Universiteit
Leiden
The Netherlands

Paragangliomas: Clinical Picture

Niemeijer, N.D.

Citation
Niemeijer, N. D. (2017, March 29). *Paragangliomas: Clinical Picture*. Retrieved from https://hdl.handle.net/1887/47852

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/47852

Note: To cite this publication please use the final published version (if applicable).

Cover Page

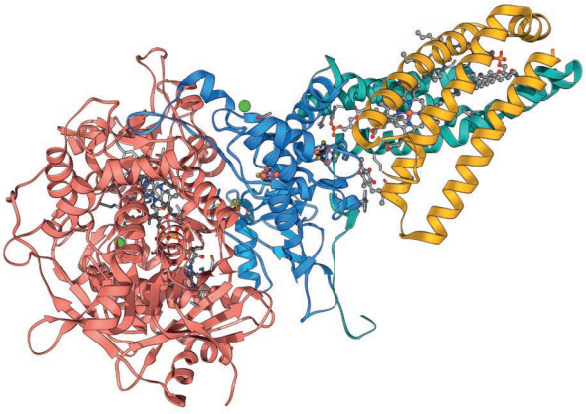
Universiteit Leiden

The handle http://hdl.handle.net/1887/47852 holds various files of this Leiden University dissertation

Author: Niemeijer, N.D.
Title: Paragangliomas: Clinical Picture
Issue Date: 2017-03-29

Chapter 8

Summary and conclusions



In the current thesis, we evaluated the clinical characteristics of *SDHx* mutation carriers, described genotype-phenotype correlations, assessed which (nonparaganglionic) tumors can also be linked to *SDHx* mutations and reviewed various treatment options for malignant pheochromocytoma (PCC)/paraganglioma (PGL).

Mutations in any one of the genes encoding succinate dehydrogenase (SDH) complex subunits or co-factors (*SDHA, SDHB, SDHC*, *SDHD*, and *SDHAF2*) can lead to formation of hereditary PGL syndromes. Mutations in *SDHB* and *SDHD* are generally the most common. In the Netherlands, the majority of the *SDH* mutation carriers harbor one specific mutation of *SDHD*, the c.274G>T, pAsp92Tyr.[1,2] *SDHB* mutations are less common, but the majority of *SDHB* mutation carriers also harbor known Dutch founder mutations, specifically the c423+1G>A mutation or the exon 3 deletion, c.201-4429_287-933del.[1] The reported penetrance of *SDHB* mutations (26-75%) is lower than the penetrance of *SDHD* or *SDHAF2* mutations (88-100% and 87-100%, respectively).[3-12] In **chapter 2**, an extended family with a founder exon 3 deletion in the *SDHB* gene was studied. From the 17 mutation carriers, 6 were clinically affected PGL patients. The calculated penetrance in this study was 9% at 50 years. The lower 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. However, it might also reflect an overestimation of *SDHB*-linked penetrance in the literature due to various forms of bias. In the literature, penetrance calculations are prone to overestimation because of the limited inclusion of unaffected mutation carriers and because the mutation carriers are identified via index patients. This might give a higher chance of selecting other mutation carriers with the disease (ascertainment bias). We included a relatively large number of unaffected mutation carriers and corrected for ascertainment bias. Also we excluded the index patient from the calculations. This resulted in reduced estimates of *SDHB*-linked penetrance and might be very important in the (genetic) counseling of *SDHB*-linked patients.

In **chapter 3**, we determined phenotypical characteristics of a large Dutch cohort of *SDHB* mutation carriers and assessed differences in clinical phenotypes related to specific *SDHB* mutations. We conducted a retrospective descriptive study in seven academic centers and included 196 *SDHB* mutation carriers. The study contained 65 (33.2%) index patients and 131 (66.8%) relatives. Fifty-four mutation carriers (27.6%) had one or multiple head and neck PGLs (HNPGLs), 4 (2.0%) had a PCC and 26 (13.3%) had one or more sympathetic PGLs. The figures for PCC en sPGL we found in our study were lower than that reported in previous studies that have assessed clinical characteristics in *SDHB* mutation carriers.[3,7,13,14] Because we included a large number of unaffected mutation carriers, ascertainment bias might play only a minor role. Furthermore, percentages mentioned in previous studies took into

account only disease-affected subjects. However, if we excluded all unaffected mutation carriers from our cohort, we still found lower figures for PCC and sPGL.
The frequency we found for HNPGLs (27.6%) was relatively high compared with other studies (6-31%)[3,7,13,14], and when we excluded all unaffected mutation carriers, our prevalence was as high as 65.1%. This might in part be explained by the observation that in our study the proportion of HNPGL patients with a positive family history (i.e. non-index HNPGL patients) is 29·6% (16/54). The large majority of these patients had no symptoms and had not yet come to medical attention. The genetic testing of relatives and structured follow-up protocols of persons with a *SDHB* mutation in the Netherlands identifies a relatively high number of asymptomatic mutation carriers, with or without tumors, allowing for a more accurate representation of the phenotype of *SDHB* mutation carriers.
Only 15 patients (7.7%) developed a malignant PGL and 17 patients (8.7%) developed non-paraganglionic tumors, including 5 renal cell carcinomas (RCCs) and 2 gastric gastrointestinal stromal tumors (GIST).
Statistical analyses showed no significant differences in the number and location of HNPGLs, sPGLs or PCC, nor in the occurrence of malignant disease or other tumors between carriers of the two founder *SDHB* mutations (exon 3 deletion versus c.423+1G>A).
This study underlines the importance of the inclusion of unaffected identified carriers in studies that assess phenotypes of germline mutations. The results from this study are important to consider in the clinical management and genetic counseling of families with PCC/PGL syndromes. Including unaffected carriers provides a more accurate insight into the spectrum of disease.

