

Absence of close linkage between benign hereditary chorea and the locus *D4S10* (probe G8)

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SUMMARY A genetic linkage study between benign hereditary chorea and the locus *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^{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.³ The pattern of inheritance is thought to be autosomal dominant; male to male transmission is known to occur,^{4,5} and in reviewing the families reported up to 1975, Harper⁶ 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 G8,⁷⁻¹⁰ whose locus has been defined as *D4S10*.¹¹ Sixteen British HD families have been studied with the G8 probe and the results confirm tight linkage.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 *D4S10*.

Methods

The families were all examined clinically and four have been reported previously. Families 1 and 2 were described by Harper,⁶ family 4 in this series is

the third family reported by Sleigh and Lindenbaum,⁹ and family 5 has been described by Robinson and Thornett.¹³

DNA was extracted from venous blood by the method of Kunkel *et al.*¹⁴ DNA (5 µg) was digested to completion using the appropriate enzyme. Agarose gel electrophoresis, Southern blotting, hybridisation, and autoradiography were carried out by standard methods. Polymorphisms at the *D4S10* locus were identified with subclones of the G8 probe. Subclone pK082 detects polymorphisms with *HindIII*, *PstI*, and *NciI* restriction enzymes. Subclone pK083 detects the *EcoRI* polymorphism and the R7 probe (which overlaps G8) detects a *BglII* polymorphism. Genetic linkage was analysed with the computer programme LINKAGE¹⁵ using the same *D4S10* allele frequencies as for the HD study.¹²

Results

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 *HindIII* and *EcoRI* polymorphisms. Subject II.1 was also homozygous for other polymorphisms identified by the *BglII*, *PstI*, and *NciI* restriction enzymes.

The polymorphisms identified by the restriction enzymes can be combined to give a complex haplotype at the *D4S10* locus.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

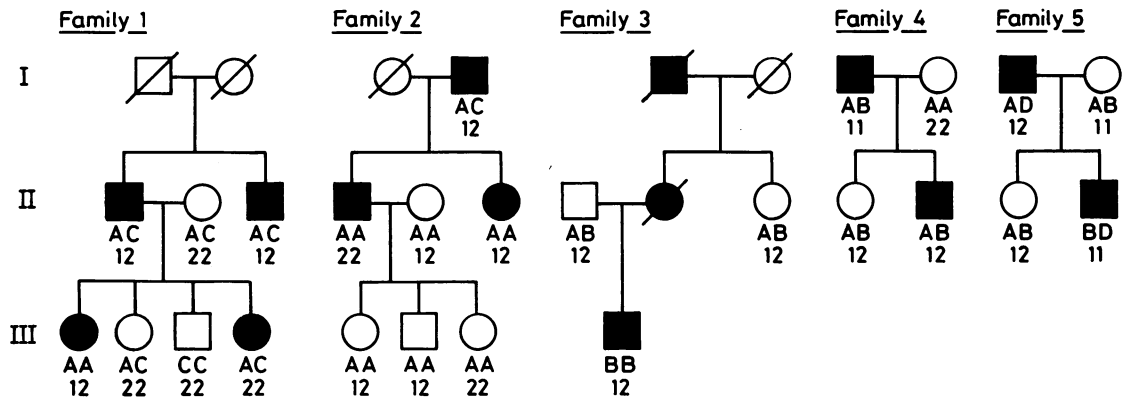


FIG 1 Five benign hereditary chorea families studied with *G8* using *HindIII* and *EcoRI* polymorphisms.

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 $\theta = 0.30$ and $\theta = 0.28$ respectively, neither representing significant evidence in favour of linkage.

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

θ	<i>HindIII</i> polymorphism	<i>EcoRI</i> polymorphism	Combined <i>HindIII</i> and <i>EcoRI</i> polymorphisms
0.01	-0.952	-1.019	-2.264
0.05	-0.244	-0.361	-0.887
0.10	0.008	-0.126	-0.372
0.15	0.102	-0.026	-0.140
0.20	0.129	0.018	-0.028
0.25	0.120	0.033	0.021
0.30	0.093	0.030	0.034
0.35	0.060	0.022	0.029
0.40	0.029	0.011	0.016
0.45	0.008	0.003	0.005

TABLE 2 Lod score for values of θ assuming reduced penetrance of benign hereditary chorea in females.

θ	<i>HindIII</i> polymorphism	<i>EcoRI</i> polymorphism	Combined <i>HindIII</i> and <i>EcoRI</i> polymorphisms
0.01	0.235	-1.209	-1.171
0.05	0.268	-0.534	-0.459
0.10	0.272	-0.274	-0.180
0.15	0.249	-0.149	-0.053
0.20	0.210	-0.079	0.007
0.25	0.164	-0.040	0.029
0.30	0.115	-0.018	0.032
0.35	0.070	-0.007	0.024
0.40	0.033	-0.002	0.013
0.45	0.009	-0.005	0.004

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*¹⁶ and by one of the families reported by Sleigh and Lindenbaum,⁵ but in that case the proposed unaffected obligatory male carrier was not examined. Reduced penetrance in males is thus unlikely to affect the outcome of this study as there is only one unaffected male in an informative family (family 1, III.3).

If benign hereditary chorea were closely linked to *D4S10* then it would be possible to suggest that this disease locus is allelic to the *HD* locus. Benign hereditary chorea could then be considered as a 'milder' form of HD in a similar manner to that suggested for the X linked Duchenne and Becker muscular dystrophies,¹⁷ where linkage studies with DNA markers have proved comparable for the two

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.

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TABLE 3 Summary of linkage data between Huntington's disease and *D4S10*.

	Z max	θ max	95% confidence limit for θ
Study 1 ¹⁸	12.14	0.02	0-0.076
Study 2 ⁹	13.59	0.06	0-0.120
Study 3 ¹²	17.6	0.02	0.004-0.063
Total	42.74	0.04	0.013-0.063

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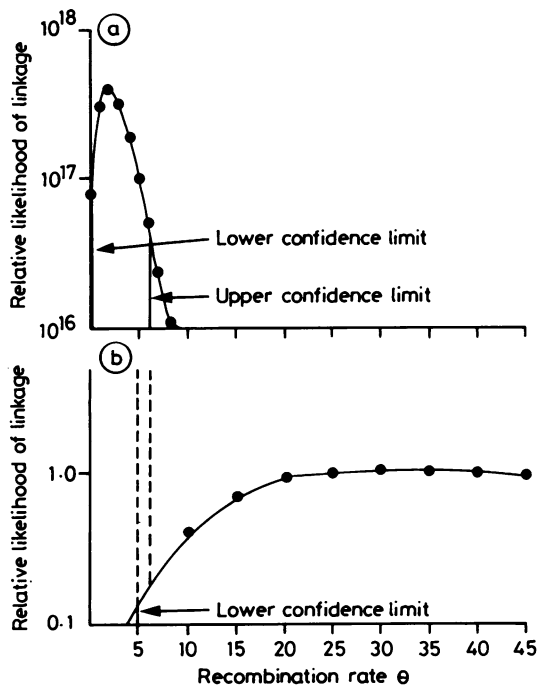


FIG 2 Relative likelihoods of linkage between locus *D4S10* and (a) Huntington's disease, South Wales study, and (b) benign hereditary chorea, illustrating the small overlap between 95% confidence intervals.

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¹⁸ Human Gene Mapping 8. Report of the committee on chromosome 3-4. *Cytogenet Cell Genet* 1985;40:107-27.

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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.