Am. J. Hum. Genet. 57:465–473, 1995

Linkage Studies on Gilles de la Tourette Syndrome: What Is the Strategy of Choice?

Peter Heutink,[1] Ben J. M. van de Wetering,[2] Andrew J. Pakstis,[3] Roger Kurlan,[4] Paul Sandor,[5] Ben A. Oostra,[1] and Lodewijk A. Sandkuijl[1]

Departments of [1]Clinical Genetics and [2]Psychiatry, Erasmus University Rotterdam; [3]Department of Human Genetics, Yale University School of Medicine, New Haven; [4]University of Rochester School of Medicine and Dentistry, Rochester, New York; and [5]Department of Psychiatry, The Toronto Hospital and University of Toronto, Toronto

Summary

For a linkage study it is important to ascertain family material that is sufficiently informative. The statistical power of a linkage sample can be determined via computer simulation. For complex traits uncertain parameters such as incomplete penetrance, frequency of phenocopies, gene frequency and variable expression have to be taken into account. One can either include only the most severe phenotype in the analysis or apply multiple linkage tests for a gradually broadened disease phenotype. Gilles de la Tourette syndrome (GTS) is a chronic neurological disorder characterized by multiple, intermittent motor and vocal tics. Segregation analyses suggest that GTS and milder phenotypes are caused by a single dominant gene. We report here the results of an extensive simulation study on a large set of families. We compared the effectiveness of linkage tests with only the GTS phenotype versus multiple tests that included various milder phenotypes and different gene frequencies. The scenario of multiple tests yielded superior power. Our results show that computer simulation can indicate the strategy of choice in linkage studies of multiple, complex phenotypes.

Introduction

Gilles de la Tourette syndrome (GTS) is a chronic neuropsychiatric disorder with unknown etiology. The syndrome is characterized by multiple intermittent motor and vocal tics. Affected individuals frequently display associated behaviors such as obsessive compulsive symptoms (OCS), attention-deficit and hyperactivity disorder, coprolalia, and echolalia (Shapiro et al. 1988). Expression of the phenotype follows a waxing-and-waning course and is influenced by gender and age. Patients are often capable of suppressing tics for limited periods of time.

Analysis of family data is consistent with an autosomal dominant mode of inheritance with incomplete penetrance (Pauls et al. 1986). It has been suggested that a number of milder behavioral problems should be considered as variant expressions of the presumed genetic defect responsible for GTS (for review, see Shapiro et al. 1988). The chronic multiple-tic syndrome (CMT) is generally agreed to be a variant phenotype of GTS (Pauls et al. 1981). There is also evidence for a genetic relationship between GTS and OCS (Pauls et al. 1986; Robertson 1989). It is unclear, however, how often CMT and OCS occur due to different genetic or nongenetic factors.

Among the human genes that have recently been characterized, no obvious candidate genes for GTS have been identified. Chromosomal regions 18q22.1 and 9p23-pter, implicated by structural rearrangements in GTS patients, have failed to generate positive evidence for linkage (Heutink et al. 1990, 1993). In a systematic global genome search, a GTS Genetic Consortium tested >600 genetic markers (Pakstis et al. 1991; Heutink et al. 1993). (Members of the Consortium are listed in the acknowledgments.) No strong and definitive evidence for linkage was obtained. Assuming locus homogeneity, and considering CMT as a variant phenotype of GTS, an exclusion map based on a well-localized subset of markers shows exclusion of $\geq 80\%$ of the human autosomes (GTS Genetic Consortium, unpublished data).

In linkage studies for bipolar disorder and schizophrenia, promising findings could be neither confirmed nor supported (Kennedy et al. 1988; Kelsoe et al. 1989; Baron et al. 1993). The failure to localize genes for psychiatric disorders via linkage analysis has generated a broad discussion in the literature, not only about the appropriateness of single-gene assumptions for complex disorders (for review, see Risch 1990) but also on the question of how genetic disease entities should be delineated in the intricate diagnostic classification schemes of today's psychiatry. Some authors propose to include only the most extreme phenotypes in the linkage analysis, assuming that these phenotypes are most likely based

Received March 16, 1995; accepted for publication April 19, 1995.

Address for correspondence and reprints: Dr. P. Heutink, Department of Clinical Genetics, Erasmus University Rotterdam, P. O. Box 1738, 3000 DR Rotterdam, The Netherlands. E-mail: heutink@kgen.fgg.eur.nl

0002-9297/95/5702-0030$02.00

on genetic factors (Byerley 1989; Baron 1990). Others have carried out multiple analyses, gradually broadening the phenotype definition to include milder or less specific diagnoses (Sherrington et al. 1988). The former suggestion might lead to severe loss of information, while the practice of multiple testing will undoubtedly give rise to an increased frequency of false-positive linkage findings if no statistical corrections for multiple testing are made. Decisions on the strategy of choice have frequently been made somewhat arbitrarily.

