Distinct Clinical Features of Paraganglioma Syndromes Associated With *SDHB* and *SDHD* Gene Mutations

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Context Germline mutations of the genes encoding succinate dehydrogenase subunits B (*SDHB*) and D (*SDHD*) predispose to paraganglioma syndromes type 4 (PGL-4) and type 1 (PGL-1), respectively. In both syndromes, pheochromocytomas as well as head and neck paragangliomas occur; however, details for individual risks and other clinical characteristics are unknown.

Objective To determine the differences in clinical features in carriers of *SDHB* mutations and *SDHD* mutations.

Design, Setting, and Patients Population-based genetic screening for *SDHB* and *SDHD* germline mutations in 417 unrelated patients with adrenal or extra-adrenal abdominal or thoracic pheochromocytomas (n=334) or head and neck paragangliomas (n=83), but without syndromic features, from 2 registries based in Germany and central Poland, conducted from April 1, 2000, until May 15, 2004.

Main Outcome Measures Demographic and clinical findings with respect to gene mutation in *SDHB* vs *SDHD* compared with nonmutation carriers.

Results A total of 49 (12%) of 417 registrants carried *SDHB* or *SDHD* mutations. In addition, 28 *SDHB* and 23 *SDHD* mutation carriers were newly detected among relatives of these carriers. Comparison of 53 *SDHB* and 47 *SDHD* total mutation carriers showed similar ages at diagnosis but differences in penetrance and of tumor manifestations. Head and neck paragangliomas (10/32 vs 27/34, respectively, $P<.001$) and multifocal (9/32 vs 25/34, respectively, $P<.001$) tumors were more frequent in carriers of *SDHD* mutations. In contrast, *SDHB* mutation carriers have an increased frequency of malignant disease (11/32 vs 0/34, $P<.001$). Renal cell cancer was observed in 2 *SDHB* mutation carriers and papillary thyroid cancer in 1 *SDHB* mutation carrier and 1 *SDHD* mutation carrier.

Conclusions In contrast with *SDHD* mutation carriers (PGL-1) who have more frequent multifocal paragangliomas, *SDHB* mutation carriers (PGL-4) are more likely to develop malignant disease and possibly extraparaganglial neoplasias, including renal cell and thyroid carcinomas. Appropriate and timely clinical screening is recommended in all patients with PGL-1 and PGL-4.

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Pheochromocytoma and paraganglioma are tumors of the autonomic nervous system. Terminology in science and clinical practice is divergent. Herein, we use the term *pheochromocytoma* for location in the adrenal glands, extra-adrenal abdominal, and thoracic locations (eg, where nearly all tumors are endocrinologically active). In contrast, the term *paraganglioma* is only used for tumors in the head and neck area where most tumors are nonfunctioning. All these tumors have been described as sporadic and as hereditary entities.[1-3] Estimated yearly incidence of

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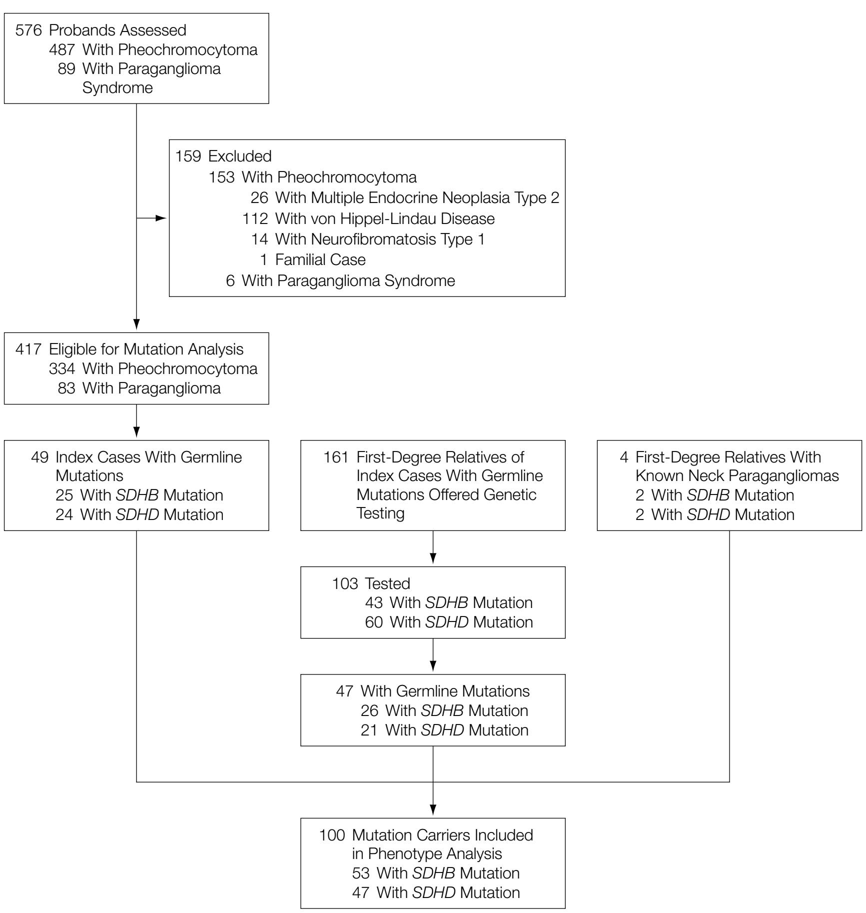
pheochromocytomas and paragangliomas is about 1 in 300 000.[4]

