



tourette syndrome association, inc.

MEDICAL LETTER

2000 Summary of the Recent Literature

Editorial

THE GENETICS OF TS

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In November 1999, the results of the TSA sponsored sibpair study were published.¹ Two areas (on chromosomes 4 and 8) were considered promising and worthy of further investigation. Before discussing the results of this study, we provide a brief review of the TS genetics story.

As readers may know, the TSA has supported the collaboration of the TSA International Genetic Consortium for over a decade. The lack of results from classic linkage studies to identify the TS gene coupled with findings from recent family studies suggesting that the inheritance of TS may be more complicated than previously assumed, a new approach to identifying the TS gene(s) was initiated about four years ago. The affected sibpairs method used in this new study is a decided change in strategy and has many advantages. The idea behind this method is to identify areas of the genome with increased *sharing* in affected sibpairs. Simply put, if two siblings have TS, then their shared genetic material will likely include the genetic material that is responsible for causing TS. If a study looks at many sibling pairs and identifies areas of the genome that are frequently shared among a group of affected sibpairs, there is a greater chance that the shared areas of the genome will include the gene(s) for TS.

Actually, the sibpairs method is a simple approach. With traditional linkage studies, it is necessary to estimate such parameters as inheritance model, penetrance, gene frequency, male to female ratio, in order to conduct data analysis. If these assumptions

are wrong, it is difficult to identify the gene(s)—even when the clinical and genetic data are carefully collected. With sibpair studies, no assumptions about the genetics of the disorder are required. If affected sibpairs can be identified relatively easily, with a bit of luck, it may be possible to identify candidate areas of the genome within the first phase of the study (100 sibpairs).

This approach has been used successfully in a number of other conditions with complex, but still relatively straightforward patterns of inheritance such as diabetes mellitus. However, one of the drawbacks is that the method does not identify specific gene locations. Thus, additional studies need to be carried out at “hot spots” to map the area for a specific gene location. Also, if the genetic inheritance of TS is really complicated (many genes), this method may not succeed at all, or it may require many more sibling pairs than originally planned to find the gene(s) in TS. With diabetes, it took approximately 600 pairs to identify the 5-6 genes involved. Despite these potential limitations, the TS sibpairs study was launched with great enthusiasm, and the Consortium has been busy ever since.

The two sites identified on chromosomes 4 and 8 have maximum likelihood scores (MLS) of >2 . This score suggests that there is a 99/100 chance that these sites are important. Although an MLS >2 is potentially meaningful, experts in the field become more excited when the MLS score is >3 or 999/1000 chance that the site is meaningful. In addition, ➤

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