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Penetrance and clinical consequences of a gross *SDHB* deletion in a large family

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Abstract

Mutations in the gene encoding subunit B of the mitochondrial enzyme succinate dehydrogenase (SDHB) are inherited in an autosomal dominant manner and are associated with hereditary paraganglioma (PGL) and pheochromocytoma. The phenotype of patients with *SDHB* point mutations has been previously described. However, the phenotype and penetrance of gross *SDHB* deletions have not been well characterized as they are rarely described. The objective was to describe the phenotype and estimate the penetrance of an exon 1 large *SDHB* deletion in one kindred. A retrospective and prospective study of 41 relatives across five generations was carried out. The main outcome measures were genetic testing, clinical presentations, plasma catecholamines and their *O*-methylated metabolites. Of the 41 mutation carriers identified, 11 were diagnosed with PGL, 12 were found to be healthy carriers after evaluation, and 18 were reportedly healthy based on family history accounts. The penetrance of PGL related to the exon 1 large *SDHB* deletion in this family was estimated to be 35% by age 40. Variable expressivity of the phenotype associated with a large exon 1 *SDHB* deletion was observed, including low penetrance, diverse primary PGL tumor locations, and malignant potential.

Keywords

paraganglioma; penetrance; pheochromocytoma; *SDHB* deletion; succinate dehydrogenase subunit B

Paragangliomas (PGLs) are neuroendocrine tumors that originate from neural crest cells in the adrenal medulla or along the sympathetic and parasympathetic ganglia. Pheochromocytoma (PHEO) specifically refers to the adrenal presentation of these tumors. Various point mutations in the gene encoding subunit B of the mitochondrial enzyme succinate dehydrogenase (SDHB) have been identified and shown to cause predominantly norepinephrine (NE)-producing PGL originating in adrenal, head and neck, and extra-adrenal abdominal locations (1–5). Extra-adrenal abdominal PGLs associated with *SDHB* point mutations have a high metastatic potential (1, 6–8) and a poor prognosis (9). However, the phenotype associated with large *SDHB* deletions is not well known as these mutations are rare and missed by standard direct sequencing methods (3, 6, 10). Recently, easier to implement methods employing multiplex amplification have been developed to detect large *SDHB* deletions (9, 11).

To date, eight families have been found to carry large deletions of exon 1, suggesting a probable recombination hot spot region (9, 11–13). The first three families identified with this exon 1 mutation originated from Brazil, Portugal, and Spain (11, 12). Recently, two new families originated from a similar region in the Iberian Peninsula as the previously reported Spanish patients were also identified as having the same exon 1 deletion breaking points (15.69 kb), suggesting a founder mutation (13). Three other families of French descent have also been affected by this large exon 1 *SDHB* deletion (9, 13). Of the 14 affected relatives identified from these eight families, 9 developed extra-adrenal abdominal PGL, 1 carotid body PGL, 1 thoracic PGL, 2 adrenal PHEO, and 1 possibly *SDHB*-related metastatic neuroblastoma. Only two other cases have been attributed to large *SDHB* deletions spanning different regions of the gene, one with a deletion of exons 3–8 (9) and another with an entire deletion of the *SDHB* gene (11). Limited information on the phenotype of patients with large *SDHB* deletions exists due to the small number of patients identified to date.

In this study, we describe the phenotype of 41 relatives of Spanish-Mexican descent found to have the same founder exon 1 *SDHB* heterozygous deletion previously reported in the literature for patients from the Iberian Peninsula. We discuss in detail the diverse clinical and biochemical phenotype of 11 relatives with PGL/PHEO and provide a Kaplan–Meier estimate of the penetrance of the gross deletion in this family.