Classic syndromes associated with pheochromocytomas are multiple endocrine neoplasia type 2 due to mutations of the *RET* gene, von Hippel-Lindau disease (VHL), and neurofibromatosis type 1.[2,5,6] Recently, the paraganglioma syndromes (PGL) have attracted attention especially after identification of the succinate dehydrogenase subunit D (*SDHD*) gene as the susceptibility gene for PGL type 1 (PGL-1), and succinate dehydrogenase subunit B (*SDHB*) gene as the susceptibility gene for PGL type 4 (PGL-4).[7,8] A considerable number of cases with germline mutations in 1 of these 2 genes has been reported in both population-based and referral-based series of cases presenting with pheochromocytomas, and from hospital referral–based and selected series of cases presenting with head and neck paragangliomas.[7-14] In contrast, only 4 PGL type 3 (PGL-3) families have been identified with a germline mutation of the succinate dehydrogenase subunit C (*SDHC*) gene, whereas the susceptibility gene for PGL type 2 (PGL-2) remains unidentified.[15-18]

Our research on *SDHB* and *SDHD* gene mutations started with analyses of *SDHD* in 17 blood-tumor pairs, resulting in the first description of *SDHD* germline mutations in patients with pheochromocytoma.[3] Subsequently, we extended our work to blood DNA of all available patients with pheochromocytoma and characterized germline mutations of the *RET*, *VHL*, *SDHB*, and *SDHD* genes in nonsyndromic pheochromocytomas.[10] Although it is accepted that carriers of *SDHB* and *SDHD* mutations are at risk for tumors of the entire paraganglial system, systematic clinical investigations of mutation carriers have not been reported to date.

Our current endeavor was therefore to clinically characterize the diseases based on mutations of the *SDHB* and *SDHD* genes using a complex approach based on our updated Freiburg-Warsaw Pheochromocytoma Registry, which includes Germany and central Poland, and a newly founded German Head and Neck Paraganglioma Registry, which includes all of Germany. We examined a population-based series of registrants with pheochromocytomas and/or paragangliomas and their relatives for mutations in *SDHB* and *SDHD* and systematically clinically characterized all carriers found among index cases and their first-degree and second-degree relatives.

Figure 1. Flow of Study Population With Germline Mutations for Paraganglioma Syndrome



SDHB indicates succinate dehydrogenase subunit B; SDHD, succinate dehydrogenase subunit D.

METHODS

Patients

Our study used patients who were registered to 2 population-based registries (**Figure 1**). The updated Freiburg-Warsaw Pheochromocytoma Registry, as of May 15, 2004, comprised 487 patients with adrenal and abdominal or thoracic extra-adrenal pheochromocytomas. We systematically included patients who presented with symptomatic disease and histologically confirmed pheochromocytoma from Freiburg, Germany, and Warsaw, Poland, since 1985, from Essen, Germany, and Würzburg, Germany, since 1995, from Padova, Italy, since 1998, and German pediatric patients from 1979-1999, who came for diagnosis, treatment, or reevaluation, and who consented to participate in scientific research studies. All individuals presenting with symptomatic pheochromocytoma or paraganglioma in their respective geographic regions were registered. In addition, we included 27 patients from whom we received blood DNA throughout Germany and from clinicians abroad.

For this study, syndromic features and known family history were exclusion criteria. We excluded 153 patients with pheochromocytoma who had clinical, familial, and/or molecular genetic evidence for multiple endocrine neoplasia type 2, VHL disease, or neurofibromatosis type 1 based on extended personal history, pedigree evaluation, and genetic analyses of the *RET* and *VHL* genes. We also excluded patients with mutations of the *SDHC* gene because of the rarity of the condition. After exclusions, the study population consisted of 334 cases compared with the Freiburg-Warsaw pheochromocytoma registry[10] of 228 cases as of December 1, 2001, which included 191 unrelated German, 113 Polish, and 30 index cases from other countries.

In January 2000, we founded a new German registry that ascertained the population base by head and neck paraganglioma presentations. This registry comprised 77 unrelated patients, as of May 15, 2004, and an additional 6 paraganglioma index cases from other countries. For this registry, 100 otorhinolaryngology departments throughout Germany participated. Patients who developed head and neck paragangliomas as well as adrenal and extra-adrenal pheochromocytomas entered the registry after the first symptomatic tumor presentation.

In total, 417 unrelated patients were studied from April 1, 2000, until May 15, 2004, for germline mutations of the *SDHB* and *SDHD* genes. Mutation analysis for the 8 exons and flanking intronic regions of *SDHB* and the 4 exons and flanking intronic regions of *SDHD* was performed as previously described using a combination of single-strand confirmation polymorphism and direct sequencing.[3,8] Missense mutations were regarded as pathogenetically relevant if not found in 300 control patients, whereas truncating mutations are predicted to be deleterious because of structure-function consequences. The 300 blood DNA controls came from white healthy blood donors from blood banks in Freiburg, Germany, and Warsaw, Poland, and from Switzerland (ie, region-matched, race-matched normal controls), as well as a small minority from Columbus, Ohio.

The research protocols were approved by the ethical committees of the University of Freiburg, the Institute of Cardiology, Warsaw, Poland, and the Human Subjects' Protection Committee, The Ohio State University, Columbus. All participants gave oral or written informed consent.

Mutation Carriers

Identification of mutation carriers among eligible registrants was followed by genetic screening of the family members. Once a germline mutation was identified, we extended our work in 2 directions. First, the mutation carriers were reevaluated in depth. The clinical screening program included magnetic resonance imaging (MRI) of the neck and skull base, MRI or computed tomography (CT) of the thorax, and MRI or CT of the abdomen and 24-hour urine assays for norepinephrine, epinephrine, and vanillylmandelic acid. Second, we offered all first-degree relatives of mutation-positive index cases molecular genetic testing for the mutation identified in the index patient. When a germline mutation was detected in a relative of the index case, the same clinical screening procedure was used.