In **chapter 4** we investigated which nonparaganglionic tumors belong to the SDH-associated tumor spectrum. If mutations occur in the *SDHA*, *SDHB*, *SDHC*, *SDHD*, or *SDHAF2* genes with corresponding loss of the wild-type allele or a second inactivating mutation, SDHB immunohistochemical staining will become negative.[15] This negative staining for SDHB is now a validated and highly sensitive marker for germline mutations of any of the SDH subunits and is a broadly accepted indication of pathogenicity of an *SDH* mutation.[16] In addition, SDHA immunohistochemistry is a proven marker for *SDHA* mutations, showing loss of immunoreactivity exclusively in *SDHA*-mutated tumors.[15] We analyzed 35 nonparaganglionic tumors from 26 *SDH* mutation carriers. Eight tumors showed negative staining for SDHB and positive staining for SDHA: a pancreatic neuroendocrine tumor (NET), a macroprolactinoma, two gastric GISTs, an abdominal ganglioneuroma, and three RCCs. A prolactinoma in a patient with a germline *SDHA* mutation was the only tumor immunonegative for both SDHA and SDHB. Sanger sequencing of this tumor revealed a somatic mutation (p.D38V) as a likely second hit leading to biallelic inactivation of SDHA. Our study strengthens the etiological association of *SDH* genes with pituitary neoplasia, renal

tumorigenesis, and gastric GISTs. Furthermore, our results indicate that pancreatic NET also falls within the SDH-related tumor spectrum. Our report was the first report of an association between a germline *SDHD* mutation and pancreatic NET. This finding might have potential implications for the surveillance of patients with a germline *SDHD* mutation, because in the existing surveillance protocol, abdominal imaging is only advised when there is evidence of catecholamine excess. It might be advisable to amend surveillance protocols, with the addition of standard abdominal imaging studies. However, the occurrence rate in our study was rare, and further studies are needed to definitely amend surveillance protocols.

Paragangliomas in the head and neck region can arise from the carotid body, vagal body, or jugulotympanic tissue (i.e. paraganglioma of the temporal bone). Due to their location in close proximity to important neurovascular structures, tumor growth may lead to serious morbidity and cranial nerve impairment. With removal of these tumors, branches of the carotid sinus nerves may not be spared. Bilateral carotid body tumor resection (bCBR) may thus result in arterial baroreflex dysfunction. In **chapter 5** we investigated the role of the baroreflex during sleep. We found that bCBR was associated with decreased low frequency power during sleep, suggesting impaired baroreflex function. The effect of sleep on heart rate was similar in bCBR patients and their matched controls, suggesting that the sleep-related heart rate decrease primarily results from non-baroreflex mediated pathways.

The risk of malignant transformation is 10% for PCC and 10-20% for extra-adrenal non-HNPGLs.[17] Treatment of malignant disease remains basically palliative. Radionuclide therapy using ^{131}I-MIBG has been investigated in several studies, however, with varying success rates. Because the precise effect of ^{131}I-MIBG therapy for the treatment of malignant PCC/PGL remained unclear, we performed a systematic review and meta-analysis. The results of this meta-analysis assessing the effects of ^{131}I-MIBG therapy on tumor volume in patients with malignant PCC/PGL are reported in **chapter 6**. We included 17 studies in our meta-analysis, with a total of 243 patients. We showed that stable disease following ^{131}I-MIBG therapy could be achieved in 52% of the patients and a partial hormonal response in 40%. Reported 5-year survival rates were 45% and 64% and mean progression-free survival times 23·1 and 28·5 months. The most frequent side effect was haematologic toxicity. In the included studies, the protocol when to initiate treatment differed widely. Many of the studies included patients irrespective of evidence of progressive disease. Therefore it might be possible that stable disease is not merely a therapy effect, but also a reflection of the natural course of the disease, with slow progression in a subset of patients.

