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# Chapter 5

## Penetrance and phenotype of the *SDHD.D92Y* mutation

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## Abstract

Germline mutations in *SDHD* predispose to the development of head and neck paragangliomas, and pheochromocytomas. The risk of developing a tumor depends on the sex of the parent who transmits the mutation: paragangliomas only arise upon paternal transmission. In this study, both the risk of paraganglioma and pheochromocytoma formation, and the risk of developing associated symptoms were investigated in 243 family members with the *SDHD.D92Y* founder mutation. By using the Kaplan-Meier method, age-specific penetrance was calculated separately for paraganglioma formation as defined by magnetic resonance imaging (MRI) and for paraganglioma-related signs and symptoms. Evaluating clinical signs and symptoms alone, the penetrance reached a maximum of 57% by the age of 47 years. When MRI detection of occult paragangliomas was included, penetrance was estimated to be 54% by the age of 40 years, 68% by the age of 60 years and 87% by the age of 70 years. Multiple tumors were found in 65% and pheochromocytomas were diagnosed in 8% of paraganglioma patients. Malignant paraganglioma was diagnosed in one patient (3%). Although the majority of carriers of a paternally inherited *SDHD* mutation will eventually develop head and neck paragangliomas, we find a lower penetrance than previous estimates from studies based on predominantly index cases. The family-based study described here emphasizes the importance of the identification and inclusion of clinically unaffected mutation carriers in all estimates of penetrance. This finding will allow a more accurate genetic counseling and warrants a 'wait and scan' policy for asymptomatic paragangliomas, combined with biochemical screening for catecholamine excess in *SDHD*-linked patients.

## Introduction

Paragangliomas of the head and neck are rare, usually benign tumors that arise in the paraganglion tissue associated with the parasympathetic nervous system[1]. The carotid body in the carotid bifurcation is most frequently affected, followed by the jugulo-tympanic bodies at the jugular bulb and tympanic nerve, and the vagal bodies at the ganglions of the vagal nerve. Symptoms are usually mild and tumor progression is characteristically slow, and therefore diagnosis of the disease is often not made before adulthood[2]. An estimated 10-50% of head and neck paragangliomas are hereditary[3]. The natural course of the disease in hereditary cases does not seem to be different from sporadic paragangliomas, but patients with inherited disease are more likely to develop multiple paragangliomas[4]. Hereditary head and neck paragangliomas can be caused by germline mutations in several genes encoding subunits of the mitochondrial succinate dehydrogenase (SDH) complex: the *SDHB*, *SDHC* and *SDHD* gene[5-7]. *SDHB* (1p36.1-p35), encodes a catalytic subunit, whereas *SDHC* (1q21) and *SDHD* (11q23) encode membrane-anchoring subunits of SDH involved in electron transport. Furthermore, a yet unidentified gene (*PGL2*) on 11q13.1 causes paraganglioma in at least one family[8]. Mutations in *SDHB*, *SDHC* and *SDHD* are also associated with the development of (extra-) adrenal paragangliomas or pheochromocytomas[9-12].

As paragangliomas can cause incapacitating symptoms, accurate disease risk estimates are of paramount importance in clinical decision making and genetic counseling of paraganglioma patients. The chance of developing disease is dependent on the gene that is affected: in *SDHB*- and *SDHC*-linked families, inheritance is autosomal dominant, whereas in *SDHD*- and *PGL2*-linked families, the inheritance pattern shows a parent-of-origin effect[6,12]. As a rule, individuals are at risk only when they inherit the mutant *SDHD* allele from the father (regardless of his clinical status) and not when the mutation is maternally inherited[13,14]. Thus, proper genetic counseling of *SDHD*-linked paraganglioma families requires knowledge about the risk of developing head and neck paraganglioma upon paternal transmission of a *SDHD* mutation (penetrance), the risk of developing clinical symptoms, the age at onset of the disease, the risk of developing multiple tumors and the risk of developing pheochromocytoma. To date, two reports have discussed the risk of developing paraganglioma or pheochromocytoma upon inheritance of a *SDHD* mutation[15,16]. Both studies found that no tumors developed after maternal transmission of the *SDHD* mutation, and that penetrance of disease was 100% at the age of 70 years upon paternal transmission. However, both studies have evaluated a heterogeneous population of *SDHD* mutation carriers with different *SDHD* mutations, relatively large numbers of index cases (16 different *SDHD* mutations in 19 index patients and 15 different

