

Long-term prognosis of patients with pediatric pheochromocytoma

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Abstract

A third of patients with paraganglial tumors, pheochromocytoma, and paraganglioma, carry germline mutations in one of the susceptibility genes, *RET*, *VHL*, *NF1*, *SDHAF2*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, and *MAX*. Despite increasing importance, data for long-term prognosis are scarce in pediatric presentations. The European-American-Pheochromocytoma-Paraganglioma-Registry, with a total of 2001 patients with confirmed paraganglial tumors, was the platform for this study. Molecular genetic and phenotypic classification and assessment of gene-specific long-term outcome with second and/or malignant paraganglial tumors and life expectancy were performed in patients diagnosed at < 18 years. Of 177 eligible registrants, 80% had mutations, 49% *VHL*, 15% *SDHB*, 10% *SDHD*, 4% *NF1*, and one patient each in *RET*, *SDHA*, and *SDHC*. A second primary paraganglial tumor developed in

Key Words

- ▶ pheochromocytoma
- ▶ long-term follow-up
- ▶ relapse
- ▶ germline mutations

38% with increasing frequency over time, reaching 50% at 30 years after initial diagnosis. Their prevalence was associated with hereditary disease ($P=0.001$), particularly in *VHL* and *SDHD* mutation carriers (*VHL* vs others, $P=0.001$ and *SDHD* vs others, $P=0.042$). A total of 16 (9%) patients with hereditary disease had malignant tumors, ten at initial diagnosis and another six during follow-up. The highest prevalence was associated with *SDHB* (*SDHB* vs others, $P<0.001$). Eight patients died (5%), all of whom had germline mutations. Mean life expectancy was 62 years with hereditary disease. Hereditary disease and the underlying germline mutation define the long-term prognosis of pediatric patients in terms of prevalence and time of second primaries, malignant transformation, and survival. Based on these data, gene-adjusted, specific surveillance guidelines can help effective preventive medicine.

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Introduction

Pheochromocytomas and paragangliomas are tumors of the overall paraganglial system, mainly the adrenal glands, the retroperitoneum, the pelvis, the thorax, and the skullbase and neck regions (Neumann 2008). Such paraganglial tumors occur at any age, from early childhood until late in life with mean age at diagnosis ~40 years. Their clinical presentation is historically characterized by the 'rule of tens': 10% of pheochromocytomas are bilateral, 10% extraadrenal, and 10% malignant. Paraganglial tumors confer high morbidity and mortality. Their diagnosis provides a correctable cause of hypertension and can prevent life-threatening complications such as heart failure and arrhythmias. Over one-third of all patients with paraganglial tumors carry germline mutations in one of the ten susceptibility genes: *VHL*, *RET*, *NF1*, *SDHAF2*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *MAX*, and *TMEM127* (Neumann et al. 2002, 2004, Mannelli et al. 2007, 2009, Bayley et al. 2010, Burnichon et al. 2010, Qin et al. 2010, Comino-Mendez et al. 2011). Mutations in these genes cause pheochromocytoma-associated cancer syndromes such as von Hippel-Lindau disease (VHL), multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), the paraganglioma syndrome types 1–4 (PGL1–4), and the familial pheochromocytoma syndromes. Patients with hereditary pheochromocytoma have a lifelong risk of second paraganglial tumors and relapse and frequently have life-threatening, syndrome-specific, extraparaganglial tumors, such as hemangioblastomas of the retina and CNS in VHL, medullary thyroid carcinoma in MEN2, and renal cell carcinoma in VHL, PGL1, PGL3, and PGL4 (Asari et al. 2006, Khorram-Manesh et al. 2006, Timmers et al. 2008, Grubbs et al. 2013). Early onset of disease, bilateral,