Materials and methods

Patients

In 2002, a genetically determined form of PGL was suspected in the 41-year-old proband, IV-1, due to her family history of PGL and metastatic disease, 9 years after excision of a 10-cm left adrenal PHEO. Computed tomography (CT) scan revealed a recurrence in the left adrenal bed of 4.5 cm, two metastatic liver lesions (the largest being 7 cm), and bone lesions in the lumbar spine. Her biochemical evaluation showed elevated plasma NE levels of 11,350 (80–498 pg/ml) and normetanephrine levels of 7304 (18–112 pg/ml). During this visit, she was accompanied by her younger sister, IV-11, with a medical history of pelvic PGL. No genetic mutations were detected after direct sequencing of the succinate dehydrogenase (*SDHB*, *SDHC*, and *SDHD*), von Hippel-Lindau (*VHL*), and multiple endocrine neoplasia type 2 (*RET*) genes. However, we still had a high clinical suspicion for

an *SDHB* mutation due to the proband's malignant phenotype and family history of PGL. In the hypothesis of a large *SDHB* deletion not detectable by direct sequencing, both sisters were tested with the quantitative multiplex polymerase chain reaction of short fluorescent fragments (QMPSF) method.

Subsequently, clinical and family history information was obtained on 40 of the proband's relatives, defined as those sharing a common ancestor across five generations (Fig. 1).

Informed consent was obtained from all subjects in accordance with and approval by the Institutional Review Board of the National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH).

Mutation analysis

Genomic DNA was extracted using standard methods (GENTRA Systems, Inc., Minneapolis, MN). Direct sequencing for point mutations in the *SDHB*, *SDHC*, *SDHD*, *VHL*, and *RET* genes was performed in IV-1 and IV-11 as previously described (14). The QMPSF method was employed to screen for large rearrangements of the *SDHB* gene. The eight coding exons of the *SDHB* gene were amplified in one multiplex polymerase chain reaction (PCR). An additional fragment, from the *HMBS* gene, was co-amplified as a control in each PCR. The size of the fragments ranged from 208 to 341 bp. A 5' extension, consisting of a rare combination of 10 nucleotides preceding the exon-specific sequence, was added to the primers as previously described (15). The forward primer of each pair was 5' end labeled with 6-FAM fluorochrome. After amplified DNA fragments were separated using an ABI PRISM 3730 DNA Analyzer sequencer (Applied Biosystems, Foster City, CA), data were analyzed using the GENEMAPPER software version 4.0 (Applied Biosystems).

Deletion breaking points

To establish the deletion break points occurring in these patients with germ line exon 1 *SDHB* deletion, we performed a PCR amplification specific of the Iberian Peninsula founder deletion (13).

We designed a pair of primers flanking the break points of the 15.69-kb deletion previously described.

Forward primer: GTAAAATAGATACGAGCCATCACTGG

Reverse primer: TAGTAGGGTAAGTGGGACAATATGCC

The amplification of a 228-bp fragment with this pair of primers is specific of the presence of the 15.69-kb heterozygous deletion.

Evaluation of phenotype

Medical records were requested from relatives with a previous diagnosis of PHEO/PGL at outside institutions and invited for clinical screening at NIH. In addition, carriers identified through mutation testing were invited to the NIH for appropriate screening. Family history

reports from close relatives described the health status, age of diagnosis, and symptoms of relatives who were not available for clinical screening.

Clinical screening at NIH consisted of examination by standardized inventory of symptoms and signs as previously described (16). Radiological tumor screening at NIH included a whole-body CT of the head/neck, chest, abdomen, and pelvis (CT scans were performed using a GenesisHi-Speed scanner; General Electric Healthcare Technologies, Waukesha, WI). Section thickness was up to 3 mm in the neck, 5 mm through the chest and abdomen, and 7.5 mm through the pelvis. Most studies were performed with a rapid infusion of non-ionic water-soluble contrast agent and oral barium contrast.

Loss of heterozygosity studies of non-PGL tumors

DNA was extracted from frozen tissue using standard techniques (GENTRA Systems, Inc.). Loss of heterozygosity (LOH) studies were performed as previously described (8). LOH analysis was performed for tumoral and germ line DNA samples using eight fluorescent microsatellite markers (D1S468, D1S244, D1S507, D1S436, D1S2697, D1S2644, D1S478, and D1S2749) overlapping a 50-cM region between telomere and 1p35, including *SDHB* locus.

Kaplan–Meier analysis

Penetrance of the gross exon 1 *SDHB* deletion in this family was estimated by cumulative incidence functions using Kaplan–Meier analysis where survival time was substituted by age at diagnosis (17). Only 23 of the 41 relatives identified as carriers were used for the analysis as the 18 relatives who have not been clinically evaluated at NIH may have an asymptomatic PHEO/PGL.

