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Genomewide Scan of Hoarding in Sib Pairs in Which Both Sibs Have Gilles de la Tourette Syndrome

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A genome scan of the hoarding phenotype (a component of obsessive-compulsive disorder) was conducted on 77 sib pairs collected by the Tourette Syndrome Association International Consortium for Genetics (TSAICG). All sib pairs were concordant for a diagnosis of Gilles de la Tourette syndrome (GTS). However, the analyses reported here were conducted for hoarding as both a dichotomous trait and a quantitative trait. Not all sib pairs in the sample were concordant for hoarding. Standard linkage analyses were performed using GENEHUNTER and Haseman-Elston methods. In addition, novel analyses with a recursive-partitioning technique were employed. Significant allele sharing was observed for both the dichotomous and the quantitative hoarding phenotypes for markers at 4q34-35 ($P = .0007$), by use of GENEHUNTER, and at 5q35.2-35.3 ($P = .000002$) and 17q25 ($P = .00002$), by use of the revisited Haseman-Elston method. The 4q site is in proximity to D4S1625, which was identified by the TSAICG as a region linked to the GTS phenotype. The recursive-partitioning technique examined multiple markers simultaneously. Results suggest joint effects of specific loci on 5q and 4q, with an overall *P* value of .000003. Although *P* values were not adjusted for multiple comparison, nearly all were much smaller than the customary significance level of .0001 for genomewide scans.

Introduction

In his original description of Gilles de la Tourette syndrome (GTS [MIM *137580]) in 1885, Gilles de la Tourette noted the presence of obsessive-compulsive symptoms in several of the patients he studied. Subsequent studies have shown prevalences of obsessive-compulsive symptoms of 11%–80% among individuals with GTS (King et al. 1998). This wide range in prevalence likely reflects differences not only in the sample composition but also in the assessment instrument and criteria used. Although obsessive and compulsive features are common in individuals with GTS, the proportion whose symptoms are sufficiently severe to warrant a diagnosis of obsessive-compulsive disorder (OCD [MIM 164230]) is considerably smaller, with only ~30% of adults with GTS meeting the full criteria for obsessive-compulsive disorder. These elevated prevalences of obsessive-compulsive symptoms are found not only in clinical samples composed of patients with GTS but also in nonreferred individuals with tics who were identified in community samples (Apter et al. 1993), as well as in first-degree relatives of individuals with tics (Pauls et al. 1991). The obsessions and compulsions found in individuals with GTS cover a broad range in terms of content, intensity, persistence, impairment, degree of perceived ego-syntonicity, and relationship to the individual's tic symptoms. A growing number of studies examining symptom type, natural history, sex ratio, family-genetic data, neurobiological correlates, and treatment response lend increasing support to the hypothesis that tic-related obsessive-compulsive disorder constitutes a distinctive obsessive-compulsive disorder phenotype (Leckman et al. 2000*a*).

OCD, considered separately from GTS, is a chronic disability affecting 1%–3% of the general population (Horwath and Weissman 2000). Patients with OCD describe the sudden intrusion into consciousness of unwanted worries or unpleasant images, as well as repeated urges to perform seemingly senseless acts. Standard nomenclatures designate OCD as a unitary nosological entity (American Psychiatric Association 1994). Although this parsimony has a certain appeal, it is misleading. The symptoms used to define OCD are diverse and include various intrusive thoughts, pre-