multifocal, extraadrenal, and malignant tumors are the clinical hallmarks of hereditary disease (Neumann et al. 2002). Over the last decade, numerous studies have discovered the molecular basis and clinical characteristics of pheochromocytoma and paraganglioma. The insights into their etiopathogenesis and phenotypic characteristics help to reduce their morbidity and mortality by the possibility of a more efficient and gene-specific tailored preventive medical management. However, the subgroup of pediatric pheochromocytoma is poorly studied, despite their important clinical consequences. Approximately 20% of pheochromocytomas and paragangliomas are diagnosed in children, predominantly males (Stackpole et al. 1963, Kaufman et al. 1983, Ciftci et al. 2001, Barontini et al. 2006). Children usually suffer from symptomatic and potentially life-threatening occurrence with bilateral and extraadrenal tumors (Stackpole et al. 1963, Ein et al. 1990, Ciftci et al. 2001, Barontini et al. 2006). Prevalence of hereditary and malignant tumors is controversial, but of utmost importance for quality-of-life considerations and survivorship (Ross 2000, Barontini et al. 2006, De Krijger et al. 2006, Pham et al. 2006, King et al. 2011). So far, no data from large population-based registries or long-term surveillance are available. Reports focused on pediatric patients are mostly based on few cases (Stackpole et al. 1963, Kaufman et al. 1983, Ein et al. 1990, Ross 2000, Ciftci et al. 2001, Barontini et al. 2006, De Krijger et al. 2006, Pham et al. 2006, King et al. 2011). Therefore, we sought to systematically perform molecular and clinical characterization of pediatric pheochromocytoma and paraganglioma to determine the long-term prognosis and outcomes in an international population-based registry.

Patients and methods

Patients

The platform of this study was the European-American-Pheochromocytoma-Paraganglioma-Registry based in Freiburg/Germany with a total of 2001 patients histologically confirmed with symptomatic paraganglial tumors. Inclusion criteria were age at initial diagnosis younger than 18 years and EDTA-anticoagulated blood available for genetic testing. In cases of several tumors, the youngest age at diagnosis was used. Patients who initially presented with syndrome-associated features and/or a known family history were also included. We excluded relatives in whom paraganglial tumors were diagnosed by family screening at an asymptomatic stage. All patients provided written informed consent.

Molecular genetic analysis

EDTA-anticoagulated blood leucocyte genomic DNA was analyzed for mutations in *RET* (MEN2), *VHL*, *NF1*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD* (PGL1–4), and the new genes *TMEM127*, *MAX*, and *SDHA* (familial pheochromocytoma syndromes). In addition, an investigation of large deletions was carried out in *VHL*, *NF1*, *SDHB*, *SDHC*, and *SDHD*. Mutation scanning was performed by denaturing HPLC using the WAVE analysis system and by bidirectional Sanger sequencing. Large deletions and duplications were sought by quantitative real-time PCR with SYBR Green I detection and by multiplex ligation probe amplification (MLPA) assays. Genomic DNA samples from 100 anonymous, healthy blood donors were analyzed as matching controls.

Clinical studies

All registrants provided demographic and clinical information including gender, age at diagnosis, symptoms, biochemical, and imaging data as well as family health histories. Paraganglial tumors were classified according to tumor number (solitary or multiple), location (adrenal, extraadrenal abdominal, thoracic, head, and neck), and biology (benign or malignant) (Table 1). Criteria for malignancy were presence of metastases in lymph nodes or distant tissues (Tischler 2008). Patients who were identified as having one of the hereditary syndromes underwent clinical reevaluation. The clinical screening program comprised for MEN2 serum calcitonin and parathormone, for VHL magnetic resonance imaging (MRI) of the CNS, MRI of the abdomen and retinoscopy,

and for the paraganglioma syndromes (PGL1–4) MRI of the abdomen, thorax, and neck.

All patients were provided a follow-up clinical investigation. These included surveillance to detect new tumors, e.g. second paraganglial tumors, extraparaganglial tumors, and malignant transformation. Second tumors were classified as ipsilateral tumors, tumors of the contralateral adrenal gland, and of extraadrenal origin. The frequency of second tumors and gene-specific differences was evaluated. Finally, age and causes of death were documented.

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies and compared by two-sided χ^2 test. Scale variables were expressed as median and range and compared by two-sided Mann–Whitney *U* test. Censored data were analyzed and plotted by Kaplan–Meier method and compared by two-sided log-rank test. The 95% CI for proportions was calculated according to the modified method of Wilson by Newcombe (Wilson 1927, Newcombe 1998). Significance level was set to $P=0.05$ for statistical testing. All statistical calculations were carried out with IBM SPSS, version 17 (SPSS, Inc.).

