effects on schizophrenia susceptibility in other populations, or that the pathways in which these genes participate will have more major effects. Identifying such genes to elucidate the pathogenesis of this devastating disorder remains a major goal of schizophrenia research.

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13. The eight samples and references to their methods are as follows: AU/US (*24, 25*) (molecular methods apply also to JHU and NIMH), University of Bonn (*26*), Cardiff (*27*), University of Chicago (*28*), CNRS (*29, 30*), JHU (*31*), NIMH (*32*) [for a publicly available data set, see (*33*)], and VCU/Ireland (*34, 35*). Research diagnostic interviews were completed by research clinicians and best-estimate diagnoses were made based on interviews, records, and informant reports. Affected cases had DSM-IIIR/DSM-IV diagnoses of schizophrenia or schizoaffective disorder. Predominant ethnic origins were as follows: Bonn, German, Israeli/Sephardic; Chicago, AU/US, JHU, and NIMH, European, African American; CNRS, French, French/African/Indian mixtures (Reunion Island); VCU/Ireland, Irish; Cardiff, English, Welsh. The NIMH sample was ethnically diverse. For details of sample sizes, see Web table 1 (*14*).
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23. The recessive model described above (*22*), assuming 75% of families linked (*6*), predicts a population-wide λ_{sibs} of 3.55 (*36*). With 800 ASPs there is 100% power to detect MLS = 3 at λ_{sibs} = 1.8 (10-cM map), with expected MLS > 20 for λ_{sibs} = 3 (no parents typed) (*37*). For comparable families containing 800 ASPs, simulation studies determined power (to detect genome-wide significant linkage) ranging from 66 to 94% (dominant model) as λ_{sibs} varied from 1.27 to 1.36, and from 48 to 68% (recessive) for λ_{sibs} from 1.24 to 1.31 (*38*).
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Influence of Gene Action Across Different Time Scales on Behavior

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Genes can affect natural behavioral variation in different ways. Allelic variation causes alternative behavioral phenotypes, whereas changes in gene expression can influence the initiation of behavior at different ages. We show that the age-related transition by honey bees from hive work to foraging is associated with an increase in the expression of the *foraging* (*for*) gene, which encodes a guanosine 3′,5′-monophosphate (cGMP)–dependent protein kinase (PKG). cGMP treatment elevated PKG activity and caused foraging behavior. Previous research showed that allelic differences in PKG expression result in two *Drosophila* foraging variants. The same gene can thus exert different types of influence on a behavior.

Some genes influence behavior via genetic polymorphisms, whereas other genes influence behavior via developmental polymorphisms. But little is known about whether the same gene, or orthologs of a gene, can influence behavior in both ways. This knowledge is necessary to develop a comprehensive understanding of how genes and the environment influence behavior, because both involve genomic responsiveness, albeit over vastly different scales of time.

The *foraging* gene (*for*) affects naturally