**VHL** c.505 T>C mutation confers a high age related penetrance but no increased overall mortality

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Abstract

**Background**—Germ line mutations of the **VHL** gene cause von Hippel-Lindau syndrome (**VHL**). In southern Germany, a specific mutation in this gene, c.505 T>C, is one of the most frequent alterations owing to a founder effect.

**Methods**—This study was conducted to evaluate morbidity, specific clinical risk profile, and mortality among a series of **VHL** c.505 T/C mutation carriers. A total of 125 eligible subjects carrying **VHL** c.505 T/C underwent ophthalmoscopy and gadolinium enhanced magnetic resonance imaging of the brain, the spinal cord, and the abdomen. Age related penetrance, morbidity, and mortality were assessed.

**Results**—Frequently observed lesions were phaeochromocytoma (47%), retinal angiomas (36%), haemangioblastomas of the spine (36%), and haemangioblastomas of the brain (16%). Four patients developed renal cell carcinoma. **VHL** was symptomatic in 47% of subjects; 30% were asymptomatic despite the presence of at least one **VHL** related tumour and 23% of the carriers had no detectable **VHL** lesion. Of the 19 patients who had died (15%), 10 died of symptomatic **VHL** lesions. Overall penetrance by cumulative incidence functions is estimated at 48% by 35 years and 88% by 70 years. In contrast to the only existing published report based on patients with presumably unselected **VHL** germ line mutations, the mortality rate for c.505 T/C mutation carriers is comparable to that of the general population of Germany.

**Conclusions**—Our results are an important example that a specific genotype, at least in the case of **VHL** c.505 T/C, can favourably impact on mortality despite a high age related penetrance. Our study also indirectly provides objective data which might be useful for the life and health insurance industry; it would appear that c.505 T>C mutation positive subjects have similar disease specific mortality to that of the general population owing to a combination of phenotype and timely detection of mutation carrier status followed by aggressive clinical screening and, if necessary, treatment.

**Keywords:** **VHL** gene; c.505 T/C germline mutation; **VHL** morbidity; **VHL** mortality

Von Hippel-Lindau disease (**VHL**, MIM 193300) is an autosomal dominant inherited tumour syndrome with morbidity and mortality related to the inherited predisposition, namely, retinal angiomas, haemangioblastomas of the central nervous system, renal cell carcinoma, and phaeochromocytomas.1 **VHL** is caused by germline mutations in the von Hippel-Lindau tumour suppressor gene (**VHL**).2 There have been more than 130 different germline inactivating **VHL** mutations described, and reported alterations include larger deletions and rearrangements as well as point mutations.4–5 **VHL** patients develop different spectra of **VHL** tumours depending on the type of mutation. Certain centres have classified the different phenotypic spectra into four subtypes:2 VHL type 1 is characterised by predisposition to the typical syndromic lesions with the exception of phaeochromocytomas; **VHL** type 2A is characterised by the classical component features with the exception of renal cell carcinoma; subjects with **VHL** 2B may be affected by the complete spectrum of **VHL** type tumours; and patients with **VHL** 2C develop only phaeochromocytomas. VHL subtype 1 is associated with deletions of **VHL** and nonsense mutations, whereas missense point mutations predominantly predispose to VHL type 2. According to a previous study performed before the identification of the **VHL** gene, the life span in this unselected series of **VHL** patients was found to be reduced by approximately 15 years compared to that of the general population.6 Germline **VHL** c.505 T>C mutation (Y98H) (mutation nomenclature is as recommended by the Nomenclature Working Committee)7 predisposes to **VHL** 2A* and has been
identified especially in the Black Forest region of Germany; because of a common founder effect, the VHL c.505 T/C mutation has been detected in 15 branches of the founding family from this area. In addition, there are two large families with this mutation in Pennsylvania, of which at least one originates from the Black Forest. This family was traced to the Schuttertal, a circumscribed area of the Black Forest, and one branch probably migrated from Germany to the USA in the early 1800s.

