Dear Editor

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare neuroendocrine tumors that arise from the adrenal medulla or from the extra-adrenal sympathetic and parasympathetic paraganglia respectively. Now we know that more than 30% of patients develop extra-adrenal tumors (Cascon et al. 2009b, Mannelli et al. 2009), the percentage of malignant cases depends on tumor location and/or genetic background (from ~3% in RET- or VHL-related cases to 31% described for SDHB mutation carriers; Welander et al. 2011), and the probability of carrying a germline mutation in one of the PCC/PGL susceptibility genes is approaching 50%. Regarding the latter, up to four genes (SDHAF2, SDHA, TMEM127, and MAX) have recently been incorporated into the ‘catalog’ of PCC/PGL susceptibility genes (Hao et al. 2009, Burnichon et al. 2010, Qin et al. 2010, Comino-Mendez et al. 2011). Before the discovery of these genes, 30–40% of PCC/PGL cases were thought to be hereditary with autosomal inheritance caused by germline mutations affecting one of six major susceptibility genes: RET, VHL, SDHB, SDHC, SDHD, and NF1 (Cascon et al. 2009b, Mannelli et al. 2009). Recent international collaborations, focused on establishing the involvement of the novel identified genes, suggested that overall they could explain an additional 6% of the negative-tested patients (Bayley et al. 2010, Yao et al. 2010, Burnichon et al. 2012). In addition to this high and heterogeneous genetic predisposition, there is an unknown percentage of familial cases (i.e. with familial antecedents of PCC/PGL and/or with other clinical characteristics suggesting a hereditary disease) that do not harbor mutations in any of the susceptibility genes mentioned earlier.

Although PCCs/PGLs are infrequently diagnosed during childhood, it is possible to find pediatric patients (diagnosed under the age of 18 years) either carrying germline alterations in the major susceptibility genes or without known mutations (Welander et al. 2011). The identification of a genetic predisposition in children has obvious implications regarding follow-up and treatment. In the case of PCC/PGL patients with germline mutations in SDHB, early genetic characterization is even more crucial considering their malignancy-associated risk. Given that four of the ten major PCC/PGL susceptibility genes were identified very recently, there are still not enough genotype–phenotype association studies to properly guide pediatric genetic diagnosis. In the present study, we describe clinical and genetic findings of 36 pediatric patients and compare them with data from 411 genetically characterized non-pediatric cases. The study includes the analysis of the nine major PCC/PGL susceptibility genes.

Consecutively registered patients included in this study were clinically diagnosed with PCC/PGL in public Spanish hospitals and referred to us for the genetic testing in the major PCC susceptibility genes: VHL, RET, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, and MAX. No patients presented with the clinical features of neurofibromatosis type 1. DNA was obtained by standard procedures from blood samples from 447 apparently non-related index cases collected between 1995 and 2012, with 36 patients classified as pediatric cases. Written informed consent was obtained for each patient or a legal tutor in the case of children. Complete genetic characterization of the susceptibility genes included, except for the RET oncogene, point mutation analysis of all exons and intron–exon boundaries, and assessment of gross deletions either by means of multiplex ligation-dependent probe amplification or by multiplex PCR. In the case of RET, point mutations affecting exons 10, 11, 13, 14, 15, and 16 were analyzed. We used DNA from 1000 unrelated and unaffected individuals as a control population for the study of variants of unknown significance. Differences between pediatric and non-pediatric probands were assessed using a χ² test or Fisher’s exact test when appropriate. Statistical analyses were carried out using SPSS Software, version 17.0 (SPSS, Inc.). To check whether there was any association between the type of mutation and the age at onset, we subclassified SDH mutations into...
two different groups according to the predicted effect of
the variant: truncating mutations (frameshift, non-
sense, splicing, and gross deletion) and non-truncating
mutations (missense and in-frame insertions/deletions).
We compared the frequency of mutations from each group
in pediatric with non-pediatric cases.

Clinical and genetic characteristics of the two series of
patients compared in this study are described in Table 1.
In total, 69% of pediatric cases carried a germline
mutation in one of the susceptibility genes investigated,
compared with 36% of non-pediatric probands (P < 0.001).
Thirty-one percent (11/36) of pediatric probands pre-

dented a family history of PCC/PGL, with mutations
identified in 91% (10/11) of them. An additional 42%
(15/36) of cases, without family history, harbored a
germine mutation. The involvement of each suscep-
tibility gene in the pediatric cases was 11 SDHB cases, 8
VHL cases (four de novo alterations), 4 SDHD cases, 1 MAX
case, and 1 RET case. VHL and RET mutations were
significantly more and less frequently detected (P = 0.02,
P = 0.004) respectively in children compared with non-
pediatric cases. Table 2 and the Supplementary Material,
see section on supplementary data given at the end of this
article provide a clinical description of the 36 pediatric
cases included in the study. When we compared the
frequency of truncating and non-truncating SDHB
mutations between pediatric and non-pediatric probands,
we found an over-representation of truncating mutations
in the pediatric group (P = 0.06). We did not find such
differences in the distribution of the SDHD mutations.