The use of computer simulations to evaluate the adequacy in size of a linkage sample is becoming more common (Greenberg 1984; Boehnke 1986); its use has also been suggested for the assessment of the expected frequency of false-positive findings in a multiple-test situation (Weeks et al. 1990). Terwilliger and Ott (1992) proposed efficient procedures to reduce the time needed for this analysis.

In this simulation study, we are addressing the following questions concerning the available set of GTS families: (*i*) Which of the available families contains sufficient linkage information for linkage mapping? (*ii*) What approach should be taken in the analysis with respect to the spectrum disorders, CMT and OCS? We systematically investigated whether a narrowly defined phenotype would give a better probability to detect a true linkage, compared with a strategy where several diagnostic models with a broadening in the spectrum of included clinical characteristics were used. In addition, we repeated these simulations with a much higher gene frequency. (*iii*) Finally, what is the impact of diagnostic instability on the probability to detect a true linkage? Our findings are of relevance to researchers involved in the mapping of psychiatric disorders, but the approaches presented here are also applicable to mapping projects of other complex disorders.

Material and Methods

Family Material

In the study reported here, we used pedigree information and diagnostic data on 32 GTS families ascertained by the GTS Genetic Consortium: Erasmus University Rotterdam (12 families); Yale University School of Medicine, (2 families); Marshfield Medical Research Foundation (1 family); Hospital for Sick Children (1 family); and University of Iowa (16 families).

All families have previously been included in linkage studies and have been described elsewhere (Kurlan et al. 1986; Pauls et al. 1990; Devor 1992; Heutink et al. 1992; Wilkie et al. 1992), except for the family that was contributed by the research group from Toronto. This set of families was also used in a segregation analysis, which will be reported elsewhere. A detailed description of the pedigrees is available on request.

All diagnosed subjects were personally interviewed by investigators from the contributing centers. For diagnostic assessment, a structured questionnaire was used with a section on GTS and CMT (D. L. Pauls, K. K. Kidd, and D. J. Cohen, unpublished information). A separate questionnaire was used for OCS. Diagnoses were confirmed by independent clinical investigators who had no prior knowledge of family history.

Statistical Analysis

The assumptions concerning the mode of inheritance of GTS made in the analysis presented here were identical to those adopted in our previous collaborative linkage studies (Pakstis et al. 1991; Heutink et al. 1993) and were based on the findings of Pauls and Leckman (1986). GTS was taken to be caused by an autosomal dominant mutation, incompletely penetrant, with a population gene frequency of 0.003. Children <15 years of age were not included in the analysis unless diagnosed as "affected." Persons with CMT or OCS were treated in the simulations in various ways, depending on the diagnostic model chosen (table 1). Three different diagnostic models were applied in these analyses: a broad, intermediate, and narrow model. In the broad model, it was assumed that the GTS gene also predisposes to development of both the CMT and the OCS phenotypes. In the intermediate model, subjects with OCS were treated as "phenotype unknown," which implies that they did not contribute directly to the linkage analysis, although their marker genotypes may have aided in the reconstruction of marker genotypes for unavailable persons. In the narrow diagnostic model, subjects with CMT were also treated as "phenotype unknown."

Estimates of the population frequency of CMT and OCS vary widely, with a maximum of 3%–5% (Kurlan 1993). In the simulations described above, a gene frequency of 0.003, in combination with high penetrance values, leads to a population frequency of 1.5% (table 1). We included an additional model (labeled "High") in the simulations with a more frequent gene (0.015), leading to a population frequency of 7.5% for the milder phenotypes. In order to maintain the population frequency for the GTS phenotype at 1% in this model, the penetrance values for the GTS phenotype were lowered considerably. Male and female recombination fractions were assumed to be equal in all analyses.

The computer simulations that we carried out will be described in three separate steps: (*i*) the construction of marker data for a hypothetical marker either closely linked or unlinked to the GTS gene, (*ii*) the linkage analysis of those marker results, and (*iii*) the evaluation of the resulting lod scores.

i. Marker data were generated for all family members for whom DNA was available in reality, using the com-

Table 1

Genetic Parameters for Different Diagnostic Schemes Used in the Simulation Analyses

Gene Frequency and Diagnostic Model	Parameters[a]					
	Sex[b]	f_0	f_1	f_2	K_p	Ph
Gene frequency of .003:						
Narrow	M	.005	.810	.810	.0098	.506
	F	.003	.310	.310	.0048	.616
Intermediate	M	.010	.900	.900	.0153	.648
	F	.006	.560	.560	.0093	.640
Broad	M	.010	.900	.900	.0153	.648
	F	.006	.710	.710	.0102	.584
Gene frequency of .015:						
High[c]						
GTS	M	.005	.160	.160	.0096	.505
GTS	F	.003	.061	.061	.0047	.616
CMT	M	.050	.900	.900	.0753	.644
CMT	F	.030	.560	.560	.0458	.636
OCS	M	.050	.900	.900	.0753	.644
OCS	F	.030	.710	.710	.0502	.579

[a] f_0 = penetrance disease phenotype of homozygote normal; f_1 = penetrance of heterozygote; f_2 = penetrance of homozygote affected; K_p = population frequency of phenotype; Ph = phenotype frequency.