*SDHD* mutations in 24 index cases, respectively) and small numbers of asymptomatic family members[15,16]. This study design is prone to overestimation of penetrance if the index cases are selected from families with multiple affected individuals and if insufficient asymptomatic family members are included. Moreover, different mutations may confer different risks[17]. In this study, we have therefore evaluated age-specific risk of developing a paraganglioma and/or pheochromocytoma in an extended family consisting of 243 family members, in which the D92Y germline mutation in the *SDHD* gene segregates. As a significant number of paragangliomas remain asymptomatic even at advanced ages, the age-specific risk of developing paraganglioma-related symptoms is as important in counseling paraganglioma patients as the age-specific risk of developing a paraganglioma. For that reason, we have evaluated the penetrance of symptomatic disease and the penetrance of tumor development separately.

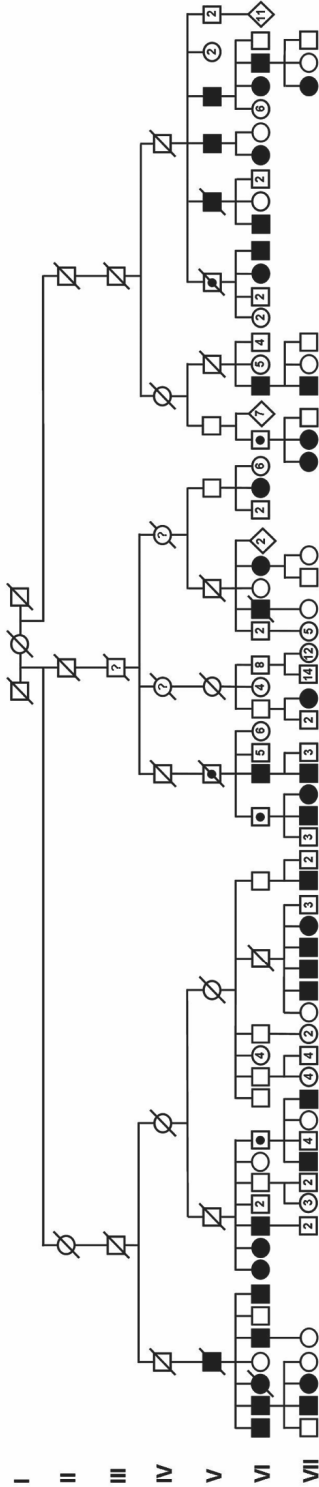
## Materials and methods

### Clinical status

The disease status of 243 relatives belonging to a seven-generation family with head and neck paragangliomas (family FGT189) was established between 1990 and 2008. The pedigree of this family has been published before and was updated for this study (Figure 1)[18-20]. For the evaluation of clinical characteristics, data from the family members of generations V, VI and VII were used, because patients in older generations were not available for adequate clinical analysis. Family members from generation V, VI and VII underwent magnetic resonance imaging (MRI) of the head and neck if they showed signs or symptoms of paragangliomas. All non-symptomatic carriers of a paternal mutation, who were identified during genetic counseling, were offered clinical evaluation and MRI screening as well. In addition, the data acquired in a previous research protocol were used, in which 83 members of this family were examined with MRI, regardless of their disease status and sex of the carrier parent[18]. To detect occult pheochromocytomas, head and neck paraganglioma patients were biochemically screened for catecholamine excess. If screening was positive, MRI of the abdomen and <sup>123</sup>I-MIBG scintigraphy was performed.

### Age at onset

As initial symptoms can be very mild and growth of paragangliomas is usually slow, there may be a substantial delay before a patient comes under medical attention. It can therefore be difficult to establish the exact age at onset of paraganglioma formation. We have defined 'age at onset' as the age at onset of complaints and/or symptoms, that



**Figure 1.** Pedigree of family FGT189. Roman numerals correspond to the subsequent generations of the FGT189 family. Squares depict males, circles depict females and diamonds depict multiple siblings of both sexes. Open symbols represent unaffected family members, dotted symbols represent unaffected obligate carriers of a paternally inherited *SDHD* mutation and solid symbols represent affected family members. A question mark within a symbol stands for a possibly affected family member, as inferred from carrier status of offspring. A number within a symbol indicates the number of siblings.

is, the age at which the patient retrospectively first experienced complaints of a head and neck paraganglioma or pheochromocytoma, as opposed to the age at diagnosis, that is, the age at which the patient came under medical attention and the diagnosis of paraganglioma and/or pheochromocytoma was established.

