No evidence for genetic linkage of Gilles de la Tourette syndrome on chromosomes 7 and 18


Abstract
Gilles de la Tourette syndrome is a heritable neuropsychiatric disorder. In order to determine the chromosomal localisation of the locus involved, genetic linkage studies were initiated in six extended families. The Gilles de la Tourette gene has been tentatively assigned to chromosome 18q22.1. In our present study no evidence for genetic linkage on chromosome 18 and chromosome 7 was obtained. Data from the markers tested made it possible to exclude the whole of chromosome 18 and the chromosome 7q21.3–qter region as a site for the Gilles de la Tourette gene.

Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder with an unknown aetiology. The syndrome is characterised by recurrent, involuntary, repetitive, multiple motor and vocal tics. In many patients associated behavioural problems like obsessive compulsive behaviour and copro- and echophenomena are observed.1 There is strong evidence that GTS is genetically determined. The exact mode of inheritance, however, is still a matter of discussion. Both single major locus and multifactorial models have been proposed.1–6 The most widely held hypothesis states that a single autosomal dominant gene with reduced penetrance is involved.6 However, it has been discussed that associated behavioural symptoms should be considered as variant expressions of the presumed genetic defect responsible for GTS. There is general agreement that the chronic tic syndromes, according to DSMIII-R criteria,7 in families afflicted with GTS are variant phenotypes of the GTS gene defect.6

Comings et al6 presented evidence for the localisation of the GTS gene. They reported a 46,t(7;18) (q22;q22.1) reciprocal translocation in six relatives suffering from GTS. No support for linkage was found between the breakpoint on chromosome 7q22 and the COLA1 locus at 7q21.3–q22.1, suggesting a localisation of the GTS gene near the 18q22.1 breakpoint. Donnai9 reported a GTS patient with a deletion of the long arm of chromosome 18 at 18q22.2. These findings led to the tentative assignment of the GTS gene to chromosome 18q22.1. At 18q21, a candidate gene, gastrin releasing peptide (GRP), has been localised coding for a neuropeptide-like protein.10 11

In order to determine the chromosomal location of the GTS gene, we started genetic linkage studies in five families of Dutch origin and in one family of Norwegian origin. In our present study we found no support for linkage on either chromosome 18 or chromosome 7, including the COLA1 locus (7q21.3–q22.1) near the translocation breakpoint.

Material and methods
FAMILY MATERIAL
Clinical and genetic studies were performed in five Dutch families and one Norwegian family. Complete pedigree data and methods of ascertainment will be published elsewhere (van de Wetering et al, in preparation) and are briefly summarised here.

All subjects were investigated using a standardised
psychiatric interview with an added section on GTS and tics (Yale Scale, Dr D L Pauls, New Haven). Only those with GTS or tic syndrome, according to DSMIII-R criteria,1 were regarded as affected. The interviews were reviewed by an independent psychiatrist and a neurologist without previous knowledge of the family history. A total of 236 subjects was investigated, of whom 48 were considered to be affected.

Pedigrees of the families used in this study are not shown to protect the privacy of the subjects that collaborated in this study. However, pedigrees can be sent to investigators only, on request.

DNA ANALYSIS
DNA was isolated from peripheral blood lymphocytes of family members as described by Miller et al.12 DNA was digested with various restriction enzymes (Boehringer, Pharmacia, BRL) according to the manufacturer's instructions. Gel electrophoresis of 8 μg DNA samples on 0.7% agarose gels, and DNA immobilisation by alkaline blotting onto nylon membranes (Gene Screen plus), were performed according to standard procedures.13 Hybridisation conditions were as described by Maniatis et al13 and washing was performed at 65°C in 0.1×SSC final stringency. DNA was labelled by random hexamer priming according to Feinberg and Vogelstein.14

Markers B74 (D18S3), OLVIIA8 (D18S7), OS-4 (D18S5), pHF12–62 (D18S1), and pERT25 (D18S11) were used as reference points for chromosome 18, as they had been mapped previously by physical methods, and were used for the construction of a continuous linkage map for chromosome 18.15 They were kindly provided by Drs J L Mandel, H Olek, H Tateishi, R White, and U Müller, respectively. Markers OLVIE10 and GRP have previously been described16 17 and shown to map to chromosome 18.

Markers pJ2 (TCRB), Cgamma (TCRG), pMetH (MET), NJ3 (COL1A), pTHH28 (D7S371), pRMU7.4 (D7S370), pYNB3.1R (D7S372), C33 (D7S126), TM102L (D7S135), and pB79A (D7S13) have previously been mapped on chromosome 7 and used in a linkage map.18 In our present study they were used as reference points for chromosome 7. These markers were kindly provided by Drs T W Mak, R White, P Tsipouras, Y Nakamura, L Tsui, and J Schmidtke, respectively. Markers pXV–2C (D7S23) and TN127 (D7S144) have been described previously and shown to map to chromosome 7.19 20

Results and discussion
Chromosome 18 markers were tested in six extended families and a linkage map was constructed using the continuous linkage map of O'Connell et al15 as a basis. Mapping the genetic distances of corresponding markers B74, pHF12–62, OLVIIA8, OS-4, and pERT25 with our own material differed only marginally from the O'Connell mapping distances. Additional markers OLVIE10 and GRP were then mapped, with our family material, onto the fixed O'Connell linkage map.