[b] M = male; F = female.

[c] GTS = Gilles de la Tourette syndrome; CMT = chronic multiple-tic syndrome; OCS = obsessive-compulsive syndrome.

puter program SLINK (Weeks et al. 1990). Markers of various informativeness (2, 4, and 8 alleles), with a PIC values of .375, .70 and .86, respectively, were simulated to be either linked to the GTS gene with 5% recombination or unlinked. For each family, 100 or 400 distinct replicates were prepared, depending on the size of the family. Simulations were carried out separately for each of the four selected models (for the linked marker only; in the absence of linkage, the choice of the diagnostic model will not influence the construction of the hypothetical marker data).

ii. Analysis of the resulting data was carried out for each replicate of each family separately, with a slightly modified version of the MLINK option of the LINKAGE package, version 5.03 (Lathrop and Lalouel 1984). All simulated data were analyzed under the diagnostic model used for simulation but also under the other diagnostic models. Lod scores for each replicate were calculated for recombination fractions ranging from 0.0 to 0.5 in steps of 0.01. The resulting lod score lists were manipulated via the computer programs SIMSUM and SIMCOMP (L. A. Sandkuijl, unpublished programs) to yield expected lod scores for individual families and for sets of families. Expected lod scores for individual families were calculated for each marker and each model. For each replicate of a given family, the maximum lod score was identified. The mean of those maxima (>100 or 400 replicates) was taken to represent the expected lod score in that family.

iii. The expected maximum lod score in a set of families was obtained via a bootstrap procedure, as proposed by Terwilliger and Ott (1992). For each family of a given set, a replicate was selected at random. Lod scores for the selected replicates were summed for each value of the recombination fraction, and the resulting lod score curve was taken to represent one simulated replicate of that set of families. Analyses of sets of families were based on 1,000,000 bootstrapped replicates. Corrections for multiple testing were as proposed by Risch (1991): lod score threshold = 3 + LOG(t), where t represents the number of tests carried out.

Results

Informativity of the Family Material

Expected lod scores varied widely between the 32 families, and, for a given family, between different diagnostic models. With a four-allele marker, 13 of the families yielded mean lod scores of ≥ 0.5 under the broadest diagnostic model (data not shown). Differences in lod score between the broader models and the narrow one showed marked variation between families, since there was a large variation in the contribution of the spectrum disorders between families. Kindred S14 (fig. 1) was the

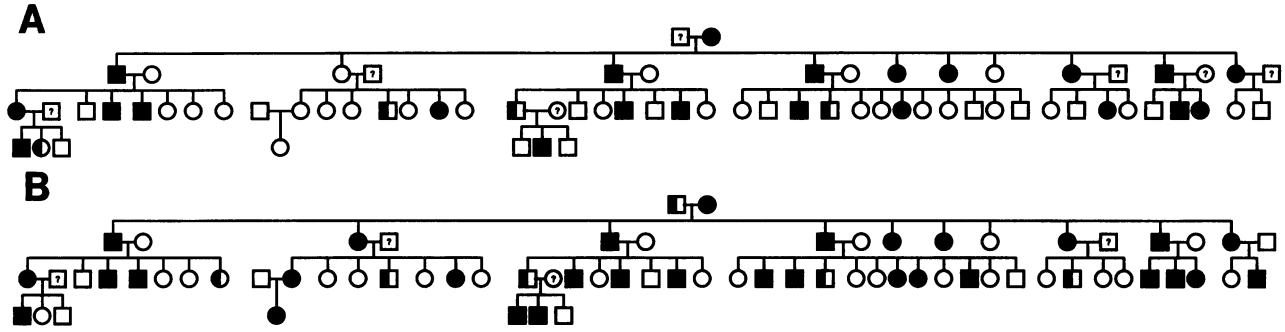

Figure 1 Pedigree of family S14. *A*, Old diagnoses. *B*, New diagnoses. Completely filled symbols depict individuals with full-blown GTS. Half-filled symbols depict individuals with chronic multiple-tic syndromes. Question marks indicate individuals with uncertain diagnosis.

most informative family under all diagnostic models; this family generated an average lod score of 4.5 under the narrow model with a four-allele marker. Kindred S14 is the largest family available, and the contribution of spectrum disorders is smaller in S14 than in the other families. Three other kindreds yielded mean lod scores close to or >3.0 with a four-allele marker but only for the broader diagnostic models.