Results

As of July 1, 2013, the European-American-Pheochromocytoma-Paraganglioma-Registry comprised 2001 registrants with symptomatic paraganglial tumors. Of these 2001 registrants, 177 (9%) were diagnosed <18 years. There were 164 unrelated index cases and 13 first- or second-degree relatives of the index cases. Age distribution at initial diagnosis was 4–17 years, with mean 13 years (95% CI 12–13), with 116 males and 61 females (Table 1). Among the 164 index patients, 105 patients (64%) presented with apparently sporadic disease, whereas 51 patients (31%) had a positive family history for paraganglial tumors. Six patients presented with neurofibromas and thus met diagnostic criteria for NF1. Ten patients were identified as having the prototypic lesions of VHL-disease, retinal hemangioblastoma, and/or hemangioblastoma of the CNS.

The 164 (94%) index patients were symptomatic and had hypertension, palpitations, headache, or profuse sweating. The diagnosis was clinically confirmed by elevated catecholamines or metanephrines and by radiological imaging. Elevated values of 24 h-urinary catecholamines, metanephrines, and of plasma metanephrines

Table 1 Gene-specific clinical characteristics of the 177 registry-based pediatric pheochromocytoma patients at initial presentation

| | Sporadic (n = 33) | Hereditary (n = 144) | VHL (n = 93) | MEN2^a (n = 1) | NF1^b (n = 6) | PGL1 (n = 17) | PGL3^a (n = 1) | PGL4 (n = 25) | Familial pheochromocytoma syndrome^a (n = 1) | P value |
|--------------------------|-----------------------------|--------------------------------|---------------------|------------------------------------|--------------------------------|-------------------------|------------------------------------|-------------------------|--|--------------------------------------|
| Total (n = 177) | 19% | 81% | 53% | 1% | 3% | 10% | 1% | 14% | 1% | |
| Gene | | | | | | | | | | |
| Gender (m:f) | 116:61 | 90:54 | VHL 64:29 | RET 1 (f) | NF1 3:3 | SDHD 8:9 | SDHC 1 (m) | SDHB 13:12 | SDHA 1 (m) | – |
| Age at diagnosis (years) | 13 (12–13) | 13 (12–13) | 12 (12–13) | 17 | 16 (15–16) | 14 (12–15) | 12 | 14 (13–16) | 15 | P = 0.788 |
| Mean (95% CI) | 4–17 | 4–17 | 4–17 | 17 | 14–17 | 5–17 | 12 | 8–17 | 15 | P = 0.001, P = 0.026* |
| Range | 4–17 | 4–17 | 4–17 | 17 | 14–17 | 5–17 | 12 | 8–17 | 15 | |
| Pheochromocytoma | 95% (168/177) | 95% (137/144) | 100% (93/93) | 100% (1/1) | 100% (6/6) | 71% (12/17) | 0 | 96% (24/25) | 100% (1/1) | |
| Bilateral | 24% (43/177) | 28% (40/144) | 39% (36/93) | 100% (1/1) | 0 | 18% (3/17) | 0 | 0 | 0 | P = 0.000 [†] |
| Extraadrenal | 30% (53/177) | 32% (46/144) | 20% (19/93) | 0 | 17% (1/6) | 53% (9/17) | 0 | 68% (17/25) | 0 | P < 0.001, P = 0.029 [†] |
| Thoracic | 5% (9/177) | 6% (9/144) | 3% (3/93) | 0 | 0 | 24% (4/17) | 0 | 8% (2/25) | 0 | P < 0.001 [§] |
| HNP | 5% (8/177) | 4% (6/144) | 0 | 0 | 0 | 24% (4/17) | 100% (1/1) | 4% (1/25) | 0 | P < 0.001 |
| HNP/pheochromocytoma | 1% (1/177) | 1% (1/144) | 0 | 0 | 0 | 6% (1/17) | 0 | 0 | 0 | |
| Malignant | 6% (10/175) | 6% (9/141) | 3% (3/92) | 0 | 33% (2/6) | 0 | 0 | 17% (4/23) | 0 | P = 0.005 [†] |