Because of the high prevalence of the VHL c.505 T/C mutation in the catchment area of our medical centre, and to tailor medical management of these subjects better based on molecular data, we carried out a systematic examination of the causes of morbidity and mortality related to VHL in a series of subjects with the c.505 T/C germline mutation.

Subjects and methods

STUDY SUBJECTS

The subjects included 64 patients belonging to 15 families with a known VHL c.505 T/C mutation. Other subjects included in the present study were people found to be mutation positive at c.505 from our programme, which genetically tests subjects with apparently sporadic VHL component tumours, such as retinal angiomia (n=125 patients), renal cell carcinoma (n=189), haemangioblastoma of the central nervous system (n=141), and phaeochromocytoma (179 patients). From this test programme, another 10 c.505 T/C mutation carriers were identified. Finally, all consenting first degree relatives (at risk subjects) of mutation carriers, irrespective of disease status, were subjected to mutation analysis, resulting in another 51 mutation carriers detected. In total, 125 (64 + 10 + 51) c.505 T/C mutation carriers were identified to be eligible for our mortality and morbidity study. Most of the mutation positive subjects were born in Germany, are living in the administrative district of Freiburg (approximately 1.9 million inhabitants), and have been seen at the University Hospital Freiburg between 1970 and 2000. Of the subjects who had died, the diagnosis of VHL could be genetically confirmed in five, but in 14 cases no archival material was available for genetic testing. In eight of the dead subjects, necropsy had been performed. All living patients gave informed consent for the genetic and clinical investigations. The next of kin of dead subjects gave consent.

MUTATION ANALYSIS

Mutation analysis was performed using the polymerase chain reaction (PCR) and modified primers (5' GGC CGG TGC TG C GCT CCG TGA ACT 3' and 5' CGG CCC GTG CCA GGC GGC AGC GTT GGA T 3', see below). For PCR, constitutional DNA from blood leucocytes was isolated by phenol/chloroform extraction according to standard protocols. After PCR, the amplicons were subjected to restriction digestion with FokI according to the manufacturer's recommendations (Boehringer Mannheim). The primers were modified so that only PCR products with the c.505 T/C mutation were cleaved by FokI resulting in two bands after electrophoresis. Restriction fragments were separated on agarose gels containing 2% SeaKem ME agarose and visualised with UV transillumination after ethidium bromide staining.

CLINICAL STUDIES

Available clinical data were systematically evaluated in already known as well as newly diagnosed mutation carriers and their relatives. Most of the living carriers of the c.505 T/C mutation were subjected to clinical surveillance which included direct ophthalmoscopy and gadolinium enhanced magnetic resonance imaging (MRI) of the brain, spinal cord, and abdomen, and 24 hour urine for catecholamines. The following aspects were of special interest and noted for purposes of the study: (1) age at detection of the lesions, (2) involvement of the eyes, the CNS, the adrenal glands and paraganglia, and other organs, (3) morbidity caused by the lesions (symptomatic/asymptomatic), and (4) mortality from c.505 T/C associated VHL syndrome.

STATISTICAL ANALYSIS

Patient characteristics are reported as means and ranges for quantitative variables and as absolute and relative frequencies for qualitative variables. Penetration of VHL syndrome and its components in relation to the patients’ age was estimated by cumulative incidence functions eliminating the competing risk of death without syndrome manifestations. Survival probabilities of VHL c.505 T/C mutation positive patients were estimated by the method of Kaplan-Meier but substituting patients’ age for survival time. These estimates and their pointwise 95% confidence intervals were compared with the sex adjusted survival probabilities of the general population of Germany in 1995-1997. Data storage and

Table 1  Results for overall VHL penetrance and manifestation of its components, phaeochromocytoma, angiomatosis retinae, and haemangioblastoma of the brain and spine. Penetration at 35 and 70 years was estimated by cumulative incidence functions eliminating the competing risk of death without syndrome manifestation

