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A Complete Genome Screen in Sib Pairs Affected by Gilles de la Tourette Syndrome

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Summary

Gilles de la Tourette syndrome is a neuropsychiatric disorder characterized by waxing and waning multiple motor and phonic tics with a complex mode of inheritance. Previous attempts, which used large multigenerational families to localize susceptibility loci, have been unsuccessful. In this report, the results of the first systematic genome scan, using 76 affected-sib-pair families with a total of 110 sib pairs, are summarized. While no results reached acceptable statistical significance, the multipoint maximum-likelihood scores (MLS) for two regions (4q and 8p) were suggestive (MLS > 2.0). Four additional genomic regions also gave multipoint MLS scores between 1.0 and 2.0.

Introduction

Gilles de la Tourette syndrome (GTS) (MIM 137580) is a chronic neuropsychiatric disorder with onset in childhood. It is characterized by multiple, fluctuating motor and vocal tics of variable severity. Prevalence estimates are higher in males than in females, and range from 1/20,000 to 1/2,000, depending on the age group studied and on the diagnostic inclusion criteria (Apter et al. 1993). More recent studies in school-age populations suggest that the prevalence may be somewhat higher (e.g., 1% in males) (Robertson and Stern 1998). Support for a genetic component in the etiology of GTS comes from several lines of evidence, including twin studies (Price et al. 1985; Hyde et al. 1992) and family studies (Pauls et al. 1991). Family studies also provide support for a common genetic basis for GTS, chronic tic disorder (CT), and obsessive-compulsive disorder (OCD) (Pauls et al. 1986). In addition, a relationship with other psychiatric disorders has been suggested (Comings and Comings 1985). While the relationship between GTS and other conditions has been somewhat controversial, the recurrence risk for GTS among first-degree relatives appears to be quite consistent among studies. Pauls et al. (1991) reported a recurrence risk for GTS of 7/61 (11.5%) in brothers and 4/83 (4.8%) in sisters of probands. Walkup et al. (1996) and Hebebrand et al. (1997) observed recurrence risks that were not significantly different from those reported by Pauls and colleagues.

Segregation analysis generally supports the presence of a major locus, but the characteristics for this predisposing gene vary. Pauls et al. (1990) reported that the pattern of transmission was consistent with autosomal dominant inheritance with incomplete penetrance, whereas Hasstedt and colleagues (1995) found the pattern in large multigenerational families in which there was bilineal transmission to be consistent with a genetic model in which the penetrance of the heterozygote was between the penetrance of the two homozygotes. Walkup et al. (1996) reported a similar solution but with a significant multifactorial background. Several studies have reported the frequent occurrence of bilineal families, in which either GTS, CT, or OCD occurs in both parents of a proband or in one of the parents' first-degree relatives (McMahon et al. 1992; Kurlan et al. 1994; McMahon et al. 1996; Walkup et al. 1996).

Attempts to localize the responsible gene(s) have not yielded consistent results thus far. Linkage analysis of data from a series of multiply affected families resulted in the exclusion of ~80% of the genome (for review, see Barr and Sandor 1998). These analyses were completed assuming a dominant mode of inheritance and locus homogeneity for GTS and spectrum disorders. This data set included several very large families, which, on their own, could yield significant evidence for linkage (Heutink et al. 1995). It is possible that incorrect specification of genetic parameters (e.g., penetrance and gene frequency) of the GTS susceptibility gene could have led to false exclusion of one or more relevant genomic regions.

More recently a genome scan was completed on a series of multigenerational families (Barr et al. [1999]) that included two families that had also been examined

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by Heutink et al. (1995). This genome scan used more informative markers that were evenly spaced throughout the genome. The data were analyzed using both parametric (autosomal dominant with reduced penetrance) and nonparametric methods. LOD scores >1.0, calculated with the parametric method, were observed for 24 of the markers in at least one of the families. No LOD scores >2.0 were observed. When the Affected Pedigree Method (APM; Weeks and Lange 1988) modified by Ward (1993) was used, eight markers were observed with a $P < .00005$ in at least one of the families. APM has been shown to be more likely to give false positive results (Field and Kaplan 1998), so these results should be interpreted with caution.