Use of Incorrect Model for Analysis

The results presented above were obtained by generating marker data for a given diagnostic model and analyzing the data under the identical model. We have also analyzed the data for the subset of the Dutch families under different, "incorrect," models, thereby obtaining an indication for the loss of statistical power when incorrect diagnostic models are used.

The simulated data for these families were analyzed separately with each of the four models. For simulated marker data generated under the broadest model, the analyses almost always yielded significant results with the intermediate and broad models, but with the narrow model only in 47.6% of the cases (table 2). Using the broad diagnostic model in the analysis when the simulated, "true," model was narrow resulted in a dramatic loss of power: significant results were obtained in only 2.8% of all replicates.

Similar analyses were carried out on data simulated under the absence of linkage in order to count the rare occurrences of false-positive linkage findings. The frequency of incorrect linkage findings was remarkably low: 28–59/1,000,000 (table 2).

The population frequencies for the spectrum disorders CMT and OCS are uncertain but could be as high as 5%. We therefore performed a second set of simulations on the broadest diagnostic model but now with a higher gene frequency (table 1). The results for this "high" model only give a slightly better probability to detect linkage than those obtained with the broad model. The gene frequency does not appear to influence the linkage results very much.

In addition to testing single models, we analyzed various multiple-test scenarios and scored how frequently a lod score >3 + LOG(t) was obtained under at least one of the diagnostic models. In this latter analysis, a higher lod score threshold was chosen, in order to compensate for the increased probability of false-positive linkage findings due to multiple tests (Risch 1991) (tables 2 and 3).

Several multimodel scenarios performed very favor-

Table 2

Expected Frequency (%) of Lod Scores >3.0 in the Dutch Data Set for Various Models of Simulation and Analysis

	Model of Simulation (True Model)				
Model of Analysis	Narrow	Intermediate	Broad	High	Unlinked
Narrow	**78.60**	73.85	47.60	47.51	.0059
Intermediate	13.46	**99.71**	98.28	90.41	.0038
Broad	2.84	85.52	**99.98**	98.76	.0028
High	6.16	89.38	99.96	**99.48**	.0029

Note.—Diagonal indicated in bold-faced type represents analysis with correct diagnostic model.

Table 3

Expected Frequency (%) of Lod Scores >3 + LOG(t) in the Dutch Data Set for Combinations of Models

Model of Analysis[a]	Model of Simulation				
	Narrow	Intermediate	Broad	High	Unlinked
N/I	74.19	99.43	97.75	88.60	.0049
N/B	73.94	88.92	99.96	98.43	.0046
N/H	73.99	90.45	99.95	99.22	.0047
I/B	10.72	99.45	99.97	98.46	.0026
I/H	11.70	99.46	99.96	99.24	.0028
B/H	4.41	86.82	99.96	99.24	.0016
N/I/B	71.08	99.36	99.96	98.16	.0039
N/I/H	71.11	99.36	99.96	99.09	.0039
N/B/H	70.87	89.18	99.96	99.05	.0031
I/B/H	9.91	99.37	99.97	99.09	.0019
N/I/B/H	68.79	99.30	99.96	98.99	.0028

[a] N = narrow; I = intermediate; B = broad; H = high.

ably, compared with the single-model analysis. A combination of narrow, intermediate, and high diagnostic models (N/I/H) appeared particularly attractive. When the combination of N/I/H models is compared with the perfect single-model analysis (table 2, along diagonal as indicated), the N/I/H model leads to only minor loss of power, while the dramatic losses that occurred in the single-model analysis with model misspecification were completely prevented.

Impact of Diagnostic Instability

For family S14, a second round of diagnostic interviews was performed. Comparing diagnoses based only on this second round of interviews with diagnoses based on the first round showed a change in diagnosis for several family members. Additional diagnoses were obtained for subjects who had not been interviewed previously. For 10 subjects hitherto regarded as unaffected, the diagnosis of GTS was established in the second interview. For three subjects, previously regarded as unaffected, the diagnosis of CMT was established in the second interview. Diagnosis for one subject changed from GTS to unaffected, and diagnosis of one subject changed from CMT to unaffected, on the basis of the second interview (fig. 1*A* and 1*B*).

In order to evaluate the possible impact of diagnostic instability, we carried out simulations in this family under the assumption that the recently updated diagnoses are correct. Subsequent lod-score calculations were carried out, once with the updated diagnoses and once with the older diagnostic information. The intermediate diagnostic model was used in both the simulations and the analyses. The average loss in peak lod score due to use of the older diagnoses was 91.5% (peak lod score 4.07) (fig. 2). In an attempt to reduce this damaging effect of diagnostic instability, we carried out an additional analysis under the narrow diagnostic model. An approximately equal reduction in the peak lod score of 91.0% was obtained (peak lod score 4.01).

Discussion

In planning a linkage study, the use of computer simulations for evaluation of the adequacy in size of a linkage sample is becoming common practice. For the mapping of complex disorders additional questions have to be considered: what linkage strategy is most likely to be successful, and what is the effect of diagnostic uncertainties on the power to detect linkage in the available family set?

