Contrasting clinical manifestations of SDHB and VHL associated chromaffin tumours

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Abstract

Mutations in succinate dehydrogenase-B (SDHB) and the von Hippel-Lindau (VHL) genes result in an increased risk of developing chromaffin tumours via a common aetiological pathway. The aim of the present retrospective study was to compare the clinical phenotypes of disease in subjects developing chromaffin tumours as a result of SDHB mutations or VHL disease. Thirty-one subjects with chromaffin tumours were assessed; 16 subjects had SDHB gene mutations and 15 subjects had a diagnosis of VHL. VHL-related tumours were predominantly adrenal pheochromocytomas (22/26; 84.6%), while SDHB-related tumours were predominantly extra-adrenal paragangliomas (19/25; 76%). Median age at onset of the first chromaffin tumour was similar in the two cohorts. Tumour size was significantly larger in the SDHB cohort in comparison with the VHL cohort (P=0.002). Multifocal disease was present in 9/15 (60%) of the VHL cohort (bilateral pheochromocytomas) and only 3/16 (19%) of the SDHB cohort, while metastatic disease was found in 5/16 (31%) of the SDHB cohort but not in the VHL cohort to date. The frequency of symptoms, hypertension and the magnitude of catecholamine secretion appeared to be greater in the SDHB cohort. Renal cell carcinomas were a feature in 5/15 (33%) of the VHL cohort and 1/16 (6%) of the SDHB cohort. These data indicate that SDHB-related tumours are predominantly extra-adrenal in location and associated with higher catecholamine secretion and more malignant disease, in subjects who appear more symptomatic. VHL-related tumours tend to be adrenal pheochromocytomas, frequently bilateral and associated with a milder phenotype.

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Introduction

Recent studies have shown that ~25% of apparently sporadic pheochromocytomas and paragangliomas are due to germ line mutations in one of several familial syndrome genes, including von Hippel-Lindau (VHL), RET, succinate dehydrogenase-B (SDHB), SDHC, SDHD or NF1 (Neumann et al. 2002, 2004, Amar et al. 2005). Pheochromocytomas are tumours arising from catecholamine-producing chromaffin cells in the adrenal medulla, while paragangliomas are extra-adrenal chromaffin tumours of either sympathetic (secretory) or parasympathetic (mainly non-secretory) origin, located between the base of skull and the pelvis. VHL disease and familial paraganglioma syndrome
type 4 are caused by mutations in the VHL and SDHB genes respectively (Latif et al. 1993, Astuti et al. 2001). Functional investigations of the VHL and SDHB gene products have revealed overlapping functions. Firstly, inactivation of VHL and SDHB results in activation of hypoxic gene response pathways through stabilization of the HIF-1 and HIF-2 transcription factors (Maxwell et al. 1999, Selak et al. 2005). However, VHL mutations associated with a phaeochromocytoma only phenotype (type 2C VHL disease) retain the ability to regulate HIF transcription factors (Clifford et al. 2001) implicating additional pathways in the pathogenesis of phaeochromocytoma. Subsequently, it was demonstrated that VHL and SDHB mutations are both associated with a failure of normal developmental apoptosis of phaeochromocytoma precursor cells (Lee et al. 2005). However, despite the similar functional consequences of VHL and SDHB inactivation, clinical differences have been described and analysis of VHL- and SDHB-associated tumours have shown some differences in patterns of gene expression (Pollard et al. 2006).


In this study, we have compared the detailed clinical presentations of phaeochromocytomas and paragangliomas in these two syndromes with a common aetiological pathway. We note an early onset of disease in both cohorts but significant differences with respect to location of disease, size of tumours, multifocality and metastatic potential of disease. We also note differences with respect to associated symptoms and catecholamine secretion.