Other approaches have also been employed in the search for GTS-susceptibility loci. Several families have been reported with apparent cosegregation of balanced translocations with GTS (for a review, see Robertson and Boardman 1996), but these candidate regions have not been supported by positive linkage findings in other families (Heutink et al. 1990). In addition, a number of association studies have been published examining a variety of candidate genes in GTS patients and controls (Comings et al. 1991; Comings et al. 1993; Nöthen et al. 1994*a*, 1994*b*; Grice et al. 1996). Finally, Simonic and colleagues (1998) performed a genomewide search (with genetic markers at an average spacing of 3 cM) using a case-control strategy in a sample of unrelated patients with GTS from an Afrikaner population. These investigators reported positive associations between GTS and markers on chromosomes 11, 14, 20, and 21 that were highly significant before correction for multiple testing. While these are potentially interesting leads, association studies should be interpreted with caution. It has been demonstrated that false positive findings can occur when controls are not perfectly matched with respect to their genetic background (Kidd 1993). It should be noted that none of the positive reports from association studies have been replicated.

Analysis of affected sib pairs has been proposed as an alternative to parametric linkage analysis and association studies. The sib-pair approach is suited for diseases with an unclear mode of inheritance and has been used successfully in studies of other complex disorders. Thus, given the lack of conclusive results from more traditional linkage and association studies, an affected-sib-pair study appears to be an appropriate strategy to identify chromosomal regions linked to GTS.

The overall contribution of genetic factors to disease susceptibility can be measured conveniently by comparing the risks for various types of relatives of probands with the risk of the disease in the general population (Risch 1990*a*). When calculated in this way, the relative risk for sibs of GTS probands is sufficiently high ($\lambda_{sib} > 10.0$) to suggest that affected sib-pair analysis is a viable alternative to traditional parametric linkage analysis for GTS. In this report, the results of a complete genome screen using 370 highly polymorphic DNA markers is reported. The sample for this genome scan consisted of 76 affected-sib-pair families with at least one parent available for clinical evaluation and genotyping. These 76 families yielded a total of 110 sib pairs. Correcting for nonindependence resulted in a sample that was equivalent to 91 independent pairs.

Material and Methods

Sample

All affected-sib-pair families consisted of at least two sibs affected with GTS. Furthermore, in the ascertainment of families, if both parents were affected with GTS or if one parent had GTS, CT, OCD, and/or subclinical OCD and the other parent also received a diagnosis of CT, OCD, and/or subclinical OCD the family was not included in the analyses reported here. All diagnoses were made using DSM-III-R criteria. The criteria for subclinical OCD were the same as those used to make a diagnosis of OCD, with the exception that the individual did not perform the compulsions or obsessions for at least an hour, did not experience them as egodystonic, or did not report any impairment. These were the same criteria used in the family study of OCD reported by Pauls et al. (1995). The final sample included in the genome scan consisted of 76 families with at least two sibs affected with GTS. Both parents were included in the tests for 72 families. Among these 72 families, there were 19 in which neither parent was affected with GTS, tics, or OCD; 32 in which the father was affected and the mother was unaffected; and 21 in which the mother was affected and the father was unaffected. In the remaining four families, only one parent was tested; in every case that parent was unaffected. Of the 76 families, 64 had only two children who were affected, 10 had three affected sibs, and the remaining 2 had four and five affected sibs, respectively.

Phenotypic Evaluation

When a family entered the study, information concerning both affected siblings and their parents was collected in a two-stage process. The initial stage consisted of the collection of information concerning symptoms associated with GTS and OCD using a self-and-family report based on the tic inventory and ordinal severity scales of the Yale Global Tic Severity Scale (Leckman et al. 1989) and the symptom checklist and ordinal scales of the Yale-Brown Obsessive-Compulsive Scale (Goodman et al. 1989). Earlier versions of these instruments have been used in prior studies of individuals with GTS and OCD and have been shown to have a high level of

