SDH mutations in tumorigenesis and inherited endocrine tumours: lesson from the pheochromocytoma-paraganglioma syndromes

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SDH MUTATIONS IN TUMOURIGENESIS AND INHERITED ENDOCRINE TUMOURS

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Abstract

A genetic predisposition has been recognized for paragangliomas and adrenal or extra-adrenal pheochromocytomas was recognized years ago. Well known syndromes associated with an increased risk of pheochromocytoma include Von Hippel Lindau disease, multiple endocrine neoplasia type 2, and neurofibromatosis type 1 and are discussed elsewhere. The study of inherited predisposition to head and neck paragangliomas led to the discovery of three genes encoding subunits of the succinate dehydrogenase (SDH) enzyme (*SDHB*, *SDHC* and *SDHD*) thus opening an unexpected connection between mitochondrial tumour suppressor genes and neural crest-derived cancers. In this review we summarize the most recent knowledge about the role of SDH in tumorigenesis, including spectrum and prevalence of mutations, related phenotypes, and the biological hypotheses attempting to explain tumorigenesis, as well as current questions and ongoing research.

Keywords

Succinate dehydrogenase; neuroendocrine tumours; tumour suppressor genes

Introduction

Hereditary susceptibility to paragangliomas, mainly of the head and neck region, was recognized at least two decades ago and led to the identification through linkage analysis of three loci on chromosome 11 and 1, named PGL1 on 11q23 [1–4], PGL2 on 11q11.3 [5, 6] and PGL3 on 1q21–23 [7, 8]. Co-occurrence of both paragangliomas and pheochromocytomas was also well recognized [9]. Following the discovery of *SDHD* [succinate dehydrogenase (SDH) subunit D gene, OMIM 602690] as the gene responsible for PGL1 in familial head and neck paragangliomas [10], it was thereafter recognized that two other subunits of this mitochondrial enzyme, *SDHC* (PGL3, OMIM 602413) and *SDHB* (PGL4, 1p36, OMIM 185470) were associated with heritable pheochromocytoma and/or paraganglioma [11, 12]. To date, the gene for PGL2 has not been identified.

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Conflict of Interest Statement
The authors declined any conflict of interest.

Paragangliomas and pheochromocytomas

Paraganglia comprise a diffuse neuroendocrine system dispersed from the middle ear and the skull base to the pelvic floor. They play an important role in the homeostasis against hypoxia, bleeding, cold and hypoglycaemia. Non-chromaffin paragangliomas (PGLs) are usually benign and slow-growing tumours of the parasympathetic ganglia with an incidence of roughly 1:30.000 – 1:100.000 in the general population. They are more frequently located in the head and neck region (HNPGLs) at the carotid bifurcation (carotid body tumour), along the vagal nerve, in the jugular foramen and in the middle ear space. Less common sites are close to the larynx, thyroid, urinary bladder and the upper mediastinum. Known risk factors for HNPGLs include conditions associated with chronic hypoxia such as living at a high altitude, respiratory and heart diseases with chronic arterial hypoxaemia and relates states. However, in 7–10% to 50% of cases a genetic predisposition has been suspected based on positive family and/or development of bilateral or multiple primary tumours [13–16]; more recently the proportion of tumors due to an inherited predisposition has been identified to be close to 35% [17].

The sympatho-adrenal system includes the adrenal medulla, the Zuckerkandl body at the root of the inferior mesenteric artery, and a series of chromaffin cells clustered in the paravertebral chain, kidney and liver hila, aortic bifurcation, bladder and mediastinum. Pheochromocytoma (PHEO) arises in 80–90% of cases within the adrenal medulla (more frequently the right) while extra-adrenal PHEOs (more properly called “paragangliomas”) are described in 10–20% of cases. Hypertension and other symptoms of increased catecholamines secretion occur in approximately 90% of cases and tumours are malignant at first operation in 4–7% of cases. The life-time risk of metastases seems greater for extra-adrenal PGLs (23.9% vs. 6.7% for adrenal PHEOs), younger patients and larger tumours [18–20]. Adrenal PHEO, often bilateral, is a feature of the inherited cancer syndromes multiple endocrine neoplasia type 2 and Von Hippel Lindau disease and can occur in 0.1–5.7% of neurofibromatosis type 1 patients [21, 22]. Recently, additional genes/loci predisposing to PHEO have been recognized on chromosome 1p36 (*KIF1B*β) [23, 24], 2q and 6p [25] but their causative role is still to be confirmed.

Succinate dehydrogenase and encoding genes

SDH or succinate-ubiquinone reductase is the complex II of the mitochondrial respiratory chain located in the mitochondrial matrix [26]. SDH couples the oxidation of succinate to fumarate in the Krebs cycle with electron transfer to the terminal acceptor ubiquinone in a way to prevent formation of potentially dangerous reactive oxygen species (ROS) [27]. SDH is an enzyme complex composed by four subunits encoded by four nuclear genes (*SDHA*, *SDHB*, *SDHC* and *SDHD*). SDHC (cybL, 15 kDA) and SDHD (cybS, 12 kDa) subunits are hydrophobic and provide membrane anchor and the binding site for ubiquinone. SDHA (flavoprotein, 70 kDa) and SDHB (iron-sulfur protein, 27 kDa) are hydrophilic with the former involved in substrate binding and oxidation and the latter in electron transfer [27]. Both the *SDHB* and the *SDHC* genes are located on chromosome 1, the short and long arm respectively. The *SDHC* gene spans 50.3 kb and contains 6 exons transcribed in an mRNA of 2858 nucleotides (long isoform) corresponding to the precursor peptide of 169 amino acids. The *SDHB* gene spans 35.4 kb and contains 8 exons transcribed in an 1161 nucleotides (nt)-long mRNA encoding a protein of 280 amino acids. The *SDHD* gene located on 11q23.1 spans 8.9 kb and contains four exons transcribed in an 1313 nt-long mRNA encoding a protein of 159 amino acids. Finally *SDHA* lies on the short arm of chromosome 5 (5p15) and it is composed by 15 exons spread in a genomic region of 38.4 kb. Its mRNA, 2405 nucleotides long, is transcribed in a protein of 664 amino acids. While homozygote germline mutations affecting the *SDHA* gene cause Leigh syndrome, a subacute necrotizing encephalomyelopathy during infancy [28–30], *SDHD*, *SDHB* and *SDHC*