Materials and Methods
Subjects for this study were identified at St Bartholomew’s Hospital from records collated by SLC, with additional subjects identified by LW, SAA and ABG. SDHB subjects from other UK centres who were related to members of the initial St Bartholomew’s Hospital cohort were included in this study. VHL subjects, with a history of chromaffin tumours were included in the study, if they had a VHL mutation identified or they fulfilled the clinical criteria for disease as delineated by Melmon and Rosen (1964). Subjects were included in the study if they had complete imaging from the base of the skull to the pelvis and measurements of urinary or plasma catecholamines. The case-notes and hospital databases were examined for the required data, which included: age at first symptom/diagnosis, family history, disease penetrance, site and size of tumour, symptoms, secretion of catecholamines, multifocal disease, metastatic disease, treatment and disease outcome. The tumour size was taken as the widest diameter recorded on examination of the pathological sample or radiologically, if the tumour had not been removed. A comparison between cohorts was made along with a subgroup analysis of associated features corrected for tumour size and genetic mutation. The SDHB subjects in this study have been reported previously (Astuti et al. 2001, 2003, Lawrence et al. 2004, Srirangalingam et al. 2008), as have some of the VHL subjects with respect to pancreatic lesions (Mukhopadhyay et al. 2002). The study was classified as a service evaluation and therefore did not require formal ethical approval. Each subject provided informed consent within the screening process, which included appropriate genetic counselling.

Phaeochromocytomas were defined as tumours arising from chromaffin tissue in the adrenal medulla, while all extra-adrenal chromaffin tumours were designated paragangliomas. Paragangliomas originate in the abdomen, pelvis, thorax or head and neck regions. Multifocal disease was defined as a subject having multiple tumour foci, presenting synchronously or metasynchronously to the original tumour in areas normally containing chromaffin tissue. Metastatic disease was defined as evidence of distant spread in tissue not normally containing chromaffin tissue i.e. bone, liver, lung or lymph nodes.

The statistical software package GraphPad Prism version 4 was used for this analysis. Mean data with standard deviations or median data with interquartile range (IQR) are presented where appropriate. Twotailed tests with a significance level of 5% were used. The $\chi^2$ or Fisher’s exact test was employed to test for association between categorical variables. Continuous data were assessed for normality and appropriate parametric (t-test) or non-parametric (Wilcoxon signed-rank test) statistical testing applied. Odds ratios were calculated in relation to mutation type and location of tumours.
Results

Basic demographics

Thirty-one subjects were included in this study consisting of 16 SDHB mutation carriers and 15 subjects with VHL disease followed-up between 1975 and 2008. Median follow-up time overall was 11.0 years (IQR 3.5–15.0, range 1.1–31); 8.7 years (IQR 3.3–15.8, range 1.1–31) in the SDHB cohort and 11 years (IQR 3.5–15.0, range 3–28) in the VHL cohort. The index case in family 3 was excluded because the original data were unavailable. Further demographics are given in Table 1.

There were 11 index subjects in the SDHB cohort and 9 index subjects in the VHL cohort. Evidence of familial disease was only noted in 2/11 (18%) SDHB index cases compared with 4/9 (44%) VHL index cases. Apparently sporadic presentations of disease occurred in 6/11 (55%) of SDHB index subjects compared with 2/9 (22%) of VHL index subjects. In 3/11 SDHB subjects and 3/9 VHL subjects, there was a suggestive but inconclusive history of familial disease.

The median age at first diagnosis of a chromaffin tumour was similar between the groups; 26.5 years (IQR 16–40.5) in the SDHB mutation carriers versus 19 years (IQR 12–29) in the VHL group (P = 0.15, Mann–Whitney test). The initial manifestation of disease in VHL group was a chromaffin tumour in 9/15 (60%) subjects, retinal angiomas in 4/15 (27%) subjects, cerebellar haemangioblastoma and renal cell carcinoma in 1/15 (7%) subjects each. Where a chromaffin tumour was not the first presentation of disease, this lagged the initial diagnosis by a median period of 3.5 years (IQR 2–14).

Mutations

Ten mutations in the SDHB gene (nine exonic and one intronic) and five mutations in the VHL gene were noted. Of the 15 VHL subjects, 12 subjects were mutation positive (subject 29 – genetic linkage suggested 99% chance of carrying affected mutation carried by affected father (subject 28) but mutation analysis not done), while three fulfilled clinical criteria for VHL disease. Mutations are listed in Table 2.

