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Linkage Analysis of Tourette Syndrome in a Large Utah Pedigree

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Abstract

Tourette Syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor and phonic tics. The heritability of TS has been well established, yet there is a lack of consensus in genome-wide linkage studies. The purpose of this study was to conduct a genome-wide linkage analysis on a unique, large, high-risk TS Utah pedigree. We examined a qualitative trait (TS1) where cases had a definitive diagnosis of TS as observed by a clinical interviewer (n=66) and a quantitative phenotype based on the total Yale global motor and phonic tic severity scores (n=102). Both parametric and non-parametric multipoint linkage analyses based on MCMC methods were performed using a 10cM spaced micro-satellite autosomal marker set. Two regions of interest were identified under affecteds-only recessive models; a LOD score of 3.3 on chromosome 1p for Yale tic severity and a LOD score of 3.1 on chromosome 3p for the TS1 phenotype. Twenty-seven individuals shared linked segregating haplotypes for the 1p region. They had significantly higher Yale tic phonic scores than non-sharers (p=0.01). There were 46 haplotype sharers on chromosome 3p with significantly higher percentage of females among these individuals compared to the non-sharers (p=0.03). The significant linkage peaks on chromosomes 1p and 3p are in new areas of the genome for TS, and replication of these findings is necessary.

Keywords

Linkage analysis; Tourette Syndrome

Introduction

Tourette Syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor and phonic tics that wax and wane over a lifetime(Leckman and others 2001). The prevalence of TS is estimated to be between 26 to 115 per 10,000(Scahill 2004). Males are more likely to have TS with a ratio as high as 4 to 1(Leckman and others 2001; Robertson 2000). The age at onset for motor tics ranges from 2 to 14 with a mean age of 7 years; vocal tics usually occur 2 to 3 years later(Leckman and others 2001; Robertson 2000). Over half of all TS patients experience remission of symptoms in early adulthood(Leckman and others 2001; Robertson 2000).

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The heritability of TS has been well established (Baron and others 1981; Devor 1984; Eapen and others 1993; Hasstedt and others 1995; McMahon and others 2003; McMahon and others 1992; McMahon and others 1996; Nestadt and others 2000; Pauls and Leckman 1986; Pauls and others 1991; Price and others 1985). Early segregation analysis suggested the existence of a single major gene (Baron and others 1981; Devor 1984) and an autosomal dominant mode of inheritance was proposed(Eapen and others 1993; Pauls and Leckman 1986). However, reports of bilineal transmission(Hanna and others 1999; Hasstedt and others 1995; Kurlan and others 1994; McMahon and others 1996) and a lack of consensus from the many linkage studies undertaken to identify major genes suggests that the mode of inheritance is likely more complex.

The lack of consensus in genome-wide linkage studies for TS is characteristic for psychiatric disorders and points to a more complex disease model than a single major gene. However, the fact that large multigenerational pedigrees have arguably been the more successful study design in TS linkage studies (Barr and others 1999; Curtis and others 2004; Merette and others 2000; The Tourette Syndrome Association International Consortium of Genetics 2007; Verkerk and others 2006) indicates that rarer, more highly penetrant susceptibility variants may exist for TS. Early linkage studies of large pedigrees were restricted to analyses based on one or two markers at a time due to the lack of software capable of performing multipoint analyses (Barr and others 1999a; Merette and others 2000; Curtis and others 2004). Ignoring results obtained from the affected-pedigree-member method that have been shown to be invalid (Field and Kaplan 1998), these studies indicated suggestive regions on chromosomes 5p, 19p (Barr and others 1999a) and 5q, 10p and 13q (Curtis and others 2004), and a significant region on chromosome 11q (Merette and others 2000). However, linkage scores from these analyses were based on only one or two markers, so that it is possible that the results are inflated, calling for caution when interpreting these earlier findings. Two more recent studies including multigenerational pedigrees have performed multipoint analyses using SIMWALK2(The Tourette Syndrome Association International Consortium of Genetics 2007; Verkerk and others 2006). A suggestive region on chromosome 3q was found in one study (Verkerk and others 2006). Additionally, a suggestive region on chromosome 5p and a significant region on 2p were found in a large collaborative study (The Tourette Syndrome Association International Consortium of Genetics 2007). The Tourette Syndrome Association International Consortium of Genetics (TSAICG) also included 308 sib-pairs; however the significant score on chromosome 2p was primarily driven by the multigenerational pedigrees.