heterozygous mutations cause a genetic predisposition to HNPGLs and adrenal / extra-adrenal PHEOs [10–12] called “paraganglioma-pheochromocytoma syndrome”. This inherited cancer predisposition is transmitted in an autosomal dominant fashion with age-dependent and incomplete penetrance. However, for loci located on chromosome 11q (*SDHD* and PGL2) a parent-of-origin effect is apparent since the disease is observed almost exclusively when the mutation is transmitted from the father [6, 15]. A maternal imprinting has therefore been postulated for 11q PGL genes but, despite the pattern of inheritance, *SDHD* shows bi-allelic expression in normal tissues and neural crest derived cancers including lymphoblastoid cell lines from affected and carriers, brain tissue, fetal kidney, PGLs, PHEOs and neuroblastomas [10, 31, 32]. Moreover, *SDHD* promoter methylation has not been found in neuroendocrine tissues and related tumours [32, 33]. Based on the frequent somatic loss of the entire maternal chromosome 11 in *SDHD*-related PGLs, it has been postulated a possible involvement of imprinted genes in other regions of the same chromosome such as those of the Beckwith-Wiedemann (BW) locus on 11p15.5 [34, 35]. Hensen *et al*. hypothesized that, the somatic selective loss of the whole maternal chromosome 11 (targeting both the wild type *SDHD* allele and a maternally-expressed tumour suppressor gene) (TSG) can explain the exclusive paternal transmission of the disease. Indeed, loss of the maternal 11p15 occurs frequently in paediatric tumors including Wilm’s tumours, embrional rhabdomyosarcoma, hepatoblastoma and adrenocortical carcinoma thus suggesting the involvement of *CNKN1C* ($p57^{Kip2}$) and/or *H19-IGF2* dysregulation in tumourigenesis [36, 37]. Interestingly, loss of 11p has been demonstrated in 33–50% of HNPGLs, in 27% of abdominal PGLs, in 17–48% of sporadic PHEOs and in 40% to 86% of PHEOs from MEN2A and Von Hippel Lindau (VHL) patients, respectively [38–41]. Moreover, a decreased expression of *CNKN1C* ($p57^{Kip2}$) and *H19* has been found in PHEOs [42] and the preferential loss of the maternal rather than paternal 11p15.5 has been confirmed in the same tumours [43] thus supporting the hypothesis proposed by Hensen *et al*. Possible evidence supporting the involvement of the BW locus in the parent-of origin effect is given by the work of Pigny and colleagues on a family with an affected child who inherited the *SDHD* mutation p.Trp43X from his mother [44]. The child developed a jugulo-tympanic PGL at 11 years of age and genetic analysis revealed hyper-methylation of two CpGs within the seventh region (CTS7) of binding for the CCCTC-binding factor (CTCF) in the differentially methylated region 1 (DMR1) upstream the *H19* gene. Long-range PCR excluded the presence of genomic deletions in the region. A normal pattern of methylation was shown in the affected mother, the healthy brother who had inherited the *SDHD* germline mutation, and the healthy father. However, no further information was given about the presence of clinical signs related to the BW syndrome in the child affected by the cervical PGL, as expected in case of imprinting changes at DMR1 (i.e. silencing of *H19* - *IGF2* over expression).

SDH germline mutations associated with inherited predisposition to neuroendocrine tumours

For the purpose of this study, 95 papers have been reviewed dealing with *SDH* germline mutations (57 in *SDHD*, 54 in *SDHB* and 13 in *SDHC*) in patients affected by tumours related with the “paraganglioma/pheochromocytoma syndromes” [10–12, 31, 33, 35, 44, 45–134]. They include all published reports cited in the LOVD *SDH* gene databases at July 2008 (SDHB 080626: June 26, 2008; SDHC 080520: May 20, 2008; SDHD 080703: July 03, 2008) [135] and 13 recent publications. Data have been collected in a database with the aim to define the mutation spectrum of the three genes and the clinical characteristics of affected carriers.

Two-hundred-twenty-seven index cases carriers of *SDHB* germline mutations have been reported to date, including 216 deleterious mutations and 11 variants (missense and intronic

substitutions) of unknown biological significance (VUS) for a total of 275 affected patients including 48 family members. Germline mutations are scattered along exon 1 to 7 whit the fewer mutations identified in exon 5 and no point mutations involving exon 8 (figure 1.1). Twenty-seven percent (58/216) of mutated index cases carry unique mutations while 73% (158/216) have 40 mutations that are recurrent in 2 to 14 independent families. Among the 98 different germline mutations, 46% are missense, 23% frameshift, 13% splicing defect, 9% nonsense, 2% deletion/insertion of one amino acid and 7% are large genomic deletions involving the whole gene [64], exon 2 to 8 [47], exon 6 to 8 [100, 113] or limited to exon 1 [47, 65]. At least two different exon 1 deletions have been described, one of 15.7 kb that was recurrent in Spain and another, 20 kb long, that was found in French families. Despite the presence in *SDHB* intron 1 of eleven Alu repeats covering 36% of the sequence, the mechanism underlining the Spanish deletion seems to be the DNA polymerase α frameshift hot spot GGGGGA at position + 2 while no obvious motif has been recognized that could be responsible for the French deletion [64, 65, 99]. Other recurrent mutations include the splice site IVS2+1G>T (c.72+1G>T) identified in 9 cases of Scottish origin, p.Arg46X identified in 9 families from UK and US, p.Arg242His in 9 families from Germany and Belgium, p.Arg90X and p.Arg46Gln in 9 and 14 different families, respectively, of various ethnical origin.

Two-hundred-ninety-nine index cases have been reported as carriers of *SDHD* germline mutations including 289 deleterious mutations and 10 VUS in a total of 405 affected patients including 106 family members. Germline mutations are scattered along exon 1 to 4 with the exon 3 mutated in 60% of cases (figure 1.2). Fourteen percent (40/289) of mutated index cases carry unique mutations while in 86% (249/289) of cases 28 mutations have been identified, recurrent in 2 to several independent families. Among the 68 different germline mutations reported to date, 40% are frameshift, 25% nonsense, 19% missense (clustered in exon 3 and 4), 9% splicing defect, 4% in-frame deletions of 1 to 4 amino acids and 2% are large genomic deletions involving the whole gene [99] or exon 3 [75]. Well known recurrent mutations with a founder effect include p.Asp92Tyr, p.Leu95Pro and p.Leu139Pro in Dutch patients, p.Gln109X in central Italy and p.Met1Ile in Chinese families while the p.Pro81Leu has been suggested as hot spots for new mutations due to C>T transition.

Only nineteen index cases have been reported to date as carriers of *SDHC* germline mutations with a total of 30 affected patients including 11 family members. Germline mutations are scattered along exon 1 to 6 with a few missense mutations involving exon 4 and 6 (figure 1.3). Sixty-three percent (12/19) of mutated index cases carry unique mutations while 37% (7/19) have 3 recurrent mutations in 2 to 3 independent families. Among the 15 different germline mutations reported to date, 7 (47%) are nonsense, 5 (33%) splicing defect, 2 (19%) missense and one (7%) Alu-mediated genomic deletion of 8.4 kb involving exon 6 [56].

