Genotype-phenotype correlation in von Hippel-Lindau disease: identification of a mutation associated with VHL type 2A

F Chen, L Slife, T Kishida, J Mulvihill, S E Tisherman, B Zbar

Abstract

A family with von Hippel-Lindau disease (VHL) type 2A has been shown to have a T to C missense mutation at nucleotide 547 of the VHL gene. This gives further support for the proposal to associate the 547 T to C mutation with phenotype VHL 2A.

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Key words: von Hippel-Lindau disease; genotype-phenotype correlation; VHL type 2A.

Von Hippel-Lindau (VHL) disease (MIM No. 199300) is a multisystem, inherited disease characterised by a predisposition to develop retinal angiomas, central nervous system haemangioblastomas, clear cell renal carcinomas, pancreatic cysts, and pheochromocytomas.1 The VHL tumour suppressor gene has been isolated by positional cloning.2 Germline mutations were identified in 75% of US and Canadian VHL families.3 Somatic mutations in the VHL gene were found in sporadic clear cell renal carcinomas,4 sporadic central nervous system haemangioblastomas,5 and a sporadic cystadenoma of the epididymis.6 The VHL tumour suppressor gene has been isolated by positional cloning.2 Germline mutations were identified in 75% of US and Canadian VHL families.3 Somatic mutations in the VHL gene were found in sporadic clear cell renal carcinomas,4 sporadic central nervous system haemangioblastomas,5 and a sporadic cystadenoma of the epididymis.6 The VHL tumour suppressor gene has been isolated by positional cloning.2 Germline mutations were identified in 75% of US and Canadian VHL families.3 Somatic mutations in the VHL gene were found in sporadic clear cell renal carcinomas,4 sporadic central nervous system haemangioblastomas,5 and a sporadic cystadenoma of the epididymis.

One of the authors (ST) has studied a large Pennsylvanian pheochromocytoma family (1190) of German origin for the past 30 years.3,4 This family contains 19 affected subjects, 19 with pheochromocytoma, four with retinal angioma, one with central nervous system haemangioblastoma, and none with renal cell carcinoma. Based on these clinical findings, this family has been classified as VHL type 2A. Because VHL family 1190 was classified as VHL type 2A, and was of German origin, we tested whether this family had a mutation at nucleotide 505 or another distinct mutation. Blood samples from five affected (4612, 4613, 4796, 4799, 4801) and seven unaffected members of family 1190 were tested by single strand conformational polymorphism analysis (SSCP) with primers for the three exons of the VHL gene. The exon 1 SSCP labelling reactions were performed as described previously4 using primers 9B (5' CAT CTT CTG CAA TCG CAG TCC GCC GTG CGT 3') for the sense strand and primer 101 (5' CCC TGC TGG GTC GGC CCT AAC CGC CGG GCC GCT 3') for the antisense strand. A novel migrating fragment was identified in all five affected members of family 1190 in exon 1. None of the tested samples from seven unaffected members showed this alteration (fig 1A). DNA from patients 4612 and 4613 of the family was amplified by PCR and subcloned. A T547C (Y111H) mutation was shown in clones derived from patients 4612 and 4613 (fig 1B). Sequencing in both directions confirmed this result. The other three affected subjects (4796, 4799, 4801) were not sequenced.

The nucleotide T547C mutation was previously observed in a family (3738) that contains three affected subjects (3/3 with pheochromocytoma and 0/3 with renal cell carcinoma). Because of the small size of family 3738, it was not possible to assign the 547 mutation to VHL type 2A or 2B. Including family 1190, 22 affected subjects with the T547C mutation have been identified and 19/22 members had pheochromocytoma; 0/22 had renal cell carcinoma. (In family 1190, pheochromocytoma

### Clinical classification of VHL

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Without pheochromocytoma</td>
</tr>
<tr>
<td>2</td>
<td>With pheochromocytoma</td>
</tr>
<tr>
<td>A</td>
<td>Without renal cell carcinoma or pancreatic cysts</td>
</tr>
<tr>
<td>B</td>
<td>With renal cell carcinoma or pancreatic cysts</td>
</tr>
</tbody>
</table>

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and angiomas segregated in 3/11 branches of the family; there was no history of renal cell carcinoma in the 619 members of these three branches.) The 547 T to C mutation identified in this large VHL family (1190) enables us to assign this mutation clearly to VHL type 2A. Both the nucleotide 505 and 547 mutations change a tyrosine to a histidine in exon 1. The fact that both the nucleotide 505 and 547 mutations change a tyrosine to histidine may provide a clue to the structural changes in the VHL protein that produce phaeochromocytoma but not renal cell carcinomas.

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