agreement with expert clinician ratings of tic and obsessive-compulsive symptom severity (Leckman et al. 1993, 1994, 1997). In a second stage, the validity of these symptom ratings were reviewed by an experienced clinician to insure their accuracy and validity. These instruments are currently being used in family studies of both GTS and OCD. Earlier versions have been shown to be both valid, when compared to clinician diagnoses (the rates of agreement between interview derived diagnoses and clinical diagnoses were .98 for GTS and .97 for OCD), and reliable, for the diagnoses of GTS (κ = 1.00) and OCD (κ = .97) (Pauls et al. 1995). For the assessment of other psychopathology, the Kiddie Schedule for Affective Disorders and Schizophrenia (Chambers et al. 1985; Kaufman et al. 1995) was used for children aged <18 years and the Structured Clinical Interview for DSM-III-R (Spitzer et al. 1992) was used for adults. Both interviews have established reliability. For this report, only sibs with a diagnosis of GTS were considered to be affected. Future analyses will include information about chronic tics, OCD, attention deficit hyperactivity disorder, and other comorbid conditions.

Best-Estimate Diagnoses

All diagnoses were made using the best-estimate approach (Leckman et al. 1982). The best-estimate procedure used in the present study followed a standard protocol. Before the initial diagnostic estimate was made, separate files for each individual were prepared. These files contained all available information about the individual, including the completed interview packet and medical records, when available. All of this information was reviewed by three clinicians (B. v.d.W., Rotterdam site; W. M., Utah site; R. A. K., Yale site) who independently made diagnostic assessments. All three diagnosticians were blind to the prior diagnosis of the individual and to his/her relationship to the proband. Each interview was evaluated by two raters. The best estimates of the two diagnosticians were then compared. The rate of agreement between any two diagnosticians was very high (κ = .97) for the diagnosis of GTS. When there was disagreement between the two raters, the individual files were reviewed by the third diagnostician and a final consensus diagnosis was assigned. These consensus diagnoses were then compared with the diagnosis assigned by the clinician at the site where the family was recruited. If there were differences, the clinical materials were reviewed via a conference call and consensus was reached if possible. If there was still disagreement, more data were requested to help resolve the differences. If there was still disagreement, the family was removed from the sample. For the current report, only diagnoses of GTS, chronic tics, OCD, and ADHD were made.

DNA Markers

Short tandem-repeat polymorphisms (STRPs) from Marshfield Screening Set 8 (Yuan et al. 1997) were genotyped in Marshfield. The markers chosen were at a 10-cM average density.

Data Analysis

Allele frequencies for the genetic markers were established by gene counting in genotyped parents. Tests for linkage were done under the direction of LS (Rotterdam site) and were performed following the maximum-likelihood–score (MLS) approach (Risch 1990*b*). In general, the MLS does not depend on marker allele frequencies when the parents' genotypes are available, which was the case for almost all families in the present study. For each pair of affected sibs, the identity-by-descent (IBD) distribution was estimated by single-point and multipoint analysis. In the single-point analysis, the IBD distribution was estimated given the marker genotypes for each marker individually. In the multipoint analysis, MLS values were computed for >4,000 different locations relative to the markers (average step size <1 cM).

For all calculations the MAPMAKER-SIBS program (Kruglyak and Lander 1995) was used. In the estimation of the IBD distribution, this program only considers IBD vectors that are biologically consistent, lying within the "possible triangle" as described by Holmans (1993). All MLS calculations allowed for dominance variance. In addition to these MLS calculations, the information content of the marker map was evaluated, and likelihoods were calculated for a fixed value of λ_s of 2.0 under the assumption of no dominance variance, which leads to an IBD vector of (z_0, z_1, z_2) = (.125, .5, .375). A comparison of these likelihoods with the likelihoods obtained for the Mendelian expectation (z_0, z_1, z_2) = (.25, .5, .25) yields exclusion LOD scores for a GTS-predisposing gene with a λ_{sib} = 2 (Kruglyak and Lander 1995).

For families with more than two affected siblings, all possible pairs were evaluated, and the results were weighted by a factor equal to $2/n$, where n indicates the number of affected children in the sibship.