Prevalence of germline mutations in the *SDH* genes

As it will be shown in the next paragraph, germline mutations in *SDH* genes are associated with sporadic and familial PGLs involving either sympathetic paraganglia (mainly abdominal, adrenal or extra-adrenal) or parasympathetic organs in the head and neck region. Despite the parent-of-origin effect of *SDHD* germline mutations, 61% of mutated index cases have a positive family history for PGLs while 69% of *SDHB* mutations carriers have an apparent negative family history. The few *SDHC* mutated cases described to date have a positive family history in 62.5% of the cases. Therefore, the prevalence of *SDHB* germline mutations among sporadic cases (tables 1 and 4) is somewhat higher than that one of *SDHD* (6% versus 3% for PHEOs/PGLs, 6.5% versus 2.4% for HNPGLs).

Very few sporadic cases have been reported with *SDHC* germline mutations (0.6%, table 4). The general prevalence of *SDH* mutations among sporadic and non-syndromic cases of adrenal and extra-adrenal PGLs is around 6% (50/795) with 9% of frequency in cases tested negative for *RET* and *VHL* mutation. However, the prevalence of *SDH* mutations is considerably higher in sporadic extra-adrenal tumours (15/45, 33%), malignant tumours (38%, table 2) and paediatric cases (29%, table 3) with strong preponderance of *SDHB* mutations in all categories. *SDH* mutations seem less frequent than *RET* and *VHL* in bilateral or familial adrenal PHEOs with a prevalence around 10–17% while in familial aggregations of adrenal and extra-adrenal tumours (including HNPGLs) the frequency reaches 85% (11/13) (table 3). Similar *SDH* mutations frequencies can be found in cases affected by HNPGLs outside the area of Low Countries (table 4). The general prevalence of mutations among sporadic, multiple and familial HNPGLs is 9.5%, 71% and 88%, respectively, with a predominance of *SDHD* germline mutations among multiple and familial cases, in accordance to the overall higher penetrance of mutations of this gene. In the Netherlands and Belgium (table 5) due to the presence of founder mutations associated with the low altitude (which decreases the hypoxic stimulation of paraganglia) the prevalence of *SDH* mutations among sporadic cases is remarkably higher (29%) and all familial cases that are not linked to PGL2 are caused by *SDHD* germline mutations.

Clinical manifestations and penetrance of *SDH* germline mutations

Analysis of the clinical manifestations of 689 published carriers of deleterious mutations in *SDHB* (264), *SDHC* (30) and *SDHD* (395) led to the recognition of a genotype-phenotype correlation. Affected carriers of *SDHD* and *SDHC* mutations have more frequently a positive family history (61% and 62.5%, respectively) than *SDHB* mutation carriers (31%). Median age at diagnosis of the first tumour is similar in *SDHB* and *SDHD* mutations carriers (32 and 33 years of age, respectively) and lower than that in *SDHC* mutation carriers (38 years). As shown by the analysis of the mean ages at diagnosis (figure 2, left panels), 25% of affected *SDHB* carriers have been diagnosed in the first and second decades of life while only 15% of *SDHD* mutation carriers and no *SDHC* mutation carriers have been diagnosed in the first decade of life. Multiple primary tumours are frequently observed in *SDHD* mutation carriers (79%, 167/211 with available information) while patients with *SDHB* and *SDHC* mutations have single tumours in 67% and 73% of the cases, respectively. As shown in figure 2 (right panels) the most frequent phenotype associated with *SDHB* germline mutations is the development of extra-adrenal PGL (53%, 140/264), mainly abdominal (including pelvis and retro-peritoneum) but also thoracic, mediastinal and cervical. Twenty percent of cases presents with adrenal PHEO alone or associated with PGL (52/264) and another 20% of cases develops only HNPGL (52/264). On the contrary, *SDHD* affected carriers presented with only HNPGL, single or multiple, in 78% of cases (305/395) while adrenal PHEO and/or extra-adrenal PGL are the sole manifestations in 8% (31/395) and 1% (1/395) of cases. Among the 30 *SDHC* affected carriers reported to date, 87% (26/30) presented with HNPGL alone while PGL and PHEO occurred more rarely. Tables 6, 7 and 8 summarize the clinical manifestations of *SDH* subunit mutation carriers as per published reports and including data included in the present report.

The penetrance of *SDH* germline mutations has been addressed by two major studies [58, 106]. According with data from the “Freiburg-Warsaw registry” [106] *SDHB* mutation carriers have a life time cancer risk of 76% with 50% penetrance by age 35 while *SDHD* carriers who inherited the mutation from their father seem to have a life time cancer risk of 100% with penetrance of 50% by age 31 and 86% by age 50. A penetrance of 50% by age 33 for *SDHD* has been confirmed for a founder mutation in the Italian population [122]. Slightly lower numbers have been reported for *SDHB* germline mutations by the “International *SDH* consortium” [58] with an estimated penetrance of 29% by age 30 years

and 45% by age 40 while for *SDHD* carriers the penetrance was similar to the one previously reported (48% by age 30 years and 73% by age 40). Considering the tumour location, both studies recognized a prevalence of extra-adrenal abdominal paragangliomas in *SDHB* mutation carriers (50% of *SDHB* carriers vs 21% of *SDHD* in Neumann HP *et al.* − 67% of *SDHB* carriers vs 18% of *SDHD* in Benn DE *et al.*) and a prevalence of HNPGLs in *SDHD* mutation carriers (79% of *SDHD* carriers vs 31% of *SDHB* in Neumann HP *et al.* − 89% of *SDHD* carriers vs 27% of *SDHB* in Benn DE *et al.*). Results were conflicting for adrenal PHEOs (53% of *SDHD* carriers vs 28% of *SDHB* in Neumann HP *et al.* − 7% of *SDHD* carriers vs 18% of *SDHB* in Benn DE *et al.*) and slightly different for thoracic PGLs (18% of *SDHD* carriers vs 9% of *SDHB* in Neumann HP *et al.* − 11% of *SDHD* carriers and 18% of *SDHB* in Benn DE *et al.*). In *SDHD* mutation carriers, life at high altitude has been shown to increase the risk of developing multiple primary tumors and PHEOs. An increased risk of PHEOs has also been recognized for truncating mutations [49]. In light of these data, the very low altitude in the Netherlands associated with the presence of recurrent missense mutations can explain the peculiarly high rates of *SDHD* germline mutations among sporadic cases of HNPGL (table 5) and the overall low risk of PHEO among Dutch carries.