Simulation studies performed on the available family set for GTS, assuming locus homogeneity, showed that in a genome search a mean lod score much >3 can be expected for a true linkage, even with a two-allele marker and with the most narrow diagnostic model (data not shown). In the simulation studies presented here, we investigated the power to detect a true linkage in each family separately. Family S14 was sufficiently informative to detect linkage under all diagnostic models, while three other families yielded significant evidence for linkage under the two broader diagnostic models. We conclude that the available family material is sufficiently informative to detect linkage. Even under locus heterogeneity, some of the families should provide significant evidence for linkage individually. However, analyzing families separately will not protect us from missing a linkage due to locus heterogeneity within families. For GTS, this possibility is difficult to exclude, in

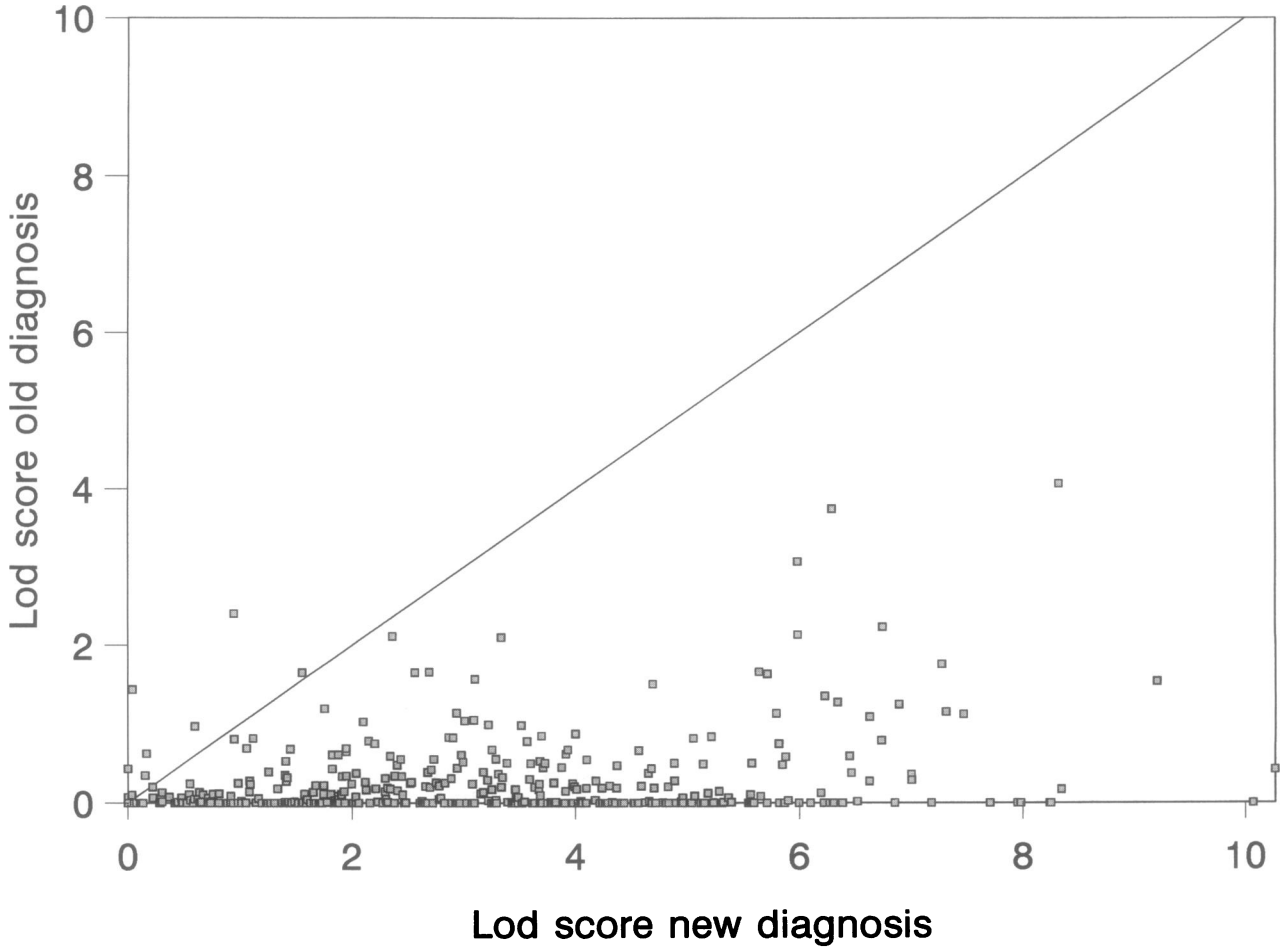

Figure 2 Effect of changed diagnosis in family S14. Simulation of a four-allele marker (PIC = .7) under the intermediate diagnostic model with new diagnoses is shown. Analysis under the intermediate model with the new diagnoses is given on the X axis, and the old diagnoses is given on the Y axis.

light of the reduced penetrance and the waxing-and-waning course of the disorder. Instances of possible bilineal segregation were identified by investigating individuals who marry into the families for a family history of tics and GTS.

