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Detailed genetic mapping of the von Hippel-Lindau disease tumour suppressor gene

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Abstract

Von Hippel-Lindau (VHL) disease is an autosomal dominant inherited familial cancer syndrome characterised by a predisposition to the development of retinal, cerebellar, and spinal haemangioblastomas, renal cell carcinoma, and phaeochromocytoma. The gene for VHL disease has been mapped to chromosome 3p25–p26 and flanking markers identified. We report the detailed genetic mapping of the VHL disease locus in 38 families. Significant linkage was detected between VHL disease and *D3S601* (Zmax = 18·86 at θ = 0·0, CI 0·0–0·025), *D3S18* (Zmax = 11·42 at θ = 0·03, CI 0·005–0·08), *RAF1* (Zmax = 11·02 at θ = 0·04, CI 0·007–0·01), and *D3S1250* (Zmax = 4·73 at θ = 0·05, CI 0·005–0·15). Multipoint linkage analysis mapped the VHL disease locus between *D3S1250* and *D3S18* close to *D3S601*. There was no evidence of locus heterogeneity. This study has (1) confirmed the tight linkage between VHL disease and *D3S601*, (2) identified *D3S1250* as the first marker telomeric to *RAF1* which maps centromeric to the VHL disease gene, and (3) narrowed the target region for isolation of the VHL disease gene by positional cloning techniques to a 4 cM interval between *D3S1250* and *D3S18*. These findings will improve the clinical management of families with VHL disease by improving the accuracy of presymptomatic diagnosis using linked DNA markers, and will enhance progress towards isolating the VHL disease gene.

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Von Hippel-Lindau (VHL) disease is a dominantly inherited familial cancer syndrome with variable expression. The minimum birth incidence is 1/36 000 and the most frequent complications are haemangioblastomas of the central nervous system and retina, renal cell carcinoma, and phaeochromocytoma.[1 2] However, many different tumour types have been reported in this disorder.[3] Clinical heterogeneity has been noted with some families showing a high incidence of phaeochromocytoma and others a very low frequency.[2 4–6] The variable expression and age dependent penetrance (mean age at diagnosis is 26·3 years) make the follow up of affected patients and their relatives problematical, so that although the morbidity and mortality of VHL disease can be reduced by regular ophthalmological and systemic screening,[7] long term compliance with the complicated screening protocol may be difficult to achieve.

The gene for VHL disease was mapped to the short arm of chromosome 3 by Seizinger *et al*,[8] and subsequently we and others have localised the VHL locus telomeric to the *RAF1* oncogene in chromosome 3p25–p26.[9–11] In a previous genetic linkage study of 22 VHL disease families, we localised the VHL gene to a 10 cM interval between *RAF1* and *D3S225*, but were unable to orientate the VHL disease gene with respect to *D3S18* which lies within this interval.[10] However, Hosoe *et al*[9] mapped the VHL disease gene between *RAF1* and *D3S18*. We now report a genetic linkage study of 38 VHL disease families using chromosome 3p25–p26 markers which refines further the localisation of the VHL disease gene.

Methods

PATIENTS

Subjects from 38 families with VHL disease were investigated using a panel of polymorphic DNA markers from chromosome 3p25 to p26. A total of 167 affected patients (at least two from each family) and 171 relatives and spouses were genotyped. VHL disease was diagnosed using standard criteria.[2 12] All affected patients had proven retinal angioma, central nervous system haemangioblastoma, renal cell carcinoma, or phaeochromocytoma. Six families contained patients with phaeochromocytoma.

DNA ANALYSIS

High molecular weight DNA was isolated from peripheral blood or lymphoblastoid cell lines by conventional methods. After digestion with the appropriate restriction endonuclease, electrophoresis, Southern analysis, and autoradiography were performed as described previously.[10 13] Details of the DNA probes used are shown in table 1. Families were initially typed with the *Taq*I RFLP at *D3S601* and then the two other RFLPs if this was uninformative. *D3S225* was found to be poorly informative and was not typed in all families.