Tumour characteristics

Twenty-five tumours in the SDHB mutation carriers and twenty-six tumours in the VHL group were noted (Fig. 1). Of the SDHB-related tumours, 19/25 (76%) were extra-adrenally located compared with 6/25 (24%) adrenal phaeochromocytomas. This is in contrast to the VHL-related tumours, where the majority, 22/26 (84.6%) were adrenal phaeochromocytomas and only 4/26 (15.4%) tumours were extra-adrenally located. A further breakdown of tumour distribution is given in Table 2. The majority of extra-adrenal tumours were abdominal paragangliomas in SDHB mutation carriers, whereas extra-adrenal disease was equally distributed between the abdomen and head-and-neck regions in the VHL group (Fig. 1). There were no cases of bilateral adrenal phaeochromocytomas in the SDHB cohort in comparison with 9/15 (60%) in the VHL cohort. Of these, 5/15 (33%) VHL subjects had synchronous phaeochromocytomas and 4/15 (27%) had asynchronous tumours. As a result, multifocal disease was more common in the VHL group in comparison with the SDHB group; 9/15 (60%) compared with 3/16 (19%) respectively. The median diameter of tumours associated with SDHB mutation carriers was significantly higher at 6.0 cm (IQR 4.5–7.3) than tumours in the VHL group of 3.7 cm (IQR 2.9–5.0) (P = 0.0016, Mann–Whitney test). The odds ratio of developing a phaeochromocytoma or an extra-adrenal paraganglioma according to genetic mutation was calculated. In comparison with an SDHB mutation carrier, a subject with VHL disease has an odds ratio of 17.42 (95% CI, 4.1–71.1; P < 0.0001) of developing an adrenal phaeochromocytoma.

Table 1 Basic demographics of the succinate dehydrogenase-B and von Hippel-Lindau cohorts

<table>
<thead>
<tr>
<th></th>
<th>SDHB cohort</th>
<th>VHL cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Males</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Females</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Index subjects</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Median follow-up time/years</td>
<td>8.7 (IQR 3.3–15.8)</td>
<td>11 (IQR 3.5–15.0)</td>
</tr>
<tr>
<td>Number of families</td>
<td>3 (7 subjects)</td>
<td>4 (10 subjects)</td>
</tr>
<tr>
<td>Isolated subjectsa</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Definite family history</td>
<td>2/11 (18%)</td>
<td>4/9 (44%)</td>
</tr>
<tr>
<td>No family history (apparently sporadic)</td>
<td>6/11 (55%)</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>Number of tumours</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Multifocal disease</td>
<td>3/16 (19%)</td>
<td>9/15 (60%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>5/16 (31%)</td>
<td>0/15 (0%)</td>
</tr>
</tbody>
</table>

Index subjects are defined with respect to present study i.e. index subject in this cohort (true index subject may not be followed up in this cohort).

aIsolated subjects in this study, however, may have a family history outside of this cohort.
Table 2 Genetic mutations and disease phenotype in the succinate dehydrogenase-B and von Hippel-Lindau cohorts