An explanation for the failure to detect or replicate a "true" linkage for many complex disorders could be that the phenotype was not correctly defined. For GTS, the delineation of the phenotypic spectrum is still a matter of discussion. Associated behavioral problems such as CMT and OCS are likely to be variant expressions of the GTS gene defect but can also be caused by other genetic or nongenetic factors. Furthermore, GTS shows a waxing-and-waning course, and patients are often able to suppress symptoms for a limited time. This may lead to an incorrect diagnosis or to the inclusion of phenocopies. Both the role of spectrum disorders and uncertainty of diagnosis were studied in our simulations by testing various diagnostic models and evaluating the impact of diagnostic instability on the statistical power to detect linkage. As a remedy against false-positive linkage findings, it has been proposed to include only the most severe phenotypes in a linkage analysis (Byerly 1989; Baron 1990). This will result in a loss of information, but it seems more likely that the severe phenotype is the result of a genetic factor. This method does not protect us, however, against the consequences of diagnostic instabilities. An alternative solution that has been proposed is to define different models with a broadening in diagnostic criteria (Sherrington et al. 1988). There is an increased risk of false positive results, which can be addressed by a correction for multiple testing (Risch 1991). In the simulated data of the Dutch families, we investigated whether the use of three diagnostic models would better protect us against false negative findings than the use of a single model that carries the risk of misspecification.

If CMT and OCS are variant expressions of the GTS gene defect, analysis of the two broadest models was very powerful. In >98% of the replicates, linkage was

detected (tables 2 and 3). Analysis with the narrow model showed a considerable loss in information; the power to detect linkage was lowered to 47.6% as linkage information from individuals expressing CMT or OCS was lost. If OCS is not part of the GTS spectrum (table 2, column: true model is intermediate model), the probability of detecting linkage is high for all models of analysis, between 73.9%–99.7%. The penalty of using an incorrect analysis model is much more severe if the most narrow model is the correct one, with power reduced to as little as 2.8%.

These results can be explained by the fact that individuals with CMT and OCS will be classified inappropriately as gene carrier and frequently will be scored as recombinants in the analysis. Limiting the analysis to a single diagnostic model apparently leads to a dramatic loss of power, except if by chance the correct model is chosen. As a remedy, the application of several diagnostic models is very effective (tables 2 and 3). Whatever diagnostic model is correct, the probability of detecting linkage always is >70%.

Estimates of the population frequencies of CMT and OCS as milder expressions of the GTS gene are difficult to make but could be as high as 0.01. To investigate the influence of the gene frequency on the linkage analysis, another set of simulations was performed with the broadest diagnostic model and a high gene frequency. This additional model did not perform considerably better than the previous models.

When multiple models are tested, an increased lod-score threshold should be adhered to, to compensate for an increased probability of false-positive findings. We evaluated the appropriateness of the correction proposed by Risch (1991). When only a single model was tested, the frequency of false-positive findings was extremely low (<1/17,000; see tables 2 and 3). When three tests were applied simultaneously, each with a threshold of 3.0, an approximately twofold increase in false-positive findings was observed (1/7,812; data not shown). The proposed correction dealt appropriately with this (in $\leq$1/20,000 cases the lod score threshold of 3 + LOG(t) was exceeded).

In conclusion, a combination of the narrow, intermediate, and high diagnostic models in the analysis gave the highest probability to detect a true linkage. For GTS, a scenario of performing multiple tests gives a much higher probability of detecting linkage than does the use of a single narrowly defined phenotype.

The impact of diagnostic instability on linkage findings has been discussed (Egeland et al. 1990; Hodge and Greenberg 1992; Maziade et al. 1992). We fully agree with the recommendation of Hodge and Greenberg to include a sensitivity analysis as a standard part of reporting the results of a linkage analysis for complex disorders. The simulation studies here are not so much an a posteriori sensitivity analysis as a practical example of the impact of diagnostic instability observed for GTS.