### **Genetic status**

Paraganglioma patients in family FGT189 were shown to harbor the D92Y missense mutation (g.7882 T>C; p.Asp92Tyr) in the *SDHD* gene[21]. This Dutch founder mutation was detected by direct sequencing of PCR products obtained from peripheral blood lymphocyte DNA, as described previously[7].

### **Penetrance**

For penetrance calculations, only the data from generations VI and VII were used, because insufficient data were available to identify asymptomatic mutation carriers in older generations (Figure 1). In this way, the risk of bias in penetrance calculations is minimized. Given the typical inheritance pattern of *SDHD*-linked paragangliomas, children of female mutation carriers were considered not to be at risk[13,22]. For children of affected fathers, the risk of inheriting the mutation was estimated to be 50%. Penetrance was calculated by comparing the actual number of patients with and without symptoms with the expected number of family members at risk of inheriting the mutation[23]. Next, we combined genetic and clinical data to calculate age-related penetrance in this family. Penetrance was expressed as a Kaplan-Meier curve, representing the probability of a *SDHD* mutation carrier to have developed either paraganglioma-related signs or symptoms, or a detectable paraganglioma at a given age. Calculations were performed for symptomatic and asymptomatic paragangliomas confirmed by radiology and for symptomatic paragangliomas alone.

## **Results**

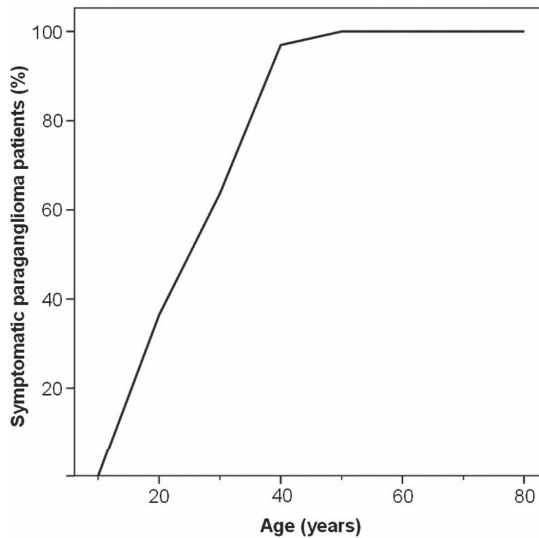
### **Clinical status**

Figure 1 shows the pedigree of family FGT189. In generations V, VI and VII, paragangliomas were diagnosed in 40 family members (25 men, 15 women). Seven of these individuals (18%) had no signs or symptoms, and their diagnosis was made only after MRI screening. Multiple tumors were present in 26/40 patients (65%), to a maximum of five per patient. The most frequently encountered location was the carotid body (29 patients, 39 tumors) followed by jugulo-tympanic tumors (20 patients, 23 tumors) and the vagal body (13 patients, 16 tumors). Furthermore, 3/40 patients (8%) with head and neck

paragangliomas also had an adrenal pheochromocytoma as diagnosed by  $^{123}\text{I}$ -MIBG scintigraphy and MRI. In 1/40 paraganglioma patients (3%), metastatic paraganglioma tissue was found in the lung and spinal column, and this tumor was thus classified as malignant paraganglioma.

### Age at onset of symptoms

In generations V, VI and VII, 33 paraganglioma patients experienced symptoms. The age at onset of symptoms ranged from 14 to 47 years (mean 26.5 years; 95% CI, 23.5-29.6 years), with a mean delay of 2.6 years (95% CI, 1.4-3.7 years) until diagnosis (Figure 2).



**Figure 2.** Age at onset of symptoms in *SDHD*-linked paraganglioma patients. Cumulative chart of the age at which the first symptoms of a head and neck paraganglioma or pheochromocytoma became evident in the symptomatic family members in generation V, VI and VII ( $n = 33$ ).

### Genetic status

In generation VI and VII, a total of 211 family members were alive at ascertainment and in Mendelian line of inheriting the D92Y founder mutation in the *SDHD* gene. Of these 211, 22 asymptomatic family members declined the invitation to be tested for the mutation. A total of 63 of the remaining 189 family members tested positive, 52 of whom inherited the mutation from their father. One of the 22 asymptomatic family members who could not be tested was identified as an obligate carrier of a paternally inherited mutation,

because of affected offspring. In all, 53 paternal and 11 maternal mutation carriers were thus identified in generation VI and VII.