Results

As noted above, the 76 families yielded a total of 110 sib pairs. Weighting by a factor of $2/n$ resulted in a sample equivalent to 91 independent sib pairs. The power of this sample is sufficient to detect linkage when λ_{sib} is $\geq$4. When equations published by Risch and Merikangas (1996) are used, this sample of 91 sib pairs has power of 59% to map a given locus with λ_{sib} = 2, and 99.9% when λ_{sib} = 4.

The panel of markers genotyped included 370 DNA

markers with an average spacing of 9.1 cM in the male meiotic map. The observed average heterozygosity of this set of markers was .77. Single-point analyses with dominance variance yielded MLS values of 2.38 and 2.09, respectively, for markers D4S1625 and D8S1106. Twelve additional markers (D1S1728, D4S403, D4S2623, D4S1644, D6S1053, D8S1130, D8S1145, D8S136, D10S1213, D11S912, D14S592, and D17S1298) yielded MLS values between 1.0 and 2.0. Two of these markers (D4S2623 and D4S1644) are located in the vicinity of D4S1625, and three (D8S1130, D8S1145, and D8S136) are in the vicinity of D8S1106. Graphs of multipoint MLS values are shown infigure 1. Two regions show suggestive MLS values $\geqslant$2.0. On chromosome 4, MLS values exceeded 2.0 over a region of ~12 cM, including markers D4S1644 and D4S1625, with a peak MLS value of 2.3 at ~3 cM telomeric of D4S1625. The estimated IBD values at this location were $(z_0, z_1, z_2) = (.185, .370, .445)$. On chromosome 8, MLS values reached 2.0 in two adjacent intervals, bounded by markers D8S1106, D8S1145, and D8S136, respectively. Here the estimated IBD values were $(z_0, z_1, z_2) = (.146, .442, .412)$. As can be seen in figure 1, four additional regions show multipoint MLS values >1.0. These regions are on chromosomes 1, 10, 13, and 19. Finally, summing over all regions for which the LOD score was <-2.0 suggests that ~35% of the genome has been excluded, assuming $\lambda_{sib} = 2$.

Discussion

When judged purely on the basis of twin and family studies (Price et al. 1985; Pauls et al. 1991; Hyde et al. 1992; Hebebrand et al. 1997), the evidence for a substantial genetic contribution to the etiology of GTS is convincing. Even when the highest estimates for the population prevalence of GTS are considered, the risk for first-degree relatives of probands is increased by at least a factor of 10. Thus, it is surprising that genetic linkage studies have so far been unsuccessful. It is possible that such an increased risk in close relatives of probands could be due to shared environmental factors. If such factors exist, the outlook for their detection is much better than that for the detection of similar factors in some late-onset diseases, such as multiple sclerosis, because the time window, between birth and onset of disease, for such factors to act would be quite small. That no clear risk factors have yet been identified in the familial shared environment is in agreement with the results of segregation analysis. To date, all segregation analyses for GTS consistently yield evidence that the risk for GTS is transmitted in a Mendelian fashion and that there are genes of major effect that contribute to its manifestation (Pauls et al. 1990; Hasstedt et al. 1995; Walkup et al. 1996).

The results of segregation analysis are also consistent with the observed high relative risks for close relatives of probands. Given these high relative risks, many investigators believed that it should be relatively simple to map the gene(s) responsible for GTS in one or a few large multiply affected families. These efforts have not resulted in convincing linkage findings, even when the existing large families were considered separately (Heutink et al. 1995; Barr et al. [1999]). It is conceivable that extensive locus heterogeneity might preclude one from detecting linkage in a series of unrelated families. In that case, however, one would expect to find suggestions for linkage in the existing large families, albeit for each family in a different location. It is noteworthy that Barr and colleagues (1999) did observe suggestive evidence for regions on chromosomes 5 and 19p.

One potential pitfall in the study of large families has been discussed (Pauls 1993): the very unpredictable and highly biased ascertainment procedure that leads to the identification of large multiply affected families may lead to identification of families segregating for more than a single disease gene, even when those disease genes are rare in the general population. A general problem in the early statistical analyses of linkage in family data was the choice of genetic model parameters—most importantly, the gene frequency and the penetrances for the different genotypes. Serious misspecification of these parameters may lead to false exclusion of the region of interest (Heutink et al. 1995). Furthermore, it is not appropriate to rely completely on the results of segregation analysis for this purpose. When locus heterogeneity exists, and some loci act recessively while others act dominantly, the joint segregation analysis of these families may yield intermediate results that are inadequate for analysis of linkage in each individual family. The models chosen in earlier mapping efforts were broadly in agreement with the results of segregation analysis and family studies: dominant, with a low gene frequency and a relatively low phenocopy frequency, leading to a high recurrence risk in families.