GENETIC LINKAGE ANALYSIS

LIPED and LINKAGE computer programs were used for two point and multipoint linkage analysis in VHL disease families as described previously.[10 13] Age dependent penetrance

Table 1 Details of restriction fragment length polymorphisms used in this study.

Locus	Probe	Restriction enzyme	Allele sizes (kb) (allele frequency)	Frequency of heterozygosity	Ref
RAF1	p627	*Taq*I	6·8(0·74)/6·3(0·26)	0·34	9 10 27
RAF1	p627	*Bgl*I	4·0(0·54)/3·3(0·46)	0·49	9 10 27
D3S732	LIB 4A-52″	*Hin*dIII	9·0(0·65)/7·5+1·5(0·35)	0·46	14–16
D3S1250	c-LIB-56	*Eco*RI	2·8(0·2)/1·2(0·8)	0·32	This paper
D3S601	LIB 19-63′	*Taq*I	4·3(0·47)/3·9(0·53)	0·5	15 16
D3S601	c-LIB-11.8	*Bam*HI	11·0(0·85)/9·6(0·05)/7·3(0·10)	0·27	16
D3S601	c-LIB-7.1	*Bgl*II	3·7(0·7)/2·0+1·7(0·3)	0·42	16
D3S18	c-LIB-I	*Bam*HI	8·7(0·69)/4·7(0·31)	0·43	9 15
D3S225	42-26′	*Hin*dIII	9·8(0·72)/5·5(0·28)	0·40	9 15

values were as follows: age 10 years = 0·08, 15 = 0·19, 20 = 0·37, 25 = 0·52, 30 = 0·67, 35 = 0·78, 40 = 0·86, 45 = 0·91, 50 = 0·94, 60 = 0·98.[1 14] The multipoint linkage maps were constructed with the LINKMAP program of the LINKAGE package using five point analyses. Recombination fractions were assumed to be equal in males and females.[15 16] Genetic distances were calculated using Haldane's function and confidence intervals were determined by taking values of the recombination fractions corresponding to a lod score one unit less than the maximum. Formal heterogeneity testing was performed with the HOMOG program.[17]

Genetic linkage studies in 60 CEPH families have established the marker order as: (*RAF1*, *D3S732*)-*D3S601*-*D3S18*-*D3S225*.[9 15 16] The position of a new marker, *D3S1250*, within this framework map was established by genetic linkage studies in 40 CEPH families. The CRI-MAP computer program was used to localise *D3S1250* within the existing genetic map.[18]

Results

BACKGROUND MAP: GENETIC AND PHYSICAL MAPPING OF MARKER LOCI

The most likely background map is shown in fig 1. The order (*RAF1*, *D3S732*)-*D3S1250*-*D3S601*-*D3S18*-*D3S225* was 26 times more likely than *D3S1250*-(*RAF1*, *D3S732*)-*D3S601*-*D3S18*-*D3S225*. The localisation of *D3S1250* between (*RAF1*, *D3S732*) and *D3S601* is consistent with the results of physical mapping experiments using chromosome suppression in situ hybridisation studies and pulse field gel electrophoresis (unpublished observations).

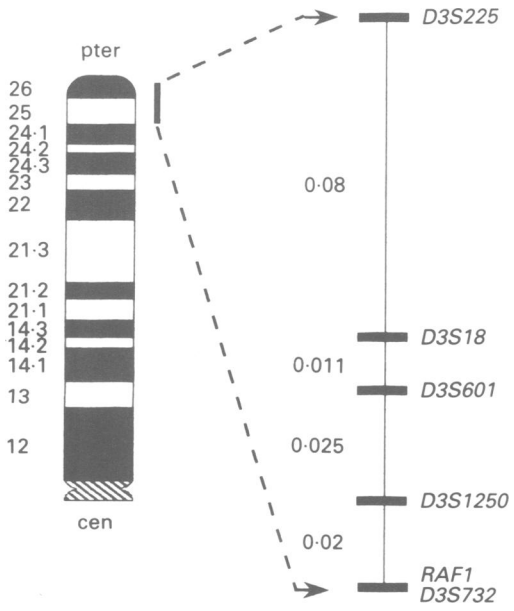

Figure 1 Background map of chromosome 3p25–p26 markers.

