Clinical aspects of SDHx-related pheochromocytoma and paraganglioma

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Abstract

Paragangliomas (PGLs) derive from either sympathetic chromaffin tissue in adrenal and extra-adrenal abdominal or thoracic locations, or from parasympathetic tissue of the head and neck (DeLellis et al. 2004). A PGL arising from chromaffin cells of the adrenal medulla is also referred to as pheochromocytoma (Lenders et al. 2005, Pacak et al. 2005). Typical locations for extra-adrenal sympathetic tissue-derived PGLs are: (1) the Zucker carnal body, a sympathetic ganglion located at the root of the inferior mesenteric artery, (2) the sympathetic plexus of the urinary bladder, the kidneys, and the heart, and (3) the sympathetic ganglia in the mediastinum. Throughout the manuscript, the abbreviation ‘sPGL’ refers to sympathetic paraganglioma, i.e., pheochromocytoma and extra-adrenal sympathetic PGL. When referring to tumors of parasympathetic origin, the term ‘head and neck PGL’ (HNPG) will be used. The vast majority of sPGLs produce catecholamines, whereas only 5% of the HNPG do (Erickson et al. 2001). Typical symptoms and signs of catecholamine excess include headache, palpitations, diaphoresis, and hypertension.
sPGLs are rare tumors (incidence 2–8 per million) that occur either sporadically or as part of a hereditary syndrome. The ‘classical’ familial syndromes with which sPGL is associated are multiple endocrine neoplasia type 2 (RET mutations), von Hippel-Lindau disease (VHL mutations), hereditary PGL/pheochromocytoma syndromes (SDHx mutations), and rarely neurofibromatosis type 1 (NF1 mutations). The hereditary PGL/pheochromocytoma syndromes have been more recently identified. These familial PGL syndromes are associated with three different genes that encode subunits D, C, and B of the mitochondrial enzyme succinate dehydrogenase (SDH): SDHD (locus PGL1 on 11q23), SDHC (locus PGL3 on 1q21), and SDHB (locus PGL4 on 1p35-p36.1; Baysal et al. 2000, Niemann & Muller 2000, Astuti et al. 2001). An up-to-date overview of all reported SDHx allelic variants that give rise to familial PGL syndromes is available online at http://chromium.liacs.nl/lovd_sdh/ (Fokkema et al. 2005). In addition to these established hereditary PGL syndromes, novel susceptibility loci for pheochromocytoma are being identified (Dahia et al. 2003).

Within a European–American registry of patients with PGL, the prevalence of underlying SDHx mutations was 10% among 371 patients with apparently sporadic sPGL (6% SDHB, 4% SDHD) and 28% among 121 patients with HNPGL (7% SDHB, 4% SDHC, and 17% SDHD; Schiavi et al. 2005). Important information on the clinical characteristics of different SDHx-related PGL syndromes was gathered by large multinational PGL study consortia (Neumann et al. 2004, Amar et al. 2005a, Schiavi et al. 2005, Benn et al. 2006). SDHB mutations mainly predispose to extra-adrenal, and to a lesser extent, adrenal sPGLs, with a high malignant potential (Young et al. 2002, Neumann et al. 2004, Benn et al. 2006, Brouwers et al. 2006, Pham et al. 2006, Timmers et al. 2007a). SDHD mutations are typically associated with multifocal HNPGL and usually benign adrenal and extra-adrenal sPGL (Neumann et al. 2004, Benn et al. 2006). SDHC mutations appear to be a rare cause of mainly HNPGL (Schiavi et al. 2005) and sPGL (Mannelli et al. 2007). More recently, germ line SDHB, SDHC, and SDHD mutations have implicated in a new clinical syndrome, the Stratakis–Carney dyad associating gastrointestinal stromal tumor and PGL (Pasini et al. 2008).

In this review, distinct clinical expressions associated with mutations in different subunits of the SDHx gene will be discussed, as well as present insights in to optimal strategies for establishing the biochemical diagnosis, tumor localization, and therapy of PGL. We will present our recommendations regarding genetic testing and tumor screening among relatives of patients with SDHx-related PGL.