Statistical Analysis

We used demographic data, including age, sex, as well as number, location, and benign or malignant status of the tumor specimens. Criterion for malignancy was only presence of distant metastases. Clinical screening results enabled us to calculate penetrance for the development of tumors (the percentage of mutation carriers who had developed a tumor). Only index cases and relatives who underwent clinical screening, or previous MRI and CT results that were positive, have been included for penetrance calculations. For calculation of the registry-based prevalence of *SDHB* and *SDHD* gene mutations in patients with pheochromocytoma, paraganglioma, or both, we only included all cases from Germany and Poland but excluded those from other countries to avoid any bias. Differences in clinical parameters among *SDHB*-associated and *SDHD*-associated pheochromocytomas were compared by 2-tailed Fisher exact test. Penetrances of *SDHB*-related and *SDHD*-related tumors were estimated by cumulative incidence functions, by the method of Kaplan-Meier but substituting patients' age for survival time. For comparison of age distributions and age-related penetrances, Wilcoxon signed rank test and Cox-Mantel test were used, respectively. $P<.05$ was regarded as significant. To avoid spurious positive results due to multicomparison, Bonferroni adjustment was applied to *P* values for differences in tumor location and malignancy. The software Mathematica version 5 (Wolfram Research Inc, Champaign, Ill) was used for all statistical analyses.

RESULTS

In the combined pheochromocytoma (n=334) and paraganglioma (n=83) registries, 49 patients (12%) showed a mutation in the *SDHB* or *SDHD* gene. A total of 25 index cases had 18 different germline mutations of the *SDHB* gene (TABLE 1) and 24 index cases had 15 different germline mutations in the *SDHD* gene (TABLE 2). No patients had more than 1 germline mutation. The prevalence of mutations for both genes was approximately 10% overall (5% *SDHB* and 5% *SDHD*) (TABLE 3). *SDHB* and *SDHD* gene mutation frequencies were similar among all registries: *SDHD* mutation frequencies in the Freiburg and Warsaw Pheochromocytoma Registries and the German Head and Neck Paraganglioma Registry were 4% for each registry; *SDHB* mutation frequencies were 6%, 4%, and 5%, respectively. The prevalence data did not include 36 study patients from countries outside Germany and Poland (30 with pheochromocytomas and 6 with head and neck paragangliomas) of whom 10 were shown to be carriers of *SDHB* or *SDHD* mutations (Tables 1 and 2). In the *SDHB* gene, mutations occurred in exons 1 to 7 but not in exon 8, whereas in the *SDHD* gene, the mutations were distributed throughout all 4 exons but tended to cluster in exon 1. In both genes, missense, nonsense, frameshift, and splice site mutations were found. In addition, in the *SDHB* gene, a single codon insertion was noted. The spectra of mutations did not differ statistically between the 2 genes: 50% (9 of 18) of *SDHB* mutations compared with 27% (4 of 15) of *SDHD* mutations were missense ($P=.16$). Eight *SDHB* mutations and 5 *SDHD* mutations have not been described previously. Five *SDHB* and 11 *SDHD* mutation carriers had available consenting parents who could be tested for the presence of mutations. Among these, there were 2 confirmed cases with de novo mutations (defined as first cases in a family, both parents without mutations) in *SDHD* (c. 33 C/A), which did not occur on the same haplotype. Mean (SD) ages at diagnosis of disease of the index cases were 29.8 (15.2) years for *SDHB* mutation carriers and 30.6 (14.3) years for *SDHD* mutation carriers and thus not significantly different ($P=.77$).

All 161 eligible first-degree relatives of mutation-positive index cases were offered genetic testing. Of these, 103 proceeded with testing, 43 for *SDHB* and 60 for *SDHD*. Among these 103 relatives, 26 were newly identified as *SDHB* mutation carriers and 21 as *SDHD* mutation carriers. In addition, we included 4 further first-degree relatives with known neck paragangliomas for whom we did not have DNA or paraffin-embedded surgical specimens. Thus, the study comprised a total of 53 *SDHB* and 47 *SDHD* mutation carriers. In the parental generation, *SDHD* mutations were only found in fathers, consistent with known maternal imprinting. Maternal imprinting is caused by methylation and hence silencing of the maternal allele. Therefore, individuals who inherit a mutation from the mother would not manifest tumors.[19]

After comprehensive clinical investigation in mutation carriers, we detected nonfunctioning tumors of the neck in 7 carriers of an *SDHD* mutation, of the thorax in 1 *SDHB* and 1 *SDHD* carrier each, and of the abdominal paraganglia or adrenal gland in 3 *SDHD* carriers. No tumors at all have been found in 10 carriers of an *SDHB* mutation and 9 carriers of an *SDHD* mutation; all the latter were classified as maternally imprinted cases. The mean (SD) age of carriers at tumor diagnosis was not significantly different from those without tumors (*SDHB*: 31.3 [15.4] years vs 34.7 [15.8] years, $P=.49$; and *SDHD*: 32.4 [16.1] years vs 47.6 [25.3] years, $P=.08$).