*P = 0.788 refers to the age at diagnosis of sporadic patients vs hereditary patients. P = 0.001 refers to the significant age difference of pediatric VHL mutation carriers vs SDHB mutation carriers and P = 0.026 to the age difference of VHL mutation carriers vs NF1 patients. P < 0.001 refers to the high prevalence of bilateral pheochromocytoma in VHL patients vs others (sporadic, SDHB and SDHD patients). †P < 0.001 refers to the high prevalence of extraadrenal pheochromocytoma in SDHB patients vs others (sporadic, VHL) and P = 0.029 refers to the high prevalence of extraadrenal pheochromocytoma in SDHD patients vs others (sporadic, VHL). ‡P < 0.001 refers to the high prevalence of thoracic pheochromocytoma in SDHD patients vs others (sporadic, VHL and SDHB). ||P < 0.001 refers to the high prevalence of head and neck paraganglioma (HNPs) in SDHD patients vs others (sporadic, VHL and SDHB). ††P = 0.005 refers to the high prevalence of malignant pheochromocytoma in SDHB vs others (sporadic, VHL and SDHD).

‡‡The total number of NF1 patients and other mutation carriers (SDHA, SDHC, and RET) was so small that in most statistical questions a reasonable calculation was impossible.

were recorded in 101 (89%) patients. Head and neck paragangliomas (HNPs) were identified in 8 (5%) patients. There were 43 (24%) patients with bilateral adrenal tumors and 53 (30%) with extraadrenal tumors. Ten (6%) patients had malignant paraganglial tumors (Table 1).

Molecular genetic characterization

Of the 164 index patients, 131 (80%) had a germline mutation in one of the susceptibility genes, of which 80 (49%) were *VHL*, 25 (15%) *SDHB*, 17 (10%) *SDHD*, and 6 (4%) *NF1*. Mutations of *RET* and of the new susceptibility genes, *SDHC* and *SDHA*, were observed in one patient each. Mutations of *SDHAF2*, *MAX*, and *TMEM127* were not present in this cohort. Of 131 different mutations, 123 were found within the exons, namely missense mutations, stop codon mutations, small deletions or insertions. Eight mutations (6%) were large deletions encompassing 1–3 exons. All eight deletions affected the *SDH*-genes, *SDHB*, *SDHC*, and *SDHD*.

Patients with sporadic ($n=33$) and hereditary ($n=144$) paraganglial tumors did not differ in their mean age at initial diagnosis of 13 years of age ($P=0.8$). But hereditary paraganglial tumors caused by *VHL* mutations occurred earlier in childhood than those caused by *SDHB* and *NF1* ($P=0.001$ and $P=0.026$) and with a trend compared with *SDHD* ($P=0.07$) (Table 1). Bilateral adrenal tumors occurred significantly more frequent in *VHL* mutation carriers than in *SDHB* or *SDHD* mutations carriers or patients with sporadic disease ($P<0.001$). Extraadrenal tumors were significantly more often associated with *SDHB* and *SDHD* mutations (*SDHB* vs others, $P<0.001$ and *SDHD* vs others, $P=0.029$). Thoracic paraganglial tumors ($n=9$) were mostly associated with *SDHD* mutations (*SDHD* vs others, $P<0.001$). At initial diagnosis, 10 (6%) registrants had malignant paraganglial tumors and most of them had *SDHB* (*SDHB* vs others, $P=0.005$). HNPs were mostly hereditary and caused by *SDHD* mutations (*SDHD* vs others, $P<0.001$; Table 1).

Long-term surveillance

Follow-up data were available for 5 years in 78% and for 10 years in 48% of the registrants (Fig. 1). Of the 177 registrants, 68 (38%) developed second paraganglial tumors after a mean interval of 25 years. Incidence of second tumors increased with time from 25% at 9 years to 50% at 31 years (Fig. 2A). Seventeen (16%) patients had an ipsilateral tumor. Twenty-one (13%) had a second contralateral adrenal tumor and 28 (18%) second extraadrenal paraganglial tumor. Fifteen of the 17 patients with

ipsilateral tumors developed another contralateral or extraadrenal tumor. Contralateral and extraadrenal tumors occurred more often than ipsilateral ones (95% CI 31–46 vs 13–28%). However, the period of latency did not differ in the three groups.