**SDH and tumorigenesis**

SDH is part of the mitochondrial electron transport chain (complex II, succinate-ubiquinone oxidoreductase) and catalyses the oxidation of succinate to fumarate in the Krebs cycle (Scheffler 1998). Subunits A and B of this complex (SDHA, SDHB) constitute the catalytic core of the enzyme, while SDHC with SDHD anchor the complex to the matrix face of the mitochondrial inner membrane. Abnormal SDH function due to mutations of nuclear DNA encoding for one of its subunits results in two completely different phenotypes. Defects in SDHA cause metabolic neurodegenerative disorders like congenital Leigh syndrome (Bourgeron et al. 1995) and late-onset optic atrophy, ataxia and myopathy (Birch-Machin et al. 2000), whereas SDHB, SDHC, and SDHD mutations predispose to familial PGL. The molecular and cellular mechanisms linking these latter SDHx mutations and tumorigenesis have not been fully elucidated. Also, the pathophysiology of distinct clinical phenotypes associated with abnormalities in different SDH subunits remains to be unraveled.

Consistent with Knudson’s two-hit hypothesis for tumorigenesis involving in a tumor suppressor gene, a heterozygous germ line mutation in an SDHx gene is usually associated with somatic loss of the non-mutant allele in the tumor, i.e., loss of heterozygosity (Gimenez-Roqueplo et al. 2003). In SDHB and SDHD-associated PGL, this was shown to result in a complete abolition of SDH enzymatic activity and an activation of the hypoxic–angiogenic pathway via an activation of the transcription hypoxia-inducible factor (HIF1-α) and its main target genes such as VEGF (Gimenez-Roqueplo et al. 2001, 2002). Actually, the abnormal SDH function induces an accumulation of succinate. It was shown in vivo in tumoral tissues and in vitro in different cellular models that the succinate accumulation induces an inhibition of the prolyl hydroxylase activity and consequently a stabilization of HIF1α (Lee et al. 2005). HIF1α regulates the transcription of a number of genes that are known to be involved in tumorigenesis and angiogenesis (Selak et al. 2005). Mitochondrial dysfunction and activation of the hypoxic pathway might be interlinked with other mechanisms of tumorigenesis involving oxidative stress and apoptosis resistance (Gottlieb & Tomlinson 2005). Another important theory interlinking the pathogenesis of different hereditary forms of PGL pertains to the developmental culling of sympathetic...
neuronal precursor cells. Specifically, in the case of SDHx-related PGL, c-Jun-dependent neuronal apoptosis following withdrawal of neuronal growth factor is decreased through inhibition of prolyl hydroxylase by succinate (Lee et al. 2005).

Apart from a role in the pathogenesis of PGL in patients with germ line mutations, somatic SDHx mutation may also be rarely involved in the development of sporadic PGL (Gimm et al. 2000, van Nederveen et al. 2007).

SDHB (PGL4)
Typically, SDHB-related sPGLs arise in extra-adrenal locations and have strong tendency for metastatic spread (Neumann et al. 2004, Amar et al. 2005a, Benn et al. 2006; Table 1). Malignant PGL is defined as the presence of metastatic lesions at sites where chromaffin tissue is normally absent, e.g., lymph nodes, bone, lung, and liver (Linnoila et al. 1990). Among 84 patients with an apparently sporadic sPGL, eight had an SDHB mutation, 62.5% of them had an extra-adrenal tumor, and 84% had a malignant disease. In this series, in the presence of an SDHB mutation, the odd ratio for an extra-adrenal tumor as primary site was calculated to 19.8 and for a malignant to 19 (Gimenez-Roqueplo et al. 2003). Among 32 patients with SDHB-associated PGL(s) in the German/Polish cohort (Neumann et al. 2004), 28% had an adrenal PHEO, 59% had an extra-adrenal abdominal or thoracic sPGL, and 31% had a HNPGL. Twenty-eight percent had multifocal tumors. A similar percentage of extra-adrenal sPGL was reported by the International SDH Consortium (Benn et al. 2006). In the NIH cohort of SDHB-mutation carriers with mainly metastatic sPGL, as many as 96% presented with an extra-adrenal tumors (Timmers et al. 2007a).