Table 1. Germline Mutations of the *SDHB* Gene Mutation in Unrelated Index Cases

Nationality of Origin	Initial Tumor	Index Case	Sex	Age at Onset, y	Mutation (cDNA Nucleotide)	Consequence (Codon and Amino Acid)	Exon	Carriers*
German	Extra-adrenal pheochromocytoma	1	F	31	155 del C†	Frameshift	1	1
German	Extra-adrenal pheochromocytoma	2‡	F	13	213 C/T	Arg27→stop	2	1
Polish	Adrenal pheochromocytoma	3‡	F	48	221 ins CCAG	Frameshift	2	1
German	Extra-adrenal pheochromocytoma	4‡	F	14	270 C/G	Arg46→Gly	2	2
German	Extra-adrenal pheochromocytoma	5‡	M	15	270 C/G	Arg46→Gly	2	2
German	Nonfunctional head and neck paraganglioma	6	M	34	271 G/A	Arg46→Gln	2	1
Canadian	Adrenal pheochromocytoma	7	M	50	271 G/A	Arg46→Gln	2	3
German	Adrenal pheochromocytoma	8	F	36	291 G/A	Gly53→Arg	2	1
Spanish	Adrenal pheochromocytoma	9	M	19	300-4 del CCTCA†	Frameshift	2	2
German	Adrenal and extra-adrenal pheochromocytoma	10	M	15	328 T/C†	Leu65→Pro	2	3
German	Adrenal pheochromocytoma	11	F	17	394 T/C†	Leu87→Ser	3	1
German	Extra-adrenal pheochromocytoma	12	F	42	394 T/C†	Leu87→Ser	3	6
French	Extra-adrenal pheochromocytoma	13	F	54	394 T/C†	Leu87→Ser	3	1
German	Nonfunctional head and neck paraganglioma	14	F	43	421-2 A/G†	Splice	4	1
German	Nonfunctional head and neck paraganglioma	15	M	45	421-2 A/G†	Splice	4	1
German	Extra-adrenal pheochromocytoma	16‡	F	10	436 G/A	Cys101→Tyr	4	2
Spanish	Extra-adrenal pheochromocytoma	17	M	65	558-3 C/G†	Splice	5	3
Polish	Extra-adrenal pheochromocytoma	18‡	F	26	708 T/C	Cys192→Arg	6	4
Polish	Extra-adrenal pheochromocytoma	19‡	M	19	721 G/A	Cys196→Tyr	6	3
Polish	Extra-adrenal pheochromocytoma	20‡	F	16	847 del TCTC	Frameshift	7	4
Polish	Adrenal pheochromocytoma	21‡	F	34	847 del TCTC	Frameshift	7	1
German	Adrenal pheochromocytoma	22‡	M	35	859 G/A	Arg242→His	7	5
German	Functional head and neck paraganglioma	23	M	31	859 G/A	Arg242→His	7	2
German	Adrenal pheochromocytoma	24‡	M	12	881 C/A	Cys249→stop	7	1
German	Functional head and neck paraganglioma	25‡	M	21	899 + 1 G/A†	Splice	7	1

Abbreviations: cDNA, complement DNA; F, female; M, male; *SDHB*, succinate dehydrogenase subunit B.
*Number of carriers in the given family, including the index case.
†Novel (so far not described) mutations.
‡Denotes previously reported cases.[10]

Table 2. Germline Mutations of the *SDHD* Gene in Unrelated Index Cases

Nationality of Origin	Initial Tumor	Index Case	Sex	Age at Onset, y	Mutation (cDNA Nucleotide)	Consequence (Codon and Amino Acid)	Exon	Carriers (No. With Maternal Imprinting)*
German	Adrenal pheochromocytoma	1†	F	5	14 G/A	Trp5→stop	1	4 (2)
German	Adrenal and extra-adrenal pheochromocytoma	2	M	26	14 G/A	Trp5→stop	1	3
German	Nonfunctional head and neck paraganglioma	3	F	18	14 G/A	Trp5→stop	1	1
Polish	Adrenal and extra-adrenal pheochromocytoma	4†	F	20	33 C/A	Cys11→stop	1	3 (2)
Polish	Adrenal pheochromocytoma	5†	M	21	33 C/A‡	Cys11→stop	1	1
Polish	Adrenal pheochromocytoma	6†	F	27	33 C/A‡	Cys11→stop	1	1
German	Adrenal and extra-adrenal pheochromocytoma	7†	F	13	33 C/A	Cys11→stop	1	2 (1)
Polish	Nonfunctional head and neck paraganglioma	8	M	29	33 C/A	Cys11→stop	1	1
Polish	Functional head and neck paraganglioma	9	M	60	33 C/A	Cys11→stop	1	1
Polish	Functional head and neck paraganglioma	10	F	27	33 C/A	Cys11→stop	1	1
German	Adrenal pheochromocytoma	11†	M	26	36,37 del TG	Frameshift	1	3 (1)
German	Adrenal pheochromocytoma	12†	M	35	52 + 2 T/G	Splice	1	2
German	Adrenal pheochromocytoma	13†	F	33	112 C/T	Arg38→stop	2	2
French	Nonfunctional head and neck paraganglioma	14	F	31	112 C/T	Arg38→stop	2	2
Polish	Adrenal pheochromocytoma	15†	F	47	112 C/T	Arg38→stop	2	1
Moroccan	Adrenal pheochromocytoma	16	M	15	204-216 del 13 bp§	Frameshift	3	5
German	Nonfunctional head and neck paraganglioma	17	M	49	242 C/T	Pro81→Leu	3	2
French	Functional head and neck paraganglioma	18	F	43	252 T/G§	Tyr84→stop	3	2
Polish	Extra-adrenal pheochromocytoma	19†	M	31	274 G/T	Asp92→Tyr	3	3 (1)
German	Nonfunctional head and neck paraganglioma	20	M	55	337-40 del GACT	Frameshift	4	1
German	Functional head and neck paraganglioma	21	F	38	341 A/G	Tyr114→Cys	4	1
German	Adrenal pheochromocytoma	22†	F	15	361 C/T§	Gln121→stop	4	1
German	Adrenal and extra-adrenal pheochromocytoma	23	M	13	441 del G§	Frameshift	4	3 (2)
German	Nonfunctional head and neck paraganglioma	24	F	49	443 G/T§	Gly148→Val	4	1

Abbreviations: cDNA, complement DNA; F, female; M, male; *SDHD,* succinate dehydrogenase subunit D.
*Number of carriers in the given family, including the index case.
†Denotes previously reported cases.[10]
‡De novo mutations.
§Novel (so far not described) mutations.