Finally, both studies underlined the prevalence of multiple tumours among *SDHD* mutation carriers (74% of *SDHD* carriers vs 28% of *SDHB* carriers in Neumann HP *et al.*− 30% of *SDHD* carriers vs 12% of *SDHB* in Benn DE *et al.*) and the increased risk for malignant tumours in *SDHB* carriers, although with different extent (34% of *SDHB* carriers vs 0% of *SDHD* in Neumann HP *et al.*– 37.5% of *SDHB* carriers vs 8% of *SDHD* in Benn DE *et al.*). Even higher risk for malignancy (defined as the presence of metastases or histologically documented lymph-node invasion) in *SDHB* mutation carriers has been reported by other groups (71.4% by Amar L *et al.*) [46, 127] most likely reflecting differences in clinical evaluation, follow-up, and sources of recruitment between different centres. In malignant tumours the presence of an *SDHB* germline mutation seems to correlate with worse prognosis including a five-year probability of survival of 36% compared to 55% and a median time from presentation to first metastasis of 4 months compared to 20 months in the absence of *SDHB* mutations [47]. However, longer survival and longer disease-free interval have been reported by other authors [60, 123, 127, 132]. In carriers of *SDHD* mutations, development of malignant tumors has been reported occasionally giving a life time risk of malignancy between 2.5% and 7.7% [49, 58, 74, 82–84, 111, 112, 128]. In the present survey, the prevalence of malignant tumours among affected carriers has been determined as 41% (105/256) for *SDHB*, 4% (20/395) for *SDHD* and 3% (1/30) for *SDHC*. In an attempt to define the risk for malignancy for each type of tumour, it is interesting to note that malignant disease has been reported for *SDHB* mutations in 12% of patients affected by HNPGL alone, in 35% of patients with only adrenal PHEO and in 48% of cases with only extra-adrenal PGLs. A similar trend for an increased risk of malignancy related to extra-adrenal PGL is present also in *SDHD* mutation carriers in whom malignant tumours are reported in 4% of patients with HNPGL alone, 6% of cases with only adrenal PHEO and 17% of patients with extra-adrenal PGLs.

Other tumours associated with *SDH* germline mutations

The best known association of *SDH* germline mutations with other tumours is the Carney-Stratakis syndrome (or dyad) of PGLs and gastrointestinal stromal tumours (GIST) [100, 113]. Germline point mutations or large deletions were identified in *SDHB*, *C* and *D* genes in 7 out of 9 index cases with GIST and/or PGLs. Loss of the normal allele was demonstrated in all GIST samples analysed (3 for *SDHB*, 2 for *SDHC* mutations). An additional family with extra-adrenal PGLs and a relative affected by GIST has been reported in association with an *SDHB* missense mutation [59].

The identification of *SDHB* germline mutations (c.713_716delTCTC) in two siblings affected by paraganglioma and clear cell renal carcinoma at 21 and 26 years of age [106] suggested a possible involvement of *SDH* genes in renal tumorigenesis. Indeed both renal tumors showed losses of the normal allele as it was shown for another renal cancer (with apparent mixture of clear cells and cells with granular-eosinophilic cytoplasm) developed at 28 years of age by a carries of the *SDHB* p.Arg27X germline mutation. The latter patient inherited the mutation from her mother affected by heart PGL at 55 years [129]. However, no additional *SDHB* or *SDHD* mutations have been identified in a cohort of 95 renal cell tumours while a renal angiomiolipoma and a renal oncocytoma were found in two carriers of *SDHB* large deletions [64, 65] and a malignant papillary type II renal cell cancer in a carrier of an *SDHB* nonsense mutation [123]. Recently, screening of 68 patients affected by familial or multiple/early-onset renal cell cancer for germline *SDH* mutations led to the identification of 3 additional carriers of *SDHB* mutations (p.Arg11His, p.Arg46X, p.Arg46Gln) [119] thus confirming a possible increased risk for RCC limited to carriers of *SDHB* germline mutations. A unique case of testicular seminoma has been reported among carriers of *SDHD* mutations (p.Trp43X); the causative role of the germline mutation is suggested by the loss of the normal allele in this tumour [77]. Interstingly, both RCC and testicular tumours have been reported in carriers of *FH* germline mutations, another gene with tumor suppressor function encoded by a mitochondrial enzyme (fumarate hydratase or fumarase). The prevalent manifestations of FH mutations are cutaneous and uterine leiomyomas, RCC (manly papillary type II); testicular (Leydig cell tumours) and adrenocortical tumors can also occur [136–138].

Finally, it has been suggested that germline *SDHD* mutations could be responsible for hyperplasia of thyroid C-cells secreting calcitonin. However, the mutation identified in a family with four members affected by hypercalcitoninemia (p.His50Arg) is indeed a common polymorphism [63, 139]. Germline *SDHB* and *SDHD* variants have been identified in 10 patient out of 74 (13.5%) affected by Cowden-like clinical manifestations (breast, thyroid, uterine benign and malignant diseases) [108]; although some of these sequence changes are considered polymorphisms (*SDHB* p.Ser163Pro, *SDHD* p.Gly12Ser and p.His50Arg), they appear to function as low penetrance alleles.

It remains unclear if *SDH* mutations can be associated with other tumours that are occasionally found in affected carriers or their relatives such as papillary thyroid cancers [106, 127], adrenal neuroblastoma [65], pituitary adenoma [58, 93], bronchial carcinoid [94], ependymoma, melanoma, bone and soft tissue sarcoma [49], B-cell lymphoma [111] and colon cancer [58, 99].

Somatic second hits associated with *SDH* germline mutation

Germline loss of function mutations associated with frequent somatic deletions of the wild type (wt) allele suggest that *SDH* genes behave as classical tumour suppressor genes (TSG) as they need two events for inactivation. PGLs and PHEOs are tumours composed by cancer cells, normal sustentacular cells and a variable amount of small vessels. In light of this particular histology (characterized by an intrinsic relatively large component of normal cells), the classical approach to search for somatic deletion of the wt allele through loss-of-heterozygosity (LOH) (i.e. microsatellite analysis or sequencing of the mutated exon) on whole tumour DNA can fail to detect the second hit while loss of the wt allele is unequivocally shown on aneuploid tumour fraction [126], microdissected tumours cells [122] or tumour RNA [31]. However, even by simple LOH analysis or allelic-imbalance, somatic deletion of the wt allele is present in at least 78.5% of *SDHD*-related tumours (33/45 HNPGLs and 11/11 adrenal or extra-adrenal PHEOs [10, 31, 34, 35, 51, 70, 81, 122, 126, 130], 60% of *SDHB*-related tumours (15/25 adrenal or extra-adrenal PHEOs) [12, 66, 79, 80, 85, 95, 113, 129, 132] and in all 5 tumours studied from carriers of *SDHC* germline

mutations [11, 56, 93, 113]. No somatic point mutations or promoter hyper-methylation have been reported to date as a possible "second hit". The somatic deletion of the wt *SDH* allele seems therefore the preferential second hit and this observation can suggest the need of concomitant loss of neighbouring TSG/s. Indeed, *SDHD* germline mutations seem invariably associated with somatic loss of the entire chromosome 11 implying the concomitant loss of maternally-expressed TSGs on 11p15.5 [34] and perhaps other TSGs on the long and the short arms of the same chromosome. Loss of the whole maternal chromosome 11 would therefore provide with a single event a great growth advantage thus explaining the almost complete penetrance of *SDHD* germline mutations upon paternal transmission. Interestingly, somatic gains of genomic material of 11cen-q13 (i.e. the opposite somatic alteration) have been shown in 36% of extra-adrenal PHEOs and in 25% of malignant PGLs [40] which are relatively infrequent clinical manifestations in *SDHD* mutation carriers. An association between 11q13 gain and malignant PHEOs and PGLs has been confirmed also in an another study [39]. In the case of *SDHB* germline mutations, deletions of the short arm of chromosome 1 can be associated with the concomitant loss of TSGs located in 1p36.2–1p36.3 (the neuroblastoma-TSG region) or even more centromeric such as 1cen-p31 and 1p32.1–1p32.3 (the PHEOs-TSG regions) [41, 140, 141].