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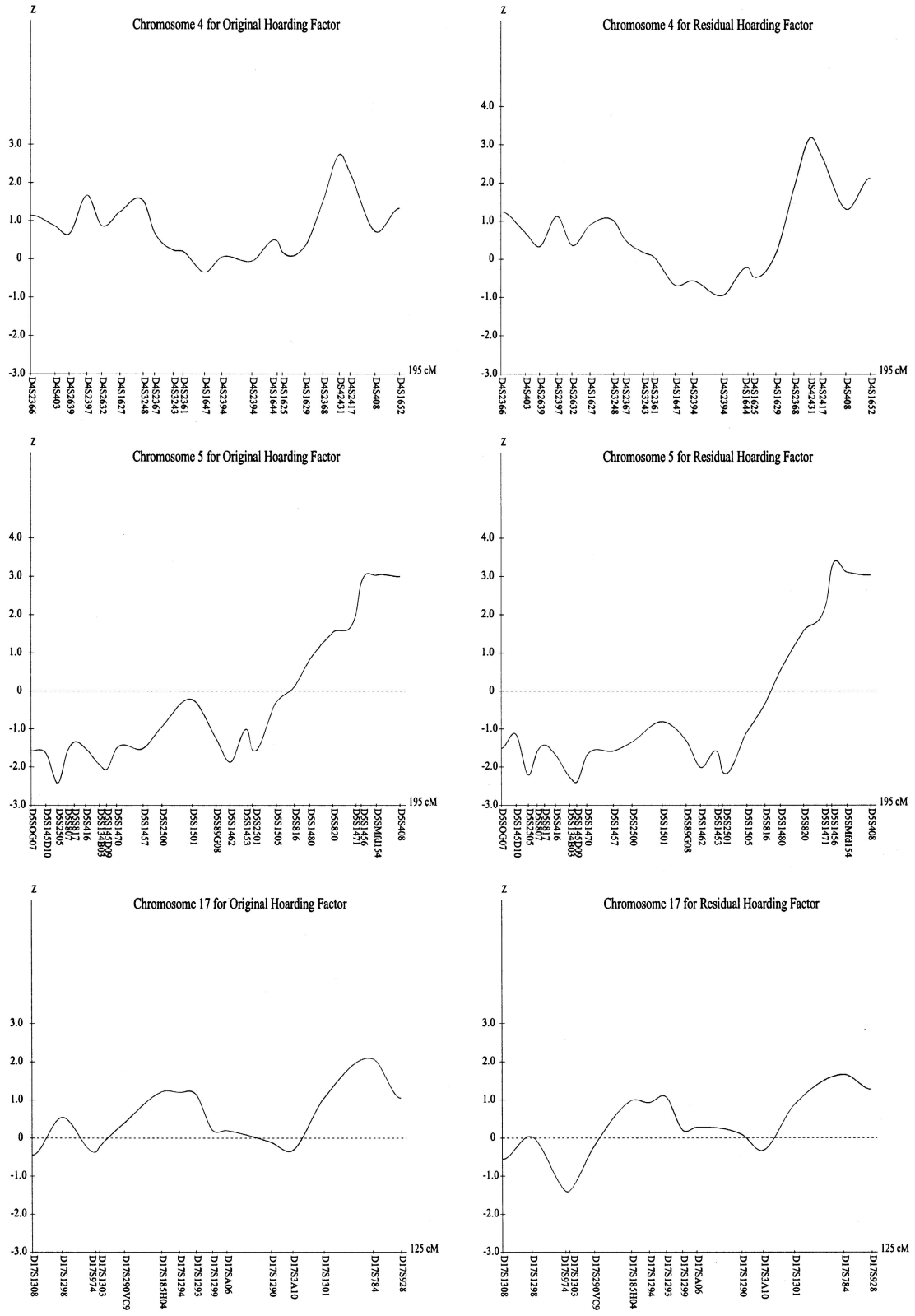

Figure 1 Nonparametric *Z* scores produced by GENEHUNTER for original and residual hoarding factor scores on chromosomes 4q (*top*), 5q (*middle*), and 17q (*bottom*).

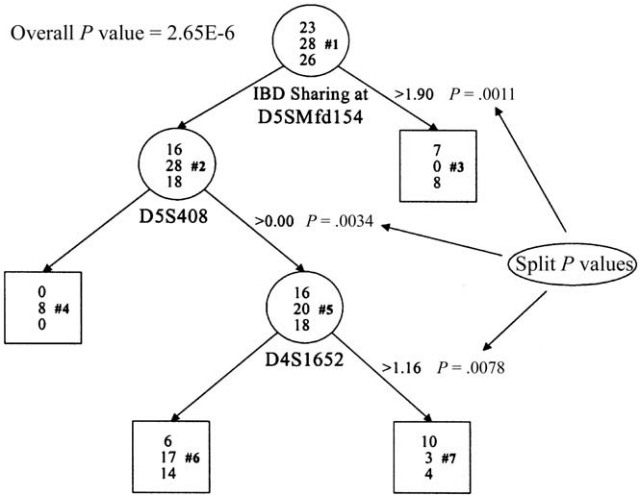

Figure 2 Tree-based genome scan for linkage to hoarding. Nodes are labeled "1"–"7." Inside each node, the numbers of sib pairs in which both members are affected (*top number*), only one member is affected (*middle number*), and neither member is affected (*bottom number*) are given. Thus, the three numbers indicate, from top to bottom, the numbers of both affected, discordant, and both unaffected pairs in any given node. IBD sharing is used to split nodes. Selected markers and cut-off values are below and to the bottom right of the node, respectively. *P* values calculated using Fisher's exact test are presented for each node split and for the distribution among all terminal nodes (*boxes*).

occupations, rituals, and compulsions, many of which are found at lower frequencies in unaffected populations.