The mean age at diagnosis of PGL in SDHB mutation carriers in previous series was ~30 years (Neumann et al. 2004, Timmers et al. 2007a). However, initial tumors may occur between age 7 and 65 (Elston et al. 2006, Pham et al. 2006, Timmers et al. 2007a). In the International SDH Consortium population, age-related penetrance (the proportion of gene carriers manifesting the signs or symptoms of the disease by a given age) among SDHB mutation carriers was 29% by age 30 and 45% by age 40 (Benn et al. 2006). Genetic and/or environmental factors responsible for this large variability in penetrance are unknown.

Patients with SDHB-associated sPGL frequently develop metastatic disease. Reported malignancy rates in patients with SDHB-associated sPGL vary from 34 to 70% (Neumann et al. 2004, Amar et al. 2005a, Benn et al. 2006, Timmers et al. 2007a) versus 10% for sPGL in general (Plouin et al. 1997, Goldstein et al. 1999, Amar et al. 2005b, Khorrmaneshe et al. 2005). Reversely, the prevalence of deleterious SDHB mutations among patients with malignant sPGL is 30%, and even higher (48%) if the tumor originates from an extra-adrenal location (Brouwers et al. 2006). In another NIH study, nearly one-third of patients had evidence of malignant disease at the initial diagnosis of sPGL, which is similar to the previous finding of 22% (Benn et al. 2006). The overall 5-year survival rate of patients with malignant sPGL varies between 34 and 60% (Mundschken & Lehner 1998, John et al. 1999). An underlying SDHB mutation was shown to be an independent predictor of mortality (Amat et al. 2007): in 54 patients with malignant sPGL, the 5-year probability of survival was 36% in SDHB mutation carriers and 67% in the absence of SDHB mutation. Median survival after the diagnosis of the first metastasis was 42 months for the SDHB mutation carriers and 244 months for patients with no SDHB mutation. Finally, in multivariate analysis, only the presence of SDHB mutations was significantly and independently associated with survival: the presence of SDHB mutations was associated with an excess mortality (relative risk 2.7).

Of note is that the diagnosis of SDHB-related sPGL is frequently delayed due to an atypical clinical presentation (Timmers et al. 2007a). A majority presents with

### Table 1 Characteristics of SDHx-related PGL and HNPGL

<table>
<thead>
<tr>
<th>PGL syndrome</th>
<th>PGL1</th>
<th>PGL3</th>
<th>PGL4</th>
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<tr>
<td>SDH subunit defect</td>
<td>SDHD</td>
<td>SDHC</td>
<td>SDHB</td>
</tr>
<tr>
<td>Gene locus sPGL</td>
<td>11q23</td>
<td>1q21</td>
<td>1p35–36.1</td>
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<tr>
<td>Adrenal</td>
<td>Frequent</td>
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<tr>
<td>Extra-adrenal</td>
<td>Frequent</td>
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<tr>
<td>Multifocal</td>
<td>Possible</td>
<td>Not reported</td>
<td>Frequent</td>
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<tr>
<td>Malignant</td>
<td>Rare</td>
<td>Not reported</td>
<td>Very frequent</td>
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<td>Norepinephrine secreting</td>
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<tr>
<td>Dopamine secreting</td>
<td>Unknown</td>
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<td>Frequent</td>
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<td>HNPGL</td>
<td>Very frequent</td>
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<td>Multifocal</td>
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SDH, succinate dehydrogenase; PGL, paraganglioma; HNPGL, head and neck paraganglioma. aOnly in adrenal paraganglioma.
pain and other problems related to the space occupying effects and invasive growth of the tumor, rather than to signs and symptoms related to catecholamine excess. Apart from malignant sPGL, SDHB mutations have been suggested to be associated with renal cell carcinomas of early onset (Neumann et al. 2004, Vanharanta et al. 2004, Ricketts et al. 2008).

Previously, genotype–phenotype correlations failed to distinguish differences in tumor location and malignant potency of SDHB-related PGL between different mutations (Benn et al. 2006). In addition, clinical phenotypes may largely differ between family members with the same SDHB mutation. In our recent study, features that are associated with aggressive tumor behavior, including young age at presentation, large tumor size, metastatic disease at presentation, and hypersecretion of dopamine were equally distributed among patients with missense versus truncating mutations and were independent of exon locations (Timmers et al. 2007a). Identical mutations may result in SDHB-related tumors of variable location and severity.