Table 3. Prevalence of *SDHB* and *SDHD* Mutations in Index Patients of the Subregistries*

	No. of Patients/Total (%)		
Subregistry	*SDHB* Mutations	*SDHD* Mutations	Either Mutation
Freiburg Pheochromocytoma Registry	11/191 (6)	8/191 (4)	19/191 (10)
Warsaw Pheochromocytoma Registry	5/113 (4)	5/113 (4)	10/113 (9)
Freiburg-Warsaw Pheochromocytoma Registry	16/304 (5)	13/304 (4)	29/304 (10)
German Head and Neck Paraganglioma Registry	5/77 (6)	5/77 (6)	10/77 (13)
All	21/381 (5)	18/381 (5)	39/381 (10)

Abbreviations: *SDHB*, succinate dehydrogenase subunit B; *SDHD,* succinate dehydrogenase subunit D.
*Data do not include 6 patients with head and neck paragangliomas from outside Germany and 30 patients with pheochromocytomas from countries outside Germany and Poland, of whom 10 were shown to be carriers of *SDHB* or *SDHD* mutations (see "Tables 1 and 2").

Blood pressure and catecholamine levels at the time of initial pheochromocytoma diagnosis were available for 41 patients (n=21 for *SDHB* and n=20 for *SDHD* mutation carriers). All had at least paroxysmal hypertension. Levels of catecholamine excretion were available from 20 patients: norepinephrine level was increased in 19 patients and normal in 1 case; whereas, epinephrine level was increased in 7 and normal in 13 patients, respectively. None of the patients with head and neck paragangliomas in the absence of pheochromocytoma had elevated blood pressure or catecholamine excretion.

For purposes of comparing various tumor characteristics among *SDHD* and *SDHB* mutation carriers, we excluded 9 carriers of *SDHD* mutations from further calculations. This included 7 patients without evidence of tumors who likely (n=6 fathers; mean [SD] age, 61.8 [7.3] years; range, 51-71) or definitely (n=1 mother) have inherited the mutation from their mothers, and 2 children of mothers who have been recognized as mutation carriers by this study but will not develop tumors because of maternal imprinting of the *SDHD* gene.

A total of 55 mutation carriers, including 20 relatives, had complete clinical screening; in an additional 19 carriers, positive findings were already available for the neck or thorax, and/or abdominal area, or all 3. In total, information was available for head and neck tumors in 67 (including 20 index cases operated for symptomatic neck tumors), for thoracic tumors in 56 (including 5 index cases operated for

Table 4. Tumor Characteristics*

Tumor Characteristics	*SDHB* Mutation (n = 32)		*SDHD* Mutation (n = 34)		*SDHB* vs *SDHD*		Non-*SDHB/SDHD* Pheochromocytoma and Paraganglioma (n = 368)†		*SDHB/SDHD* vs Non-*SDHB/SDHD*	
	No. of Tumors	% (95% CI)	No. of Tumors	% (95% CI)	*P* Value‡	*P* Value§	No. of Tumors	% (95% CI)	*P* Value‡	*P* Value§
Adrenal	9	28 (14-47)	18	53 (35-70)	.049	.58	286	78 (73-82)	<.001	<.001
Abdominal extra-adrenal	16	50 (32-68)	7	21 (8-38)	.02	.23	21	6 (4-9)	<.001	<.001
Thoracic	3	9 (2-25)	6	18 (7-35)	.48	>.99	5	1 (0-3)	<.001	<.001
Head and neck	10	31 (16-50)	27	79 (62-91)	<.001	.002	69‖	19 (15-23)	<.001	<.001
Multifocal tumors	9	28 (14-47)	25	74 (56-87)	<.001	.006	30	8 (6-11)	<.001	<.001
Carriers with malignant tumors	11	34 (19-53)	0	0 (0-10)	<.001	.001	14	4 (2-6)	<.001	.005

Abbreviations: CI, confidence interval; *SDHB*, succinate dehydrogenase subunit B; *SDHD,* succinate dehydrogenase subunit D.
*Percentage values with 95% CIs for a binomial distribution are given, referring to the number of tumors for the given body area divided by the number of patients with any tumor.
†Location of tumors in *SDHB* and *SDHD* mutation carriers compared with 300 patients with sporadic pheochromocytoma and 68 patients with paraganglioma.
‡Calculated by Fisher exact test.
§Calculated by the Bonferroni correction.
‖One patient with a primary sporadic pheochromocytoma also developed an asymptomatic neck tumor.

