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Paragangliomas: Clinical Picture

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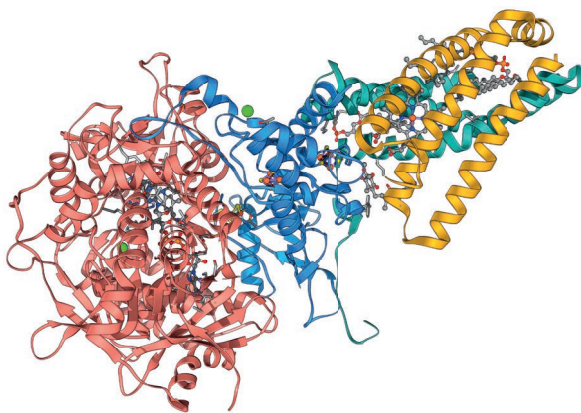
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Chapter 2

Low penetrance of paraganglioma and pheochromocytoma in an extended kindred with a germline *SDHB* exon 3 deletion

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Abstract

In the Netherlands, the majority of hereditary paragangliomas (PGL) is caused by *SDHD*, *SDHB* and *SDHAF2* mutations. Founder mutations in *SDHD* are particularly prevalent, but several *SDHB* founder mutations have also been described. Here, we describe an extended PGL family with a Dutch founder mutation in *SDHB*, c.201-4429_287-933del. The proband presented with apparently sporadic head and neck paraganglioma at advanced age. Subsequently, evaluation of the family identified several unaffected mutation carriers, asymptomatic and symptomatic PGL patients, and patients presenting with early-onset malignant pheochromocytoma. The calculated penetrance of the *SDHB* mutation in this kindred is lower than the risk suggested for *SDHB* mutations in the literature. This may represent a characteristic of this particular *SDHB* mutation, but may also be a reflection of the inclusion of relatively large numbers of asymptomatic mutation carriers in this family and adequate statistical correction for ascertainment bias. The low penetrance of *SDHB* mutations may obscure the hereditary nature of *SDHB*-linked disease and is important in the counseling of *SDHB*-linked patients. Risk estimates should preferably be based on the specific mutation involved.

Introduction

Paragangliomas (PGL) are rare, usually benign tumors that originate from the neuroendocrine paraganglia along the paravertebral axis. PGLs can be subdivided into head and neck paraganglioma (HNPG), pheochromocytoma (PHEO) and thoracic and abdominal extra-adrenal PGL. A genetic predisposition for PGL or PHEO formation can be identified in about one third of the patients.

In the Netherlands, the majority of hereditary PGLs are caused by a limited number of specific Dutch founder mutations, predominantly in *SDHD*, but also in *SDHB* and *SDHAF2*.¹ Patients with *SDHD* and *SDHAF2* mutations are mainly characterized by the occurrence of HNPGs, whereas *SDHB* mutation carriers more frequently develop extra-adrenal PGLs, PHEOs and metastatic PGLs.²⁻⁷

The reported penetrance of *SDHB* mutations (26–75%) is lower than the penetrance of (paternally inherited) *SDHD* or *SDHAF2* mutations (88–100% and 87–100%, respectively).^{5,8-17} The majority of the earlier reports on the penetrance of *SDHB* or *SDHD* mutations were largely based on groups of affected PGL patients and a limited inclusion of asymptomatic family members. The penetrance calculations in these studies are prone to overestimation of risk if the bias that is introduced by the inclusion of predominantly symptomatic mutation carriers is not adequately corrected for. Recent family-based studies that involve more comprehensive screening of asymptomatic family members of index patients have shown lower penetrance rates for *SDHB* and *SDHD* mutations.^{10,16,17}

Here, we present the penetrance and clinical characteristics of an extended PGL-PHEO kindred linked to a recently identified Dutch founder mutation in *SDHB*, c.201-4429_287-933del.¹⁵ The index patient presented with HNPG at advanced age and the family history for the nuclear family was negative for PGL or PHEO. However, through genealogical study and comprehensive screening of the extended kindred, we identified several affected PGL-PHEO patients as well as asymptomatic mutation carriers, allowing the further assessment of the penetrance and variable phenotype associated with this *SDHB* mutation.