<table>
<thead>
<tr>
<th>Overall VHL penetrance</th>
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<th>Overall VHL penetrance</th>
<th>Overall VHL penetrance</th>
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<tbody>
<tr>
<td>Investigated subjects</td>
<td>125</td>
<td>118</td>
<td>115</td>
</tr>
<tr>
<td>Genetically confirmed subjects</td>
<td>111</td>
<td>109</td>
<td>108</td>
</tr>
<tr>
<td>No lesion</td>
<td>29 (23%)</td>
<td>63 (53%)</td>
<td>74 (64%)</td>
</tr>
<tr>
<td>Patients with tumour(s)</td>
<td>96 (77%)</td>
<td>58 (47%)</td>
<td>41 (36%)</td>
</tr>
<tr>
<td>Females/males with tumour(s)</td>
<td>54/43</td>
<td>24/31</td>
<td>23/18</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>38 (30%)</td>
<td>25 (21%)</td>
<td>28 (24%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>59 (47%)</td>
<td>30 (25%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Estimated overall penetrance at 35 y</td>
<td>48%</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>Estimated overall penetrance at 70 y</td>
<td>88%</td>
<td>60%</td>
<td>46%</td>
</tr>
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</table>
Of the 125 mutation carriers, 118 had available well documented information regarding the status of the adrenal glands. Among these 118 (109 genetically confirmed mutation carriers and nine relatives with clinical evidence of VHL), 55 (47%) subjects (31 males, 24 females) developed phaeochromocytoma during their lifetime (table 1). Overall penetrance for phaeochromocytomas was, therefore, estimated to be 31% by the age of 35 and 60% by the age of 70 (fig 2). Of these 55 patients who developed phaeochromocytoma during the course of our study, 55% were symptomatic and 45% asymptomatic (table 1). The penetrance estimations among patients with symptomatic and asymptomatic phaeochromocytomas are given in fig 3A.

Other frequent lesions were retinal angiomata (36%), haemangioblastoma of the spine (36%), and, to a lesser extent, haemangioblastoma of the brain (16%). As can be seen from table 1, one third of patients with angiomatosis retinae were symptomatic (13 out of 41), whereas two thirds were asymptomatic. Only 9% of spinal haemangioblastomas were symptomatic and 91% were asymptomatic. By contrast, the majority of brain haemangioblastomas were symptomatic (12 versus six asymptomatic tumours). The estimations of age related overall penetrance rates are shown in fig 2; of special note, the calculated penetrance for spinal haemangioblastomas was only 8% at 35 years, but owing to late occurrences the estimated 49% penetrance at 70 years is second only to phaeochromocytomas and, indeed, is higher than the penetrance of retinal angiomas at that age (46%). The different penetrance rates for the frequent VHL lesions among symptomatic and asymptomatic presentations as well as overall syndromic manifestation are shown in fig 3.

With respect to all frequent lesions, carriers of VHL c.505 T/C mutations, like almost all carriers of cancer predisposing mutations, also had a tendency to multifocal and/or bilateral manifestations. One patient with angiomatosis retinae developed at least 25 retinal angiomas, whereas the remaining patients had an average of two angiomas with no more than five lesions in one patient; 15 patients had bilateral and 25 unilateral involvement of the retinae. Pheochromocytoma was observed as a single tumour with adrenal or extra-adrenal localisation in 32 patients, but 23 mutation carriers developed multiple phaeochromocytomas.

In addition to the frequent tumours, there were several rare neoplasms. Four patients developed renal clear cell carcinoma (estimated overall penetrance 13% by the age of 70). Two of these patients died of metastases. All renal clear cell carcinomas were unilateral, single tumours, and no kidney showed renal cysts. Three of the patients with renal cell carcinoma were female. The kidney tumours were detected at the ages of 46 (male patient), 48, 63, and 74 years. Two patients with renal cell carcinoma also had multiple spinal haemangioblastomas. Other rare tumours were one pancreatic islet cell tumour and one pituitary...

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**Results**

Our series comprised 125 eligible subjects with germline VHL c.505 T/C mutation, including 64 previously known and 61 newly diagnosed mutation carriers. Of the 125 mutation carriers, 67 were females (54%) and 58 males (46%). Ages ranged from 4 to 86 years (mean 46 years).