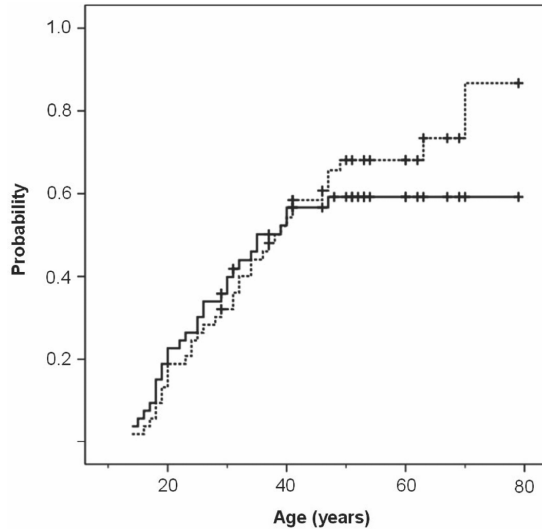
### Penetrance

As expected, penetrance of the disease was parent-of-origin-dependent. No paragangliomas were found by clinical investigation or MRI in the offspring of female *SDHD* mutation carriers, and they were therefore not included in the risk calculations. We identified 11 male mutation carriers in generation V and 17 in generation VI on the basis that they were either affected themselves or had an affected offspring. In total, we identified 138 children of male mutation carriers (83 in generation VI and 55 in generation VII), who were thus all at 50% risk of inheriting the *SDHD* mutation. Of the 138 family members, 36 (26%) had one or more radiologically proven head and neck paragangliomas and/or a pheochromocytoma. A total of 30 of these 36 patients (83%) experienced symptoms at the time of diagnosis or developed symptoms in the follow-up period. Under the assumption that 50% of the children of paternal mutation carriers are at risk, this corresponds with an estimated overall penetrance of 36/69 (52%) and an estimated overall clinical penetrance of 30/69 (43%)[23].

Using the genetic data, 53 of the 138 children (38%) at risk of a paternally transmitted mutation in generation VI and VII were shown to actually have inherited the mutation (Table 1). A total of 30 of these carriers at risk presented with paraganglioma- or pheochromocytoma- related symptoms, accounting for an overall clinical penetrance of 30/53 (57%). To correct for the age at onset, a Kaplan–Meier curve was made representing the chance to be symptom free as a function of time (Figure 3). As none of the carriers developed symptoms after the age of 47 years, the penetrance reached a maximum of 57% at this age. Of the 23 clinically non-penetrant carriers of the disease gene, 12 were examined with MRI. In six cases (50%), one or more paragangliomas were diagnosed, raising the overall penetrance to 36/53 (68%) (Table 1). If these cases were included in a Kaplan–Meier curve, the penetrance increased to 87% by 70 years of age (Figure 3).

**Table 1.** Penetrance in generations VI and VII.

Carriers of a paternally inherited <i>SDHD</i> mutation (n)			Symptomatic paraganglioma patients (n)			MRI diagnosed paraganglioma patients (n)		
<i>total</i>	<i>male</i>	<i>female</i>	<i>total</i>	<i>male</i>	<i>female</i>	<i>total</i>	<i>male</i>	<i>female</i>
53	31	22	30(57%)	18	12	36(68%)	21	15



**Figure 3.** Penetrance of *SDHD*-linked head and neck paragangliomas. Inverted Kaplan–Meier curve indicating the probability of developing a MRI-detectable paraganglioma (dotted line) or the probability of developing paraganglioma-related symptoms (solid line) at a certain age for carriers of a paternally inherited *SDHD* mutation. Vertical markers indicate censored patients.