Comings et al8 and Donnai9 postulated that the gene responsible for GTS resides on chromosome 18q22.1. Markers OLVIE10 at 18q21.3, GRP at 18q21, OS-4 at 18q21–qter, and pERT25 at 18q23
map in the region surrounding the t(7;18)(q22;q22.1) translocation breakpoint.24 Given the linkage map and the cytogenetic maps15 24 (fig 1), the most likely localisation for the translocation breakpoint is between markers OLVIEI0 and OS-4.

Lod scores for the two point analysis of chromosome 18 between GTS and marker loci are shown in table 1. Only subjects presenting GTS and tic syndrome were included as affected in our present study. None of the markers tested showed evidence for linkage and they excluded linkage for the genetic distance mentioned in table 1. Using multipoint analysis (fig 2), we obtained lod scores of at least -5 for the translocation breakpoint region between markers OLVIEI0 and OS-4. A lod score of at least -2 was obtained for the complete linkage map of chromosome 18. This value is generally accepted as evidence for the exclusion of linkage.23 We therefore conclude that chromosome 18 can be excluded as a site for the GTS gene. These results are not in agreement with the findings of Comings et al6 and Donnai.9

Another possible site for the GTS gene would be the breakpoint of the translocation on chromosome 7q22 reported by Comings et al.8 We have tested several RFLP markers on chromosome 7 with our family material, and a linkage map was constructed (table 2). Comparison of our linkage map with the primary linkage map of O'Connell et al18 gave marginal differences only, except for marker C33, which we mapped at θ=0·01 telomeric to pMetH instead of θ=0·11 in the O'Connell data. Our results are consistent with the findings of Rommens et al.19 To avoid possible mapping errors we did not include marker C33 in the multipoint analysis. Marker TN127, not on the primary linkage map of O'Connell et al,18 was mapped using our family material and added to the combined linkage map (fig 1).

For none of the markers tested on chromosome 7 did we find evidence for linkage, including the COLA1 locus which is located proximal to the EPO locus at 7q21 and thus must be located proximal to the presumed breakpoint of the translocation.24 With multipoint analysis we have been able to exclude part of chromosome 7p and the 7q21.3–qter region including the translocation breakpoint region. The region around marker C33 is excluded by flanking markers pMetH, pXV2C, and TCRB in the two point analysis as well as in the multipoint analysis, even if we assume that marker C33 is localised at θ=0·11 to pMetH.

With the exclusion of chromosome 18 as a possible site for the GTS gene and the exclusion of the 7q21.3–qter region of chromosome 7, we conclude that the 46,t(7;18)(q22;q22.1) reciprocal translocation is not linked to the gene responsible for the Gilles de la Tourette syndrome. However, genetic heterogeneity could mask a positive result. In this study, all families

![Figure 2](http://jmg.bmj.com/)

**Figure 2** Multipoint linkage analysis showing the exclusion of the GTS locus from chromosome 7q21.3–qter (a) and chromosome 18 (b). Dotted line represents a value of -2.

**Table 1 Two point linkage data for chromosome 18.**

<table>
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<tr>
<th>Probe</th>
<th>0·0</th>
<th>0·05</th>
<th>0·1</th>
<th>0·15</th>
<th>0·2</th>
<th>0·3</th>
<th>0·4</th>
<th>Exclusion</th>
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<td>-23·46</td>
<td>-6·68</td>
<td>-4·24</td>
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<td>pHF12–62</td>
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<td>-3·92</td>
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<td>-1·84</td>
<td>-1·30</td>
<td>-0·91</td>
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</tr>
<tr>
<td>OS4</td>
<td>-12·77</td>
<td>-4·32</td>
<td>-2·83</td>
<td>-1·93</td>
<td>-1·31</td>
<td>-0·51</td>
<td>-0·11</td>
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<tr>
<td>pERT25</td>
<td>-25·07</td>
<td>-8·04</td>
<td>-4·47</td>
<td>-2·61</td>
<td>-1·50</td>
<td>-0·44</td>
<td>-0·11</td>
<td>18</td>
</tr>
</tbody>
</table>

*Centimorgans definitely excluded on either site of the tested marker. A lod score of -2 or less was assumed as definite proof of exclusion.*
contributed to the negative lod scores on both chromosomes.

Currently, we are performing collaborative genetic linkage studies on other parts of the genome in order to find the location of the GTS gene.25 Chromosomal rearrangements in families suffering from GTS could facilitate the localisation of the GTS gene, but should be followed by extensive linkage studies in order to obtain definite proof for genetic linkage.

This work was supported by the University Hospital Rotterdam–Dijkzigt and the American Tourette Syndrome Association, New York. The authors wish to thank Dr D L Pauls for providing the Yale Scale, and Professor Dr H Galjaard and Mrs S L Levi for their continuous support.

Table 2 Two point linkage data for chromosome 7.

<table>
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<th>Probe</th>
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<th>0.05</th>
<th>0.1</th>
<th>0.15</th>
<th>0.2</th>
<th>0.3</th>
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<tr>
<td>TN127</td>
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<td>-1.99</td>
<td>-1.31</td>
<td>-0.52</td>
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<tr>
<td>pYNB3.1</td>
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<td>-2.63</td>
<td>-1.45</td>
<td>-0.82</td>
<td>-0.43</td>
<td>-0.05</td>
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<td>5</td>
</tr>
</tbody>
</table>

*Centimorgans definitely excluded on either site of the tested marker. A lod score of -2 or less was assumed as definite proof of exclusion.

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