Second paraganglial tumors were significantly more common in hereditary than in sporadic disease ($P=0.001$). Ipsilateral tumors and third paraganglial tumors were exclusively associated with hereditary disease without gene-specific differences in frequency. Notably, second contralateral adrenal and extraadrenal tumors were more often associated with *VHL* and *SDHD* mutations (*VHL* vs others, $P=0.001$ and *SDHD* vs others, $P=0.042$; Table 2). Second tumors occurred 10 years earlier in hereditary than in sporadic disease (period of latency 23 vs 33 years respectively, $P=0.031$). The time to second tumors showed gene-specific differences with the shortest latency in *SDHD* and *VHL* with 18 and 21 years (*SDHD* vs sporadic, $P=0.01$ and *VHL* vs sporadic, $P=0.01$; Fig. 2B).

HNPs as a second tumor were observed in 7 (4%) patients. There was no difference in the period of latency among ipsilateral, contralateral, and extraadrenal paraganglial tumors compared with HNPs. HNPs were mostly caused by *SDHD* mutations at initial diagnosis (*SDHD* vs others, $P<0.001$) and during follow-up (*SDHD* vs others, $P=0.002$) (Table 2).

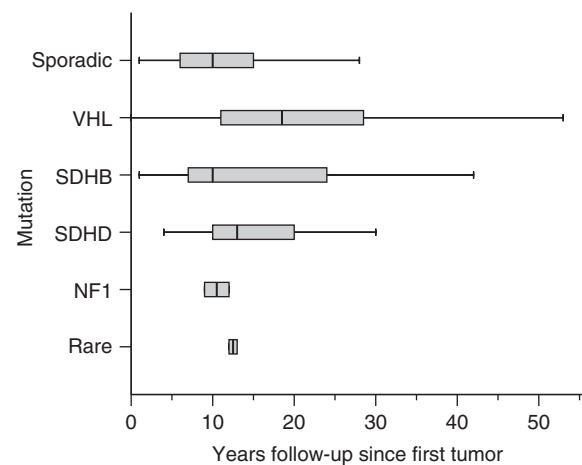


Figure 1

Overview of the gene-specific follow-up in years considering the period of time from initial diagnosis up to July 1, 2013. The black vertical line indicates the mean follow-up, the box includes time range of 50% of all cases and the whiskers present the 95% CI. Patients harboring a *SDHA*-, *SDHC*- and *RET*-mutation are summarized as rare/other mutation carriers. They were only observed in single cases. The mean follow-up interval was 16 years. The mean, gene-specific follow-up was 10 years (range 1–45) for sporadic patients, 19 years (range 0–53) for *VHL*, 10 years (range 1–42) for *SDHB*, 13 years (range 4–46) for *SDHD*, 11 years (range 2–12) for *NF1*, and 13 years (range 12–13) for other/rare mutation carriers.