<table>
<thead>
<tr>
<th>Subject</th>
<th>Family</th>
<th>Gender</th>
<th>Mutations</th>
<th>Site</th>
<th>Mutation type</th>
<th>Amino acid</th>
<th>Age at diagnosis</th>
<th>Disease</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>F</td>
<td>c.268 C&gt;T</td>
<td>3</td>
<td>Nonsense</td>
<td>p.Arg90X</td>
<td>41</td>
<td>AP</td>
<td>No further disease</td>
<td></td>
</tr>
<tr>
<td>2(^a)</td>
<td>M</td>
<td>c.487 T&gt;C</td>
<td>5</td>
<td>Missense</td>
<td>p.Ser163Pro</td>
<td>40</td>
<td>H, AP, P</td>
<td>Died 20 years after diagnosis second stroke</td>
<td></td>
</tr>
<tr>
<td>3(^a)</td>
<td>M</td>
<td>c.590C&gt;G</td>
<td>6</td>
<td>Missense</td>
<td>p.Pro197Arg</td>
<td>24</td>
<td>Pe, mets</td>
<td>Mother had CBT – died aged 32 years</td>
<td></td>
</tr>
<tr>
<td>4(^a)</td>
<td>F</td>
<td>c.423 +20 T&gt;A</td>
<td>4(l)</td>
<td>Splice site(^b)</td>
<td>--</td>
<td>41</td>
<td>P</td>
<td>No further disease</td>
<td></td>
</tr>
<tr>
<td>5(^a)</td>
<td>M</td>
<td>c.423 +20 T&gt;A</td>
<td>4(l)</td>
<td>Splice site(^b)</td>
<td>--</td>
<td>48</td>
<td>P</td>
<td>Carotid artery dissection, PFO, PTE, stroke</td>
<td></td>
</tr>
<tr>
<td>6(^a)</td>
<td>F</td>
<td>c.141 G&gt;A</td>
<td>2</td>
<td>Nonsense</td>
<td>p.Trp47X</td>
<td>10</td>
<td>AP, RCC</td>
<td>Chemo for RCC mets</td>
<td></td>
</tr>
<tr>
<td>7(^a)</td>
<td>M</td>
<td>c.292 T&gt;C</td>
<td>4</td>
<td>Missense</td>
<td>p.Cys98Arg</td>
<td>47</td>
<td>Pe, mu, mets</td>
<td>Died second PGL mets</td>
<td></td>
</tr>
<tr>
<td>8(^a)</td>
<td>M</td>
<td>c.136 C&gt;T</td>
<td>2</td>
<td>Nonsense</td>
<td>p.Arg46X</td>
<td>18</td>
<td>AP</td>
<td>No further disease</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>c.136 C&gt;T</td>
<td>2</td>
<td>Nonsense</td>
<td>p.Arg46X</td>
<td>26(^c)</td>
<td>AP, mets</td>
<td>Died metastatic PGL</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>c.136 C&gt;T</td>
<td>2</td>
<td>Nonsense</td>
<td>p.Arg46X</td>
<td>39(^c)</td>
<td>T</td>
<td>Awaiting excision</td>
<td></td>
</tr>
<tr>
<td>11(^a)</td>
<td>M</td>
<td>c.72+1 G&gt;T</td>
<td>1</td>
<td>Splice site</td>
<td>--</td>
<td>14</td>
<td>P</td>
<td>No further disease</td>
<td></td>
</tr>
<tr>
<td>12(^a)</td>
<td>F</td>
<td>c.406 del A</td>
<td>4</td>
<td>Frameshift</td>
<td>p.Ile136X</td>
<td>29</td>
<td>AP, mets</td>
<td>Died PGL mets intra-operatively</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>c.406 del A</td>
<td>4</td>
<td>Frameshift</td>
<td>p.Ile136X</td>
<td>14</td>
<td>P</td>
<td>No further disease</td>
<td></td>
</tr>
<tr>
<td>14(^a)</td>
<td>M</td>
<td>c.137G&gt;A</td>
<td>2</td>
<td>Missense</td>
<td>p.Arg46Gln</td>
<td>11</td>
<td>AP, P, T, mu, mets</td>
<td>Mother had PGL mets, died aged 38 years</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>c.590C&gt;G</td>
<td>6</td>
<td>Missense</td>
<td>p.Pro197Arg</td>
<td>18</td>
<td>Pe</td>
<td>Lost to follow-up</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>c.590C&gt;G</td>
<td>6</td>
<td>Missense</td>
<td>p.Pro197Arg</td>
<td>18</td>
<td>Pe</td>
<td>Lost to follow-up</td>
<td></td>
</tr>
</tbody>
</table>