For GTS, the waxing-and-waning course of phenotype expression and the possibility that patients suppress tics lead to diagnostic instabilities. This can result in a dramatic loss in lod score, as was observed with the updated diagnoses in one of the families (fig. 1). Diagnostic instability could vary between different families, but could also be the result of the long time span between subsequent interviews. In an attempt to account for the diagnostic instabilities, the GTS Genetic Consortium is now using a best-estimate diagnosis from senior investigators in the field that is based on structured interviews with subjects (see Material and Methods) and the participation of a panel of psychiatrists blind to proband's and relatives' clinical status. The diagnoses are based on personal diagnostic interviews, all available medical records, and family history data. In addition to this, we propose, in the case of GTS, to establish a lifetime diagnosis via repeated interviews. Individuals who have been diagnosed as "affected" will remain affected in the linkage analyses even if in subsequent diagnostic evaluations no disease phenotype is observed. Until now, the *Diagnostic and Statistical Manual of Mental Disorders* (3d edition, revised) (APA, [American Psychiatric Association] 1994), criteria were the basis of classification, but in addition a "Diagnostic Confidence Index" is being developed for GTS by the clinical investigators within the GTS consortium. This index consists of weighing factors for diagnostic items that strengthen or weaken the diagnostic confidence. In the linkage analysis, the confidence index could be used as a quantitative measure for GTS. In addition, linkage information from unaffected individuals can be omitted from the analysis applying alternative analytic methods as the "affected-only analysis" and "sib-pair analysis."

By using simulation techniques, the strategy of choice for a linkage study can be determined systematically instead of being made arbitrarily. In the case of GTS, the simultaneous testing of several diagnostic schemes was shown to give the best probability of detecting linkage. This conclusion does not necessarily apply to other disorders. In this specific case, a large amount of the information is obtained from associated behaviors of GTS. For other disorders, the gain in information that results from using broader models might not be enough to compensate for the increase in the lod score threshold, but this can be determined only after performing systematic simulation studies as presented here.

For each complex disorder, specific problems such as diagnosis, phenocopies, gene frequencies, or even the mode of inheritance have to be defined and translated into models that can be used for linkage analysis. Furthermore, simulation studies can be used to determine which of the available statistical approaches will give

the highest probability of detecting true linkage. When systematic simulation studies on these models or statistical methods are performed prior to starting a linkage study, which strategy is most likely to succeed can be determined.

In order to make independent replication of linkage studies possible, we propose that each study should summarize the clinical methods that were used and give a clear definition of phenotypical criteria and genetic parameters. Only in this way can the seemingly conflicting linkage results reported for many complex disorders be judged for their validity.

Acknowledgments

The authors wish to acknowledge Drs. J. L. Weber and E.J. Devor and all other collaborators taking part in the consortium working on the genetics of GTS who kindly provided us with all the family information used in this study. We thank the American Tourette Association and Prof. Dr. H. Galjaard for continuing support. This work was supported in part by the Dutch Praeventiefonds. R.K. was supported by U.S. Public Health Service grant NS24278. The GTS Genetic Consortium consists of the research groups of the following investigators: Dr. B. A. Oostra, Department of Clinical Genetics, Erasmus University Rotterdam; Drs. K. K. Kidd and D. L. Pauls, Department of Human Genetics, Yale University School of Medicine; Dr. R. Kurlan, University of Rochester School of Medicine and Dentistry; Dr. J. L. Weber, Marshfield Medical Research Foundation; Dr. L. C. Tsui, Department of Genetics, Hospital for Sick Children, Toronto; Dr. P. Sandor, Department of Psychiatry, The Toronto Hospital and University of Toronto; and Dr. E. J. Devor, Department of Psychiatry, College of Medicine, University of Iowa.

References

APA (American Psychiatric Association) (1994) Diagnostic and statistical manual of mental disorders, 3d ed rev. Washington, DC, APA

Baron M (1990) Genetic linkage in mental illness. Nature 346:618

Baron M, Freimer NF, Risch N, Lerer B, Alexander JR, Straub RE, Asokan S, et al (1993) Diminished support for linkage between manic depressive illness and X-chromosome markers in three Israeli pedigrees. Nat Genet 3:49–55

Byerley WF (1989) Genetic linkage revisited. Nature 340:340–341

Boehnke M (1986) Estimating the power of a proposed linkage study: a practical computer simulation approach. Am J Hum Genet 39:513–527

Devor EJ (1992) Linkage studies in 16 St. Louis families: present status and pursuit of an adjunct strategy. Adv Neurol 58 181–188

Devor EJ, Grandy DK, Civelli O, Litt M, Burgess AK, Isenberg E, van de Wetering BJM, et al (1990) Genetic linkage is excluded for the D_2-dopamine receptor lambda HD2G1 and flanking loci on chromosome 11q22-q23 in Tourette syndrome. Hum Hered 40:105–108

Egeland JA, Sussex JN, Endicott J, Hostetter AM, Offord DR, Schwab JJ, Allen CR, et al (1990) The impact of diagnoses on genetic linkage study for bipolar affective disorders among the Amish. Psychiatr Genet 1:5–18

Greenberg DA (1984) Simulation studies of segregation analysis: application to two-locus models. Am J Hum Genet 36:167–176

Heutink P, Breedveld GJ, Niermeijer MF, van de Wetering BJM, Oostra BA (1993) Progress in gene localization. In: Kurlan R (ed) The handbook of Tourette's syndrome and associated tic and behavioral disorders. Marcel Dekker, New York, pp 317–335