Materials and methods

Data were collected from two tertiary referral centers for PGL in the Netherlands: the Leiden University Medical Center (Leiden) and the VU University Medical Center (Amsterdam). Screening for *SDHB* mutations was performed by direct sequencing using the Sanger method on an ABI 377 Genetic Analyser (Applied Biosystems, Carlsbad, CA) and by multiplex ligation-dependent probe amplification (MLPA) using the P226 MLPA kit (MRC Holland, Amsterdam, the Netherlands). In the index patient, the c.201-4429_287-933del mutation in *SDHB* was identified, previously described as a Dutch founder mutation.¹⁵ Family members at risk were invited for genetic counseling and DNA testing. The identification of at-risk

family members was facilitated by a previous genealogical study of this kindred; however, some of these family members could not be reached or declined DNA testing. Mutation carriers were referred to the outpatient clinic of the departments of Otorhinolaryngology and Endocrinology and Metabolic Diseases. All carriers of the *SDHB* mutation were offered annual clinical evaluation, biochemical screening for catecholamine excess and magnetic resonance (MR) imaging of the head and neck, thorax and abdomen. Additionally, two mutation carriers underwent DOPA-PET scanning, one underwent FDG-PET scanning, and one metaiodobenzylguanidine (MIBG) scintigraphy. Biochemical screening included the annual measurement of (nor)metanephrine and 3-methoxytyramine in two 24-h urinary samples. Clinical characteristics including gender, age, the occurrence and location of *SDHB*-linked tumors, and age at diagnosis were recorded. All the participating family members gave informed consent for the clinical study and DNA testing.

Statistics

We estimated the age-specific penetrance function for mutation carriers by maximizing the non-parametric conditional likelihood function for all individuals in the pedigree, except the proband, given the positive mutation status of the proband. The likelihood also included those individuals who had not been tested. We assumed that the penetrance functions for male and female mutation carriers are equal and, in addition, assumed that non-mutation carriers have zero risk to be affected.

We found an estimated lower bound of the penetrance function by assuming that all untested individuals are carriers and next estimating the penetrance function by the Kaplan–Meier estimate based on all positive tested individuals. Similarly, we found an upper bound by assuming that all untested individuals are non-carriers and next estimating the penetrance function by the Kaplan–Meier estimate. Computations were performed in R, version 3.0.1.

Results

The index patient was referred for the evaluation of a tinnitus in the right ear at 77 years of age. Otoscopy revealed a purple-red mass behind the right tympanic membrane. Computed tomography of the mastoid showed partial opacification of the right middle ear with irregular erosion of the bone surrounding the jugular bulb. T1- and T2-weighted MR imaging of the head and neck showed a mass extending from the right jugular foramen into the hypotympanum, suggestive of a jugulotympanic PGL. No other masses in head and neck region were found. Blood pressure was normal and 24-h urine analysis showed no increased catecholamine excretion. The family history in this branch of the family was negative for PGL. However, DNA analysis revealed a germline mutation in *SDHB*, the c.201-4429_287-933del Dutch founder mutation.

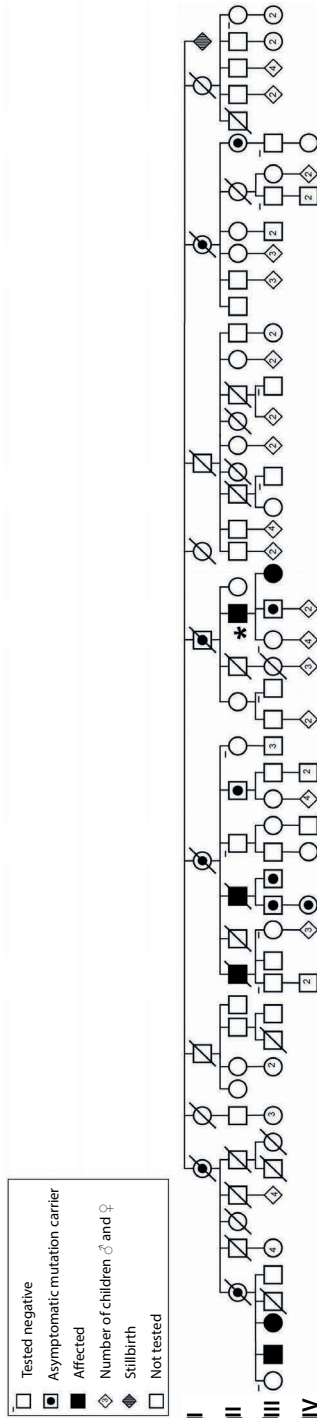


Figure 1. The pedigree of the *SDHB*-linked family. The asterisk shows the index patient.