**VHL group**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Family</th>
<th>Gender</th>
<th>Mutations</th>
<th>Site</th>
<th>Mutation type</th>
<th>Amino acid</th>
<th>Age at diagnosis</th>
<th>Disease</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>17(^a)</td>
<td>M</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>58</td>
<td>P</td>
<td>RCC</td>
</tr>
<tr>
<td>18(^a)</td>
<td>M</td>
<td>c.555C&gt;G</td>
<td>3</td>
<td>Nonsense</td>
<td>p.Tyr185X</td>
<td>30</td>
<td>AP</td>
<td>Retinal angiomas aged 16</td>
<td></td>
</tr>
<tr>
<td>19(^a)</td>
<td>M</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>32</td>
<td>H</td>
<td>Cerebellar HB aged 28</td>
</tr>
<tr>
<td>20(^a)</td>
<td>M</td>
<td>c.499 C&gt;T</td>
<td>3</td>
<td>Missense</td>
<td>p.Arg167Trp</td>
<td>14</td>
<td>P, mu</td>
<td>Left phaeochromocytoma identified on adrenal catheter</td>
<td></td>
</tr>
<tr>
<td>21(^a)</td>
<td>M</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>23</td>
<td>P, mu</td>
<td>Asynchronous</td>
</tr>
<tr>
<td>22(^a)</td>
<td>F</td>
<td>c.499C&gt;T</td>
<td>3</td>
<td>Missense</td>
<td>p.Arg167Trp</td>
<td>8</td>
<td>P, mu</td>
<td>Asynchronous</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>c.499C&gt;T</td>
<td>3</td>
<td>Missense</td>
<td>p.Arg167Trp</td>
<td>14</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26(^a)</td>
<td>M</td>
<td>c.509T&gt;G</td>
<td>3</td>
<td>Missense</td>
<td>p.Val70 Gly</td>
<td>29</td>
<td>P, mu</td>
<td>Synchronous</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>c.509T&gt;G</td>
<td>3</td>
<td>Missense</td>
<td>p.Val70 Gly</td>
<td>12</td>
<td>P</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Symptoms

The difference between the groups in median duration of symptoms prior to initial chromaffin tumour did not reach significance at 1.3 years (IQR 0.2–2.8) for the SDHB mutation carriers and 0.09 years (IQR 0.0–3.5) for the VHL group ($P < 0.088$, Mann–Whitney test). SDHB mutation carriers were more frequently hypertensive (11/16; 69%) than subjects in the VHL group (5/15; 30%) ($P < 0.048$, $\chi^2$ test). A breakdown of symptom frequency for each group is given in Fig. 2.

The classic triad symptoms (headache, palpitations and diaphoresis) were the commonest features of disease; however, the SDHB mutation carriers appeared more symptomatic overall. While the classical triad symptoms was present in 8/16 (50%) of SDHB mutation carriers, the full set of symptoms was not present in any VHL subject ($P = 0.002$, Fisher’s exact test).

Catecholamines

Catecholamines were raised in the majority of subjects with both syndromes. Twelve of fifteen (80%) SDHB mutation carriers and thirteen of fourteen (93%) of the VHL group had raised catecholamine levels (Table 3). Of those subjects in both cohorts with elevated catecholamines, noradrenaline levels were raised in all subjects, while adrenaline levels were raised in 3/15 (20%) compared with 1/15 (7%) and dopamine levels were raised in 1/15 (8%) compared with 3/15 (20%) subjects in the SDHB and VHL groups respectively.
However, further analysis of the magnitude of the noradrenaline rise over the upper limit of the normal range (99th centile) in these subjects reveals that SDHB mutation carriers produced significantly more noradrenaline than VHL group \((P=0.0126,\) Mann–Whitney test). Statistical analysis was not undertaken for adrenaline and dopamine secretion as the numbers of subjects with elevated levels were too small for comparison.

**Functional imaging**

Radiolabelled MIBG scanning was carried out in 12 SDHB mutation carriers and 12 of the VHL group. Proportionally, more of the VHL group demonstrated MIBG uptake in comparison with the SDHB mutation carriers i.e. 11/12 (92%) vs 6/12 (50%) subjects, though this difference did not reach statistical significance \((P=0.068,\) Fisher’s exact test). Out of the five VHL subjects with synchronous adrenal phaeochromocytomas, only 2/5 (40%) had bilateral uptake on radiolabelled MIBG imaging. One SDHB subject with a thoracic paraganglioma did not show evidence of radiolabelled MIBG uptake but had positive uptake with FDG PET scanning.

**Metastatic disease**

Metastatic paragangliomas were noted in 5/16 (31%) SDHB mutation carriers at a median of 4 years (range 1.5–25) after the initial tumour. To date, no member of the VHL group has developed evidence of malignant disease.