Given that the early mapping studies were inconclusive, a new series of families with sib pairs affected with GTS were ascertained for a complete genome scan. It should be emphasized that all affected sibs met diagnostic criteria for GTS. That is, in contrast to linkage studies in large families, no relatives with CT or OCD were considered as affected in the sib pairs. Furthermore, all linkage analyses were done using nonparametric methods.

Two areas, one on chromosome 4q and another on chromosome 8p, are suggestive of linkage. When viewed from a pessimistic standpoint, the results are disappointing, in that no single area of the genome showed significantly increased IBD sharing in the affected siblings. It is possible that the increased allele sharing in either

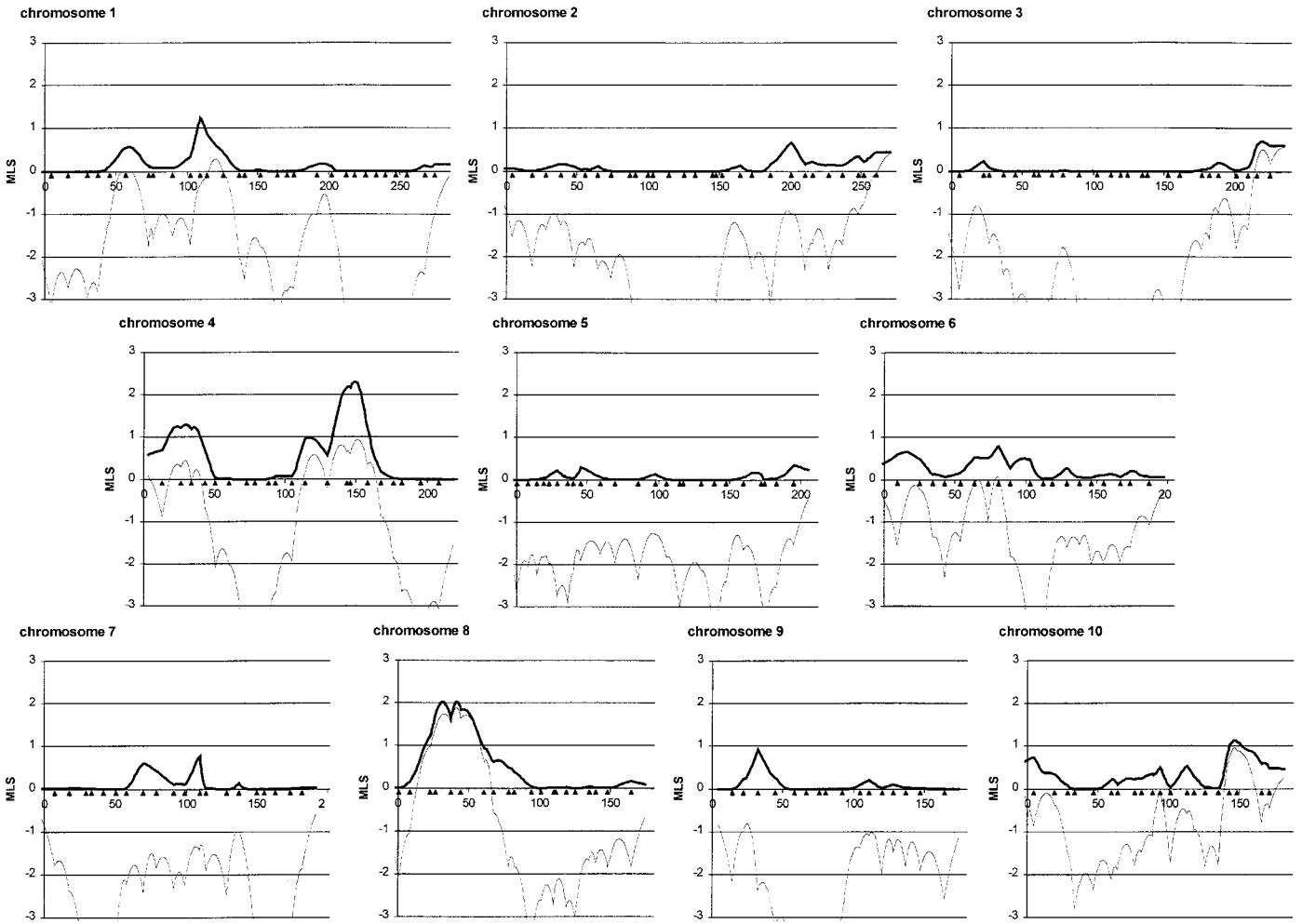

Figure 1 Graphs of multipoint maximum-likelihood scores for all chromosomes. The bold top line represents evidence for linkage; the bottom line represents exclusion. The triangles represent the location of the genotyped markers. All exclusions are based on an assumption that $\lambda = 2.0$s.