Heutink P, van de Wetering BJM, Breedveld GJ, Oostra BA (1992) Genetic study on Tourette syndrome in the Netherlands. Adv Neurol 58:167–172

Heutink P, van de Wetering BJM, Breedveld GJ, Weber J, Sandkuijl LA, Devor EJ, Heiberg, et al (1990) No evidence for genetic linkage of Gilles de la Tourette syndrome on chromosome 7 and 18. J Med Genet 27:433–436

Hodge SE, Greenberg DA (1992) Sensitivity of lod scores to changes in diagnostic status. Am J Hum Genet 50:1053–1066

Kelsoe JR, Ginns EI, Egeland JA, Gerhard DS, Goldstein AM, Bale SJ, Pauls DL, et al (1989) Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. Nature 342:238–243

Kennedy JL, Giuffra LA, Moises HW, Cavalli-Sforza LL, Pakstis AJ, Kidd JR, Castiglione CM, et al (1988) Evidence against linkage of schizophrenia to markers of chromosome 5 in a northern Swedish pedigree. Nature 336:167–170

Kurlan R (ed) (1993) Handbook of Tourette's syndrome and related tic and behavioral disorders. Marcel Dekker, New York

Kurlan R, Behr J, Medved L, Shoulson I, Pauls DL, Kidd JR, Kidd KK (1986) Familial Tourette syndrome: report of a large pedigree and potential for linkage analysis. Neurology 36:772–776

Lathrop GM, Lalouel JM (1984) Easy calculations of lod scores and genetic risks on a small computer. Am J Hum Genet 36:460–465

Maziade M, Roy MA, Fournier JP, Cliche D, Merette C, Caron C, Garneau Y, et al (1992) Reliability of best-estimate diagnosis in genetic linkage studies of major psychosis: results from the Quebec pedigree studies. Am J Psychiatry 149:1674–1686

Pakstis AJ, Heutink P, Pauls DL, Kurlan R, van de Wetering BJM, Leckman JF, Sandkuijl LA, et al (1991) Progress in the search for genetic linkage with Tourette syndrome: an exclusion map covering more than 50% of the autosomal genome. Am J Hum Genet 48:281–294

Pauls DL, Cohen DJ, Heimbuch R, Detlor J, Kidd KK (1981) Familial pattern and transmission of Gilles de la Tourette syndrome and multiple tics. Arch Gen Psychiatry 38:1091–1093

Pauls DL, Leckman JF (1986) The inheritance of Gilles de la Tourette's syndrome and associated behaviors. N Engl J Med 315:993–997

Pauls DL, Pakstis AJ, Kurlan R, Kidd KK, Leckman JF, Cohen DJ, Kidd JR, Como P, Sparkes R (1990) Segregation and linkage analyses of Tourette's syndrome and related disorders. J Am Acad Child Adolesc Psychiatry 29:195–203

Pauls DL, Towbin KE, Leckman JF, Zahner GE, Cohen DJ (1986) Gilles de la Tourette's syndrome and obsessive-compulsive disorder: evidence supporting a genetic relationship. Arch Gen Psychiatry 43:1180–1182

Risch N (1990) Genetic linkage and complex diseases, with special reference to psychiatric disorders. Genet Epidemiol 7:3–16

——— (1991) A note on multiple testing procedures in linkage analysis. Am J Hum Genet 48:1058–1064

Robertson MM (1989) The Gilles de la Tourette syndrome: the current status. Br J Psychiatry 154:147–167

Shapiro AK, Shapiro ES, Young YG, Feinberg TE (1988) Gilles de la Tourette syndrome, 2d ed. Raven Press, New York

Sherrington R, Brynjolfsson J, Petursson H, Potter M, Dudleson K, Barraglough B, Wasmuth J, et al (1988) Localization of a susceptibility locus for schizophrenia on chromosome 5. Nature 336:164–167

Terwilliger JD, Ott J (1992) A multisample bootstrap approach to the estimation of maximized-over-models lod score distributions. In: MacCluer JW, Chakravarti A, Cox D, Bishop DT, Bale SJ, Skolnick MH (eds) Genetic analysis workshop 7: issues in gene mapping and detection of major genes. Cytogenet Cell Genet 59:142–144

Weeks DE, Lehner T, Squires-Wheeler E, Kaufmann C, Ott J (1990) Measuring the inflation of the lod score due to its maximization over model parameter values in human linkage analysis. Genet Epidemiol 7:237–243

Weeks DE, Ott J, Lathrop GM (1990) Slink: a general simulation program for linkage analysis. Am J Hum Genet Suppl 47:A204

Wilkie PJ, Ahmahn PA, Hardacre J, LaPlant RJ, Hiner BC, Weber JL (1992) Application of microsatellite DNA polymorphisms to linkage mapping of Tourette syndrome gene(s). Adv Neurol 58:173–180