**Subgroup analysis**

A subgroup analysis was carried out to correct for possible confounding factors by matching subjects for tumour size (within 1 mm) and ensuring that no subject within the subgroup had the same mutation. This comparison resulted in the inclusion of seven subjects from each group with tumours ranging in size from 3.5 to 6.5 cm. The trend for higher levels of noradrenaline secretion (magnitude rise over the upper limit of the normal range; median level 6.1 vs 1.8), frequency of the classic triad of symptoms (2/7 vs 0/7) and an increased malignancy rate (2/7 vs 0/7) was noted for the SDHB subjects compared with VHL subjects, but these differences were not statistically significant \((P=0.37, 0.46\) and 0.46 respectively).

**Associated disease**

As reported previously, one SDHB mutation carrier developed a metastatic type II papillary renal cell carcinoma 16 years after the initial presentation of an abdominal paraganglioma at the age of 10 years. The metastatic renal carcinoma in this subject has responded to the multi-target tyrosine kinase inhibitor, sunitinib. Along with other manifestations of VHL disease (which we have not discussed), 5 out of 15 (33%) VHL subjects developed clear-cell renal carcinomas.

**Treatment**

All the SDHB mutation carriers have had surgery for their tumours and five subjects required repeat surgery for recurrent tumours or metastatic disease. Fourteen out of the fifteen VHL group have had surgery for their tumour, while four subjects required further surgery for multifocal disease. Two VHL subjects have tumours in situ. Subject 31 has an adrenal phaeochromocytoma...
Table 3  Catecholamines/metabolite secretion and radiolabelled MIBG imaging

<table>
<thead>
<tr>
<th>Subject</th>
<th>Disease</th>
<th>Catecholamines (urinary)</th>
<th>Catecholamines (plasma)</th>
<th>Additional information</th>
<th>Radiolabelled MIBG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>A</td>
<td>D</td>
<td>NA</td>
</tr>
<tr>
<td>1</td>
<td>AP</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>H (bilateral) AP, P, mu</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Pe, mets</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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</table>

+ signifies elevated level or positive uptake (MIBG); – signifies non-elevated level or negative uptake (MIBG); blank box indicates test not done. NA, noradrenaline; A, adrenaline; D, dopamine; AP, abdominal paraganglioma; P, phaeochromocytoma; Pe, pelvic paraganglioma; T, thoracic paraganglioma; H, head-and-neck paraganglioma; RCC, renal cell carcinoma; Mu, multifocal; Mets, metastatic.
and is awaiting surgery, while subject 28 has a non-functioning neck paraganglioma which is $^{123}$I MIBG negative but FDG-PET positive which remains under observation. Out of the five SDHB mutation carriers with metastatic paragangliomas, two have had $^{131}$I MIBG therapy, while two have had chemotherapy. Out of the two SDHB subjects requiring radiolabelled MIBG therapy, one has responded to therapy while the other subject has had progressive disease. The two subjects requiring chemotherapy (MIBG non-avid disease) did not respond to therapy.

**Outcome**

Out of the 16 SDHB subjects, four subjects are dead. In three cases, this was directly disease related and in the other subject this was indirectly disease related (multiple strokes secondary to hypertension). The 12 remaining subjects continue under follow-up. To date, 9 out of the 16 SDHB mutation subjects have had no further disease after their initial tumour. There was no associated mortality in the VHL cohort with chromaffin tumours.

**Discussion**

In this study, we have made a comparison of the clinical manifestations of phaeochromocytomas and paragangliomas in a cohort of 16 subjects with SDHB mutations and 15 subjects with VHL disease. Despite a common aetiological pathway in the pathogenesis of disease, there appear to be distinct clinical features in terms of tumour distribution, symptomatology, associated disease and malignancy rates. Limitations of this study include the small sample size and variations in follow-up regimens between cohorts. Differences in tumour size and the inclusion of family members with the same mutation may introduce further sources of bias. A subgroup analysis, correcting for tumour size and genetic mutations, noted a trend for higher noradrenaline secretion, symptom frequency and malignancy rates with SDHB-related tumours, but was probably under-powered and did not confirm these differences statistically. The higher malignancy rate in the SDHB mutation carriers made it difficult to meaningfully correct our data for tumour size as some of these subjects suffered rapid tumour development between annual surveillance scans.