Table 5. Malignant Pheochromocytoma and Paraganglioma

Case	Sex	Location	Status and Age in 2004 or at Death	Duration of Disease, y	*SDHB* Mutation
1	F	Thoracic	Living 34 y	3	155 del C
2	M	Abdominal extra-adrenal*	Living 35 y	20	270 C/G
3	M	Neck	Living 45 y	11	271 G/A
4	M	Adrenal	Living 56 y	6	271 G/A
5	F	Abdominal extra-adrenal	Dead 45 y	32	300-4 del 5bp
6	F	Adrenal†	Dead 28 y	11	394 T/C
7	M	Abdominal extra-adrenal	Living 68 y	3	558-3 C/G
8	F	Adrenal†	Dead 36 y	2	847 del TCTC
9	M	Neck	Dead 64 y	32	859 G/A
10	M	Neck	Dead 64 y	2	859 G/A
11	M	Abdominal extra-adrenal	Living 66 y	6	899 + 1 GA

Abbreviation: F, female; M, male; *SDHB*, succinate dehydrogenase subunit B.
*Later associated with benign neck paraganglioma and thoracic pheochromocytoma.
†Multiple malignant tumors at this location.

symptomatic thoracic tumors), and for abdominal tumors in 68 (including 35 index cases operated for symptomatic abdominal tumors) mutation carriers.

TABLE 4 summarizes the percentages of tumor locations and characteristics in relation to the total number of patients with tumors. Relating these numbers to all mutation carriers who underwent adequate clinical workup for the single body regions, a very similar picture can be drawn. Multiple tumors occurred in 34 patients, 9 of 32 carriers with *SDHB* and 25 of 34 with *SDHD* mutations ($P<.001$). Fifty-three percent (18 of 34) of *SDHD* mutation carriers were found to have adrenal pheochromocytomas compared with 28% (9 of 32) of *SDHB* mutation carriers ($P=.049$). Interestingly, 79% (27 of 34) of all adequately investigated *SDHD* mutation-positive individuals had head and neck paragangliomas compared with only 31% (10 of 32) in *SDHB* mutation carriers ($P<.001$). For non-*SDHB/SDHD* mutation carriers with pheochromocytoma or paraganglioma, the studied features are all statistically significantly different (multiple tumors, adrenal location, head and neck paragangliomas, for all $P<.001$).

Eleven *SDHB* mutation–positive individuals (34% of tumor patients with an *SDHB* mutation) but no *SDHD* mutation carriers were found to have malignant pheochromocytomas or paragangliomas. All 11 individuals were found to have distant metastases, defined as tumors in the lungs or bones (TABLE 5). There was a difference in the prevalence of malignant disease between *SDHB* and *SDHD* mutation carriers (11 of 32 vs 0 of 34, $P<.001$). Malignant pheochromocytoma was present in 14 of 368 non-*SDHB/SDHD* mutation carriers ($P<.001$ for *SDHB* vs non-*SDHB/SDHD* mutation carriers, $P=.28$ for *SDHD* vs non-*SDHB/SDHD* mutation carriers). In addition, there were 3 *SDHD* mutation–positive patients who were initially misdiagnosed with malignant disease because of multiple abdominal tumors in 2 cases and abdominal and thoracic tumors in another case. Because of our clinical investigations, these patients were actually found to have multifocal benign tumors.

Tumors of the extraparaganglial system were observed in 5 carriers of *SDHB* mutations. Two carriers of the *SDHB* c. 847-50 del TCTC mutation, belonging to 1 family, were found to have clear cell renal carcinoma at ages 21 and 26 years. Tumor tissue (paraffin blocks) showed loss of the wild-type allele.[20] Two patients, 1 carrier of the *SDHB* c. 328 T/C mutation and 1 carrier of the *SDHD* c. 14 G/A mutation, showed a papillary thyroid carcinoma at ages 14 and 26 years, respectively.

Age-related penetrance based on symptomatic and asymptomatic tumors is shown for *SDHB* mutation carriers and for *SDHD* mutation carriers in FIGURE 2. Ten (24%) of 42 carriers of an *SDHB* mutation with adequate clinical investigation had no tumors, in contrast with *SDHD* mutation carriers, all of whom (34 of 34) were found to have tumors (*P*=.002). Fifty percent of *SDHB* mutation carriers were estimated to develop at least 1 tumor by 35 years (*SDHB* mutations have 50% penetrance by 35 years). Penetrance increases to 77% by 50 years. In comparison, *SDHD* mutations confer 50% penetrance by 31 years and 86% by 50 years. The overall age-related penetrance for *SDHB* and *SDHD* mutations was not statistically different (*P*=.67). Interestingly, there were significant differences in the age-related penetrance of tumor manifestations by site. Adrenal pheochromocytomas appeared more frequently and at an earlier age in *SDHD* mutation carriers (*P*=.03), and there was also a significant earlier onset for head and neck paraganglioma in *SDHD* mutation carriers (*P*=.007).