The "chromosomal-site-effect" could explain the rarity and the absence of germline mutations in *SDHC* and *SDHA*, respectively, in the paraganglioma-pheochromocytoma syndrome. If no relevant TSGs are located in neighbouring regions of 1q and 5p, multiple somatic events will be required to achieve a substantial growth advantage, an occurrence statistically rare or even impossible in slow growing cells such as those derived from neural crest. In adrenal or extra-adrenal PHEOs loss or gain of genomic material on chromosome 1q or 5p are very rare events: the few aberrations reported (in malignant tumours mainly) included whole chromosome 1 monosomy or chromosome 5 trisomy [40, 41, 140]. A comparative genomic hybridisation (CGH) study, comparing somatic aberrations between PHEOs and HNPGLs, underlined the presence of 1q losses only in HNPGLs [39]. Another study on HNPGLs failed to detected any 1q loss at CGH while there were two 5p deletion among the 16 tumours analysed (12.5%); in just one case the region lost included the *SDHA* gene (whole short arm deletion) and curiously this chromosomal aberration was associated with loss of 11p [38]. A more precise characterization of the somatic alterations associated with *SDHB* and *SDHC* germline mutations will improve our knowledge on the mechanisms underlining tumourigenesis.

Biological effect of *SDH* germline mutation

Gimenez-Roqueplo and colleagues [78] first studied the biological effect of a loss of function *SDHD* germline mutation (p.Arg22X): a complete loss of the maternal wt allele was found in the related extra-adrenal PGL of the mediastinum where both functions of SDH were completely abolished, i.e. the catalytic activity of succinate dehydrogenase and the electron flow to the ubiquinone pool. Six sporadic PHEOs analysed as controls showed normal SDH activity. The same tumour and three carotid body PGLs from the same family showed high expression of hypoxia inducible factors (HIF) 1α, 2α and vascular endothelial growth factor (VEGF) while large vessels strongly expressed VEGF-receptor 1 and VEGF-R2. These results strongly suggested the activation of the hypoxia/angiogenesis pathway as possible mechanism underlying tumour development. The same group [79] studied the biological effect of a missense *SDHB* germline mutation (p.Arg46Gln) in a malignant PHEO with somatic terminal deletion of 1p. Again, in tumour tissue the succinate dehydrogenase activity was abolished with increased expression of HIF2α and VEGF in tumour cells associated with increased expression of VEGF-R1 and VEGF-R2 in vascular endothelial in agreement with the high vascularization of this endocrine tumour. Moreover, a complete and selective loss of mitochondrial complex II enzymatic activity was confirmed in additional 7

tumours (extra-adrenal and/or malignant PHEOs) from carriers of *SDHB* germline mutations (frame-shift and missense) with somatic loss of 1pter–1p34.3 [80]. Even in non-malignant tumours, the presence of an *SDHB* germline mutation was associated with changes in vascular morphology (arcs, networks and parallel structures). Similar findings have been reported by Douwes Dekker PB *et al.* [71] who studied the SDH enzymatic activity in 22 HNPGLs from Dutch patients, 12 from carriers of *SDHD* and *SDHB* germline mutations, 2 from the PGL2 linked family and 8 sporadic. In all hereditary HNPGLs, including those related to PGL2, the SDH enzymatic activity was absent (78.6%) or very week (21.4%) with over-expression of the SDHA subunit which showed diffuse cytoplasmic expression at immunohistochemostry. Moreover, two *SDHD*-related PGLs analysed by electron microscopy showed increased number of mitochondria in tumour cells with swollen appearance, loss of cristae and inclusion bodies. Interestingly, unlike sporadic PHEOs, most of sporadic HNPGLs (75%) were negative for SDH enzymatic activity as well, thus suggesting that impairment of mitochondrial complex II could be a common feature in the tumourigenesis of chemoreceptor PGLs. However, no somatic point mutations have been identified in SDH genes in a number of sporadic tumours (HNPGLs) [51, 69, 101]. Finally, a severe decrease in SDH activity was demonstrated also for a germline *SDHC* mutations in a sample of GIST tumour with loss of the wt allele [100]. These data support the notion that, whenever an *SDH* subunit gene is mutated, SDH enzymatic activity is strongly compromised. To further investigate the metabolic consequences of SDH deficiency, Pollard and colleagues analysed frozen PGLs from carriers of two *SDHB* missense mutations (p.Ser100Pro and p.Ile127Ser) with somatic loss of the entire wt 1p or whole 1 chromosome. Compared to sporadic tumours, SDH deficient PGLs showed gross accumulation of succinate, positive succinate to fumurate ratio and increased expression of HIF1α and VEGF with high density of micro-vessels [142]. *In vitro* inactivation of SDH activity and succinate accumulation was shown to inhibit prolyl-hydroxylation of HIF1α and HIF2α which is an essential step for its degradation through the complex VHL-ElonginD-C-Cul2 [143]. In fact, prolyl-hydroxilases (PHD1, 2 and 3, also known as EglN2, 1 and 3, respectively) couple their enzymatic activity with oxidation and decarboxilation of α–ketoglutarate to succinate with PHD2 (EglN1) playing the major role in HIFα downregulation. SDH deficiency finally mimics the hypoxic condition with increased activity of Hypoxia Inducible Factors able to trigger changes in cellular metabolism, angiogenesis, cell scattering and cell proliferation [144]. Consistent with the hypothesis implicating HIF dysregulation in the pathogenesis of *SDH* related tumours, gene expression micro-arrays studies have confirmed over-expression of hypoxia-induced angiogenic pathway genes in both *SDHB* and *SDHD* related PHEOs with coordinated suppression of oxidoreductase (i.e. mitochondrial function), a profile similar to neuroendocrine tumours from VHL patients [68]. Finally, prolyl-hydroxilase 3 (EglN3 or PHD3) has been shown to mediate c-Jun developmental apoptosis in sympathetic neurons when levels of nerve growth factor become a limiting condition for neuronal survival. Thus, inhibition of EglN3-PHD3 consequent to succinate accumulation can promote cell survival and proliferation also through a HIF-independent pathway [145].