VHL DISEASE FAMILY ANALYSIS

The two point linkage results between VHL disease and the six loci studied are shown in table 2. Significant lod scores (> 3) were found with *RAF1*, *D3S1250*, *D3S601*, and *D3S18*. The closest marker was *D3S601* (Zmax = 18·86 at θ = 0·0, CI 0·0–0·025), followed by *D3S18* (Zmax = 11·42 at θ = 0·03, CI 0·005–0·08), *RAF1* (Zmax = 11·02 at θ = 0·04, CI 0·007–0·01), and *D3S1250* (Zmax = 4·73 at θ = 0·05, CI 0·005–0·15).

Multipoint linkage analysis showed that the VHL locus mapped to the *D3S1250*-*D3S18* interval (fig 2). The probability of the VHL gene mapping between *D3S1250* and *D3S18* was $5{\cdot}12 \times 10^4$ times greater than that of the next most likely location telomeric to *D3S18*, and $9{\cdot}23 \times 10^8$ and $1{\cdot}52 \times 10^9$ times more likely than in a location centromeric to (*RAF1*, *D3S732*) and in the (*RAF1*, *D3S732*)-*D3S1250* interval respectively.

Three affected subjects were recombinant at the *RAF1* locus. Two of these were also recombinant at *D3S1250*, placing the VHL disease gene telomeric to *D3S1250*. The third *RAF1* recombinant subject was not recombinant at *D3S1250*. All three *RAF1* recombinant subjects were informative and non-recombinant at *D3S601*. Two *D3S18* recombinant subjects were not recombinant at *D3S601* or more centromeric markers.

Homogeneity testing with the HOMOG program provided no evidence for locus heterogeneity; the most likely proportion of linked families (alpha) was 1·0 (95% confidence interval 0·85–1·0). The maximum lod score in a multipoint analysis for the six families containing patients with phaeochromocytoma was 10·0 in the interval between *D3S1250* and *D3S601* (fig 3).

Discussion

The improved localisation of the VHL disease gene presented in this paper will (1) accelerate progress towards the identification and characterisation of the VHL disease gene by a positional cloning strategy, (2) aid the investigation of the possible role of the VHL tumour

Table 2 Combined linkage analysis of 39 families with VHL disease: pairwise lod scores for linkage between VHL disease and chromosome 3 markers.

Locus	Recombination fraction						
	0·00	0·01	0·05	0·10	0·20	0·30	0·40
RAF1	−∞	10·32	10·95	10·01	7·26	4·28	1·56
D3S732	−∞	0·52	1·52	1·62	1·22	0·65	0·18
D3S1250	−∞	4·08	4·73	4·38	3·11	1·73	0·56
D3S601	18·86	18·43	16·67	14·44	9·95	5·62	1·93
D3S18	−∞	11·13	11·17	9·99	6·94	3·80	1·23
D3S225	−∞	−2·01	−0·56	−0·03	0·26	0·23	0·12

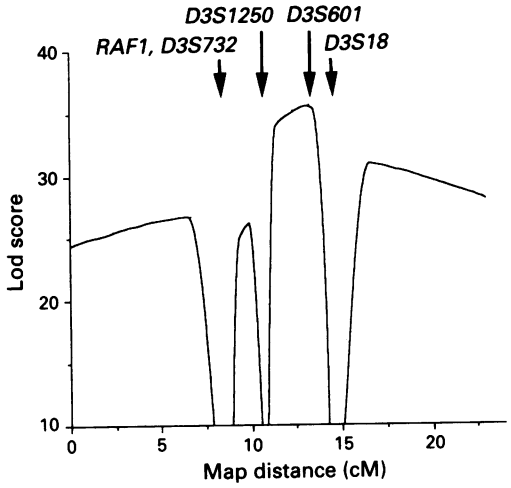

Figure 2 Multipoint genetic linkage analysis of 38 families with VHL disease. The most likely location of the VHL disease gene is between D3S1250 and D3S18 (see text for details).