This study demonstrates marked differences in the chromaffin tumour characteristics between the syndromes. SDHB mutation carriers have a predominance of extra-adrenal disease (76%) mainly in the form of abdominal paragangliomas (48%), whereas the VHL group have a predominance of adrenal disease (85%), mainly in the form of bilateral adrenal phaeochromocytomas (60%). Multifocal disease is limited to 19% of SDHB mutation carriers compared with 60% of the VHL group. The tumour size was significantly larger in the SDHB mutation carriers compared with the VHL group (6.0 vs 3.7 cm). The higher rates of malignancy seen with SDHB mutation carriers may correlate with larger tumour size. Given that VHL disease surveillance has been in place longer and that there is heightened abdominal surveillance may result in earlier identification of chromaffin tumours (Maher et al. 1990, Choyke et al. 1995) in this cohort.

The age at initial diagnosis of a phaeochromocytoma or paraganglioma was not significantly different between the groups but emphasizes the presentation of these tumours at an early age. A history of familial disease was more evident in the VHL cohort than in the SDHB mutation carriers. We have demonstrated previously the incomplete penetrance of disease in SDHB mutation carriers (Srirangalingam et al. 2008) and indeed a history of apparently sporadic disease does not rule out the possibility of an SDHB mutation as noted in 55% of SDHB mutation carriers in this study. The wide range of manifestation of VHL disease and the high penetrance of features such as cerebellar haemangioblastomas and retinal angiomas, tend to make family disease more apparent in comparison with disease in SDHB mutation carriers.

In these small cohorts, obvious genotype–phenotype correlations with respect to chromaffin tumours were not apparent. However, genotype–phenotype correlations in VHL disease in comparison with SDHB disease are more established (Ong et al. 2007). These note that missense mutations involving amino acids on the surface of the VHL protein are associated with higher rates of phaeochromocytomas (Ong et al. 2007). This study demonstrates that the VHL group appears to be significantly less symptomatic than the SDHB subjects. Both hypertension and the classic triad of symptoms were significantly less prevalent though the duration of symptoms were comparable. It is possible that documentation of symptoms of chromaffin tumours is more comprehensive in SDHB mutation carriers, where phaeochromocytomas and paragangliomas are the predominant disease manifestation in comparison with VHL disease where it is one of many manifestations. The absence of symptoms in a significant proportion of subjects with VHL disease-associated phaeochromocytomas has been noted previously (Walther et al. 1999). Again, the established surveillance programme for VHL disease may mean that disease is identified before symptoms develop.
The smaller size of tumours in the VHL group may correlate with less metabolically activate disease and hence less symptoms. Catecholamines were raised in a similar number of subjects in the 2 cohorts; however, the degree to which the catecholamines were raised may explain these differences. In both cohorts, noradrenaline was the predominant catecholamine secreted, however, the magnitude of the secretion was higher in the SDHB population that may correlate with symptomatology (Walther et al. 1999).

Functional imaging with radiolabelled MIBG was positive in significantly more subjects with VHL disease than in SDHB mutation carriers (92% vs 50%). SDHB-related tumours are larger, more malignant and may be expected to be more dedifferentiated (Timmers et al. 2007). Such tumour may lack the relevant transporter to take up MIBG. Importantly, despite high MIBG uptake in the VHL cohort overall, in the cases of synchronous bilateral adrenal tumours only 40% demonstrated bilateral uptake.

The two cohorts contrast significantly with respect to malignancy rates. In SDHB mutation carriers, malignant paragangliomais were evident in 31% of subjects, while no subjects have developed malignant disease in the VHL cohort to date. These data correlate with the larger tumour size noted in the SDHB mutation cohort compared with the VHL cohort. The literature confirms the malignant phenotype of SDHB-related disease in numerous studies (Neumann et al. 2004, Benn et al. 2006, Timmers et al. 2007, Srirangalingam et al. 2008). Though malignant disease can be associated with VHL disease, it is significantly less frequent (Neumann et al. 1993).