Results

Germ line exon 1 *SDHB* deletion

A five-generation pedigree is given in Fig. 2. Proband IV-1 and 40 additional relatives were identified as carriers of a large heterozygous exon 1 deletion of the *SDHB* gene. Nine relatives were identified as obligate carriers, based on their diagnosis of PGL or evidence of transmission of *SDHB*-related PGL to their offspring, and a gross deletion was identified in 31 relatives with the QMPSF method as shown by the twofold reduction of the corresponding exon 1 peak in the representative result in Fig. 3.

Determination of the deletion breaking points using PCR analysis revealed an identical deletion to the previously cited Iberian Peninsula founder mutation (11, 13) (Fig. 3).

Clinical presentations of PGL

Eleven mutation carriers were diagnosed with PGL in various locations, including 6 in the carotid body, 3 in the adrenal gland, 1 in the pelvis, and 1 in the thorax. The clinical presentation of the 41 mutation carriers is summarized in Table 1.

Non-PGL malignancies

Table 1 summarizes other non-PGL malignancies detected in *SDHB* deletion carriers in this family. At age 42, 3 years after being diagnosed with a carotid body PGL, the proband's sister (IV-7) was diagnosed with a 2-cm hybrid renal cell carcinoma chromophobe/oncocytoma tumor. Similarly, the proband's younger brother (IV-9) was diagnosed with papillary thyroid cancer (2-cm solitary nodule in the left thyroid lobe) at age 36. LOH analysis was performed on these two non-PGL tumors. We have detected LOH in the 1pter to 1p35 in IV-7's hybrid renal cell carcinoma chromophobe/oncocytoma tumor but not in IV-9's papillary thyroid cancer (Fig. 4). Other malignancies observed in mutation carriers included papillary bladder cancer (IV-9), uterine adenocarcinoma (III-23), and lung cancer (III-8) (Table 1). Tumor tissue was not available for genetic analysis.

Kaplan–Meier estimates of penetrance

A Kaplan–Meier analysis was used to estimate the penetrance of the gross exon 1 *SDHB* deletion in this family as a function of the age of diagnosis (Fig. 5). The penetrance of this mutation is estimated to be 23% by age 30 and 35% by age 40.

Discussion

The present study describes the phenotype associated with a previously described founder *SDHB* exon 1 deletion. A high variability in the PGL tumor sites – including a possibly *SDHB*-related hybrid renal cell carcinoma chromophobe/oncocytoma tumor – diverse biochemical profiles, and disease courses (both malignant and benign) were observed in this family. Our findings not only emphasize the importance of ruling out the presence of large *SDHB* deletions in patients with familial PGL but also have implications for the clinical management of these patients, including appropriate preventive measures and genetic counseling.

Phenotype of *SDHB* mutations vs gross deletions

Although the small number of reported *SDHB* deletion cases prevents any definite comparisons between the phenotypes of point *SDHB* mutation carriers and the large deletion carriers, the 11 relatives with PGL from this large family suggest a similar phenotype.

Previous studies of the clinical phenotype of *SDHB* point mutation carriers have shown a predisposition for head and neck, thoracic, and extra-adrenal abdominal PGL (18, 19). Similarly, *SDHB* deletion cases reported in the literature have presented with PGL in all these locations. Although the majority of *SDHB* deletion cases published (10 of 14) had extra-adrenal abdominal PGL (11–13), our family screening study found a large number of cases with carotid and adrenal PHEO as well.

The more favorable prognosis of affected *SDHB* deletion carriers in this family, compared with other patients with *SDHB* point mutations, may be due to the fact that most of the primary tumors detected in this family arose from the head/neck area. Head and neck PGL are usually symptomatic and can be rapidly diagnosed and operated on, whereas thoracic

and abdominal PGL may go undetected for a long period of time and diagnosed lately after the occurrence of first metastasis (6, 7, 20).

Non-PGL malignancies in *SDHB* deletion carriers

Previous reports detected cases of renal cell cancer caused by point mutations in the *SDHB* gene, suggesting that <3% of renal cancers may be due to an *SDHB* mutation (21–23). Herein, we present the first report of LOH study of chromosome 1p from a renal hybrid tumor. Our findings reveal a possible association between this hybrid renal tumor and *SDHB*-related PGL. Further screening of relatives of *SDHB* mutation carriers is needed to ascertain the prevalence of renal cancer in this family.