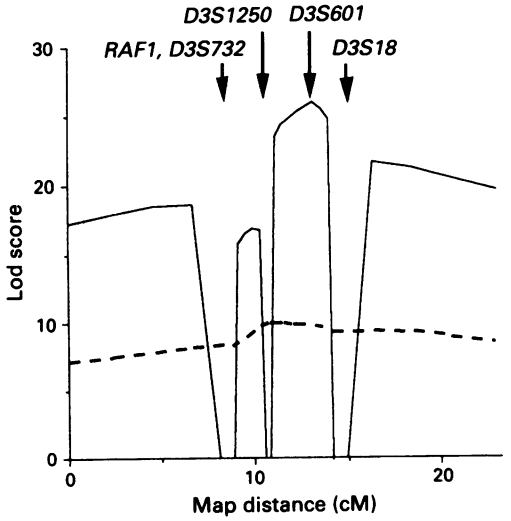

Figure 3 Multipoint genetic linkage analysis for six VHL disease families containing patients affected by phaeochromocytoma (broken line) and 32 families not containing a subject with phaeochromocytoma (unbroken line).

suppressor gene in human cancers, and (3) increase the accuracy and availability of presymptomatic diagnosis of VHL disease using linked DNA markers.

We have confirmed the findings of Latif *et al*[16] in an independent set of families that the VHL gene maps close to *D3S601* in the *RAF1–D3S18* interval. So far no recombinants have been identified between *D3S601* and *VHL* disease and the total lod score is in excess of 40 with an upper confidence interval for θ of less than 0·02. Seizinger *et al*[11] mapped the VHL disease locus to a 10 cM interval between *RAF1* and *D3S719*, and did not identify any recombinants with another marker, *D3S720*, which maps within the *RAF1–D3S719* interval. The relative positions of *D3S601* and *D3S720* are not known, but Liu *et al*[19] have reported that *D3S18* and *D3S719* are contained in a single cosmid. Thus, there is broad agreement that the VHL disease gene is localised centromeric to (*D3S18*, *D3S719*). In previous studies the proximal limit for the region containing the VHL disease gene has been defined by *RAF1*.[9–11] We have now shown that the VHL disease gene is contained within a region bounded by *D3S1250* and *D3S18*. Estimates of the genetic distances between markers flanking the VHL disease gene are variable, such that Latif *et al*[16] estimated the *RAF1–D3S18* interval as 6 to 8 cM and Seizinger *et al*[11] estimated the *RAF1–D3S719* interval as 10 cM. We have estimated the *RAF1–D3S18* interval as about 6 cM, and the genetic distance between *D3S1250* and *D3S18* to be approximately 4 cM.

The availability of presymptomatic diagnosis of VHL disease using linked DNA markers[14 20] has improved the management of VHL disease families by enabling those relatives predicted to be at low risk to be screened less frequently. The finding that *D3S1250* is the closest centromeric polymorphic DNA marker to the VHL disease gene will increase the accuracy and informativeness of presymptomatic diagnosis of VHL disease by genetic linkage analysis. We did not find any evidence of locus heterogeneity, and it appears that the well defined clinical heterogeneity seen in VHL disease reflects allelic rather than locus heterogeneity. Glenn *et al*[6] found that one family in which 27 of 47 affected subjects developed phaeochromocytoma showed similar linkage to *D3S18* and *RAF1* as 19 VHL disease families in which only four of 209 affected patients had a phaeochromocytoma. Our findings are similar except that in the 'phaeochromocytoma VHL disease family' reported by Glenn *et al*[6] renal cell carcinoma had not been detected. However, in our six 'phaeochromocytoma VHL disease family', four families contained patients with renal cell carcinoma. Therefore, it appears that all VHL disease families, regardless of variations in predisposition to phaeochromocytoma and renal cell carcinoma, are linked to chromosome 3p25–p26 markers. Nevertheless, the possibility of locus heterogeneity in VHL disease in which only a small number of families would