VHL disease is associated with a wide range of manifestations. In relation to the present study, it is of interest that chromaffin tumours were the initial manifestation of disease in 60% of VHL group followed by retinal angiomas in 27% of subjects. Renal cell carcinomas appear to be a manifestation of disease in both cohorts. However, VHL disease is associated with a high risk of clear-cell renal carcinoma (Maher et al. 1990), whereas SDHB mutations are associated with a lower risk and a variety of renal cell carcinoma cell types (Vanharanta et al. 2004, Srirangalingam et al. 2008). In both cohorts, the renal cell carcinomas have responded to therapy with various multi-target tyrosine kinase inhibitors which work via inhibition of the VEGF-HIF pathway which is implicated in the pathogenesis of these tumours (U Srirangalingam, personal observations).

The aggressive nature of disease associated with SDHB mutations is illustrated by the fact that there have been four deaths in this cohort, three of which were as a result of metastatic disease. Despite the co-morbidity associated with VHL disease, no subjects have died within this cohort to date.

Disease surveillance regimes with respect to chromaffin tumours in VHL disease are well established and include annual history and examination, measurement of plasma or urinary catecholamines or metanephrines and CT or MRI scan of the abdomen (Maher et al. 1990, Choyke et al. 1995). Annual imaging of the abdomen in VHL subjects is driven by the surveillance requirements for renal cell carcinoma, and will also image both adrenals and much of the abdominal sympathetic chain. Table 4 summarizes our present practice for chromaffin tumour surveillance in SDH mutation carriers and subjects with VHL disease. Some patients with VHL disease have paragangliomas outside the abdomen and so additional imaging of the sympathetic chain in the neck, chest and pelvis is prudent and we suggested this should be done on a 3-yearly basis. For SDHB mutation carriers, we introduced annual surveillance in 2001 (Chew 2001), but there remains some debate about the most cost-effective method of imaging the entire sympathetic chain.

**Table 4** Disease surveillance regimes for von Hippel-Lindau and succinate dehydrogenase-B-related chromaffin tumours

<table>
<thead>
<tr>
<th>Genetic mutation</th>
<th>Catecholamines/ metanephrines</th>
<th>Imaging (preferably MRI)</th>
</tr>
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<tr>
<td><strong>Region</strong></td>
<td><strong>Frequency</strong></td>
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</tr>
<tr>
<td>Abdomen</td>
<td>Annually</td>
<td></td>
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<tr>
<td>Neck/thorax/pelvis</td>
<td>Annually</td>
<td></td>
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<tr>
<td>Neck/thorax/abdomen/pelvis</td>
<td>3 yearly</td>
<td></td>
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<tr>
<td>Abdomen</td>
<td>Annually</td>
<td></td>
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<tr>
<td>Neck/thorax/pelvis</td>
<td>Annually</td>
<td></td>
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<tr>
<td><strong>VHL</strong></td>
<td>Annually</td>
<td></td>
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<tr>
<td><strong>SDHB</strong></td>
<td>Annually</td>
<td></td>
</tr>
<tr>
<td><strong>SDHD</strong></td>
<td>Annually</td>
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</table>

Annual review includes clinical assessment, symptom enquiry, blood pressure and relevant clinical examination. All subjects should have imaging from the base of the skull to the pelvis on initial surveillance. Disease surveillance recommended from the age of 5 years for all mutations carriers. If a lesion is noted, or surveillance is suggestive of disease, imaging should be carried out early. *Change to SDHB surveillance regime for SDHD mutation associated with increased risk of malignant disease (Timmers et al. 2008).*
Despite the common pathway involved in the pathogenesis of these two syndromes and the similarities in presentation with respect to age at diagnosis of the first chromaffin tumours, predominance of noradrenaline secretion and the association with renal cell carcinoma, there are several marked differences with respect to disease location, frequency of symptoms, magnitude of catecholamine secretion, other extra-paraganglial associations, malignancy and mortality rates. While these findings may be explicable in part, as a result of different management practices, it is likely that the aggressive disease phenotype that can be associated with SDHB-related disease plays a role. Such findings should improve disease identification and future surveillance strategies.

Declaration of interest
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References


