Absence of close linkage between benign hereditary chorea and the locus \textit{D4S10} (probe G8)

**OLIVER W J QUARRELL, SANDRA YOUNGMAN, MANSOOR SARFARAZI, AND PETER S HARPER**

From the Institute of Medical Genetics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN.

**SUMMARY** A genetic linkage study between benign hereditary chorea and the locus \textit{D4S10} using the DNA probe G8 has shown two recombinations in five small families. There were negative lod scores at recombination fractions that show conclusive evidence of linkage in 16 larger British Huntington’s disease families. We suggest that although benign hereditary chorea and Huntington’s disease may have some clinical similarities they are probably at two different loci.

Benign hereditary chorea is a rare disorder. It was first described in 1967\textsuperscript{1,2} and is characterised by the onset of non-progressive chorea in childhood. There is an absence of mental deterioration, although in one family recently reported the affected subjects had a lower IQ than their unaffected family members.\textsuperscript{3} The pattern of inheritance is thought to be autosomal dominant; male to male transmission is known to occur,\textsuperscript{4,5} and in reviewing the families reported up to 1975, Harper\textsuperscript{6} suggested that there is nearly complete penetrance in males but approximately 75% penetrance in females.

Huntington’s disease (HD) is the major autosomal dominant choreiform disorder. It is distinguished from benign hereditary chorea because the onset is usually in adult life, the choreiform movements are progressive, and there is associated personality change and progressive intellectual impairment. The locus for HD has been mapped to the short arm of chromosome 4 using a DNA probe G8,\textsuperscript{7-10} whose locus has been defined as \textit{D4S10}.	extsuperscript{11} Sixteen British HD families have been studied with the G8 probe and the results confirm tight linkage.\textsuperscript{12} We have now conducted a similar study with five British benign hereditary chorea families to determine whether this disease locus is also linked to \textit{D4S10}.

**Methods**

The pedigrees and genotypes are illustrated in fig 1. The only potential phase known meioses occurred in family 2 which unfortunately was uninformative for both \textit{HindIII} and \textit{EcoRI} polymorphisms. Subject II.1 was also homozygous for other polymorphisms identified by the \textit{BglII}, \textit{PstI}, and \textit{NcoI} restriction enzymes.

The polymorphisms identified by the restriction enzymes can be combined to give a complex haplotype at the \textit{D4S10} locus.\textsuperscript{12} Two definite recombinations have been observed in families 1 and 4. In family 1, the normal male in generation III typed CC:22, establishing the phase A1:C2 in his affected parent and A2:C2 in the unaffected parent. A
crossover must have occurred as one sister inherited benign hereditary chorea and genotype A1 from her father whereas the other affected sister inherited genotype C2 with benign hereditary chorea. In family 4 the unaffected parent in generation I typed AA:22 which establishes the phase A2:B1 in the affected offspring; however, the unaffected daughter has the same genotype so a recombination must have occurred.

The lod score values (Z) for various values of recombination rate (θ) are shown in table 1 assuming complete penetrance, and in table 2 assuming reduced penetrance in females. It is clear that the recombination events are more clearly demonstrated by the EcoRI polymorphism as these lod scores are negative for greater values of θ. Reducing the penetrance has not significantly altered the results. The maximum positive lod scores are 0·034 and 0·033 at θ = 0·30 and θ = 0·28 respectively, neither representing significant evidence in favour of linkage.