Although the subtyping of patients with OCD on the basis of specific proband characteristics (e.g., age at onset or absence of motor or vocal tics) may lead to increased biological homogeneity, other quantitative approaches may prove to be of greater value in the identification of the relevant genetic risk factors. Factor analyses of patients with OCD have identified several obsessive-compulsive symptom dimensions (Baer 1994; Leckman et al. 1997; Mataix-Cols et al. 1999; Summerfeldt et al. 1999), including the following factors:

1. Obsessions about harm, sex, religion, and the body, as well as checking compulsions;
2. Obsessions about a need for symmetry or exactness, repeating rituals, counting compulsions, and ordering/arranging compulsions;
3. Contamination obsessions and cleaning/washing compulsions;
4. Hoarding obsessions and compulsions.

Data supporting the validity of these obsessive-compulsive symptom dimensions have been provided by studies of psychiatric comorbidity, functional brain imaging, treatment response, and studies of normal development (Leckman et al. 2001). Hoarding symptoms, in particular, appear to be associated with increased psychiatric comorbidity (Mataix-Cols et al. 1999; Frost et al. 2000), as well as poor response to standard pharmacotherapies and cognitive-behavioral treatments (Black et al. 1998; Mataix-Cols et al. 1999). Although these studies suggest that the presence of hoarding symptoms is useful for prognosis, there has been little examination of the familial or genetic factors that may contribute to their expression.

The mode of inheritance of OCD has been investigated by means of segregation analysis in five studies. Evidence of a gene of major effect was found in each of the studies that classified relatives according to the presence or absence of OCD as a binary outcome (Nicolini et al. 1991; Cavallini et al. 1999; Nestadt et al. 2000*a*). For example, Nestadt et al. (2000*a*) conducted complex segregation analyses of OCD in 153 families (80 case and 73 control families) that were ascertained in the Johns Hopkins OCD Family Study, and they reported strong evidence for a major autosomal dominant gene with significant sex effects.

Alsobrook et al. (1999) and J. F. Leckman, D. L. Pauls, H. Zhang, M. C. Rosario-Campos, L. Katsovich, K. K. Kidd, A. J. Pakstis, J. P. Alsobrook, M. M. Robertson, W. M. McMahon, J. T. Walkup, B. J. M. van de Wetering, R. A. King, D. J. Cohen, and the Tourette Syndrome Association International Consortium for Genetics (TSAICG) (unpublished data) have reported similar results by use of symptom-based factor scores. Thus far, only the aforementioned study by Leckman et al., which was undertaken as part of the TSAICG, has specifically focused on the role that genetic factors play in the transmission and expression of hoarding symptoms. They found evidence in support of a recessive mode of transmission for the hoarding symptom dimension in families with two affected siblings with GTS (J. F. Leckman, D. L. Pauls, H. Zhang, M. C. Rosario-Campos, L. Katsovich, K. K. Kidd, A. J. Pakstis, J. P. Alsobrook, M. M. Robertson, W. M. McMahon, J. T. Walkup, B. J. M. van de Wetering, R. A. King, D. J. Cohen, and the TSAICG, unpublished data). The same segregation analyses also indicated that the transmission of factors 1 and 2 was consistent with dominant major gene effects, whereas the pattern of transmission for factor 3 was consistent with recessive inheritance. Unlike factor 4 (i.e., the hoarding factor), the other three factors comprise more than one symptom. Thus, the understanding of the linkage analysis is more challenging, and the results will be published separately. The goal of the present study was to conduct a genome analysis focused on hoarding symptoms, treated as both a quantitative trait and a dichotomous variable.