In the absence of a family history of a particular
disease, young age at onset is an important clinical feature
that suggests a hereditary predisposition. In the case of
PCC/PGL, this association is even more important, as a
high percentage of hereditary cases is found among
apparently sporadic patients (Cascon et al. 2009a).
In our series, 69% of pediatric probands harbored a germline
mutation in one of the nine PCC genes assessed. The
percentages of probands with and without germline
mutations were inversely proportional in the pediatric
compared with the non-pediatric cases (Table 1). Our
results are in agreement with a recently published study
that described a staggering number of children with
metastatic PCC/PGL carrying a SDHB germine mutation
(King et al. 2011). Among the series of pediatric cases
without mutations, we found a significantly higher
proportion with at least one well-known clinical finding
suggestive of a hereditary condition, such as bilateral PCC
and coexistence of PCC and PGL (P = 0.008). Although no
significant difference was found between mean age of
onset among mutation-positive and -negative pediatric
probands, two of the three cases younger than 10 years
at onset belonged to the mutation-negative group.
Altogether, it seems plausible that the majority of these
negative-tested children indeed harbor a germline
mutation in an as yet unknown gene.

We found that almost 60% of VHL carriers harbored
a de novo mutation, in agreement with the 56% reported
in Chinese patients (Wu et al. 2012). However, as the
currently accepted de novo VHL mutation rate is estimated
at 20–21% (Evans et al. 2010), it is likely that the high rate
found in our series is due to sample size. As expected, none
of the informative SDH mutation carriers without familial
ancestors had de novo mutations, suggesting a low
mutation rate affecting the SDH genes. In addition, half of
the cases with antecedents showed affected second-degree
relatives, in agreement with a heredity pattern involving
imprinting and low-penetrance phenomena affecting
SDHD and SDHB respectively. Although the estimated
average penetrance of SDHB mutations at age 20 is 1%
(Schiavi et al. 2010), it is not surprising to find pediatric
cases among SDHB-mutated pedigrees. The mechanisms
behind this clinical discrepancy have remained elusive
until now, but it seems that the nature of the mutation
may be important. All 11 SDHB variants found in the
pediatric probands were truncating mutations, compared
with 72% for the non-pediatric probands. This over-
representation of truncating mutations was not found
for SDHD variants. Similar to the ‘proteotype–phenotype’
correlation found for unstable SDHD mutations and an
earlier age at onset described by Ricketts (2010), we
observed a non-significant over-representation of truncat-
ing SDHB variants in pediatric patients. Although most of
the SDHB mutations found in our pediatric probands are
founder mutations in Spain (Cascon et al. 2006, 2009b),
which may explain the high rate of SDHB mutations found
in this study, bias was avoided by comparing the
frequency between only Spanish pediatric and non-
pediatric patients from the same series. Although our
results and those of Ricketts et al. (2010) concern different
genets, it seems that as reported for VHL mutations, the
nature of the SDH variants could determine important
clinical features such as the age of onset. In the present
study, the number of mutations tested is limited and
therefore evaluation of a larger series of SDH patients is
warranted to validate these results, which could poten-
tially change PCC/PGL clinical management.

Regarding other susceptibility genes, it is not surpris-
ing that we did not find involvement of the genes
TMEM127, SDHC, SDHAF2, or SDHA in pediatric PCC/PGL
Table 1  Comparison of clinical and genetic features of pediatric and non-pediatric cases.

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Gene</th>
<th>n (%)</th>
<th>Single PCC</th>
<th>bPCC</th>
<th>TA PGL</th>
<th>H&amp;N PGL</th>
<th>TA + H&amp;N PGL</th>
<th>PCC + PGL</th>
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<tr>
<td>Pediatric probands</td>
<td></td>
<td>Germline mutation</td>
<td>VHL 8 (32.0%); P = 0.02</td>
<td>P = 0.15</td>
<td>P = 0.34</td>
<td>P = 0.03</td>
<td>P = 0.08</td>
<td>P = 0.33</td>
<td>P = 0.004</td>
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<td>Germline mutation</td>
<td>25 (69.5%)</td>
<td>RET 1 (4.0%); P = 0.004</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
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<tr>
<td>Ageb (95% CI)</td>
<td>13.8 (12.8–14.8)</td>
<td>SDHB 11 (44.0%); P = 0.07</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>11 (30.5%)</td>
<td>SDHD 4 (16.0%); P = 0.40</td>
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<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Non-pediatric probands</td>
<td></td>
<td>MAX 1 (4.0%); P = 0.55</td>
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<td>0</td>
<td>0</td>
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<td>Germline mutation</td>
<td>148 (36.0%)</td>
<td>VHL 19 (12.8%)</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td></td>
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<tr>
<td>No mutation</td>
<td>263 (64.0%)</td>
<td>RET 47 (31.8%)</td>
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<td>0</td>
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<td>SDHD 39 (26.4%)</td>
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<td>10</td>
<td>4</td>
<td>1</td>
<td></td>
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<td>SDHAF2 3 (2.0%)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>TMEM127 3 (2.0%)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Ageb (95% CI)</td>
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<td>153</td>
<td>13</td>
<td>38</td>
<td>51</td>
<td>2</td>
<td>6</td>
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</table>