COMMENT

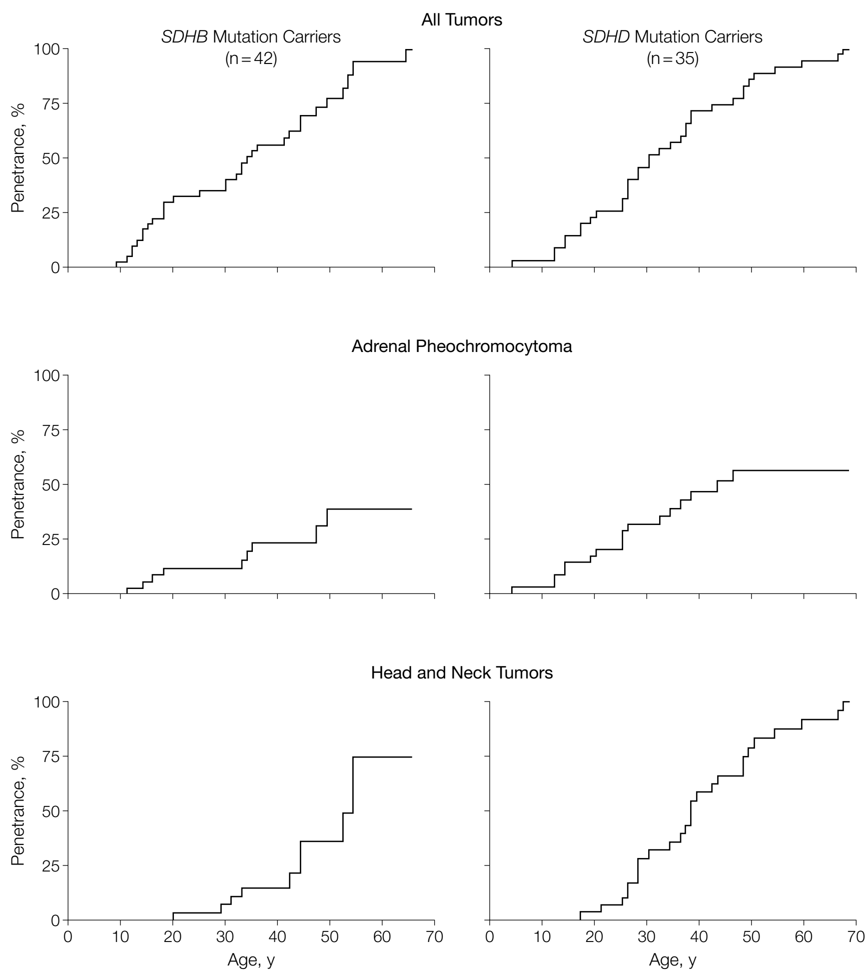
The paraganglioma syndromes have been relatively newly delineated as unique entities. Although paraganglioma has been clinically recognized for more than 40 years, only in the last 4 years have they been classified based on molecular genetics: *SDHD* mutations predispose to PGL-1, mutations in an unidentified gene on chromosome 11 to PGL-2, *SDHC* mutations to PGL-3, and *SDHB* mutations to PGL-4.[21] Our population-based study of apparently sporadic symptomatic pheochromocytoma presentations revealed that approximately 25% of such individuals carry unsuspected germline mutations in 1 of 4 genes, including *SDHB* and *SDHD*.[10] However, to date, carriers of these germline mutations were known to have a risk for paragangliomas, pheochromocytomas, or both but detailed clinical information, such as gene-specific clinical features, demographics, and penetrance, for purposes of genetic counseling, treatment, and follow-up were not known. We could not examine the gene for PGL-2, as it has yet to be identified, but we performed molecular genetic exclusion of *SDHC* mutation carriership (PGL-3); these mutations seem to be extremely rare.[15-17,22]

Our observations demonstrate that individuals carrying germline *SDHB* and *SDHD* mutations have some features in common. For example, mean age at diagnosis was 29 years for both genes. Prevalence of mutation carriers for each gene in the population-based registries of 2 countries was similar, between 4% and 6%. There were significant clinical differences between carriers of *SDHB* mutations compared with those with *SDHD* mutations.

The apparent age-related penetrance of tumors was not significantly different for *SDHB* and *SDHD* mutation carriers. Nevertheless, it is remarkable that 10 carriers of *SDHB* mutations did not develop a tumor, whereas all *SDHD* carriers, who were not likely to be subject to maternal imprinting, did have tumors. With a longer follow-up, it is quite probable that this apparent difference might also become statistically significant. Age-related penetrance for adrenal locations was higher among *SDHD* mutation carriers compared with penetrance for *SDHB* mutation carriers.

Head and neck paragangliomas were statistically more prevalent among *SDHD*

Figure 2. Age-Related Penetrance for *SDHB* and *SDHD* Mutation Carriers



SDHB indicates succinate dehydrogenase subunit B; SDHD, succinate dehydrogenase subunit D. All tumors included age-related penetrance for abdominal, thoracic, and neck tumors (*P*=.67). In 10 carriers of *SDHB*, a tumor could be excluded whereas all 35 *SDHD* carriers had tumors. The age-related penetrance of *SDHB* and *SDHD* carriers for adrenal manifestation of pheochromocytoma (*P*=.03) and head and neck paraganglioma tumors (*P*=.007) are also included.

carriers compared with those with *SDHB* mutations, although intra-abdominal extra-adrenal tumors were more prevalent among *SDHB* mutation carriers. Although most *SDHD* mutation carriers presented with multiple tumors (74%) compared with *SDHB* mutation carriers (28%), malignant tumors are more frequent in *SDHB* mutation–positive individuals (11 of 32 vs 0 of 34 in *SDHD* mutation carriers, $P<.001$). Similarly, in *SDHB* mutation carriers, a high rate of distant metastases (4 of 8 cases) has been reported recently by Giminez-Roqueplo et al[23] and no malignant pheochromocytoma or paraganglioma has yet been reported in an *SDHD* mutation carrier in the literature to date. Consistent with the apparently aggressive nature of *SDHB* dysfunction, 5 mutation carriers in our study were also found to have extraparaganglial malignancies (eg, renal cell carcinoma and thyroid papillary carcinoma). Kidney carcinomas are considered oncocytic tumors (replete with mitochondria) and thus, the involvement of a mitochondrial complex II gene in kidney carcinogenesis may be explained. The apparently more aggressive nature of the tumors in *SDHB* mutation carriers may be postulated to be a consequence of the prevention of assembly of the catalytic complex that normally comprises *SDHA* and *SDHB*, thus leaving only complexes of the structural *SDHC* and *SDHD* moieties.[24]