Table 1

Results of Genomewide Scan Significance of the Hoarding Factor Score by Use of a Nonparametric Likelihood Method and Haseman-Elston Methods

Region and Nearest Marker	*P* Value in Analysis of					
	Original Hoarding Factor			Residual Hoarding Factor		
	SIBPAIR[a]	SIBPAL2[b]	GH-NPL[c]	SIBPAIR[a]	SIBPAL2[b]	GH-NPL[c]
4q34-35:						
D4S2431	.092	.006	.003	.171	.011	7E-4
D4S2417	.111	.005	.012	.153	.005	.003
D4S408	.264	.034	.232	.216	.040	.092
D4S1652	.012	.031	.090	.005	.047	.016
5q35.2-35.3:						
D5S1471	.036	.031	.023	.022	.029	.009
D5S1456	.003	.005	.002	.002	.004	6E-4
D5SMfd154	2E-4	.001	.001	3E-4	.002	9E-4
D5S408	2E-5	2E-6	.001	6E-5	3E-6	.001
17q25:						
D17S1301	.005	1E-4	.147	.007	2E-4	.189
D17S784	3E-4	2E-5	.019	8E-4	6E-5	.047

[a] Traditional Haseman-Elston method by use of S.A.G.E. (version 6 beta).
[b] Revisited Haseman-Elston method by use of S.A.G.E. (version 6 beta).
[c] Nonparametric-likelihood method in GENEHUNTER.

Subjects, Material, and Methods

Sample

All families include at least two siblings with GTS. In the original ascertainment, families were excluded if both parents were affected with GTS or if one parent had GTS, CT (chronic tics), OCD, and/or subclinical OCD and the other parent also had CT, OCD, and/or subclinical OCD. All diagnoses were made by use of *Diagnostic and Statistical Manual*–III-R criteria (American Psychiatric Association 1994). The criteria for subclinical OCD were the same as those used to make a diagnosis of OCD, except that the individual did not perform the compulsions or obsessions for at least an hour, did not experience them as ego-dystonic, 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 51 families with a total of 77 sib pairs and 223 individuals (including parents). Of the 77 pairs, 26 are concordant for hoarding, 28 are discordant for hoarding, and 23 are concordant for being unaffected with hoarding. This is a subset of the families that were included in the original genome scan of GTS reported by the TSAICG (1999), and the rest of the families are no longer available to the TSAICG. J. F. Leckman, D. L. Pauls, H. Zhang, M. C. Rosario-Campos, L. Katsovich, K. K. Kidd, A. J. Pakstis, J. P. Alsobrook, M. M. Robertson, W. M. McMahon, J. T. Walkup, B. J. M. van de Wetering, R. A. King, D. J. Cohen, and the TSAICG (unpublished data) present detailed demographic and clinical information for sample that we studied.

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 (1) the collection of information concerning symptoms associated with GTS, (2) diagnosis of OCD through an interview developed specifically for the TSAICG (i.e., a self-and-family report [TSAICG 1999] based on the tic inventory and ordinal severity scales

Table 2

Alleles Shared by Sib Pairs for Selected Markers

Sib Pair	Shared Alleles, by Type[a]							
	1	2	3	4	5	6	7	9
Node 3:[b]								
AA	1	1	0	0		8	3	1
AU	0	0	0	0		0	0	0
UU	1	2	3	6		3	1	0
Node 5:[c]								
AA	4	0	0	12	2	0	0	
AU	3	1	1	9	4	0	1	
UU	4	0	2	8	6	2	0	
Node 7:[d]								
AA	4	8	7	0	1			
AU	1	2	1	2	0			
UU	4	3	1	0	0			

Note.—Selected markers are shown in figure 2. AA = both affected; AU = discordant; UU = both unaffected.
[a] Allele types at the selected markers were numbered consecutively from 1.
[b] IBD at D5SMfd154 > 1.9.
[c] IBD at D5SMfd154 ⩽ 1.9, and IBD at D5S408 > 0.
[d] IBD at D5SMfd154 ⩽ 1.9, IBD at D5S408 > 0, and IBD at D4S1652 > 1.16.

of the Yale global tic severity scale [Leckman et al. 1989]), and (3) the review of the symptom checklist and ordinal scales of the Yale-Brown obsessive-compulsive scale (Y-BOCS) (Goodman et al. 1989). Earlier versions have been shown to be both valid ($\kappa = 0.98$ for GTS; $\kappa = 0.97$ for OCD) and reliable ($\kappa = 1.00$ for GTS; $\kappa = 0.97$ for OCD) (Leckman et al. 1993, 1994, 1997; Pauls et al. 1995). In the second stage, these symptom ratings were reviewed by an experienced clinician during a face-to-face interview with the informant, to insure their accuracy and validity. These instruments are currently being used in family studies of both GTS and OCD.