Papillary thyroid cancer is another malignancy that was also previously discussed in the literature to possibly be a component of *SDHB*-related PGL (19). However, tumor DNA analysis of the papillary thyroid cancer tumor DNA in this study did not show LOH of the chromosome 1p. Previous studies examining the 1p chromosomal region in thyroid cancer found LOH in the 1p chromosome in thyroid adenoma and medullary carcinoma but not in papillary carcinoma (24). Our data suggest that papillary thyroid cancer is not a component of the *SDHB*-related hereditary PGL.

Other malignancies observed in *SDHB* mutation carriers in this family included papillary bladder cancer, uterine adenocarcinoma, and lung cancer. None of these tumors are currently suspected to be associated with *SDHB*, but tumor tissue was not available to rule out possible connections.

Estimated penetrance

There are only eight families affected by large exon 1 *SDHB* deletion reported in the literature to date; therefore, calculating the penetrance is at this time inappropriate due to bias of ascertainment and the small number of clinically unaffected mutation carriers investigated. Although only 23 of 41 mutation carriers in this family were available for penetrance estimates, our study suggests a slightly lower penetrance by age 40 than previously cited in the literature for *SDHB* point mutation carriers. In a previous study of 82 *SDHB* point mutation carriers, an estimated 45% developed PGL by age 40 (18). In our report, with a smaller number of subjects, the penetrance of PGL related to exon 1 large *SDHB* deletion based on a Kaplan–Meier analysis was slightly lower and estimated to be 35% by age 40.

Conclusions

SDHB large deletion testing should be considered in patients with familial PGL who lack evidence of point mutations of susceptibility genes. The clinical spectrum among large *SDHB* deletion carriers appears to be similar to *SDHB* point mutation carriers with the exception of a slightly lower penetrance. Large *SDHB* deletions may also predispose to non-PGL tumors, such as hybrid renal cell carcinoma chromophobe/oncocytomas.

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Fig. 1.
Study demographics. PGL, paraganglioma; NIH, National Institutes of Health.

Fig. 2.

Abbreviated pedigree of the large family with the gross *SDHB* exon 1 deletion, focusing on the 41 known mutation carriers. Individuals have Arabic numbers within each generation I–V. The age at presentation with PGL/PHEO and current age of unaffected mutation carriers are found at the upper right-hand corner of the symbol. An asterisk next to the age denotes those individuals clinically evaluated at NIH. The proband is designated with an arrow. PGL, paraganglioma; PHEO, pheochromocytoma.

Fig. 3.

Identification of *SDHB* exon 1 deletion with quantitative multiplex polymerase chain reaction of short fluorescent fragments and determination of deletion breaking points by direct sequencing. **(a)** Large deletion of the first exon revealed by a twofold reduction of the corresponding peak obtained for the patient IV-1 DNA (red) comparing with a control subject (blue) after adjustment of the two peaks obtained with the control polymerase chain reaction (HMBS amplicon) to the same peak height. **(b)** Direct sequencing of the 228-bp fragment showing the *SDHB* exon 1 deletion break points in this family. This 15,678-bp deletion is the deletion previously described as Iberian Peninsula founder mutation. The nucleotides numeration is based on the NCBI reference sequence AL049569.

Fig. 4. Somatic LOH analysis of eight microsatellite markers at chromosome 1pter to 1p35 for IV-7 and IV-9 tumors. LOH, loss of heterozygosity.

Fig. 5. Kaplan–Meier analysis curve displaying the probability of 23 exon 1 *SDHB* mutation carriers from the same family of remaining unaffected from birth to the age of 70 years.

