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An update on the genetics of Gilles de la Tourette syndrome

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Abstract

Objectives: To summarize the current data suggesting that Gilles de la Tourette syndrome (GTS) is inherited and genetic. **Methods:** The extant literature on family studies, segregation analyses, candidate genes studies and linkage studies of GTS was reviewed and summarized. **Results and conclusions:** There is considerable data that suggests that: (1) genetic factors play an important role in the manifestation of GTS; (2) several genes are important with some possibly having major effect; and (3) several regions of the genome have been identified as potential locations of these susceptibility genes.

Keywords: Gilles de la Tourette syndrome; Family studies; Candidate gene studies; Genetic linkage studies

Introduction

Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder with onset in childhood. Research over the last two decades has led to several notable advances in our understanding of GTS: (1) a more accurate estimate of the prevalence of the syndrome and the realization that it is much more common than had previously been thought [47]; (2) a clearer elucidation of the range of behaviors that comprise the phenotype [1,13,18,39,40,43]; (3) a more detailed documentation of the familial transmission of GTS and related conditions [17,26,27,38,41,61]; (4) an evolving understanding of the role nongenetic factors play in the manifestation of the syndrome. Nongenetic factors may be related to the severity of GTS [32,33] and the comorbid conditions that often accompany its clinical presentation [10,48–50] (Carter et al., 2000 [9]); and (5) the identification of several chromosomal regions that appear to contain susceptibility loci for GTS [3,35,52,53,58].

Family studies of GTS

Six family studies completed in the last decade clearly demonstrate that GTS and related conditions are familial [17,27,31,43,59,61]. Five of the studies included families from the United States and Europe, while one [31] reported on families collected in Japan. All six studies used structured interviews to collect data directly from all probands and available first-degree family members. Furthermore, best estimate diagnostic procedures were used in all studies to achieve consensus diagnoses for all first-degree relatives. The results from the five studies examining families from the US and Europe are remarkably similar. The morbid risk for of GTS among relatives range between 9.8% and 15% across all studies and the rate of other tics range between 15% and 20%. These rates are significantly elevated over the rates of tics in the general population and/or control samples. Rates of illness observed in Japanese families are significantly lower that those reported from the US and Europe. The age-corrected rates of GTS and chronic motor tics among the first-degree relatives were 2.0% and 12.0%, respectively. If replicated, these data suggest that there may be differences in the etiology of GTS and related behaviors in the Japanese population when compared to populations of European descent.

Segregation analyses of GTS family data

Segregation analyses are designed to test specific genetic hypotheses regarding the transmission of a disorder within families. Seven separate segregation analyses have been completed on different GTS family data sets. All but one give results that are consistent with the hypothesis that

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major genes are involved in the expression of GTS and related conditions. Three studies [17,41,59] reported a pattern consistent with autosomal dominant inheritance while three others [26,38,61] found that the most parsimonious solution was a model in which the penetrance of heterozygous individuals was between the homozygotes. In addition, Walkup et al. [61] observed evidence for a significant multifactorial (polygenic) background. These investigators estimated that the major locus accounted for more than half of phenotypic variance. In contrast to all previous studies, Seuchter et al. [51] did not find evidence for Mendelian transmission of GTS and related conditions in 108 families ascertained through a GTS proband. Of note is that the recurrence risk for GTS and tics in these families were similar to other reported rates [27]. Thus, it is not immediately clear why the results of segregation analyses are so different. Nevertheless, the majority of studies provide strong evidence for the effect of major genes in the expression of GTS. However, recent studies suggest that the inheritance patterns of GTS and related conditions are more complex than were originally thought and that the underlying genetic mechanisms are likely to involve a number of different genes.

The search for genes

Two strategies have been employed in the search for susceptibility genes for GTS and related conditions: association and linkage studies.

Association studies

Genetic association studies are appealing since analyses can be done without the need for specific assumptions about the mode of inheritance. Two types of association studies have been done: case-control studies and family-based studies.

The advantage of the case-control design lies in the fact that cases are readily obtained and can be efficiently genotyped and compared with control samples. The disadvantage of this approach is the difficulty in identifying an appropriate control group. This design has been widely used and its weaknesses are well known. Specifically, association studies are often characterized by high rates of false positive results — a statistically significant association between a phenotype and a polymorphism resulting from inappropriate matching of case and control individuals. It has been demonstrated that one cause of false positive results could be population stratification — a characteristic of a population in which cases and controls differ, not only with respect to the phenotype of interest and its genetic etiology, but also with respect to their overall population genetic ancestry (i.e., their general range and frequency of polymorphisms). The result of population stratification is that many irrelevant markers appear to be disease associated.

Although the limitations of association studies are well recognized, the association design represents an essential step in the identification and description of disease-mediating genetic variants. In the last several years, there have been a number of proposals in the literature that should help to overcome some of the limitations of case-control studies (see Grigorenko and Pauls [25] for a more detailed discussion). One of the more promising approaches has been suggested by Devlin and Roeder [15]. These investigators have described a population-based association method using what they describe as a ‘‘genomic control’’ (GC). This method should help to minimize false positive findings that are due to inappropriate matching of cases and controls. The method requires the additional genotyping of markers that are unlikely to affect liability (null loci). Chi-square statistics are calculated for both null and candidate loci. Utilizing the information on the variability and magnitude of the test statistics observed at the null loci that are inflated by the impact of population stratification, a multiplier is derived to adjust the critical values for significance tests for candidate loci, permitting analysis of stratified case-control data without an increase rate of false positives. If population stratification is not detected from null loci, then the GC method is identical to a standard test of independence for a case-control design.

In addition to the GC approach, two methods have been developed that alleviate the need for stringently defined control samples; the haplotype relative risk (HRR) method [19,57] and the transmission disequilibrium test (TDT) [54,55]. Both utilize samples of small families rather than cases and controls. To carry out these studies, DNA from affected probands and their parents is genotyped for the genes/markers under investigation. The proband’s two alleles define the ‘‘affected’’ group and the nontransmitted parental alleles constitute the control sample. Since both parents donate alleles equally to both groups they are by definition perfectly matched for ethnicity and race.

Candidate gene studies are a special case of association studies. Rather than examining anonymous DNA segments, specific genes are studied to determine if some alleles may be important in the manifestation of the disorder under study. Thus, candidate genes studies are not so much an alternative analytical method, but rather a philosophy for guiding experimental choices. Based upon available biological information about a condition (e.g., neurochemical levels in affected individuals, the mode of action of a pharmaceutical agent, or differences in brain structure and/or function), a reasoned choice can be made about what genes might be important in the expression of the disorder. These genes are referred to as ‘‘candidate genes’’ and are used as markers in an identical fashion to the vast array of ‘‘anonymous’’ DNA markers that have no known function. While this approach is more intellectually satisfying than using anonymous DNA markers, at the present time, it is limited by both the current inventory of known human genes and the limited understanding of the biological underpinnings of GTS. On the other hand, once results of linkage studies suggest regions of interest and those regions have