Subsequently, the mutation status of 49 of his relatives belonging to a four-generation family with 153 members was evaluated (Fig. 1). Twelve family members tested negative for the mutation and were considered not to be at risk, as was their offspring ($n=21$). Seventeen family members, including the index patient, were identified as mutation carriers, 12 by DNA analysis and 5 were shown to be obligate carriers. All mutation carriers agreed to the clinical evaluation for PGL/PHEO as specified above, except for five obligate carriers that had already deceased before the discovery of *SDHB* as a PGL susceptibility gene and before the discovery of the PGL syndrome in this family. All five obligate carriers deceased without signs or symptoms of PGL/PHEO (at an average age of 72 years; range 34–97). One carrier was subjected to urine measurements of catecholamines only, because of young age (7 years).

Table 1. Phenotype of the 6 affected family members carrying the c.201-4429_287-933del founder mutation in *SDHB*

	Sex	Age	Symptomatic/ screening	PGL location	Catecholamine biochemistry at diagnosis	Other tumour (at diagnosis)	Disease course
1	M	50	Symptomatic	Carotid body PGL	Normal (urine)	Negative clinical screening	Benign
2	F	59	Symptomatic	PHEO	Elevated metanephrines, normal normetanephrines (urine)	Negative clinical screening	Benign
3	M	63	Symptomatic	PHEO	N/A	Hyperparathyroid	Malignant
4	M	39	Symptomatic	PHEO	N/A	Negative clinical screening	Malignant
5	M	77	Symptomatic	Jugulotympanic PGL	Normal (urine)	Negative clinical screening	Benign
6	F	41	Screening	Extra-adrenal PGL between aorta and inferior vena cava	Normal (urine)	Negative clinical screening	Benign

Abbreviations: *M* male; *F* female; *PGL* paraganglioma; *PHEO* pheochromocytoma; *N/A* not applicable.

Six mutation carriers (35%) were diagnosed with PGL (Table 1). Three patients (3 of 6; 50%) were diagnosed with a PHEO. Two patients (2 of 6; 33%) had a HNPG (one jugulotympanic and one carotid body tumor), and one (1 of 6; 17%) patient had an extra-adrenal PGL. Metastatic disease was identified in two patients (2/6; 33%), both diagnosed with a PHEO. There was no significant difference between the average age of symptomatic carriers (average age 61 years, range 43–79 years) and asymptomatic mutation carriers (average age of 46 years, range 7–73 years) ($p=0.29$). The average follow-up of the family members

carrying the mutation was 5 years (range 1–12 years). The estimated age-dependent penetrance for this *SDHB* exon 3 deletion at the ages of 40, 50, 60 and 70 is 0.04, 0.09, 0.15 and 0.21, respectively (Fig. 2).

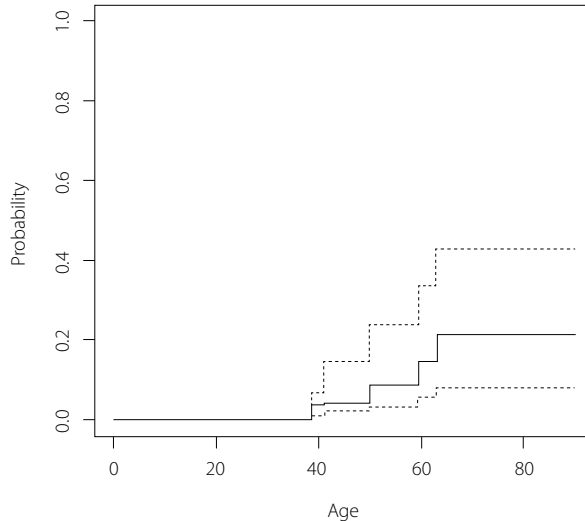


Figure 2. Estimated age-related penetrance of the *SDHB* exon 3 deletion in the family presented. Solid line: maximum likelihood estimated of the age-related penetrance. Upper dashed line: estimated upper bound of the age-related penetrance (Kaplan-Meier curve assuming all non-tested family members are non-carriers). Lower dashed line: estimated lower bound of the age-related penetrance (Kaplan-Meier curve assuming all non-tested family members are carriers without disease).