Somatic *SDH* mutations in sporadic tumours

Somatic point mutations in *SDH* genes seem very rare. To date, only a few somatic mutations have been identified in PHEO and PGL specimens. In a cohort of more than 480 tumour sample analysed (139 HNPGLs, 321 adrenal/extra-adrenal PHEO, 22 PGLs of the cauda equina, table 9) [12, 33, 50, 51, 69, 70, 80, 81, 85, 101,146–151], just two *SDHB* (p.Arg217Cys in a carotid body pgl [147], p.Ser100Phe in an extra-adrenal PGL [84, 152]) and three *SDHD* (p.81Leu in a sporadic PHEO [81], p.Met1Val in a sporadic HNPGL [35] and p.Tyr114Cys in a jugular PGL [147]) somatic mutations have been reported, all associated with LOH of the wt allele. In the same tumours, heterozygote somatic deletions (LOH) seem more frequent involving the *SDHB* locus on 1p36 in 35–58% of PHEO/PGLs

and the *SDHD* locus on 11q23 in 17–69% of the same tumours (table 9) but their causative role is still unclear giving the lack of information about the functional state of the remaining allele and of complex II enzymatic activity. The short arm of chromosome 1 and the long arm of chromosome 11 are among the chromosomal regions more frequently lost in sporadic and hereditary neuroendocrine tumours and probably they harbour other relevant TSGs.

Silencing of *SDH* genes through promoter methylation has been addressed in a few studies but never demonstrated until now (analysis of 35 PHEOs for all three *SDH* genes in Cascón A *et al.* [33], analysis of 81 neuroblastomas for *SDHD* in De Preter K *et al.* [32], analysis of 28 PHEOs and 46 neuroblastomas for *SDHB* in Astuti D *et al.* [153]). However, somatic deletion of *SDHD* in those tumours characterized by LOH at 11q23 (table 10) (group 2B neuroblastomas, midgut carcinoids, neuroendocrine tumours, PHEOs from carriers of VHL missense mutations) [32, 129, 149, 150, 153–157] could suggest a role in tumourigenesis through a mechanism of haploinsufficiency, supported by the consistent reduction of transcript levels found in some tumours [32, 41, 150]. A marked reduction of *SDHB* expression has been found in VHL-related PHEOs which are characterized by frequent loss of 1p as well [68] and the *SDHB* haploinsufficiency can be responsible for the activation of the hypoxia-angiogenesis pathway even in those tumours with VHL type 2c mutations which seems unable to interfere with HIF degradation. Moreover, HIF1α seems to be able to down-regulated *SDHB* expression thus suppressing the function of mitochondrial complex II in an auto-regulatory loop [68].

Concluding remarks

PGLs and PHEOs are mostly benign tumours although they can result in significant clinical morbiditiy related to the mass effect, cranial nerve palsies or the secretion of catecholamines. If left untreated, these tumours can also metastasise and a malignant potential has been specifically recognized for *SDHB* related adrenal and extra-adrenal PHEOs. Early treatment of these tumours can result in a significant decrease in morbidity and mortality through the identification of at risk individuals that need proper surveillance and treatment. A reasonable minimum monitoring program should start in the second decade of life and include a careful history and physical examination, annual measurement of the blood pressure and urinary catecholamines (epinephrine, norepinephrine, dopamine and vanilllylmandellic acid) in addition to bi-annual imaging by CT scan and/or magnetic resonance of the neck and skull base, thorax, abdomen and pelvis. An additional screening method, positron emission tomography with [^{18}F]fluorodopa or [^{18}F]fluorodopamine or ^{123}Iodine metaiodobenzylguanidine (MIBGE) scintigraphy may be employed as needed [58, 158]. Giving the bi-allelic expression of *SDHD*, that argues against its maternal imprinting, and the complete loss of SDH enzymatic activity whenever one of its subunits is mutated, a possible explanation of the phenotypic variability in paraganglioma-pheochromocytoma syndrome can be the size and location of the somatic deletions of the normal allele which may compromise the function of other TSGs located nearby in the form of cis or even trans effects.

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Abbreviations

BW	Beckwith-Wiedemann
CGH	comparative genomic hybridization
GIST	gastro-intestinal stromal tumours
HIF	hypoxia inducible factor
HNPGL	head and neck paraganglioma
MEN2A	multiple endocrine neoplasia type 2A
PGL	paraganglioma
PHEO	pheochromocytoma
RCC	renal cell cancer
ROS	reactive oxygen species
SDH	succinate dehydrogenase
TSG	tumour suppressor gene
VEGF	vascular endothelial growth factor
VHL	von Hippel Lindau
VUS	variant of unknown biological significance
WT	wild type

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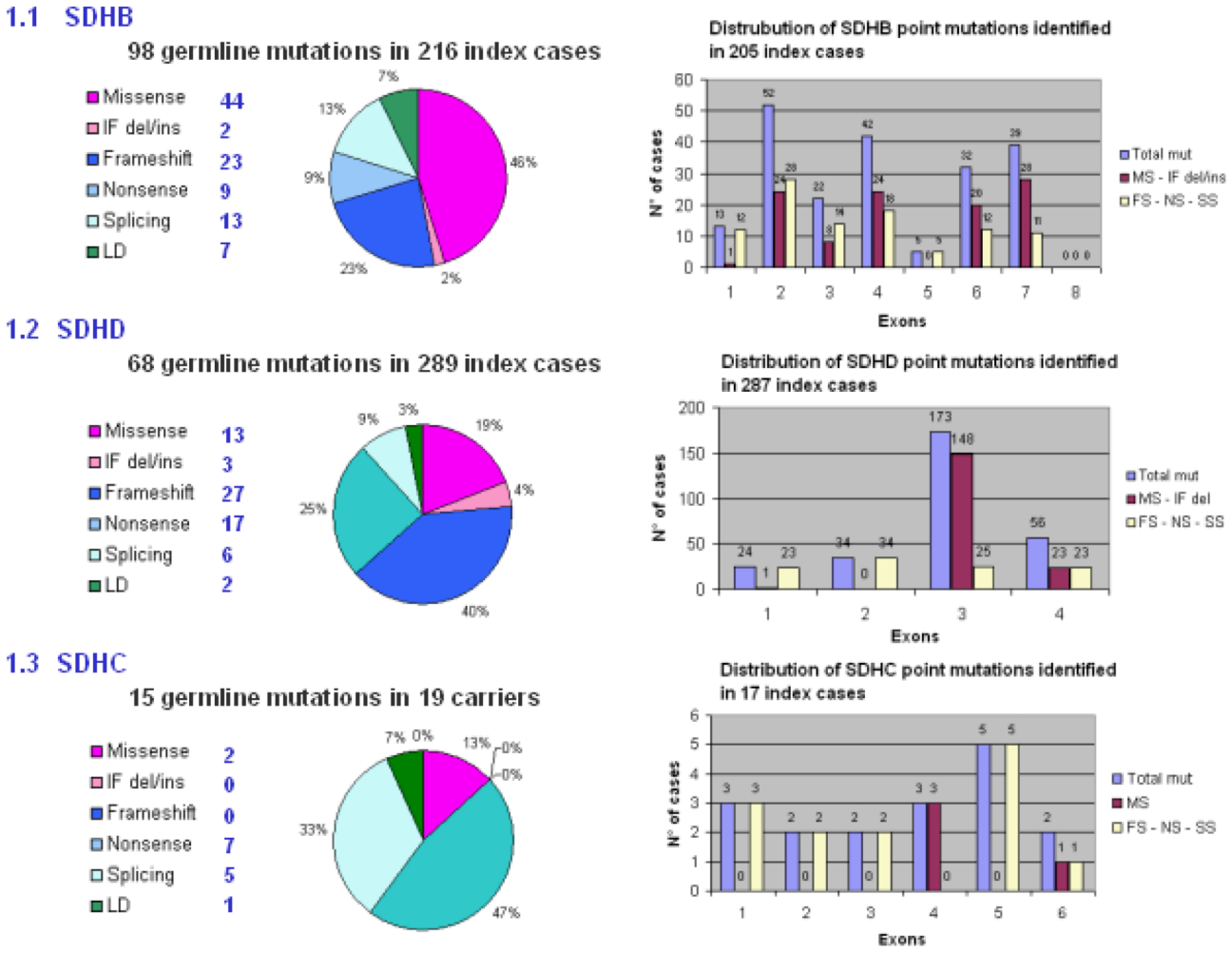