Of the 125 mutation carriers, 96 (77%) had clinical manifestations of VHL. VHL was symptomatic in 47% of the patients, 30% were asymptomatic despite the presence of at least one VHL related tumour, and 23% of the subjects had no detectable VHL lesions (table 1). Of the total of 125 patients, 51 (41%) were found to have one component tumour of VHL, 31 (25%) were affected by two different lesions, 13 (11%) patients had three neoplasms, and only one (0.8%) patient had four different VHL related tumours. Estimation by cumulative incidence functions showed an overall VHL penetrance of 48% by the age of 35 and 88% by the age of 70, whereas estimation among symptomatic mutation carriers showed a penetrance of 30% by the age of 35 and 55% by the age of 70 (fig 1). There were no differences between males and females in the manifestation of single tumours or the overall penetrance of VHL.

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**Figure 1** Estimated overall penetrance for VHL. Note the nearly complete penetrance by the age of 75 years (>95%).

**Figure 2** Estimated penetrance rates for phaeochromocytoma, angiomatisos retinae, and haemangioblastoma of the brain and spine.
adenoma; both neoplasms had been incidentally found in a dead 34 year old woman at necropsy. One 68 year old male patient was noted to have small cell lung cancer, and two other males developed testicular teratocarcinoma both at 39 years of age. With the exception of one woman with renal clear cell carcinoma, all patients with rare tumours also had at least one classical and frequent VHL neoplasm.

Of special interest was the survival rate of our c.505 T>C mutation carriers in comparison to the general population in Germany: Estimates of the survival probabilities of the 125 VHL c.505 T/C mutation positive subjects were 96% at the age of 35 (95% confidence interval (CI) 93-100%) and 79% at the age of 70 (95% CI 67-91%). These estimates are similar to the survival probabilities corresponding to the sex adjusted general population of Germany with 98% at the age of 35 and 76% at the age of 70. Furthermore, as can be seen from fig 4, the survival estimates of the control population are within the pointwise 95% confidence interval of the survival estimates of the c.505 T/C mutation carriers over the whole age range. From this, it can be concluded that the survival of patients harbouring germline VHL c.505 T/C mutation is not worse than that of the general population of Germany.

Discussion

Traditionally, the germline VHL c.505 T>C mutation is associated with VHL type 2A with a predominance of phaeochromocytoma. Our present study which includes comprehensive clinical investigation of 125 eligible subjects with the VHL c.505 T/C germline mutation followed by estimation of the overall penetrance by cumulative incidence functions showed that this mutation had an almost complete penetrance (>95% at 75 years). In contrast, the mortality and survival rate is surprisingly comparable to those of the general population of Germany. This observation is in disagreement with a previous study by Maher et al. in 1990 describing a reduced survival of about 15 years in a large cohort of VHL.
patients from Great Britain. There may be several logical reasons for the conflicting results. Since the VHL gene was only isolated in 1993, the 1990 observations were based on a genetically and clinically unselected series with a presumed broad spectrum of VHL mutation types and different VHL, phenotypic subtypes. Further, none of the investigated families in the 1990 study had the c.505 T>C mutation, and most (86%) of the cases had presented with clinical manifestations (E Maher, personal communication). In addition, the two population bases, southern Germany and Great Britain, may also contribute to the differences. The present study is based on a series from southern Germany with only one mutation, which happens to result from a founder effect, the VHL c.505 T/C alteration, which is postulated to predispose to VHL 2A, a subtype without development of renal cell carcinoma. This is of special interest because multiple previous series have documented that kidney neoplasms and brain haemangioblastomas are the main causes of VHL related mortality. In contrast, in our cohort, only four patients developed renal cell carcinoma, of which three have died. There is a comparable situation with haemangioblastoma; development of this VHL component tumour has been reported in about one half of unselected subjects with VHL. Cerebellar haemangioblastoma was detected in 18 (16%) patients in our series and only three patients died from this neoplasm. Another reason for the low rate of major VHL associated complications resulting in a comparable survival rate between c.505T/C mutation carriers and the general population might be the observed relatively high proportion of asymptomatic subjects despite the presence of one or more VHL associated neoplasms. A surprising 30% (38) of the 96 patients found to have a VHL related tumour were asymptomatic, and lesions were only identified by clinical screening after identification of the presence of the VHL mutation. This observation was especially true for spinal haemangioblastoma; of the unexpected high prevalence of spinal haemangioblastoma (33 affected patients), only three tumours were symptomatic. The relatively benign course of the VHL c.505 associated tumours may also be influenced by the ever developing molecular diagnostic, clinical screening, and interventional possibilities. For example, the prognosis of patients with operated CNS haemangioblastomas has improved over the last years; 10 patients were operated on after 1993, of whom four died after neurosurgery. The three subjects who were operated on after 1993 had no postoperative complications. Screening for phaeochromocytoma as the most frequent lesion in our study was improved by T2 weighted MRI, which has become available as standard in the last decade; all three patients with phaeochromocytoma related deaths occurred before 1984 and all three tumours were undetected by the technology of the day. All these tumours most likely would have been correctly diagnosed and successfully removed today. Presymptomatic diagnosis owing to consequent clinical VHL screening and timely treatment were also important for retinal angioma, because patients diagnosed with symptomatic ocular lesions had a poor outcome. Seven patients had amaurosis of one eye because of retinal detachment including both subjects with bilateral blindness and four patients suffered from severe impairment of visual acuity <0.3 (30% that of normal). Four of these patients developed secondary glaucoma necessitating unilateral enucleation. All the severe complications occurred in patients with no presymptomatic eye investigation. In contrast, 28 patients with asymptomatic retinal angiomas had a good outcome and no major side effects after the procedures.