All diagnoses were made by use of the best-estimate approach (Leckman et al. 1982) according to our 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 who independently made diagnostic assessments. All three diagnosticians were blind to prior diagnoses and individuals' relationships to the probands. 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 ($\kappa = 0.97$) for the diagnosis of GTS. When there was disagreement between the two raters who had evaluated the same person, 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 an attempt was made to reach consensus. If there was still disagreement, more data were requested to help resolve the differences. If there was still disagreement after more data were obtained, the family was removed from the sample.

To make the dichotomous rating of the presence of significant hoarding symptoms, we judged hoarding symptoms to be present when one or both of the hoarding items on the Y-BOCS symptom checklist were rated as present by the experienced clinician. In addition to treating hoarding as a dichotomous outcome, we also considered it as a quantitative trait that was derived from a factor analysis, on the basis of an earlier study of 292 individuals with OCD diagnosed by use of item endorsements from the Y-BOCS symptom checklist (Leckman et al. 1997). The factor loadings and algorithm derived by Leckman et al. (1997) were used to calculate the hoarding-factor scores for the present sample.

DNA Markers

The panel of markers genotyped included 370 DNA markers with an average spacing of 9.1 cM in the male meiotic map on 22 autosomal chromosomes. A detailed description of the markers and map is given by TSAICG (1999).

Data Analysis

Allele frequencies for the genetic markers were established by gene counting in genotyped parents. For each sib pair, the identity-by-descent (IBD) distribution was estimated by single-point and multipoint analyses by use of the MAPMAKER-SIBS and GENEHUNTER programs (Kruglyak and Lander 1995). In the single-point analysis, the IBD distribution was estimated on the basis of the marker genotypes for each marker individually. In the multipoint analysis, maximum-likelihood scores (Risch 1990) were computed for 4,000 different locations relative to the markers (average step size <1 cM). In the estimation of the IBD distribution, only inheritance vectors that were consistent with Mendelian inheritance were considered.

Several analytic approaches have been applied to the sib-pair analyses, as well as the analyses of nuclear families. The main results reported here are from the analysis of the quantitative hoarding-factor score. As mentioned in the "Introduction" section, Leckman et al. (1997) reported four OCD factors, the last of which is the hoarding factor. To examine the unique variability of the hoarding factor, we obtained a residual factor by regressing the original hoarding factor on the other three factor scores. Using the computer program POINTER (Lalouel 1983), J. F. Leckman, D. L. Pauls, H. Zhang, M. C. Rosario-Campos, L. Katsovich, K. K. Kidd, A. J. Pakstis, J. P. Alsobrook, M. M. Robertson, W. M. McMahon, J. T. Walkup, B. J. M. van de Wetering, R. A. King, D. J. Cohen, and the TSAICG (unpublished data) performed a complex segregation analysis for the hoarding-factor score, as a part of an effort to examine the hypothesis that there is transmission of these OCD factors in families and that that transmission is consistent with genetic modes of inheritance. Significant evidence for genetic transmission was obtained for the original hoarding factor, with a possibly recessive inheritance, although the segregation analyses did not suggest evidence for any kind of genetic transmission of the residual hoarding factor.

Linkage analyses of the quantitative hoarding-factor score were completed using the variance-component model for the nuclear families in GENEHUNTER and the traditional and revisited Haseman-Elston sib-pair methods (Haseman and Elston 1972; Elston et al. 2000). In the traditional Haseman-Elston method, the squared

difference between the phenotypes of the two siblings is regressed against their IBD sharing. In the revisited method, the mean corrected cross-product of the sibling traits is used as the dependent variable. Elston et al. (2000) indicate that the newer method is based on a test statistic that has better-understood asymptotic properties and yields better power. Furthermore, as has been noted in the literature, analysis by use of a quantitative phenotype is potentially more powerful than are analyses by use of qualitative phenotypes (Risch and Zhang 1995; Zhang and Risch 1996).