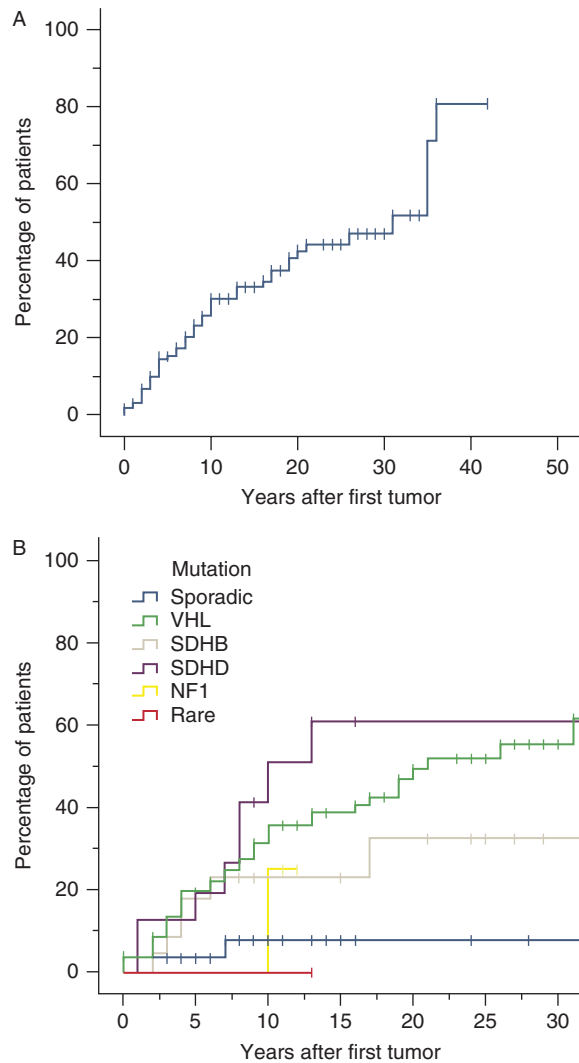


Figure 2

(A) Time-related prevalence of second paraganglial tumors. A total of 68 patients experienced a second paraganglial tumor. Ipsilateral tumors were observed in 17 (16%) patients. Contralateral pheochromocytomas were observed in 21 (13%) and extraadrenal pheochromocytomas were observed in 28 (18%) patients. The percentage increased by time reaching 25% 9 years and 50% 31 years after initial diagnosis. (B) Time-related, gene-specific prevalence of second paraganglial tumors. Four (12%) sporadic, 46 (50%) *VHL*, 6 (24%) *SDHB*, 10 (59%) *SDHD*, 1 (17%) *NF1*, and 1 (33%) *RET* patient experienced a second paraganglial tumor. Mean period of time after initial diagnosis was 33 years in sporadic and 23 years in hereditary patients. Mean period of time after initial diagnosis was 21 years in *VHL*, 30 years in *SDHB*, 18 years in *SDHD*, and 12 years in *NF1*. Patients with hereditary disease experienced significantly earlier second paraganglial tumors than sporadic patients. As for the different genes no significant time differences were identified only a trend for *SDHD* was calculated.

A third paraganglial tumor had 13 patients (7%). Time interval from detection of the second to the third tumor was 1–20, mean 5 years. All these patients had a germline mutation.

Malignant paraganglial tumors were initially present in 10 (6%) patients. During follow-up six additional patients (4%) were identified with metastases. Of these six patients, four showed metastases up to 7 years after the initial/last operation. Mutations were present in the genes *VHL*, *RET*, *NF1*, *SDHB* and *SDHD*. *SDHB* mutation-positive individuals had the highest prevalence of malignancy (*SDHB* vs others, $P < 0.001$; Table 2). Additional risk factors for malignant disease were extraadrenal and thoracic paraganglial tumors (extraadrenal: $P = 0.027$, OR 3.6 and thoracic: $P = 0.002$, OR 10.27).

Extraparaganglial tumors were only seen in mutation carriers, mostly of *VHL*. Forty percent of the *VHL* patients had retinal angiomas, 31% hemangioblastomas of the CNS, 4% renal cell carcinomas, and 12% pancreatic neuroendocrine tumors. One *SDHB* mutation carrier presented with renal cell carcinoma and one with papillary thyroid carcinoma. One *RET* mutation carrier developed a medullary thyroid carcinoma.

Eight of the 177 patients died. All had hereditary diseases, three *VHL*, three PGL4 syndrome (*SDHB*), one *NF1*, and one *SDHA*-associated disease. The causes of death were cardiac failure in one and metastases in seven patients.

Life expectancy in hereditary disease was 62 years (mean), but remarkably reduced in patients with *SDHB* and *NF1* mutations (*SDHB* vs others, $P = 0.009$; *SDHB* vs *VHL*, $P = 0.012$; and *NF1* vs *VHL*, $P = 0.008$) (Fig. 3 and Table 2).

Discussion

The multidisciplinary interrogation of hereditary neoplasia syndromes has enriched our insights into the pathogenesis of both heritable and sporadic carcinogenesis and gene-enabled clinical management. In cancer syndromes, these insights are essential for the development of targeted therapies and for the establishment of gene-specific surveillance guidelines, the cornerstone for increasing life expectancy and improving quality of life. Data are plentiful from the adult-onset side, but rare from systematic study of gene-specific clinical outcomes of pediatric neuroendocrine presentations. Paradoxically, very little is known about pediatric-onset pheochromocytoma and paraganglioma, given that the load of genetic disease in childhood-onset neoplasias should be high. This study presents molecular classification of pediatric-onset pheochromocytoma and paraganglioma with mutational and phenotypic spectra and especially, gene-associated long-term clinical outcome.