Figure 1. Spectrum of germline mutations identified in *SDHB* (1.1), *SDHD* (1.2) and *SDHC* (1.3) genes

For each *SDH* gene, the left imagine shows numbers and percentages of the different types of mutations including missense (MS), in-frame deletion/insertion (IF del/ins), frame-shift (FS), nonsense (NS), splice-site (SS) and large genomic deletions (LD). The right histogram shows the distribution of point mutations along the coding exons of each gene (blue bar = total of mutations, purple bar = missense and in-frame insertion/deletion, light-yellow bar = truncating mutations).

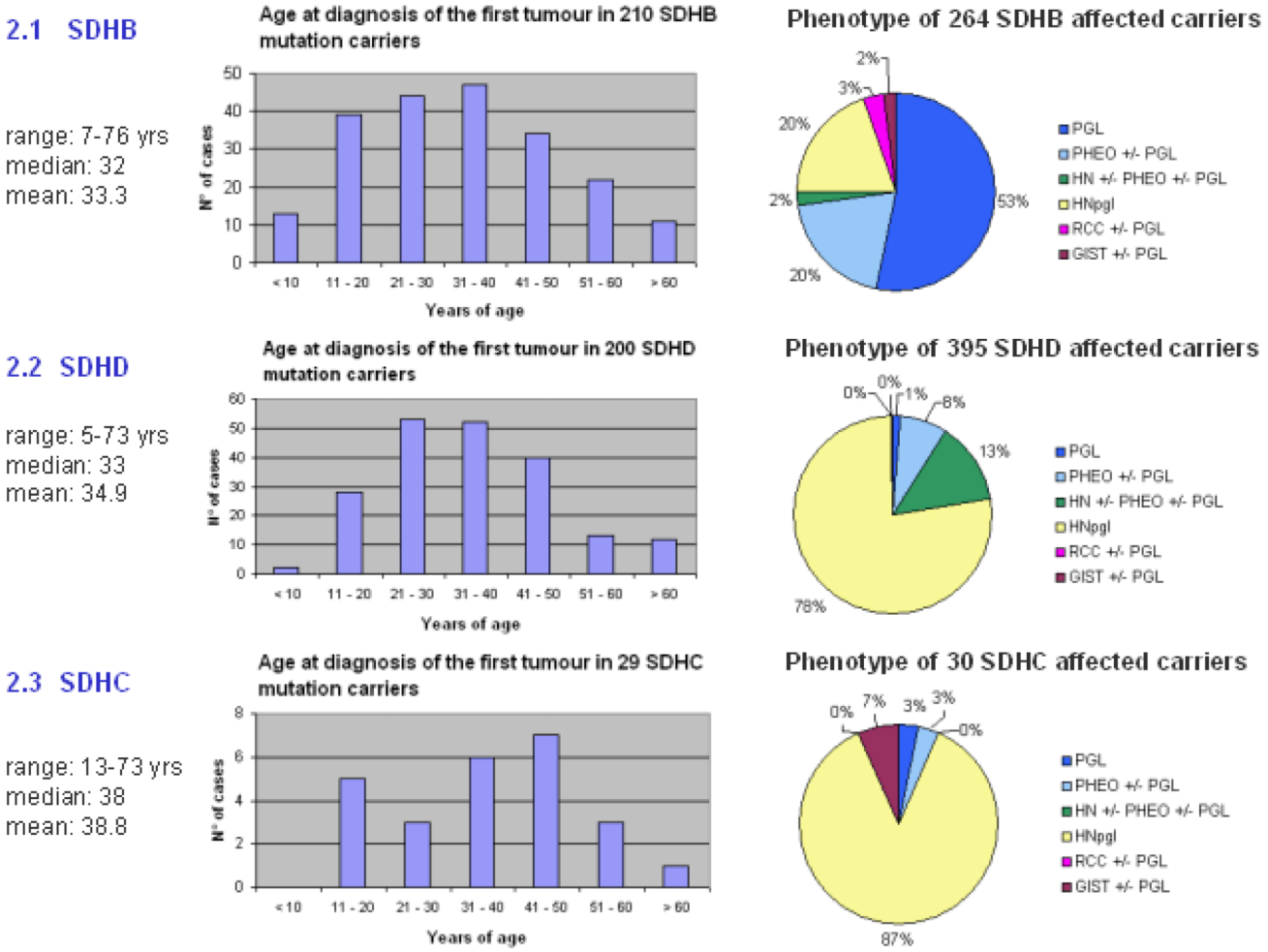

Figure 2. Clinical manifestations of *SDHB* (2.1), *SDHD* (2.2) and *SDHC* (2.3) affected carriers

For each *SDH* gene the left histogram shows the distribution of ages at diagnosis of the first tumour. The range, median and mean ages are also resumed. The right imagine shows the percentages of various tumour phenotypes, including extra-adrenal paraganglioma alone (PGL, blue), adrenal pheochromocytoma with or without extra-adrenal PGLs (PHEO +/− PGL, azure), head and neck paraganglioma alone (HNpgl, yellow), head and neck PGLs with PHEO and/or PGL (HN +/− PHEO +/− PGL, green), renal cell cancer (RCC, pink), gastrointestinal stromal tumours (GIST, purple) with or without (+/−) other neuroendocrine tumours.

Table 1

***SDH* germline mutations in series of sporadic or unselected patients with adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma**

Data on the prevalence of *SDH* germline mutations in sporadic non syndromic PHEOs/PGLs have been derived from 11 studies in which the family history was clearly indicated or the study design was adequate for the purpose of this review. When the same research group published an increasing series of cases over the time, only the last publication has been considered for the calculation of the general prevalence (marked with #). "neg" = cases negative for mutations in the given gene. "nd" = analysis not done.