The purpose of this study was to conduct a genome-wide linkage analysis on a unique, large, high-risk TS Utah pedigree containing 260 individuals with 238 having genotype data and 108 reporting TS or chronic tics. A strictly defined dichotomous TS phenotype and a quantitative tic severity score were considered and both parametric and non-parametric multipoint linkage analyses were performed.

Materials and Methods

Ascertainment and Diagnosis

Due to the unique structure of the large, high-risk TS pedigree studied and issues concerning identifiability, we cannot illustrate this family with a pedigree drawing. Descriptions of the pedigree have previously been presented elsewhere (McMahon and others 2003; McMahon and others 1992). Briefly, this pedigree was originally ascertained through a 10-year-old male proband with TS. The grandfather of the proband is the founder of the current pedigree, and although deceased, was reported to have chronic tics. The pedigree founder married 10 women and had 43 offspring. Across the total four generations descendant from this initial founder, there are over 500 descendents. Review of genealogical records indicate

no evidence for consanguinity. Here we have studied descendents from five wives. These five branches are saturated with TS and contain 260 individuals (including the original proband and 36 marry-ins) and a total of 108 with reported TS or tics. Assessment and diagnosis of TS and associated conditions was done by a consistent team of expert clinicians through an interview of the individual and/or their parents. Interviews span the past 25 years, with pedigree members from earlier generations assessed in the 1990s and those in the later generations assessed in the 2000s. TS diagnosis classification was based on criteria of the Diagnostic and Statistical Manual of Mental Disorders, IV and the developed criteria by the Tourette Syndrome Classification Study Group (The Tourette Syndrome Classification Study Group 1993). The Yale Global Tic Severity Scale (YGTSS) and the Shapiro Checklist were captured to measure tic severity (Leckman and others 1989; Shapiro and others 1978). Obsessive compulsive disorder (OCD) diagnosis and severity were reported.

Phenotype

Our primary analyses consisted of one qualitative and one quantitative phenotype. The qualitative trait (TS1) considered was a strict TS definition that consisted of cases with a definitive diagnosis of TS where tics were observed by the interviewer (n=66). Our quantitative phenotype considered tic severity based on the total YGTSS global motor and phonic tic severity scores as reported for their worst ever TS severity (n=102). Secondary analyses consisted of two further qualitative phenotypes of decreasing stringency from our primary trait: TS2 included all cases in TS1 in addition to cases who had a definitive diagnosis of TS by self report of tics, but where tics were not observed by the clinical interviewer (n=79); and TS3 additionally considered those with multiple chronic tics without TS (n=108). This final definition matches that used by the recent TSAICGC study (The Tourette Syndrome Association International Consortium of Genetics 2007).

Genotyping and Marker Characteristics

Genotyping was done at the Centre National de Genotypage in Evry, France following standard DNA amplification protocols. There were a total of 368 autosomal STR genetic markers genotyped that passed performance thresholds and these were at an average spacing of 10 cM. A total of 238 of the 260 individuals in the pedigree were successfully genotyped. Error checking of the genotypes was done using PedCheck (O'Connell and Weeks 1998) and any genotypes causing misinheritances were zeroed (see supplementary table 1). Furthermore, there were 41 individuals for whom genotyping was available but for whom a complete TS assessment or diagnosis was not available, leaving 197 individuals with both genotype and phenotype data. All genotype data were used to determine inheritance states for the linkage analysis, but LOD scores were based on sharing of individuals with phenotype of interest.

The second generation Rutgers' linkage map was used (Matise and others 2007). An EM algorithm which takes into account the pedigree structure was used to estimate the allele frequencies (Thomas and Camp 2006).

Data Analysis

A Markov Chain Monte Carlo (MCMC) software, MCLINK, was used to calculate the multipoint LOD scores for large pedigrees (Thomas and others 2000). Both parametric and non-parametric multipoint linkage analyses were performed. For the parametric analyses of the qualitative phenotypes, an “affecteds only” analysis was done using general models. For the recessive model, the disease allele frequency was set at 0.01 with a penetrance function of (0.01, 0.01, 0.90), and for the dominant model the allele frequency was set at 0.005 with a penetrance function of (0.01, 0.90, 0.90). For the quantitative analysis, the penetrance function, which depends on each individual's trait value, was determined by estimating the

mean and variance of two normal distributions from the data using an EM algorithm and deriving a ratio of odds between the distributions.