Because the status of hoarding is the chief contributor to the hoarding factor, this phenotype was also examined as a dichotomous trait. Analyses were done with both GENEHUNTER and the RTREE program, which was developed by one of the authors (H.Z.) and is available to the public from his Web site (Zhang Lab of Statistics and Bioinformatics). The RTREE program is based on a recursive-partitioning procedure described by Breiman et al. (1984) and Zhang and Singer (1999). Zhang and Bonney (2000) and Zhang et al. (2001*a*) have explored the potential use of this method in genetic linkage and association studies. Others have also noted the great promise of these techniques in genetic studies (Rao 1998; Shannon et al. 2001). The most attractive features of this method are (1) the ability to accommodate a practically arbitrary number of markers together with environmental factors and (2) the ability to identify potential epistatic (i.e., gene-gene) and gene-environment interactions. Although the method is well established in the statistical literature and the field of machine learning, it is still a novel approach in genetic studies. The key idea is that, in sib-pair analyses, genetic sharing between sib pairs is used to predict the distribution of the numbers of the concordant (both unaffected or both affected are treated as two different concordances) and discordant sib pairs. If a marker is linked to a disease locus, a high-level IBD sharing is expected to result in more concordant sib pairs. Unlike the Haseman-Elston model, the relationship can be simply monotonic, rather than having to be linear (Zhang et al. 2001*a*). In association studies, if some particular alleles are associated with an increased likelihood of a certain condition, the excess level of those allele frequencies should have predictive power to discriminate between the normal condition and the abnormal condition (Zhang and Bonney 2000). In both linkage and association analyses, the recursive-partitioning process stratifies the study sample, on the basis of the genetic information (as well as environmental variables when included in the analyses), into a number of smaller subsamples, in each of which the condition of interest for all observational units is similar (or, ideally, the same). The similarity is usually measured by an entropy function of the distribution of the condition (Breiman et al. 1984; Zhang and Singer 1999; Zhang and Bonney 2000; Zhang et al. 2001*a*). No ascertainment correction was employed for these analyses, since the ascertainment was based on the presence of GTS and not hoarding or OCD.

Results

Results of the analyses of these data suggested linkage to three regions on three chromosomes (4q, 5q, and 17q). Among different analytic methods, the significance levels are largely consistent, regardless of whether the original or the residual hoarding-factor scores were used. Specifically, in the region of 4q34-35, the best significance levels are .003, for the original factor score, and .0007, for the residual score, both of which are based on the nonparametric Z score computed by GENEHUNTER. In the region of 5q35.2-35.3, the best significance levels are .000002, for the original factor score, and .000003, for the residual score, both of which are calculated by the revisited Haseman-Elston method. In the region of 17q25, the best significance levels are .00002, for the original factor score, and .00006, for the residual score, both of which are calculated by the revisited Haseman-Elston method. A graphical presentation of the nonparametric Z scores of these results is provided in figure 1.

As noted above, the status of hoarding as a binary-outcome variable was also examined. Analyses with GENEHUNTER did not reveal any evidence of linkage for this binary trait. The power of GENEHUNTER is markedly reduced by the use of this dichotomized trait. However, by use of the RTREE program, some consistent evidence emerged from both linkage and association analyses on chromosomes 4q and 5q. The tree structure produced from the genomewide scan is shown in figure 2. In the top circle, the so-called "root node" (labeled "1") includes all 77 sib pairs (26 concordant for hoarding, 28 discordant for hoarding, and 23 concordant for being unaffected with hoarding). The IBD sharing from marker D5SMfd154 is first used to partition the sib pairs into two sets. As shown in table 1, this marker is in the region where other methods identified significance evidence of linkage to the quantitative hoarding score. The 62 sib pairs with IBD <1.9 at this marker are assigned to the left circle, the so-called "left daughter node" (labeled "2"). The remaining 15 sib pairs are assigned to the right box, the so-called "right daughter node" (labeled "3"). When IBD can be uniquely defined, the sib pairs in node 3 share exactly the same alleles at this marker. The alleles that are shared by the sib pairs in node 3 are shown in table 2. The first four alleles are shared most among seven unaffected sib pairs, and the last three alleles are mostly shared among eight affected sib pairs. The second split, which applies to the 65 sib

pairs in node 2, uses the IBD sharing at D5S408, which is next to D5SMfd154. This reaffirms the evidence of linkage in the same region. The eight sib pairs in node 4 do not share any allele at this marker, suggesting that it could be either a vulnerability allele or a protective allele. The 54 sib pairs in node 5 share one or both alleles. Finally, node 5 is further divided into nodes 6 and 7 through D4S1652, which is also within the vicinity where linkage to the quantitative-trait locus is suggested. The overall disparities in alleles that are shared among different types of sib pairs for the three selected markers are shown in table 2.