PCC, pheochromocytoma; PGL, paraganglioma; H&N, head and neck; bPCC, bilateral PCC; TA, thoraco-abdominal.

aAll cases were analyzed for germline mutations in VHL, RET, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, and MAX. Significant P values (calculated between pediatric and non-pediatric probands) are denoted in bold.
bMean age at diagnosis.
<table>
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<th>ID</th>
<th>Age at onset</th>
<th>Sex</th>
<th>Tumor (n)</th>
<th>Cause of admission</th>
<th>Secretion</th>
<th>Malignant (age/location)</th>
<th>Other tumors (age)</th>
<th>Gene</th>
<th>Variant</th>
<th>Protein</th>
<th>Familial antecedents at test</th>
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<td>15</td>
<td>15, 17</td>
<td>F</td>
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<td>bPCC, TA PGL</td>
<td>HTN, sDM</td>
<td>NE</td>
<td>No</td>
<td>No</td>
<td>VHL</td>
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<td>p.(Pro95Arg)</td>
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<tr>
<td>23</td>
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<td>PCC</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>VHL</td>
<td>c.482G &gt; A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>p.(Arg161Gln)</td>
</tr>
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<td>9</td>
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<td>Fe, He, Di</td>
<td>NE</td>
<td>Yes (17 years/2)</td>
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<td>No</td>
<td>VHL</td>
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</tr>
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<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>VHL</td>
<td>c.499C &gt; T&lt;sup&gt;b&lt;/sup&gt;</td>
<td>p.(Arg167Gln)</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>VHL</td>
<td>c.499C &gt; T&lt;sup&gt;b&lt;/sup&gt;</td>
<td>p.(Arg167Gln)</td>
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<tr>
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<td>PCC</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>VHL</td>
<td>c.500G &gt; A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>p.(Arg167Gln)</td>
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<td>–</td>
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<td>No</td>
<td>VHL</td>
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<td>M</td>
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<td>HTN, LS</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<td>c.302T &gt; G&lt;sup&gt;b&lt;/sup&gt;</td>
<td>p.(Leu101Pro)</td>
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<td>–</td>
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<td>No</td>
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<td>c.334-337delACT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>p.(Asp113Metfs&lt;sup&gt;b&lt;/sup&gt;21)</td>
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<td>–</td>
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<td>No</td>
<td>No</td>
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<td>c.1-10413-73-3866del</td>
<td>p.(Trp437)&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>He, Pa</td>
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<td>No</td>
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<tr>
<td>21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17, 21, 24, 29, 30, 33</td>
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<td>–</td>
<td>Yes (24 years/bone, lung, ovary)</td>
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<td>No</td>
<td>No</td>
<td>SDHD</td>
<td>c.166-170delICTCA&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>11</td>
<td>M</td>
<td>bPCC</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>F</td>
<td>TA PGL</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>25</td>
<td>14</td>
<td>M</td>
<td>PCC</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SDHB</td>
<td>c.49A &gt; G&lt;sup&gt;f&lt;/sup&gt;</td>
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</tr>
<tr>
<td>27</td>
<td>18</td>
<td>F</td>
<td>PCC, TA PGLs (5)</td>
<td>Pe, He, Pa, HP, LP</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>28</td>
<td>16</td>
<td>M</td>
<td>bPCC</td>
<td>Pe, HTN, He</td>
<td>E</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>No</td>
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development as patients with mutations in these genes have a higher mean age at presentation (Welander et al. 2011). Furthermore, these genes explain ~2% of all PCC/PGL cases in our series, independently of the age of onset, so only by increasing the number of pediatric cases analyzed, we should be able to confirm the absence of association of these four genes with young-age PCC/PGL development. On the other hand, the occurrence of one MAX case among pediatric probands is in agreement with its recently reported role as a PCC/PGL susceptibility gene (Burnichon et al. 2012). This finding becomes more relevant when considering that the prevalence of MAX mutations (1.1% in our whole series) is quite similar to that reported for the latest identified PCC/PGL susceptibility genes (Welander et al. 2011). Therefore, it seems justified to include MAX in the genetic screening algorithms of pediatric cases with PCC.

Further discussion of other genotype–phenotype associations is included in the Supplementary Material. Finally, the only proband with family history, and without any known germline mutation, had second-degree familial antecedents (i.e. an affected grandfather). Generation-skipping also occurred in the two familial non-pediatric probands from our series without germline mutations (data not shown), which suggests the involvement of low-penetrance variants or an imprinted gene.

In summary, genetic screening for mutations in the SDHB, SDHD, VHL, RET, and MAX genes is strongly recommended in pediatric PCC/PGL patients, starting with the metastasis-prone gene SDHB. Still unidentified PCC/PGL susceptibility genes will probably clarify the early tumor development of mutation-negative pediatric cases in the near future.

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