MCLINK calculates a multipoint LOD score, called the TLOD that we report for all parametric analyses. For a TLOD score, the inheritance vectors in the pedigree (which define identical by decent status) are determined based on all markers, but the LOD is estimated at each marker position and maximized over the recombination fraction at each point. The retention of the recombination fraction maximization in the statistic maintains robustness to model misspecification not usually characteristic of other multipoint statistics (Abkevich and others 2001). The non-parametric analysis was conducted using the methods of Camp et al, with the p-values calculated based on simulated null distribution values (Camp and others 2001). The p-values from the NPL analysis were translated to a LOD score scale for ease of comparison between results.

Due to the multiple models, standard LOD threshold values need to be adjusted. This was done using the method proposed by Camp and Farnham (Camp and Farnham 2001) After accounting for the multiple models and two primary phenotypes, LOD scores of 1, 2, and 3, corresponding to 10:1, 100:1, and 1000:1 odds in favor for the alternative hypothesis, were adjusted to thresholds of 1.6, 2.6, and 3.6, respectively. False discovery rates (FDR) results for linkage peaks are also reported for thresholds of LOD scores ≥3, ≥2 and ≥1.

For each linkage peak with LOD≥2.6 from the primary analysis, individuals carrying the linked segregating haplotype (haplotype sharers) were determined and characteristics of sharers and non-sharers were compared using Fisher's exact tests and Wilcoxon rank sum tests.

Results

Primary Linkage Analyses

Genome-wide multipoint linkage results for phenotypes TS1 and the YGTSS tic severity quantitative trait are shown in Figure 1. Two regions exceeding 2.6 were identified, indicating odds in favor of the alternative hypothesis greater than 100:1 after adjustment for multiple testing. Table 1 contains results for all peaks with a LOD score above 1.6 and Table 2 contains the FDR results.

On chromosome 1p a LOD score of 3.3 (recessive model) was found for the YGTSS tic severity phenotype, with the peak occurring at marker D1S207 (112.71 cM). A lower score was found for precisely the same marker with the dominant model (YGTSS tic severity, LOD=1.9). The same region was also identified using the NPL analysis with the TS1 phenotype (LOD=2.1).

A linkage signal was also detected under a recessive model on chromosome 3p for the TS1 phenotype, with the peak LOD score of 3.1 occurring at D3S1289 (71.83 cM). The same marker also resulted in linkage evidence under the dominant model (TS1, LOD=2.0).

Secondary Linkage Analyses

For the less stringent qualitative phenotypes (TS2 and TS3) no additional peaks were identified (Supplementary Figure 1), although, on several chromosomes these phenotypes did identify linkage evidence in the same regions as TS1 or YGTSS tic severity analyses. However, in all cases, the findings for TS2 and TS3 were less significant than for TS1 and/or YGTSS tic severity.

Haplotype Sharing: Chromosome 1p Region

For the linkage peak on 1p, we identified the individuals with high YGTSS tic severity score that shared the linked segregating chromosomal segment contributing to the 3.3 recessive linkage score, and identified these as 'haplotype sharers'. We used a YGTSS tic severity score cut-off of at least 7 for examining this peak. There were a total of 37 individuals who had scores of at least 7,of these there were 27 sharers and 9 non-sharers under a recessive model and one individual whose sharing (under a recessive model) was undetermined due to missing parental phenotype data. We compared clinical characteristics of sharers and non-sharers. There were no significant differences between the sharers and non-sharers with respect to gender, age at ascertainment, OCD diagnosis, or YGTSS motor tic severity score. We found that the chromosome 1 haplotype sharers, however, did have a significantly higher YGTSS tic phonic score compared to non-sharers (11.2 vs 8.4; p=0.01). Sharers and non-sharers had the same rate of echopraxia (22.2%), and not statistically significantly different rates of echolalia (51.9% vs. 33.3%, p=0.45), and palilalia (37.0% vs 11.1%; p=0.22). Most (n=20, 74.1%) of the chromosome 1 sharers were also haplotype sharers on chromosome 3p.

Haplotype Sharing: Chromosome 3p Region

Of the 66 genotyped individuals with definite TS observed (TS1), seven were not considered for recessive sharing because of the married-in spouses as both of their haplotypes couldn't be shared with other cases (n=5) or undeterminable due to missing parental phenotype information (n=2). Thus, of the remaining 59 individuals, 46 shared linked segregating haplotypes on chromosome 3p, under a recessive model, and 13 were non-sharers. Characteristics were compared. There were no significant difference between the chromosome 3 haplotype sharers and non-sharers with respect to age at ascertainment, YGTSS global tic severity score, and OCD diagnosis. The haplotype sharers had a significantly higher percentage of females (52.2%) compared to the non-sharers (15.4%) (p=0.03). While not statistically significant due to small sample size, it is interesting to note that sharers compared to non-sharers were more likely to report echopraxia (28.3% vs. 0.0%; p=0.52), echolalia (47.8% vs. 23.1%; p=0.20) and palilalia (32.6% vs. 7.7%; p=0.09). Coprolalia and copropraxia were reported by 2 sharers and none of the non-sharers.