be unlinked cannot yet be excluded and relatives who are predicted to be at low risk on DNA analysis should not be discharged from follow up. Presymptomatic diagnosis of VHL disease patients with flanking DNA markers has shown that many asymptomatic gene carriers have subclinical renal or pancreatic cysts.[20] The presence of only one of these features or of epididymal cysts alone does not provide an unequivocal diagnosis of VHL disease in subjects with a positive family history[11] (unpublished observations).

Many different tumour types have been associated with VHL disease and chromosome 3p allele loss has been shown in at least five types of VHL disease tumours, including haemangioblastoma, renal cell carcinoma, phaeochromocytoma, pancreatic tumour, and choroid plexus papilloma[21] (Maher *et al*, unpublished observations). This suggests a common mechanism of tumorigenesis in the diverse tumours associated with VHL disease. The extent to which the VHL disease gene is involved in the pathogenesis of sporadic tumours has not yet been well defined. Chromosome 3p allele loss has not been shown in sporadic cerebellar haemangioblastomas (although this may be because of technical difficulties), but chromosome 3p allele loss is a common finding in renal cell carcinoma.[22-24] However, chromosome 3p allele loss in sporadic renal cell carcinoma is not restricted to the region of the VHL disease locus, and there is evidence that at least three tumour suppressor genes on chromosome 3p may contribute to the pathogenesis of renal cell carcinoma.[25,26] The isolation and characterisation of the VHL disease gene will enable (1) the function of the gene to be elucidated, (2) the reliable detection of gene carriers by direct mutation detection, and (3) the role of VHL disease mutations in the pathogenesis of non-familial cancers to be defined.

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For The Blind to support gene mapping of autosomal dominant nystagmus.

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Corrections

In the paper by Richards *et al* on 'Detailed genetic mapping of the von Hippel-Lindau disease tumour suppressor gene' (*J Med Genet* 1993;**30**:104–7), an important collaborator, Dr Per Enblad, was inadvertently omitted from the authorship. The correct authorship is as follows.

Richards FM, Maher ER, Latif F*, Phipps ME, Tory K*, Lush M, Crossey PA, Oostra B†, Enblad P‡, Gustavson KH‡, Green J§, Turner G||, Yates JRW, Linehan M¶, Affara NA, Lerman M*, Zbar B*, Ferguson-Smith MA.

Cambridge University Department of Pathology, Cambridge, UK; *Laboratory of Immunobiology, National Cancer Institute, Frederick Cancer Research Facility, Frederick, USA; †Erasmus University, Rotterdam, The Netherlands; ‡University of Uppsala, Sweden; §Division of Community Medicine, Memorial University of Newfoundland, Canada; || Yorkshire Regional Genetics Service and ICRF Genetic Epidemiology Laboratory, Leeds, UK; ¶Surgery Branch, National Cancer Institute, USA.

In the paper by Padayachee *et al* on 'Mapping of the X linked form of hyper IgM syndrome (HIGM1)' (*J Med Genet* 1992;**30**:202–5), the primer sequence for DXS102[13] under the heading OLIGONUCLEOTIDE PRIMERS was referenced Luty *et al*. This is incorrect and should be:

Gedeon AK, Holmon K, *et al*. Characterization of new pcr based markers for mapping and diagnosis: AC dinucleotide repeat markers at the DXS237 (GMGX9) and DXS102 (cX38.1) loci. *Am J Med Genet* 1992;**43**:255–60.