Discussion

Hoarding is likely to be an evolutionarily conserved trait that, in times of adversity, was associated with increased survival and reproductive fitness. However, extreme forms of this trait are associated with marked disability and poor treatment response (Black et al. 1998; Mataix-Cols et al. 1999).

The current analyses provide evidence that alleles shared at specific loci on 4q, 5q, and 17q are associated with this trait. The 4q site is in proximity to D4S1625, which was identified by the TSAICG (1999) as a region linked to the GTS phenotype. The other two regions, 5q and 17q, show the strongest evidence for linkage and have not been previously identified as showing promise in kindreds with GTS or OCD. Future studies will need to evaluate this and other obsessive-compulsive–related quantitative traits in large families segregating for GTS and/or early-onset OCD, by use of highly informative marker sets in these regions of the genome. High-density mapping within these regions and replication studies with the additional GTS-affected sib pairs may also be promising endeavors.

Thus far, only one genome scan of early-onset OCD has been reported. This preliminary report found a possible vulnerability locus on 9p (G. L. Hanna, J. Veenstra-VanderWeele, N. J. Cox, M. Boehnke, J. A. Himle, and G. C. Curtis, personal communication); however, a subsequent study failed to find evidence of linkage disequilibrium at a well-characterized locus in that chromosomal region (Veenstra-VanderWeele et al. 2001). Although virtually all of the siblings with OCD in this sample had an age at onset <10 years (J. F. Leckman, D. L. Pauls, H. Zhang, M. C. Rosario-Campos, L. Katsovich, K. K. Kidd, A. J. Pakstis, J. P. Alsobrook, M. M. Robertson, W. M. McMahon, J. T. Walkup, B. J. M. van de Wetering, R. A. King, D. J. Cohen, and the TSAICG, unpublished data), we found no evidence of linkage to the hoarding trait of OCD in that 9p region.

The one weakness of this study is the small number of sib pairs. As Risch (1990) has noted, very large samples of sib pairs may be necessary to detect linkage when the relative risk is $\leqslant 2$. In the current study, it is not possible to accurately estimate the relative risk, since the population prevalence for hoarding is not known and since no family studies have been reported in which the recurrence risk for hoarding was reported. The best estimate for the relative risk for OCD that is available comes from two family studies of OCD (Pauls et al. 1995; Nestadt et al. 2000*b*). The population prevalence of OCD has been estimated to be ~2% (Karno et al. 1988). The recurrence risk for OCD is ~11%–12% (Pauls et al. 1995; Nestadt et al. 2000*b*). Thus, the best estimate of the relative risk for OCD is ~5.5–6.0. If it is assumed that the proportion of individuals with OCD who have hoarding is constant, then the relative risk for hoarding would also be ~5.5–6.0.

Another limitation is the small number of hoarding items on the Y-BOCS symptom checklist. A dimensional version of Y-BOCS (i.e., DY-BOCS), which should enhance the phenotypic characterization of this trait, is currently under development (Leckman et al. 2000*b*). Alternatively, the Questionnaire for Saving Things, developed by Frost et al. (1995), could be used for this purpose.

The recursive-partitioning methods in genomic scans have lately emerged as flexible and potentially powerful alternatives to the standard approaches (Rao 1998; Zhang and Bonney 2000; Shannon et al. 2001; Zhang et al. 2001*b*). In addition, the success of these methods in the classification of distinct colon-cancer tissues and the methods' potential for the identification of otherwise-obscure epistatic interactions suggest that such techniques may be especially valuable in efforts to identify the risk and protective factors that underlie genetically complex neuropsychiatric disorders (Zhang et al. 2001*b*). Furthermore, the identification of specific allele sharing in specific sib pairs may provide a direct approach to the confirmation of these findings in family-based association studies (Simonic et al. 2001).

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Accession numbers and URLs for data in this article are as follows:

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