Interestingly, recalculation of the survival after exclusion of all subjects without existing tumours (23% of the entire cohort) still showed no significant differences between the modified VHL cohort and the normal population (data not shown). This observation further corroborates our hypothesis that the germline VHL c.505 T/C mutation has a high penetrance but still maintains a benign natural history whether the mutation carrier presents with a VHL related tumour or not. There is little doubt that our families from Germany are two families from Pennsylvania who carry the VHL c.505 T/C germline mutation share common ancestors, that is, this mutation is a result of a founder mutation. Table 2 shows the frequencies of different VHL manifestations among the German and the American families (Nos 3127 and 3476). While the frequency of phaeochromocytoma is similar (47% for German, 55% for American families), retinal angiomas have been reported in 47% of the members of the American families, which is higher than in our German c.505 T/C mutation positive cohort (36%, p=0.2, χ² test). Of note, the reported frequency of CNS haemangioblastoma in the American families (9%) is much lower than in our patients from

<table>
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<tr>
<th>Lesion</th>
<th>Present series (c.505 T&gt;C)</th>
<th>c.505 T&gt;C positive subjects (n=55) from Pennsylvania families 3127 and 3476</th>
<th>Unsualled previous cases (n=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phaeochromocytoma</td>
<td>55/118 (47%)</td>
<td>30 (55%)</td>
<td>117 (17%)</td>
</tr>
<tr>
<td>Retinal angioma</td>
<td>41/119 (36%)</td>
<td>26 (47%)</td>
<td>406 (58%)</td>
</tr>
<tr>
<td>Spinal cord haemangioblastoma</td>
<td>33/91 (36%)</td>
<td>9 (9%)</td>
<td>393 (56%)</td>
</tr>
<tr>
<td>Haemangioblastoma of the brain</td>
<td>18/111 (16%)</td>
<td></td>
<td>176 (25%)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>4/118 (3%)</td>
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Germany (41%, p<0.0001, \chi^2 test). The explanation for this difference may be the already mentioned high proportion of asymptomatic haemangioblastomas among patients with the c.505 T/C mutation (among the present cohort, 14% of brain/spine haemangioblastomas were symptomatic); most of the haemangioblastomas in the American families were symptomatic.\(^6\) Possibly because of the less than systematic clinical surveillance programme of the previous studies, the asymptomatic CNS tumours may not have been detected (but see below). Another interesting point is the reported complete absence of renal cell carcinoma in the families from Pennsylvania, one further argument that the c.505 T/C mutation is not associated with renal cell carcinoma (see below). When a founder mutation occurs and the descendants have scattered to different parts of the world, the phenotypic outcome for each of the branches becomes a fortuitous experiment of gene-environment interactions. Barring ascertainment bias (see above), it would appear that phaeochromocytoma as a phenotypic endpoint is almost completely the consequence of gene mutation while the development of retinal angiomas and CNS haemangioblastomas might be the result of both genetic and environmental input.