Discussion

In this study of an extended family with hereditary PGL syndrome due to a founder exon 3 deletion in the *SDHB* gene, we identified 17 mutation carriers, six of whom were clinically affected PGL patients. Clinical manifestations included benign HNPGL, extra-adrenal PGL, benign PHEO and metastatic PHEO. The number of HNPGL patients in this family is low (2 of 17; 11.7%) compared with previous reports (27–31%).^{2,3} The number of PHEOs (3 of 17; 18%) is comparable to what has been reported in the literature (18–28%), malignant PHEO however occurs less frequently in this family (2 of 17; 11.7%) than previously reported (20.6–25.2%).^{2,3} We found no multifocal tumor development. The average age at diagnosis (55 years, range 39–77) is higher compared to the average age found in other studies (30 and 37 years, respectively).^{2,4}

Most mutation carriers in this family were found to be disease free (11 of 17; 65%), and the age-related penetrance of this mutation is lower than the reported penetrance estimates

for *SDHB* mutations. The decreased penetrance found in this study might reflect a clinical characteristic of this specific Dutch *SDHB* founder mutation, or the influence of a shared genetic or environmental modifier of penetrance in this family. It might however also reflect an overestimation of *SDHB*-linked penetrance in the literature due to various forms of bias. Earlier studies on *SDHB*-linked PGL syndrome reported a penetrance of respectively 50–75% by the age of 50 years.^{2,5,11} In these studies, penetrance calculations were largely based on affected, apparently non-familial individuals. These calculations are prone to overestimation because of the limited inclusion of asymptomatic mutation carriers and because the mutation carriers were identified via index patients. As index patients are affected mutation carriers per definition, the chance of selecting other mutation carriers with the disease is increased (ascertainment bias).

Family-based studies that evaluated the penetrance of specific *SDHB* mutations have found lower penetrance estimates: Solis et al. described a family with 11 PGL patients among 41 mutation carriers of a large exon 1 deletion in *SDHB*, at this time the most extended *SDHB*-linked pedigrees.¹⁶ In this study, the estimated penetrance was 35% at age 50. Hes et al. reported 3 of 15 *SDHB* c.423 + 1G > A mutation carriers who developed PGLs and found a penetrance of 26% at 48 years.¹⁷ Although both studies included relatively large number of asymptomatic mutation carriers, the index patients were included in the penetrance calculations and the ascertainment bias was not corrected for. Schiavi et al. showed that addressing these sources of bias results in even lower penetrance estimates for *SDHB* mutations (13% at the age of 50).¹⁴

In the current study of an extended family linked to the c.201-4429_287-933del mutation in *SDHB*, we have corrected for ascertainment bias by using the maximum likelihood estimate of the penetrance function and excluded the index patient from the penetrance calculations, resulting in an even lower penetrance of 9% at 50 years. This maximum likelihood estimate may represent an overestimation of the true penetrance, because of the ascertainment bias that is inevitably introduced by evaluating family members of an affected patient. In addition, when presymptomatic DNA testing is offered, individuals from affected branches of the family or individuals who experience symptoms of PGL-related disease may be more inclined to consent.

However, because the pedigree presented in this study is large and the individuals who have not been tested were included in the likelihood function, the bias is expected to be small. The estimated upper limit of the penetrance for this mutation was calculated by leaving all untested individuals out of the calculation (dashed upper line in Fig. 2). In this case, the penetrance increases to 24% at 50 years (dashed upper line in Fig. 2), which is close to the described penetrance by Solis et al. and Hes *et al.*^{16,17} The estimated lower limit of the penetrance is calculated by presuming that all untested individuals are mutation carriers without disease, which results in a penetrance of 3.7% at 50 years (dashed lower line in Fig. 2).

Although the number of mutation carriers and PGL-PHEO patients in this family is limited compared to the large patient cohorts mentioned above, family-based study designs yield more specific information on the penetrance and phenotype of specific mutations. Moreover, penetrance calculations may be more accurate because comprehensive family screening not only identifies PGL-PHEO patients but also enables the identification of asymptomatic mutation carriers. In combination with the appropriate statistical correction of the ascertainment bias, this results in reduced estimates of *SDHB*-linked penetrance. This low penetrance of *SDHB* mutations may obscure the hereditary nature of the disease, and is an important aspect of the genetic counseling of *SDHB*-linked patients.

Acknowledgements

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