**SDHC (PGL3)**

SDHC mutations are mainly associated with the development of HNPGL. A limited number of SDHC mutation carriers have been identified worldwide (Niemann & Muller 2000, Bauters et al. 2003, Niemann et al. 2003, Baysal et al. 2004, Schiavi et al. 2005, Bayley et al. 2006, Mannelli et al. 2007, Peczkowska et al. 2008). Within large population-based international registries, the prevalence of SDHC mutations varied between 0% for patients with sPGL (Amar et al. 2005a, Schiavi et al. 2005) and 4% for patients with HNPGL (Schiavi et al. 2005). In general, the clinical behavior of SDHC-related sPGL appears to be similar to that of benign sporadic sPGL. However, a malignant catecholamine-producing PGL at the carotid bifurcation has been reported in a patient with an IVS5 + 1G > T SDHC mutation (Niemann et al. 2003). SDHC mutations were originally believed to be associated only with HNPGL, but recently, adrenal and extra-adrenal sPGL were reported (Mannelli et al. 2007, Peczkowska et al. 2008).

**SDHD (PGL1)**

SDHD mutations are mainly associated with multifocal HNPGL and benign PGL. Among 34 patients with SDHD-associated PGL(s) in the German/Polish cohort (Neumann et al. 2004), 74% had multifocal PGL. Fifty-three percent had an adrenal sPGL, 39% had an extra-adrenal abdominal or thoracic sPGL, and 79% had a HNPGL. Predominant location in the head and neck was confirmed by the other consortium (89%; Benn et al. 2006).

In the German/Polish population, the mean (s.d.) ages at tumor diagnosis were 30.6 years (14.3) in SDHD mutation carriers (Neumann et al. 2004). The study by the International SDH Consortium showed that by age 40, an estimated 69% of SDHD mutation carriers are diagnosed with HNPGL, whereas by age 60, 35% are diagnosed with sPGL (Benn & Robinson 2006).

Rare cases of SDHD-associated metastatic HNPGL have been described (Neumann et al. 2004, Amar et al. 2005a, Benn et al. 2006, Ogawa et al. 2006). Among 200 carriers of the well-known Dutch founder SDHD mutation D92Y (Baysal et al. 2000), there were three patients with metastatic HNPGL and two with metastatic sPGL (Havekes et al. 2007). It was argued that SDHD-associated malignancy might be specifically linked to the D92Y mutation and/or gene–environment interactions in the Netherlands. It was later shown that SDHD-associated malignant sPGL is not exclusively linked to the Dutch founder mutation (Timmers et al. 2008a). In general, however, both parasympathetic and sPGL in SDHD mutation carriers are rarely malignant.

With respect to genotype–phenotype correlations in SDHD-related tumors, carriers of an nonsense and/or splicing mutation were suggested to develop symptoms at an earlier age than missense–mutation carriers, possibly due to the formation of a truncated protein and failure of the normal function of mitochondrial complex II (Astrom et al. 2003). Also there is a tendency for SDHD mutation carriers of truncating mutations to develop phaeochromocytoma in addition to HNPGL (Astrom et al. 2003, Benn et al. 2006).

**Biochemical diagnosis and imaging**

Suspicion of sPGL is usually prompted by (paroxysmal) symptoms suggestive of catecholamine excess, hypertension or by the incidental finding of an adrenal tumor. To establish a biochemical diagnosis of sPGL, plasma and/or 24 h urine concentrations of the catecholamines epinephrine and norepinephrine, and their O-methylated metabolites metanephrine, and normetanephrine (‘metaneprhines’) are measured. Especially, plasma-free metanephines and urinary fractionated metanephrines both have an excellent sensitivity (>97%) for detecting sPGL (Lenders et al. 2002).