Discussion

We found two linkage peaks of interest that have not previously been reported in the TS genetics literature. These two peaks correspond to 3 markers with multipoint LOD scores ≥3 which together have an FDR q-value of .08. This indicates that less than one of these markers is expected to be a false discovery, after accounting for multiple testing. The first peak (LOD=3.3), for quantitative tic severity, was on chromosome 1p31-p22 under a recessive model. The sharers of this peak had higher YGTSS tic phonic scores. The second peak was on chromosome 3p23-p13 (LOD=3.1) under a recessive model using a stringent phenotype of definite TS as observed by interviewer. The haplotype sharers at this peak were more likely to be female, with more echo-phenomena.

Both linkage peaks were found under a recessive model. Statistically, it is quite clear why such a model might generate superior linkage evidence. A large number of TS individuals share a haplotype for the chromosome 3 and chromosome 1 loci segregating from the pedigree founder whose family reported as having chronic tics. A large number of these also share a second haplotype at these loci from their marry-in parent (many of whom are also affected). This assortative mating and the presence of a segregating founder haplotype contributed to the significance of a recessive model. It is important to note that while it is likely that the underlying model that identifies the linkage peak is closer to the true

underlying inheritance model, it is not a true representation of that unknown model. Our suggestion that the model for chromosome 1 and 3 may be closer to a recessive mode is consistent with Hasstedt, et al and McMahon et al prior segregation analyses of this pedigree which indicated a penetrance level of 28% in heterozygotes compared to a 99% penetrance level for homozygotes (Hasstedt and others 1995; McMahon and others 1996). Furthermore, the recessive mode of inheritance applies only to these linkage peaks and given locus heterogeneity it is possible that TS may follow dominant modes of inheritance for other loci as proposed in prior segregation analyses as performed in other populations (Eapen and others 1993; Pauls and Leckman 1986).

The 1-LOD support interval for the chromosome 1p peak is approximately from 108.79 to 129.53 cM. However, examining the region identified by the haplotype sharers identifies a smaller region from 112.71 and 129.53 cM. This covers the region from 1p31.1 to 1p21.2 and contains 96 genes. This region has not been examined in previous TS studies. Five signal transducer genes (F3, GNG5, GPR88, PKN2, TGFBR3) reside within this region, but none of these genes have been studied in other neuropsychiatric disorders. The marker, D1S207, under the peak on this chromosome has shown linkage to the autoimmune disease of psoriasis (Veal and others 2001). This may be of interest as some recent studies have proposed an autoimmune model for TS, termed pediatric autoimmune neuropsychiatric disorder or PANDAS.(Hoekstra and others 2002) A recent blind cohort study did find significant exacerbation of tics in relationship to infections (Kurlan and others 2008) and this is worthy of note as the linkage peak was found using a phenotype related to severity of tics. The sharers under the linkage peak on chromosome 1 had higher phonic tic severity scores. Furthermore, a large percentage of sharers had echolalia (52%) and palilalia (37%). In fact, the percentage with echolalia is larger than previously reported percentage (46%) of clinical patients (Lees and others 1984). This evidence may indicate that the linkage peak is associated with verbal aspects of TS.

Our linkage peak on 3p is in the same region as the chromosomal translocation reported in 1990 by Brett et al, although their own subsequent linkage study of this region failed to find significant linkage (Brett and others 1990; Brett and others 1996). Our study represents the first linkage evidence for TS in this region. The 1-LOD support interval at 3p delineated the linkage evidence between 50.35 and 88 cM. Examination of the haplotype sharing in this region further narrowed the linkage to be between 50.35 and 71.83 cM. This is a large region from 3p24.1 to 3p14.3 and containing over 286 known genes. None of these genes have been previously examined in TS. However, a recent genome-wide association analysis of ADHD, a co-morbidity of TS, did find significant association at a marker in this region (rs9845475, p=3.95E-6) (Lasky-Su and others 2008). There are total of 39 signal transducer genes in this region. Several of these signal transducer genes have been studied in schizophrenia including CCR5 (Rasmussen and others 2006), GRM3 (Mossner and others 2008), and TGFBR2 (Numata and others 2008). Another of these signal transducer genes, CTNNB1 has been linked to memory (Maguschak and Ressler 2008). The signal transducer gene ras homolog gene family, member A (RHOA) is in this region has been shown to be associated with smoking initiation (Chen and others 2007). This might be a candidate gene as smoking has been shown to alleviate tic symptoms in a mouse model (Hayslett and Tizabi 2005) and in a small trial in the use of nicotine chewing gum in TS patients (Orth and others 2005).