In contrast to a 30% mutation frequency in adults, we have shown that 80% of 177 pediatric presentations have

Table 2 Gene-specific clinical characteristics of 177 registry-based pediatric pheochromocytoma patients during adolescence

| | Hereditary (n = 144) | | | | | P value |
|-----------------------------|-----------------------------|------------------------|-----------------------------------|-------------------------|-------------------------|----------------------|
| | Sporadic (n = 33) 19% | VHL (n = 93) 53% | NF1 ^a (n = 6) 3% | PGL1 (n = 17) 10% | PGL4 (n = 25) 14% | |
| Mean follow-up (years) | 16 | 14 | 11 | 13 | 10 | 13 |
| Range | – | – | 2–12 | 4–46 | 1–42 | 12–13 |
| 2nd paraganglial tumors | 38% (68/177) | 44% (64/144) | 17% (1/6) | 59% (10/17) | 24% (6/18) | 33% (1/3) |
| Ipsilateral | 16% (17/110) | 17% (17/98) | 0% (0/5) | 17% (2/12) | 11% (2/18) | 0 (0/2) |
| Extraadrenal | 18% (28/156) | 22% (27/125) | 17% (1/6) | 42% (5/12) | 24% (6/18) | 0 |
| Contralateral adrenal | 13% (21/157) | 16% (20/126) | 0 | 0 | 0 | 33% (1/3) |
| 3rd tumor | 13% (22/165) | 16% (22/135) | 0 | 25% (4/16) | 12% (3/25) | 0 |
| HNP | 4% (7/177) | 5% (7/144) | 0 | 24% (4/17) | 8% (2/25) | 0 |
| Extraparaganglial tumors | 43% (60/139) | 50% (60/119) | 100% (6/6) | 20% (3/15) | 10% (2/21) | 33% (1/3) |
| Malignant follow-up | 4% (6/167) | 4% (6/135) | 0 | 12% (2/17) | 11% (2/19) | 33% (1/3) |
| Total | 9% (16/175) | 12% (16/142) | 33% (2/6) | 12% (2/17) | 26% (6/23) | 33% (1/3) |
| Death | 5% (8/177) | 6% (8/144) | 17% (1/6) | 0 | 12% (3/25) | 33% (1/3) |
| Mean life expectancy | 62 | 62 | 27 | No deaths | 47 | Insufficient data |

* $P=0.001$ refers to the prevalence of second paraganglial tumors in sporadic patients vs hereditary patients. $P=0.01$ refers to the significant prevalence of second paraganglial tumors in VHL patients vs others (sporadic, SDHB and SDHD patients). $P=0.042$ refers to the significantly high prevalence of second extraadrenal tumors in SDHD patients vs others (sporadic, SDHB and VHL patients). $P<0.001$ refers to the significantly high prevalence of second contralateral tumors in VHL patients vs others (sporadic, SDHB and SDHD patients). $P=0.002$ refers to head and neck paraganglioma (HNPs) in SDHD patients vs others (sporadic, VHL and SDHB patients). $P<0.001$ refers to the high prevalence of extraparaganglial tumors in VHL disease vs others (sporadic, SDHB and SDHD patients). $P<0.001$ and $P<0.001$ refers to the high prevalence of malignant pheochromocytoma in SDHB patients during the follow-up and overall vs others (sporadic, VHL and SDHD). $P=0.009$ refers to the shorter life expectancy observed in SDHB vs others. $P=0.012$ refers to the shorter life expectancy in SDHB vs VHL and $P=0.008$ refers to the shorter life expectancy in NF1 vs VHL.

^aThe total number of NF1 patients and other mutations carriers was so small that in most statistical questions a reasonable calculation was impossible.