## Discussion

*SDHD*-linked paragangliomas and pheochromocytomas present a unique tumor syndrome with a specific, parent-of-origin-dependent risk of inheriting disease. In this study, we did not observe the development of paragangliomas or pheochromocytomas in 11 instances of maternal transmission of the *SDHD* mutation. This parent-of-origin-dependent inheritance seems to be the norm in *SDHD*-linked paraganglioma families, although one case of a tympanic paraganglioma after maternal transmission has been reported[13,14]. Recently, new insights in the mechanisms behind this peculiar inheritance pattern have emerged. We have shown previously that in *SDHD*-linked paragangliomas, not only the wild-type maternal *SDHD* allele on 11q23 but the entire maternal copy of chromosome 11 was consistently lost[22]. A model explaining the parent-of-origin-dependent inheritance in *SDHD*-linked cases was proposed, involving a second, paternally imprinted, tumor-suppressor gene (TSG) located on 11p15[22]. Within this model, paraganglioma formation occurs only when the wild type maternal *SDHD* allele on 11q23 and the active copy of the imprinted TSG on 11p15 are simultaneously lost. This model of inheritance has been supported by the report of Pigny et al., who describe the only known case of maternal transmission of *SDHD*-linked paraganglioma to date[24]. Although at first sight, this unique

case seems to contradict the model, it was shown that the patient had also acquired an altered methylation profile and, therefore, probably an altered imprinted status of H19, a known paternally imprinted TSG on 11p15[24]. This suggests that the parent-of-origin-dependent inheritance of *SDHD*-linked disease is caused by the paternal imprinting of H19, a TSG on the imprinted 11p15 region that seems to be essential for paraganglioma formation. It furthermore suggests that maternal transmission of *SDHD*-linked disease is possible only if the 'second hit' targets the wild-type paternal *SDHD* allele on 11q23 as well as the active status of the maternal H19 allele on 11p15. The fact that these events involve different regions of different copies of chromosome 11 simultaneously is likely to be the reason why maternal transmission of disease is extremely rare.

This has considerable consequences on the genetic counseling of the affected families. Although children of female mutation carriers may not be completely preserved from the risk of developing paraganglioma, maternal transmission of disease remains extremely rare. Offspring of female carriers must, however, be aware that they can be mutation carriers and transmit the disease gene to their children. On the other hand, carriers of a paternally inherited *SDHD* mutation are at risk of developing a head and neck paraganglioma and/or pheochromocytoma. In this study, the overall risk of developing a paraganglioma upon paternal transmission of the *SDHD* mutation is 68%, when evaluating the results of clinical evaluation and MRI. Age-related penetrance is 54% at the age of 40 years and 68% at the age of 60 years, reaching a maximum of 87% by the age of 70 years, that is, the large majority of patients with a paternally derived disease gene will eventually develop one or more paragangliomas and/or a pheochromocytoma (Figure 3). These figures may represent an underestimation, because MRI scanning and screening for catecholamine excess was declined by 11 of the 23 asymptomatic paternal mutation carriers. Even in the unlikely event that all these would have had one or more occult paragangliomas or a pheochromocytoma, overall penetrance is raised only marginally up to a maximum of 89%. Hence, this cannot fully explain why our estimates are slightly lower compared with those reported in the literature. Benn et al. reported an estimated age-related penetrance for *SDHD*-linked disease of 73% at the age of 40 years and 100% at the age of 70 years, whereas Neumann et al. reported a penetrance of 86% at the age of 50 years and 100% at the age of 70 years[15,16]. In the latter two studies, multiple families with multiple index patients and different *SDHD* mutations were investigated. In contrast, we have evaluated a single extended family with the D92Y Dutch founder mutation in the *SDHD* gene for the calculation of penetrance in *SDHD*-linked disease[15,16]. There is evidence that this family based approach yields more accurate estimates, because less index cases and more asymptomatic mutation carriers are included[25]. However, bias may arise if family members share unknown genetic or environmental factors that influence

disease risk[25,26]. This could lead to overestimation of penetrance in *SDHD*-linked disease, especially when high-risk families are used for penetrance calculations[25,27]. In this respect, it is interesting to note that age-related penetrance estimates of *SDHD*-linked disease found in this study are lower compared with those reported by Benn et al. and Neumann et al.[15,16]. This may reflect an upward bias in the latter two studies because of the inclusion of large numbers of index cases and relatively low numbers of asymptomatic mutation carriers. Further positive bias may have arisen in these studies because all risk factors tend to be overrepresented in case patients[28].