The majority of SDHB-related sPGLs, secrete either norepinephrine or both norepinephrine and dopamine.
(Timmers et al. 2007a), a profile that is consistent with mainly extra-adrenal and metastatic PGL (Eisenhofer et al. 2005b). Some SDHB-related sPGLs exclusively overproduce dopamine, but not other catecholamines (Eisenhofer et al. 2005a, Bonnet et al. 2006). Therefore, measurement of plasma levels of dopamine or its O-methylated metabolite methoxytyramine should be considered in SDHB-related sPGL (Eisenhofer et al. 2005a). However, a considerable number of SDHB-related sPGLs do not produce or secrete any catecholamines, e.g., are ‘biochemically silent’ (Timmers et al. 2008b). Lack of catecholamine hypersecretion results from the absence of tyrosine hydroxylase, the enzyme for the rate-limiting step in catecholamine synthesis. In these patients, lack of typical symptoms of catecholamine excess may delay the diagnosis. With respect to SDHD-associated sPGL, no studies on the biochemical phenotype have been reported so far.

Once a biochemical diagnosis of sPGL has been established, the source of catecholamine hypersecretion is subsequently localized by anatomical and functional imaging studies. Adequate localization of the tumor(s) is especially important in SDHx-mutation carriers, since they are prone to multiple and metastatic tumors at presentation. Conventional computed tomography (CT) and magnetic resonance imaging (MRI) have an excellent sensitivity (>90%) for detecting PGL, but lack specificity (Maurea et al. 1996). Tumors detected by CT or MRI can subsequently be identified as sPGL by functional imaging agents that specifically target the catecholamine synthesis, storage and secretion pathway of chromaffin cells. These include 123I-metaiodobenzylguanidine (MIBG) scintigraphy, 18F-fluorodopamine, and 18F-fluorodihydroxyphenylalanine positron emission tomography (PET; Ilia et al. 2005). However, for localizing metastatic lesions of SDHB-related sPGL, 18F-fluorodeoxyglucose PET is superior to other functional imaging techniques (Timmers et al. 2007b). Impairment of mitochondrial function due to loss of SDH function may cause tumor cells to shift from oxidative phosphorylation to aerobic glycolysis (the ‘Warburg effect’ (Warburg 1956)) and may thereby lead to 18F-fluorodeoxyglucose uptake. This possible bio-energetic signature on imaging awaits confirmation at a molecular level. Furthermore, 111In-pentetreotide scintigraphy, another less specific technique was found to have an excellent sensitivity (>90%) for HNPG (Kwekkeboom et al. 1993) and may be useful for screening for these tumors in carriers of SDHx gene mutations (Neumann et al. 2004, Benn et al. 2006).

**Treatment and prognosis**

The mainstay in the treatment of non-metastatic sPGL is surgical resection. If feasible, laparoscopic removal of intra- and extra-adrenal sPGL is preferred over conventional laparotomy (Janetschek et al. 1998). With adequate pharmacological preparation, operative mortality is down to below 1% (Niemann et al. 2002). Pre-operative management is aimed at the prevention of catecholamine-induced complications like hypertensive crisis, cardiac arrhythmias, pulmonary edema, and cardiac ischemia due to manipulation of the tumor, and to prevent hypotensive crises after tumor removal. Randomized controlled trials on different regimes for pre-operative drug treatment are lacking. The authors prefer to combine an α-adrenoceptor blocking agent (phenoxybenzamine, doxazosin), a β-adrenoceptor blocking agent (propranolol, atenolol), and α-methyl-paratyrosine, an inhibitor of catecholamine synthesis. According to previous cohort studies, the life-expectancy after surgery of benign sPGL, in general is either normal (Stenstrom et al. 1988) or mildly decreased (Khorram-Manesh et al. 2005) as compared with the general population. For obvious reasons, long-term results after surgery for SDHx-related sPGL in particular are lacking. Considering the high risk of developing additional tumors (SDHB, SDHD) and/or metastatic lesions (SDHB), we recommend indefinite post-operative follow-up with bi-annual measurement of blood pressure and annual plasma or urine metanephrines, as well as annual MRI of the neck, thorax, abdomen, and pelvis.