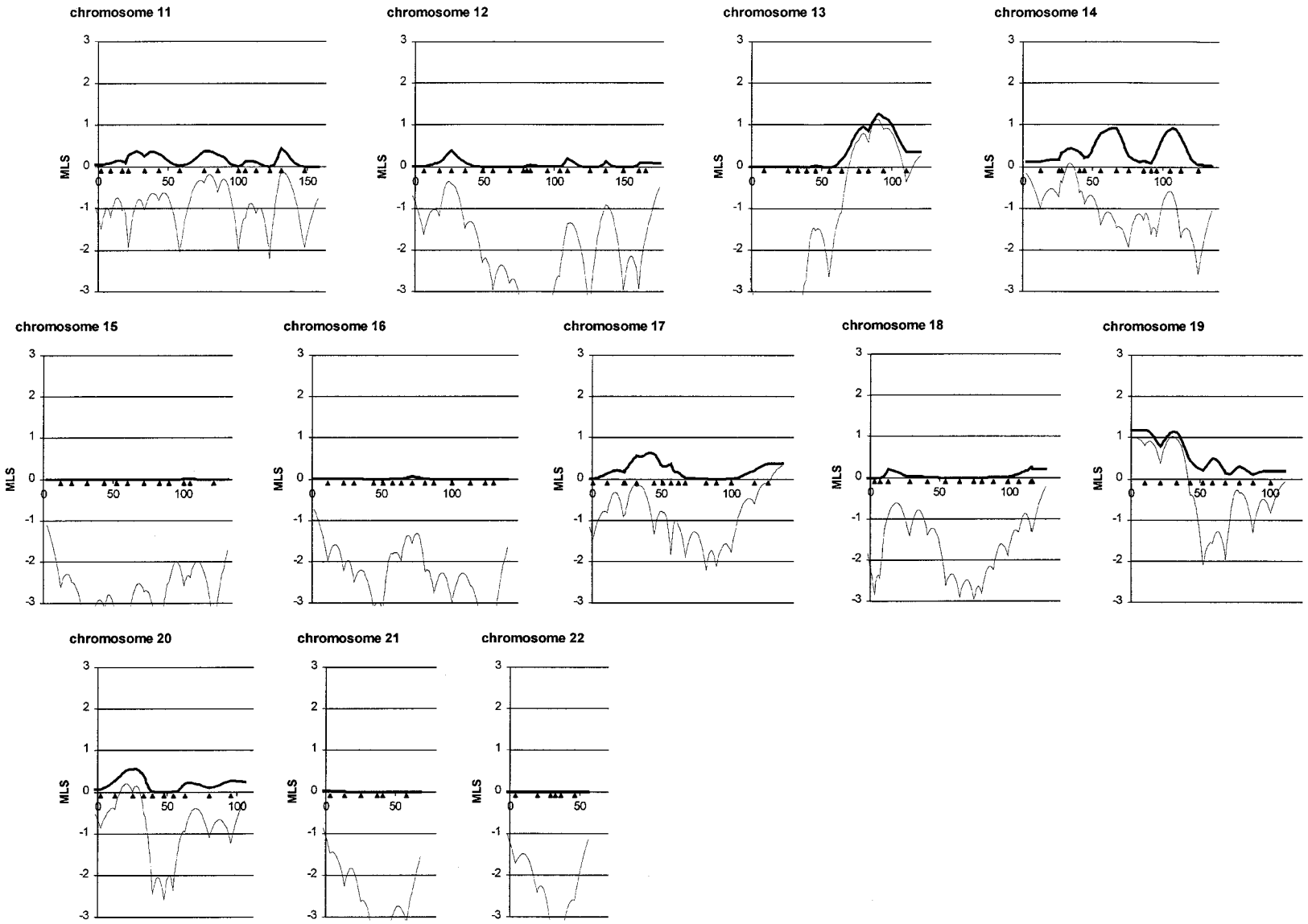

Figure 1 (*Continued*)

of these regions is only due to chance. On the other hand, these peaks in the MLS curve may reveal the true location of genetic risk factors for GTS. Certainly, these results suggest that additional typings are needed in these areas, as well as in the other regions of the genome in which there are suggestive MLS scores (i.e., $1.0 < MLS < 2.0$). At present, additional genotyping is under way in the available multigenerational families and will be completed in new affected-sib-pair families that are currently being evaluated. It should be recognized that if these peaks represent real genetic risk factors, it is likely that they only convey mildly increased risks.

It is clear that for further analysis of these regions in the available extended families, nonparametric methods should be employed. Given the relative risks of these loci, it is unlikely that the appropriate genetic mechanism could be adequately modeled. In this respect, it is important to observe that the sharing pattern observed for 4q is most consistent with a recessive contribution in this region: the increased sharing is exclusively based on an excess of affected sib pairs sharing two parental alleles. On the basis of the ascertainment procedures followed in the collection of the existing series of extended families, it is unlikely that a recessively acting gene would play a prominent role in those families, although in several of the large families there is evidence for bilineal inheritance of milder forms of the syndrome (i.e., CT and/or OCD). At the present time, there is no way of knowing whether the locus on 4q contributes to the expression of CT and/or OCD. Therefore, further analysis of this region should be mostly based on findings in additional sib pairs affected with GTS.

It is important to note that the sharing pattern for 8p is most consistent with a dominant contribution in this region. That is, the increased sharing comes from sib pairs sharing just one parental allele. This is also generally true for the other four genomic regions that have multipoint MLS scores greater than 1.0. Thus, the existing large families should be helpful in understanding more completely the genetic mechanisms in these areas. Nevertheless, more affected sib pairs are needed to follow up these results as well.