Based on these observations, preliminary guidance for genetic counseling and surveillance is possible. Although our population-based study established an approximately 25% germline mutation frequency in apparently sporadic symptomatic presentations of pheochromocytoma, this may involve any 1 of 4 genes.[10] Which gene(s) to begin testing is often a practical question for clinicians. Our present data suggest that individuals presenting with head and neck paragangliomas, multifocal tumors, or both should be targeted for *SDHD* testing in the first instance. Extra-adrenal abdominal presentations, malignant disease, renal cell carcinoma, and thyroid carcinoma may suggest *SDHB* testing initially. An older age of onset may suggest *SDHB/SDHD*-related PGL syndromes compared with VHL disease, the latter of which is usually characterized by early-onset pheochromocytoma.[10]

Conversely, if an individual was newly found to carry an *SDHD* mutation, there is a likelihood of developing head and neck paragangliomas and penetrance is relatively high in a lifetime. Thus, asymptomatic carriers should be offered 3 body region clinical screening, including MRI of the neck, thorax, and abdomen/pelvis; 18 fluorodopa or 18 fluorodopamine positron emission tomography might be an acceptable alternative.[25-27] In addition, measurement of catecholamines, preferentially of plasma metanephrines, should be performed.[28,29] Annual intervals may be considered, although rate of tumor growth is currently unknown. The only exception is perhaps the children of female *SDHD* mutation carriers who likely do not require clinical surveillance because the axiom of maternal imprinting of *SDHD* has never been reported to be violated in any case to date. Although *SDHB* mutation carriers should be subjected to annual clinical surveillance, patients should be counseled that while their disease might be less penetrant, multifocal disease, malignant disease, and early-onset renal cell carcinoma are possible.[20]

Whether thyroid malignancies are also components of *SDHB*- or *SDHD*-related disease awaits further confirmation. This may be germane to surgical decision making, if our data can be independently replicated. The current standard of care in our consortium institutions for hereditary forms of intra-adrenal pheochromocytoma is to offer adrenal sparing tumor resection, typically endoscopic resections of the tumor(s) because of the possibility of multifocal metachronous disease, and morbid consequences of total adrenalectomies.[30-33] The 2 major genes contributing to the heritable pheochromocytoma-paraganglioma syndromes, PGL-1 through PGL-4, are *SDHB* (PGL-4) and *SDHD* (PGL-1). *SDHC* (PGL-3) has only been found in 4 unrelated families[15-18] and the fourth locus (PGL-2), without an isolated gene, is germane only to 1 family in the Netherlands. Our continuing studies have suggested that clinical features are based on gene type, and therefore, knowing which gene, *SDHB* or PGL-4 vs *SDHD* or PGL-1, would be important for not only diagnosis but further clinical management and genetic counseling.

Author Contributions: Dr Neumann had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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peats expansion (57 CTG/CAG repeats) of *JPH3* (HDL2) in the same patient, while a family member with full mutation of *FMR1* and trinucleotide expansion of *JPH3* showed no symptom of parkinsonism.

Comment. Premutation of the *FMR1* gene in men is associated with various movement disorders, including tremor, ataxia, and parkinsonism, that have clinical features overlapping with PD and essential tremor.[1,6] We sought premutations in men with PD and in those with essential tremor to determine whether these 2 disorders are pathogenetically related to this genetic abnormality, but we found no *FMR1* premutation in our population of patients with PD and essential tremor. This is consistent with other reports indicating lack of *FMR1* premutation in patients with essential tremor,[7,8] atypical parkinsonism, and ataxias.[8] Thus, premutation of *FMR1* probably plays little or no role in the pathogenesis of idiopathic PD or essential tremor. Furthermore, it is unlikely that this genetic abnormality accounts for the male preponderance in patients with PD.[9]

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CORRECTIONS

Incorrect Data in Table: In the Original Contribution entitled "Comparison of Cefuroxime With or Without Intranasal Fluticasone for the Treatment of Rhinosinusitis: The CAFFS Trial: A Randomized Controlled Trial" published in the December 26, 2001, issue of THE JOURNAL (2001;286:3097-3105), there were incorrect data in Table 3. On page 3103, the number needed to treat (95% CI) for day 10 time point should have been 6 (–3 to 53).

Incorrect Sentence: In a Letter to the Editor entitled "Prevalence of Chlamydial and Gonococcal Infections Among Young Adults" published in the August 18, 2004, issue of THE JOURNAL (2004;292:801), there was an error in the first sentence. The first sentence should have read, "The article by Dr Miller and colleagues[1] complements findings from our previous studies of national samples of more than 23 000 women for chlamydia[2,3] and approximately 6000 men for chlamydia and gonorrhea.[4,5]"

Multiple Errors: In the Original Contribution entitled "Distinct Clinical Features of Paraganglioma Syndromes Associated With *SDHB* and *SDHD* Gene Mutations" published in the August 25, 2004, issue of THE JOURNAL (2004;292:943-951), there were multiple errors. On page 944, in Figure 1, the third line of the first box should have read "89 With Paraganglioma"; the last line of the second box should have read "6 With Familial Paraganglioma"; and the last 2 lines of the third box from the bottom should have read "43 for *SDHB* Mutation" and "60 for *SDHD* Mutation." On page 947, in Table 2, the mutation (cDNA nucleotide) for the Moroccan case should have read "206-218 del 13 bp§." On page 950, in the Author Contributions, "Boeoleker" cited 3 times should have read "Boedeker"; and "Mr Bausch" should have read "Ms Bausch." On page 951, in the Acknowledgment, "Weryba" should have read "Weryha"; and "Naujoks, MD, Stade; and Weber, MD, Zürich, Germany" should have read "Naujoks, MD, Stade, Germany; and Weber, MD, Zürich, Switzerland."

