Genetic heterogeneity in hereditary haemorrhagic telangiectasia

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Abstract

A locus causing hereditary haemorrhagic telangiectasia (HHT) has recently been mapped to 9q34 in four families and designated HHT1. In this paper, the results of a linkage study showing genetic heterogeneity in four families in whom HHT is segregating are reported. All the previously reported 9q34 linked families contain at least one affected member with a symptomatic pulmonary arteriovenous malformation. We postulate that clinical heterogeneity may also be a feature of HHT with a significantly higher predisposition to symptomatic PAVMs associated with the HHT1 linked families.

(J Med Genet 1994;31:925–926)

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterised by recurrent epistaxes and mucocutaneous telangiectases. The prevalence in the British population has been estimated as approximately 1 in 40 000 and is significantly higher in parts of France. Penetrance is age dependent, being almost complete by the age of 40. Mucocutaneous telangiectases in the bowel lead to significant gastrointestinal bleeding in about 20% of patients. Pulmonary arteriovenous malformations (PAVM) are a common finding occurring in about 20% of patients. They are characteristically multiple and give rise to most of the neurological complications of HHT.

Recently HHT has been mapped to 9q34 in four families. Genetic heterogeneity was suggested by Shovlin et al who found one family not to be linked, and the 9q34 locus was therefore designated HHT1.

Materials and methods

As part of a continuing collaborative study, five families with HHT and a structure suitable for linkage analysis were ascertained. Of these, one showed linkage to markers close to the HHT1 locus at 9q34 with a lod score of 2.41 (data not shown).

Fig 1 shows the pedigrees of the other four families. All family members involved were examined clinically by MP and a full medical history taken. Two of three features, recurrent epistaxes, mucocutaneous telangiectases, and a family history, were required for a positive diagnosis. Other complications are detailed in the key. Significantly, no-one in the four families had a symptomatic PAVM and there was no increased level of neurological morbidity.

Genomic DNA was extracted from peripheral white blood cells using standard techniques. Previously published PCR primers flanking short tandem repeat polymorphisms at D9S103, GSN, D9S65, and ASS were used in “hot” PCR reactions with end labelling of the forward primer.

Unaffected persons under 30 were not included in the analysis and a penetrance of 90% was assumed in persons over 30. Two point analysis between the disease and the marker was carried out using the MLINK sub-programme of the LINKAGE package. Published allele frequencies were used. The hypothesis of genetic heterogeneity was tested using the HOMOG version 3.00 program. Multipoint analysis was performed using LINKMAP and assuming a locus order cen-D9S103-GSN-D9S65-ASS with respective
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Eight families were originally included in this study. The clinical diagnosis of HHT was established 
in the absence of PAVMs, and only one family (family 1) showed evidence of telangiectasia.

Discussion

One major locus for HHT, HHT1, has been identified at 9q34, but the data presented in this paper show that at least one more is still to be found. Clinical heterogeneity has not been formally shown in HHT although there is variation between families. In particular, certain families seem to be less prone to symptomatic PAVMs and their neurological sequelae. Two large families with a total of 261 affected subjects have been reported with no mention of PAVMs, although formal oximetry was not carried out.

Three of the four families reported here (1, 2, and 3) were assessed for PAVMs using the transcutaneous oximetry method reported by Hughes and Allison and no evidence of desaturation was found. The oximeter was not available during the assessment of family 4 in which one person (III.4) had radiological evidence of a PAVM. Detailed family history failed to indicate any evidence of increased neurological morbidity in any of the families.

Genetic counselling in HHT is based at present on all families being at risk of PAVMs and their neurological sequelae. Identification of families at either high or low risk of developing symptomatic PAVMs will enable more appropriate screening protocols to be formulated. The genes underlying HHT are worthy of continued attention in view of the importance of new vessel formation in a variety of disease processes and treatments and the future potential for gene therapy in this late onset and accessible disease.

This work was supported by a project grant from the MRC and private philanthropic funds from Dame Catherine Cookson. We would like to thank Dr Alan Wright for his help with the multipoint analysis.

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doi: 10.1136/jmg.31.12.925

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