It is somewhat disappointing that none of the several chromosomal regions (e.g., 3 [3p21.3], 8 [8q21.4], 9 [9pter], and 18 [18q22.3]) in which there were cytogenetic abnormalities cosegregating with GTS and related conditions showed any strong evidence for linkage in these families. Furthermore, none of the regions in which associations had been reported with candidate genes are supported by these results (e.g., DRD2 [11q22] and DRD4 [11p15]). It is still possible that there are genetic loci in the regions identified by the cytogenetic abnormalities that confer some risk for GTS and related conditions and that the reason that they were not seen in the current study is that only GTS was examined. If that is the case, then it could be concluded that the cytogenetic abnormalities are more likely to be associated with the related conditions and that the GTS seen in these families could be etiologically different than that observed in these sib-pair families.

It is noteworthy that one region that has been suggested from a genome scan of multigenerational families (chromosome 19p; Barr et al. [1999]) is also positive in the current study. Clearly, this and the other positive regions need to be explored more thoroughly to determine whether these findings represent true linkages.

In sum, the results of the first systematic genomewide scan for GTS suggest that there are several genes of moderate effect that increase susceptibility to GTS. Further work is needed to confirm and extend these findings. While it is possible that the current results are false positives, they represent the best available data as to the location of susceptibility loci for this complex neuropsychiatric disorder of children and adults.

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Electronic-Database Information

A URL for data in this article is as follows:

Marshfield Medical Research Foundation Center for Medical Genetics, http://www.marshmed.org/genetics/ (for more information regarding the markers and typing procedures)

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