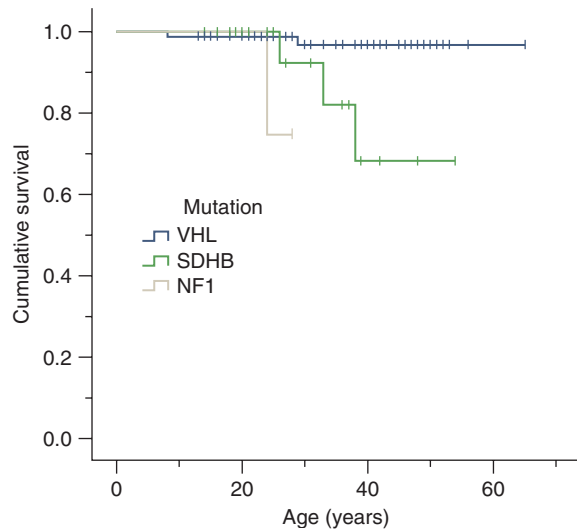


Figure 3

Gene-specific survival. Survival in years of *VHL*-, *SDHB*-, and *NF1*-affected patients. A total of 8 (5%) patients died. All patients were affected by hereditary disease, 3 (3%) *VHL* carriers, 3 (12%) *SDHB* carriers, 1 (17%) *NF1* carrier, and one *SDHA* carrier. No pediatric patient with sporadic and *SDHD*-associated pheochromocytoma died during the follow-up period. Mean life expectancy in hereditary disease was 62 years. Life expectancy in *VHL* was 64 years, whereas patients carrying *SDHB* had a shorter mean life expectancy of only 47 years.

germline mutations in one of several susceptibility genes. This population-based frequency was even higher than expected compared with published data from smaller pediatric series of 22–70% (Ciftci *et al.* 2001, Neumann *et al.* 2002, Barontini *et al.* 2006, De Krijger *et al.* 2006, Cascon *et al.* 2013). The affected genes are dominated by *VHL* followed by *SDHB*, *SDHD*, and *NF1*. Predominance of *VHL* mutations was identified by us previously and confirmed by others (Neumann *et al.* 2002, Barontini *et al.* 2006, Bausch *et al.* 2006a). The phenotypic presentation is characterized by multiple, mostly bilateral adrenal and extraadrenal tumors (Ciftci *et al.* 2001, Barontini *et al.* 2006).

The paramount implication of the high prevalence of germline mutations is the question of adequate follow-up. General agreement exists that there is a lifelong risk for the development of new tumors. Specific data are however scarce. This includes questions regarding gene-specific differences associated with potential transformation to malignant behavior of the disease (Ein *et al.* 1990, Ciftci *et al.* 2001, Beltsevich *et al.* 2004, Asari *et al.* 2006, Barontini *et al.* 2006, Khorram-Manesh *et al.* 2006, Timmers *et al.* 2008, King *et al.* 2011, Grubbs *et al.* 2013).

Our data emphasizes the need for meticulous short- and long-term follow-up. Tumor recurrences occur early,

within the first year, but they can occur 30 years after primary surgery (Fig. 2A). Ten percent develop malignant paraganglial tumors with 40% presenting after years. This underscores the importance of long-term surveillance and vigilance especially in patients with *VHL*, *SDHB*, or *SDHD* mutations.

Catecholamine storms with consequent heart failure or stroke and metastases are the major factors for reduced life expectancy in paraganglial tumors, at least in adult series. Here we see that this is rare, but we found that life expectancy is mainly influenced by malignant behavior of the disease (Fig. 3). Patients, with *SDHB* mutations, predominantly die because of metastatic disease (King *et al.* 2011). It is noteworthy that life expectancy is greatly reduced in 70% of the patients with an *SDHB* mutation. Thus, pediatric presentations with *SDHB* mutations must be aggressively followed. In time, targeted preventative or adjuvant therapies may be available for such patients relatively early.

Our results suggest general and gene-specific recommendations for adequate care of patients with paraganglial tumors diagnosed under the age of 18 years. First, all such patients need analysis for germline mutations in the susceptibility genes for such tumors, especially *VHL*, *SDHD*, and *SDHB*. *NF1* can be diagnosed clinically, but careful skin investigation is important (Bausch *et al.* 2006b). Second, all ‘high-risk’ patients should be offered surveillance, in particular mutation carriers. Third, annual surveillance is recommended for the first 3 years after initial diagnosis, because this is the period when malignant behavior becomes mostly evident, if not diagnosed initially already. Fourth, as recurrent tumors are mostly seen in carriers of *VHL* and *SDHD* mutations, such patients need close and on-going high-risk surveillance, which should be done every 3 years after yearly checks in the years 1–3 after operation because of lower but continuous risk of malignancy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors were involved in the planning of the study, have contributed data to the manuscript, and have made corrections to the manuscript. The manuscript was written by Drs B Bausch, C Eng, and H P H Neumann.

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