**Table 1** Lod scores for values of θ assuming complete penetrance of benign hereditary chorea.

<table>
<thead>
<tr>
<th>θ</th>
<th>HindIII polymorphism</th>
<th>EcoRI polymorphism</th>
<th>Combined HindIII and EcoRI polymorphisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0·01</td>
<td>−0·952</td>
<td>−1·019</td>
<td>−2·264</td>
</tr>
<tr>
<td>0·05</td>
<td>−0·244</td>
<td>−0·361</td>
<td>−0·887</td>
</tr>
<tr>
<td>0·10</td>
<td>0·008</td>
<td>−0·126</td>
<td>−0·372</td>
</tr>
<tr>
<td>0·15</td>
<td>0·102</td>
<td>−0·026</td>
<td>−0·140</td>
</tr>
<tr>
<td>0·20</td>
<td>0·129</td>
<td>0·018</td>
<td>−0·028</td>
</tr>
<tr>
<td>0·25</td>
<td>0·120</td>
<td>0·033</td>
<td>0·021</td>
</tr>
<tr>
<td>0·30</td>
<td>0·093</td>
<td>0·030</td>
<td>0·034</td>
</tr>
<tr>
<td>0·35</td>
<td>0·060</td>
<td>0·022</td>
<td>0·029</td>
</tr>
<tr>
<td>0·40</td>
<td>0·029</td>
<td>0·011</td>
<td>0·016</td>
</tr>
<tr>
<td>0·45</td>
<td>0·008</td>
<td>0·003</td>
<td>0·005</td>
</tr>
</tbody>
</table>

**Discussion**

These results are strongly against close linkage between D4S10 and benign hereditary chorea but do not completely exclude loose linkage. The form of analysis has not significantly altered the results. Reduced penetrance in males has been suggested by the pedigree of Burns et al. in Becker muscular dystrophies, where linkage studies with DNA markers have proved comparable for the two
Absence of close linkage between benign hereditary chorea and the locus D4S10 (probe G8) 193

disorders. Close linkage between D4S10 and HD is well established: a summary of the linkage data which has been published between D4S10 and HD is given in table 3. The 95% confidence limit for the linkage between D4S10 and HD is tight (0-4 to 6-3 cM) and this is illustrated in fig 2a. It would be unreasonable to expect the small benign hereditary chorea families to yield such large lod scores, but the only positive scores observed are small and lie well outside the 95% confidence limit for HD. In contrast to the HD study, the 95% confidence limit for linkage between D4S10 and benign hereditary chorea is extremely wide (5 to 50 cM) as illustrated in fig 2b. The confidence intervals for these two disorders overlap between 5 and 6-3 cM so the possibility that these disease loci are allelic has not been completely excluded. This explanation seems unlikely on the basis that two recombinations have been observed in nine phase unknown meioses from five benign hereditary chorea families, whereas the same number of recombinations were observed in 16 much larger HD families. We therefore suggest that the two diseases are the result of mutations at different loci, but this hypothesis needs to be tested further on additional families with benign hereditary chorea.

We would like to thank Professor N Nevin (Belfast) for the gift of DNA samples from family 2 and Dr James Gusella (Boston) for the gift of the DNA probes. We also thank Dr G Sleigh (Oxford) and Dr R Robinson (London) for allowing us to visit and examine their patients. This work has been supported by a grant from the Medical Research Council.

References
17 Kingston HM, Sarfarazi M, Thomas NST, Harper PS. Localisa-


Correspondence and requests for reprints to Dr O W J Quarrell, Institute of Medical Genetics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN.

---

**Announcements**

**FIFTH INTERNATIONAL CLINICAL GENETICS SEMINAR**

The Fifth International Clinical Genetics Seminar will be held in Rethymno, Crete on 25 to 30 October 1988. Main themes of the Seminar are ‘Genetics of Kidney Disorders’ and ‘Genetics of Neuromuscular Disorders’. For further information write to Dr C Bartsocas, ‘P and A Kyriakou’ Children’s Hospital, GR-11527 Athens, Greece.

**FIFTH INTERNATIONAL RETINITIS PIGMENTOSA CONGRESS**

The Fifth International Retinitis Pigmentosa Congress will be held in Melbourne, Australia on 4 to 7 November 1988. For further details contact Leonie Kelleher, Congress Convenor, 46A Oxley Road, Hawthorn, Victoria 3122, Australia. Tel: (03) 819 6590.
Absence of close linkage between benign hereditary chorea and the locus D4S10 (probe G8).

O W Quarrell, S Youngman, M Sarfarazi and P S Harper

doi: 10.1136/jmg.25.3.191

Updated information and services can be found at:
http://jmg.bmj.com/content/25/3/191

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/