The risk of developing head and neck paraganglioma and/or pheochromocytoma, or penetrance of the disease, is not the only feature that is important in counseling *SDHD* mutation carriers. The risk of developing associated symptoms is at least as relevant in counseling and clinical decision making. In this study, evaluation of the age-related occurrence of clinical symptoms upon paternal transmission of a *SDHD* mutation reveals that a significant number of individuals at risk did not develop clinical symptoms despite the fact that some of them have reached advanced ages. In actual fact, no patients developed first symptoms after the age of 47 years, and clinical penetrance reaches a maximum of 57% at this age (Figure 3). Clinical penetrance might even have been overestimated in our study, because 21 asymptomatic family members at risk of inheriting the *SDHD* mutation through the father were not tested for the *SDHD* mutation and their carrier status could not be inferred from their offspring. Assuming that 50% of these 21 untested family members would have inherited the mutation, the clinical penetrance decreases to 50%. In the unlikely event that all 21 untested family members would have inherited the *SDHD* mutation, clinical penetrance is at least 41%.

Astrom et al. observed that patients with multiple *SDHD*-linked tumors or a concurrent pheochromocytoma at the time of diagnosis had lived at higher mean altitudes as compared with those with single tumors[29]. They postulated that the low altitudes found in the western part of the Netherlands cause a milder disease phenotype, manifesting as reduced penetrance and a better fitness of *SDHD* mutations. This would explain the relatively high incidence of hereditary paragangliomas and the remarkable clustering of founder mutations in the *SDHD* gene in the Netherlands[29]. However, despite the fact that most family members of family FGT189 live in the western part of the Netherlands, a region situated at sea level, multiple tumors were ascertained in 65% of its patients, as compared with 30-74% in other studies[15,16,29]. In addition, the risk of developing pheochromocytoma is 8% for paraganglioma patients in this family, at the lower end of the spectrum of published risk estimates (7-53%), but comparable with that of patients living at higher altitudes (10%)[10,15,16,29]. Remarkably, Astrom et al. did not observe

an effect of altitude on age at onset, although age-dependent carotid body hyperplasia at high altitudes has been observed by others[29,30]. However, they did find a correlation between age at onset and mutation type[29]. Patients harboring missense mutations in the *SDHD* gene seemed to develop symptoms later in life than those harboring nonsense or splicing mutations (mean age at onset of 34.3 years vs. 25.8 years, respectively)[29]. In the present family, patients harboring the D92Y missense mutation had a mean age at onset of 26.5 years (95% CI, 23.5-29.6 years), which was in good agreement with other studies that have evaluated paraganglioma patients with different *SDHD* mutations (25.8-30.6 years)[15,16,29]. Malignancy or metastatic disease, a rare finding in *SDHD*-linked disease with an estimated prevalence of 0-10%, has not been associated with residential altitude, nor with mutation type[15,16,29,31]. In the present family too, only one patient (3%) was diagnosed with a paraganglioma metastasis. All in all, the disease phenotype of the *SDHD.D92Y* mutation in this extended family residing at sea level does not seem to represent a milder or otherwise different phenotype than that of patients living at high altitudes or those carrying other mutation types, and hence altitude is unlikely to explain the observed lower penetrance. Probably, more relevant is the fact that the *SDHD.D92Y* missense mutation has a detrimental effect on the functionality of the SDH-complex[32]. Moreover, as most patients develop first symptoms after reaching reproductive age, and symptoms are usually mild and slowly progressive even at high altitudes, it is doubtful whether negative selection plays a decisive role in the geographical distribution of *SDHD* mutations. Rather, the high incidence of founder mutations in the Netherlands is explained by specific historic and demographic factors, such as migrational patterns, endogamy and rapid population growth, factors that have contributed to the existence of a striking number of Dutch founder mutations in other disease genes[33].

In summary, we have provided risk estimates for a well-defined *SDHD*-linked population and have shown that penetrance of disease differs considerably depending on whether or not MRI-screening results are included. Whereas the large majority of paternally inherited *SDHD* mutation carriers may eventually develop one or more paragangliomas (87%), symptoms do not occur in substantial proportion of these carriers at risk (43%), probably because of the characteristic indolent growth pattern of paragangliomas[2]. Patients who do develop complaints associated with paraganglioma or pheochromocytomas generally do so before the age of 50 years; the risk of developing symptoms later in life seems small. This knowledge might reassure especially older non-symptomatic carriers and warrants a 'wait and scan' policy for patients with asymptomatic head and neck paragangliomas. Because of the elevated risk of developing a pheochromocytoma in *SDHD*-linked disease, surveillance should include screening for the detection of asymptomatic pheochromocytomas[2,10].

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