There is no effective treatment for malignant sPGL. The usefulness of surgical debulking of tumor tissue has not been established. Treatment with therapeutic doses of 131I-MIBG or combination chemotherapy (cyclophosphamide, vincristine, and dacarbazine) may induce (partial) responses (Averbuch et al. 1988, Fitzgerald et al. 2006). External beam irradiation can be useful in the treatment of local tumor complications. Symptomatic treatment by decreasing catecholamine burden can be obtained with α-adrenergic blockers and α-methyl-paratyrosine. The prognosis after diagnosis of metastatic sPGL is highly variable, with an estimated 5-year survival rate of 50% (Eisenhofer et al. 2004). Specific data on SDHB-associated malignant sPGL are lacking. In our experience, survival among these patients is highly variable as well. In one case, prolonged survival exceeding 30 years has been reported (Young et al. 2002).
Genetic testing

The SDHB, SDHC, and SDHD traits are inherited in an autosomal dominant fashion. However, as stated above, the penetrance of these traits is incomplete. Furthermore, SDHD-related disease is characterized by maternal genomic imprinting: individuals who inherit a mutation from mother remain free of PGL, but may still pass on the mutation to their offspring. Because of incomplete penetrance and genomic imprinting, a considerable number of patients with SDHx-related PGL have no apparent family history of PGL. As many as 63–90% of patients with SDHB-related PGL had an apparently sporadic presentation (Benn et al. 2006, Timmers et al. 2007a), whereas 21% of patients with SDHD-related PGL do (Benn et al. 2006). These observations indicate that a negative family history by no means rules out an underlying SDH mutation. Reversely, among patients with apparently sporadic sPGL, the prevalences of SDHB and SDHD mutations are 4–7% and 1–4% respectively (Neumann et al. 2002, Amar et al. 2005a).

According to recent expert-based recommendations, genetic testing for an underlying mutation should be considered in all patients with sPGL, regardless of family history and age (Gimenez-Roqueplo et al. 2006). In the absence of clinical evidence of other syndromic features, testing of specific genes (RET, VHL, NF1, SDHx) should be prioritized on the basis of individual clinical characteristics. More specifically, the SDHx genes should be addressed in the first line of genetic testing in case of HNPGL (SDHD, SDHB, SDHC), extra-adrenal sPGL or concurrent SGL/HNPGL (SDHB, SDHD), and malignant sPGL (SDHB). HNPGL can also occur as part of VHL syndrome (Hull et al. 1982). Apart from intragenic mutations, there are few reports on patients with PGLs relating to large deletions of the SDHB and SDHC gene (McWhinney et al. 2004, Cascon et al. 2006). These whole gene or large partial deletions remain undetected by conventional gene analysis, but can be detected using semiquantitative multiplex PCR analysis (Amar et al. 2007). Since limited clinical data on families with such deletion are available, it remains to be elucidated whether this genotype is associated with a phenotype distinct from intragenic mutations.

Tumor screening in SDHx-mutation carriers

Asymptomatic carriers of an SDHx-mutation among the relatives of affected patients may benefit from tumor screening for early detection of PGL, because the chances of post-operative morbidity and metastatic spread rise with increasing tumor size. Tumor screening may be particularly useful in SDHB-mutation carriers, who are at risk for aggressive PGLs with a delayed and atypical clinical presentation. However, genetic testing of relatives and subsequent tumor screening in mutation carriers is controversial, since unnecessary investigations can cause significant psychological distress and the screening may not be of cost-effective due to a limited disease penetrance. So far, no solid information from large family screening studies on the age-related penetrance of SDHx-related disease and on the yield of tumor screening in asymptomatic mutation carriers are available.

Until evidence-based guidelines for SDHx family screening become available, we recommend to offer genetic testing, preceded by careful genetic counseling, to all first-degree family members of patients with SDHx-related PGL (Young & Abboud 2006), and to subsequently carry out a clinical, biochemical, and radiological tumor screening among mutation carriers. The only exceptions are the children of female SDHD mutation carriers, who do not require clinical surveillance because of maternal imprinting. We recommend a surveillance protocol that includes annual history and physical examination, annual biochemical testing, e.g., plasma-free metanephrines and/or 24 h urine for fractionated metanephrines, and MRI of the neck, chest, abdomen, and pelvis every 1–2 years. In the selected cases, additional functional imaging may be of use in the screening for PGL (Kwekkeboom et al. 1993, Pacak et al. 2001). In case of SDHB mutation carriership, we recommend to commence investigations as early as before the age of 10. The approach to screening should be adjusted according to the individual history of the patient and findings on prior investigations.

Conclusion

The identification of mutations of different subunits of the SDH gene in patients with PGL is important, since it guides a tailor-made approach to the biochemical diagnosis, localization, treatment, and follow-up of these tumors.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
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