Phenotypically, although our study has confirmed that the c.505 T/C mutation is predominantly a phaeochromocytoma prone mutation,\(^6\)\(^7\)\(^8\)\(^9\) we have clearly shown that other component tumours, including the presence of renal cell carcinoma, cannot be ignored; 47% of the investigated patients developed phaeochromocytoma including 19 patients with extra-adrenal tumours. In contrast, angiomas of retinae was seen in our patients at a frequency of 36% which is somewhat lower in comparison to the approximate 50% prevalence in unselected series with VHL syndrome.\(^6\)\(^7\)\(^8\) Of note were the frequencies of CNS tumours; in previous reports, haemangioblastomas of the brain have been reported in 60-80%, whereas spinal haemangioblastomas usually have a lower prevalence of 20-40%.\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) In our series of c.505 T/C mutation carriers, the ratio of frequencies for both these tumours was inverted: 16% of mutation carriers were found to have cerebellar haemangioblastomas compared to 36% who developed spinal haemangioblastomas. Therefore, despite the low proportion of symptomatic spinal lesions (9%), clinical surveillance of c.505 T/C mutation positive subjects should always include the spine.

The observed rare neoplasms in our series, pancreatic islet cell tumour, pituitary adenoma, and teratocarcinoma of the testes, have been reported previously as part of VHL and, therefore, they may be regarded as rare c.505 T/C associated tumours as well.\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\) Pancreatic islet cell tumours occur in about 0.5% and pituitary adenomas in approximately 1% of VHL patients\(^24\) and this frequency is that observed in our c.505 T/C VHL mutation positive cohort as well. The one case of small cell lung cancer is probably not VHL related.

The four cases of renal cell carcinoma in our VHL type 2A c.505 T/C carriers is worthy of discussion. In general, the yearly incidence of renal clear cell carcinomas in Germany is 4-10 per 100 000 inhabitants.\(^25\) For comparison, we projected the annual incidence by extrapolation of our four cases of renal carcinoma among the 125 persons with a mean age of 46 years; the calculation showed a projected annual incidence of 71 cases of renal carcinoma per 100 000 inhabitants. This incidence is clearly much higher than that of the general population, but owing to small numbers, statistical significance cannot be achieved (95% CI=0-112 tumours). Therefore, whether the development of renal cell carcinoma is a true consequence of the c.505 T/C mutation is still open to speculation. Nevertheless, to avoid bias towards an artificially good outcome in our series, we considered the development of and death from renal cell carcinoma as attributable to VHL. Forthcoming further studies in patients with VHL type 2A should clarify whether the current phenotypic classification should be modified; if other cases with VHL type 2A and renal clear cell carcinoma are found, this phenotypic subtype should allow for rare cases of renal cell carcinoma.

In summary, this is a unique study which delineates the mutation specific penetrance, morbidity, and mortality for the VHL c.505 T/C germline mutation. Our systematic clinical investigation of patients with this mutation showed near complete penetrance by the age of 75 years but a mortality comparable to that of the general population of Germany. We believe there may be several reasons for this. Firstly, the c.505 T/C missense mutation might predispose to slowly growing tumours. Secondly, given that this is a founder mutation, it is altogether possible that good environmental factors, whatever they may be, may already have been selected for in the distant past. Thirdly, aggressive routine genetic screening followed by clinical surveillance and intervention must play a large role in the favourable clinical course. The demonstration of the favourable outcome in c.505 T/C associated VHL could favourably influence employment and health and life insurance of mutation carriers. Our observations should spur on other investigators to examine the morbidity and mortality from other specific VHL mutations and other cancer predisposition genes because such data can be used to practice evidence based medicine and guide clinical management.

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