Chemotherapy is another treatment option for patients with malignant PCC/PGL. Combination chemotherapy of cyclophosphamide, vincristine and dacarbazine (CVD) was

introduced in 1985 by Keiser *et al.*[18] A meta-analysis assessing the effect of CVD chemotherapy has never been performed. Therefore, in **chapter 7**, we performed a systematic review and meta-analysis addressing this effect. We included four studies concerning a total of 50 patients with malignant PCC/PGL. The meta-analysis of the effect of chemotherapy on tumor volume showed pooled percentages of complete response, partial response and stable disease of respectively 4% (95% CI: 1%-15%), 37% (95% CI: 25%-51%) and 14% (95% CI: 7%-27%). Only two studies concerning a total of 35 patients assessed the response on catecholamine excess; pooled percentages for complete, partial and stable hormonal response were 14% (95% CI: 6%-30%), 40% (95% CI: 25%-57%) and 20% (95% CI: 10%-36%), respectively. In the included studies, the protocol when to initiate treatment was not well described. Therefore it might be possible that the reported effect of chemotherapy on tumor volume reflects the natural course of the disease, at least partially.

Conclusions

The findings of this thesis can be summarized in the following conclusions:

1. The penetrance of the germline exon 3 *SDHB* mutation might be lower than previously described.
2. The inclusion of unaffected identified carriers in studies that assess phenotypes of germline mutations is very important to provide a more accurate insight into the spectrum and penetrance of disease.
3. The pancreatic NET is a new component of the SDH-related tumor spectrum. This might have potential implications for the surveillance of patients with a *SDHD* mutation, because at the moment abdominal imaging is not a standard part of the surveillance protocol.
4. After bilateral carotid body tumor resection, patients exhibit baroreflex dysfunction. Sleep-related heart rate changes are similar between bCBR patients and controls, suggesting that the effects of sleep on heart rate are predominantly generated through central, non-baroreflex mediated pathways.
5. In patients with malignant PCC/PGL, concerning tumor volume, stable disease following ^{131}I-MIBG therapy can be achieved in 52% of the patients and a partial hormonal response in 40%.
6. With CVD chemotherapy, a partial response concerning tumor volume can be achieved in about 37% of patients with malignant PCC/PGL and a partial response on catecholamine excess in about 40% of patients.

References

1. Hensen EF, van Duinen N, Jansen JC, et al. High prevalence of founder mutations of the succinate dehydrogenase genes in the Netherlands. Clinical Genet 2012;81:284-288.
2. Taschner PE, Jansen JC, Baysal BE, et al. Nearly all hereditary paragangliomas in the Netherlands are caused by two founder mutations in the SDHD gene. Genes Chromosomes Cancer 2001;31:274-81.
3. Neumann HP, Pawlu C, Peczkowska M, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA 2004;292:943-951.
4. Hensen EF, Jordanova ES, van Minderhout IJ, et al. Somatic loss of maternal chromosome 11 causes parent-of-origin-dependent inheritance in SDHD-linked paraganglioma and phaeochromocytoma families. Oncogene 2004;23:4076-4083.
5. Kunst HP, Rutten MH, de Monnink JP, et al. SDHAF2 (PGL2-SDH5) and hereditary head and neck paraganglioma. Clin Cancer Res 2011;17:247-254.
6. Hensen EF, Jansen JC, Siemers MD, et al. The Dutch founder mutation SDHD.D92Y shows a reduced penetrance for the development of paragangliomas in a large multigenerational family. Eur J Hum Genet 2010;18:62-66.
7. Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab 2006;91:827-836.
8. van der Mey AG, Maaswinkel-Mooy PD, Cornelisse CJ, Schmidt PH, van de Kamp JJ. Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. Lancet 1989;2:1291-1294.
9. Schiavi F, Milne RL, Anda E, et al. Are we overestimating the penetrance of mutations in SDHB? Hum Mutat 2010;31:761-762.
10. Solis DC, Burnichon N, Timmers HJ, et al. Penetrance and clinical consequences of a gross SDHB deletion in a large family. Clin Genet 2009;75:354-363.
11. Hes FJ, Weiss MM, Woortman SA, et al. Low penetrance of a SDHB mutation in a large Dutch paraganglioma family. BMC Med Genet 2010;11:92.
12. Bayley JP, Grimbergen AE, van Bunderen PA, et al. The first Dutch SDHB founder deletion in paraganglioma-pheochromocytoma patients. BMC Med Genet 2009;10:34.
13. Srirangalingam U, Walker L, Khoo B, et al. Clinical manifestations of familial paraganglioma and phaeochromocytomas in succinate dehydrogenase B (SDH-B) gene mutation carriers. Clin Endocrinol 2008;69:587-596.
14. Ricketts CJ, Forman JR, Rattenberry E, et al. Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. Hum Mutat 2010;31:41-51.
15. Papathomas TG, Oudijk L, Persu A, et al. SDHB/SDHA immunohistochemistry in pheochromocytomas and paragangliomas: a multicenter interobserver variation analysis using virtual microscopy: a Multinational Study of the European Network for the Study of Adrenal Tumors (ENS@T). Mod Pathol 2015;28:807-821.
16. Gill AJ, Benn DE, Chou A, et al. Immunohistochemistry for SDHB triages genetic testing of SDHB, SDHC, and SDHD in paraganglioma-pheochromocytoma syndromes. Hum Pathol 2010;41:805-814.

17. Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB. The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer 2007;14:569-585.

18. Keiser HR, Goldstein DS, Wade JL, Douglas FL, Averbuch SD. Treatment of malignant pheochromocytoma with combination chemotherapy. Hypertension 1985;7:I18-24.