Table 1

Phenotype of 41 *SDHB* deletion carriers in one kindred

Subject	Sex	Age at follow-up	Type of evaluation	Age at PGL diagnosis	Exon 1 <i>SDHB</i> deletion	PGL location	Prim. PGL size (cm)	Elevated biochemistry at diagnosis	Elevated biochemistry at follow-up	Disease course	Other tumor (age at diagnosis)
V-4	F	19	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Negative clinical screening
IV-26	F	22	Pathology report	21	Confirmed	Mediastinum	8	Unknown	Unknown	Unknown	None reported
V-9	F	22	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Negative clinical screening
V-6	F	28	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	None reported
V-1	M	29	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	None reported
V-7	F	31	NIH visit	21	Confirmed	RT carotid body	2.2	Normal	Normal	Benign	None reported
IV-11	F	33	NIH visit	24	Confirmed	Pelvis	7	Elevated	Normal	Benign	Negative clinical screening
III-13	M	33 ^b	Family history	29	Obligatory	LT adrenal gland	Unknown	Elevated	n/a	Malignant (33)	Negative clinical screening
IV-9	M	36	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Papillary thyroid cancer (36)
IV-13	F	39	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Uterine leiomyomas
III-9	F	40	Family history	24	Obligatory	Adrenal	Unknown	Unknown	Unknown	Unknown	Negative clinical screening
IV-8	M	41	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	None reported
IV-7	F	42	NIH visit	39	Confirmed	RT carotid gland	6	NE and NMN	Normal	Benign	Renal cell carcinoma/oncocytoma (42)
IV-20	F	46	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Negative clinical screening

Subject	Sex	Age at follow-up	Type of evaluation	Age at PGL diagnosis	Exon 1 SDHB deletion	PGL location	Prim. PGL size (cm)	Elevated biochemistry at diagnosis	Elevated biochemistry at follow-up	Disease course	Other tumor (age at diagnosis)
IV-4	F	47	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Adrenal nodule (1 cm)
IV-1	F	48 ^b	NIH visit	32	Confirmed	LT adrenal gland	10	NE and NMN	NE and NMN	Malignant (41)	Negative clinical screening
IV-23	F	50	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	None reported
IV-18	F	57	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Negative clinical screening
IV-15	M	62	NIH visit	n/a	Confirmed	Negative clinical screening	n/a	n/a	Normal	n/a	Papillary bladder cancer (59)
III-23	F	63	NIH visit	63	Confirmed	RT carotid body	2.1	Normal	n/a	Benign	Uterine adenocarcinoma (62)
III-2	F	75	NIH visit	65	Confirmed	RT carotid body	4	Normal	Normal	Recurrence (75)	Basocellular carcinoma precordial (74)
I-2	F	90	Family history	70+	Obligatory	Carotid body	Unknown	Unknown	Unknown	Unknown	None reported
II-2	F	93	Family history	70	Obligatory	RT carotid body	Unknown	Unknown	Unknown	Unknown	None reported
V-2	F	4	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
V-3	F	10	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
V-5	M	15	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
V-12	M	15	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
V-14	M	15	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
V-11	F	19	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
V-10	M	20	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
IV-24	F	30	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
IV-25	M	34	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported

Subject	Sex	Age at follow-up	Type of evaluation	Age at PGL diagnosis	Exon 1 SDHB deletion	PGL location	Prim. PGL size (cm)	Elevated biochemistry at diagnosis	Elevated biochemistry at follow-up	Disease course	Other tumor (age at diagnosis)
V-8	M	34	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
IV-2	M	46	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
III-25	F	51	Family history	n/a	Obligatory	None reported	n/a	n/a	n/a	n/a	None reported
III-18	F	54	Family history	n/a	Confirmed	None reported	n/a	n/a	n/a	n/a	None reported
III-19	M	55	Family history	n/a	Obligatory	None reported	n/a	n/a	n/a	n/a	None reported
II-4	M	72	Family history	n/a	Obligatory	None reported	n/a	n/a	n/a	n/a	None reported
II-11	F	83	Family history	n/a	Obligatory	None reported	n/a	n/a	n/a	n/a	None reported
I-3	M	70+ ^b	Family history	n/a	Obligatory	None reported	n/a	n/a	n/a	n/a	Unknown
III-8	F	72 ^b	Family history	n/a	Obligatory	None reported	n/a	n/a	n/a	n/a	lung cancer (72)

CA, cancer; LT, left; met, metastatic; n/a, not applicable; NE, norepinephrine; NIH, National Institutes of Health; NMN, normetanephrine; PGL, paraganglioma; PHEO, pheochromocytoma; RT, right.

^aThe 23 subjects highlighted in gray either have a family history of PGL or are currently healthy carriers as determined by a clinical evaluation at NIH. Only family history information is available for the remaining 18 subjects as they have not been evaluated at NIH.

^b Age deceased.