While not statistically significant, sharers of the haplotype on chromosome 3p were more likely to have the complex motor tic of echopraxia (30%). This rate of echopraxia is almost 10% higher than previously reported rates in clinical patients (Lees and others 1984). These haplotype sharers may represent distinct subset of TS and is reflective of the use of a stringent phenotypic definition of TS by observation of the clinical interviewer. This

phenotype definition has not been used in linkage studies of TS. It was chosen because of the larger number of individuals in the pedigree with tics and the concern over phenocopies or over reporting of tics due to the overall acceptance of tics in the family.

Due to the large overlap of chromosome 1 haplotype sharers with chromosome 3 haplotype sharers, we investigated protein or gene interactions for all the genes found in these two regions using the web tool BioGrid, but found no reported interactions involving genes from these two regions.(Breitkreutz and others 2008)

We have found several linkage peaks in new areas of the genome. The large number of haplotype sharers on chromosome 3 and chromosome 1 strengthens the evidence for linkage under these peaks. However, due to cost constraints we were unable to add additional markers for fine mapping under the linkage peaks and thus we were not able to further narrow the regions identified. These findings were from a single unique pedigree, so it is not surprising that the linkage evidence does not overlap with peaks in other studies. However, subsequent fine mapping to determine good candidate genes within such a pedigree may reveal pathways or mechanisms that will be of interest more generally for TS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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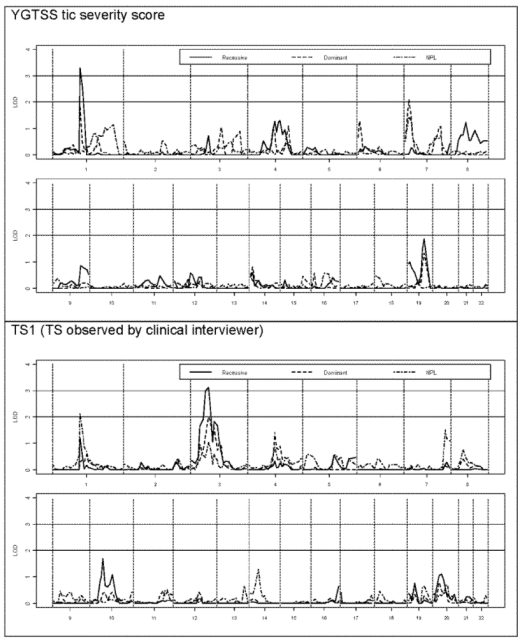

Figure 1.
Primary linkage analysis results for TS1 and quantitative trait based on the YGTSS tic severity score

Table 1

Linkage peaks with LOD scores ≥1.6 for primary analyses (LOD≥2.6 in bold)

Chromosome band	cM Position	Marker	Phenotype	Model	LOD*
1p31-p22	**112.71**	**D1S207**	**YGTSS Severity**	**Rec**	**3.3**
	112.71	D1S207	TS1	NPL	2.1
	112.71	D1S207	YGTSS Severity	Dom	1.9
3p23-p13	**71.83**	**D3S1289**	**TS1**	**Rec**	**3.1**
	71.83	D3S1289	TS1	Dom	2.0
7p21	21.10	D7S513	YGTSS Severity	Dom	2.1
10p12	90.34	D10S197	TS1	Rec	1.7
19q13	75.28	D19S902	YGTSS Severity	Rec	1.9

*LOD≥1.6 indicates a 10:1 ratio in favor of the alternative hypothesis; LOD≥2.6 indicates a 100:1 ratio in favor of the alternative hypothesis, corrected for multiple models and phenotypes.

Table 2

FDR q-values for LOD scores ≥ 1, ≥ 2 and ≥ 3, accounting for multiple testing in primary analyses.

LOD	Observed scores	Expected scores*	FDR q-value**
≥ 3	3	0.23	0.08
≥ 2	7	2.17	0.31
≥ 1	9	2.97	0.33

*Expected indicates the number of markers expected to exceed the LOD score under the null distribution;

**corresponding FDR q-value indicating the proportion of the findings exceeding the LOD score that would be expected under the null (i.e. expected/observed).