Tumor type	N° of cases	RET	VHL	SDHB	SDHC	SDHD	Tot SDH	References (population)
Sporadic PHEO-PGL	**24**	neg	neg	**2 (8.3%)**	**0**	**0**	**2 (8.3%)**	Astuti D et al. 2001 [11, 50] (English)
Sporadic PHEO-PGL 14 adrenal, 4 extra-adrenal	18	neg	neg	nd	nd	**2 (11.1%)**		Gimm O et al. 2000 [81] (German)
Sporadic PHEO-PGL		**13 (4.8%)**	**30 (11%)**	**12 (4.4%)**		**11 (4%)**		
- < 30 years (160)		4 (2.5%)	25 (15.6%)	8 (5%)		6 (3.7%)		
- adrenal (241)	271	**13 (5.4%)**	**26 (10.8%)**	**6 (2.5%)**	nd	**7 (2.9%)**	**23 (8.5%)**	Neumann H et al. 2002 [105] (German, Polish)
- extra-adrenal (30)		**0 (0%)**	**4 (13.3%)**	**6 (20%)**		**4 (13.3%)**		
- multiple tumours (26)		5 (19.2%)	12 (46.1%)	0 (0%)		4 (15.4%)		
Sporadic PHEO-PGL	304	neg	neg	**16 (5.3%)**	neg	**13 (4.3%)**	**29 (9.5%)**	Neumann H et al. 2004 [106] (German, Polish)
Sporadic PHEO-PGL	**371**	neg	neg	**21 (5.7%)**	**0**	**21 (5.7%)**	**42 (11.3%)**	# Schiavi F et al. 2005 [120] (German, Polish and other countries)
Sporadic PHEO-PGL			**2 (2.4%)**	**8 (9.5%)**				
adrenal (69)			**2 (2.9%)**	**3 (4.3%)**				
- benign (57)	84	**0**	2 (3.5%)	1 (1.7%)	nd	**0**	**8 (9.5%)**	Gimenez-Roqueplo AP et al. 2003 [80] (French)
- malignant (12)			0 (0%)	2 (16.7)				
extra-adrenal (15)			**0 (0%)**	**5 (33.3%)**				
Sporadic PHEO-PGL	**258**	**1 (0.4%)**	**9 (3.5%)**	**18 (7%)**	**0**	**3 (1.2%)**	**21 (8.1%)**	# Amar L et al. 2005 [46] (French)
Sporadic PHEO-PGL	**213**	**0**	**6/136 (4.4%)**	**1/47 (2%)**	nd	**2/126 (1.6%)**		Korpershoek E et al. 2006 [84] (Dutch)
Sporadic PHEO-PGL	**18**	**0**	**0**	**0**	**0**	**0**	**0**	Persu A et al. 2008 [115] (Belgian)
PHEO collected anonymously	**35**	**2 (5.7%)**	**0**	**1 (2.8%)**	nd	**2 (5.7%)**	**3 (8.5%)**	Cascòn A et al. 2004 [33] (Spanish)

Tumor type	N° of cases	RET	VHL	SDHB	SDHC	SDHD	Tot SDH	References (population)
Total PHEO-PGLs negative for RET-VHL mutations	**901**			43/741 **5.8%**	0/661 **0%**	28/820 **3.4%**	**9%**	combined data

Table 2

***SDH* germline mutations in series of malignant adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma**

Data on the prevalence of *SDH* germline mutations among malignant PHEOs/PGLs have been derived from 4 studies giving a general frequency of 38% with a marked predominance of *SDHB* mutations. In two studies, together with deleterious mutations, 7 vus have been identified. However, giving their absence in normal controls and in other series of cases, a pathogenic role is suspected. “neg” = cases negative for mutations in the given gene. “nd” = analysis not done.

Tumor type	N° of cases	RET	VHL	NF1	SDHB	SDHC	SDHD	References (population)
Malignant PHEO-PGL					**13 to 18* (30 to 41%)**			
- adrenal (13)	**44**	nd	nd	nd	2 (15.4%)	nd	nd	Brouwers FM et al. 2006 [60] (NIH – USA) *5 cases with genetic variants
- extra-adrenal (29)					**16 (55.2%)**			
- uncertain (2)					0 (0%)			
Malignant PHEO-PGL			**1 (1.9%)**	**2 (3.7%)**	**23 (42.6%)**			Amar L et al. 2007 [47] (French)
- syndromic (5)			0 (0%)	2 (40%)	2 (40%)			
- sporadic (49)	**54**	**0**	**1 (2%)**	**0**	**21 (42.8%)**	nd	**0**	
- adrenal (29)			ns	ns	7 (24.1%)			
- extra-adrenal (25)			ns	ns	**16 (64%)**			
Malignant PHEO-PGL					**1 (11%)**			
- adrenal (5)	**9**	nd	nd	nd	0	nd	**0**	Isobe K et al. (2007) [86] (Japanese)
- extra-adrenal (4)					1 (25%)			
Malignant PHEO-PGL					**6 to 7* (21 to 25%)**		**1–2* (3.6–7%)**	
- adrenal (12)	**28**	nd	nd	nd	0	nd	2 (16.7%)	Klein RD et al. 2008 [83] (USA) *2 cases with genetic variants
- extra-adrenal (16)					7 (43.8)		0	
Total malignant PHEO/PGLs	**135**				49/135 **36%**		2/91 **2%**	combined data

Table 3

***SDH* germline mutations in series of patients with suspected genetic predisposition to adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma**

Data on the prevalence of *SDH* germline mutations in cases suspected for a genetic predisposition giving the early age at onset, multiple or bilateral tumours or positive family history. “neg” = cases negative for mutations in the given gene. “nd” = analysis not done.

Phenotype	N° of cases	RET	VHL	SDHB	SDHC	SDHD	Tot SDH	References (population)
Paediatric PGL	**3**	**0**	**0**	**3 (100%)**	**0**	**0**	**3 (100%)**	Mora J et al. 2006 [103] (Spanish)
Paediatric PHEO	**4**	neg	neg	**2 (50%)**	**0**	**0**	**2 (50%)**	Astuti D et al. 2003 [51] (English)
Paediatric PHEO 9–18 years of age	**10**	**2 (20%)**	**1 (10%)**	**0**	nd	**0**	**0**	De Krijger RR et al. 2006 [159] (Dutch)
Multiple sporadic PHEO-PGL	**26**	**5 (19.2%)**	**12 (46.1%)**	**0**	nd	**4 (15.4%)**	**4 (15.4%)**	Neumann H et al. 2002 [105] (German, Polish)
Multiple sporadic PHEO-PGL	**10**	neg	neg	**0**	**0**	**1 (10%)**	**1 (10%)**	Astuti D et al. 2003 [51] (English)
Bilateral PHEO sporadic and familial	**33**	**21 (63.6%)**	**2 (6%)**	**0**	nd	**1 (3%)**	**10%** of cases neg. for RET - VHL	Korpershoek E et al. 2007 [85] (Dutch)
Familial PHEO adrenal and extra-adrenal	**12**	neg	neg	**2 (17%)**	**0**	**0**	**2 (17%)**	Astuti D et al. 2003 [51] (English)
Familial PHEO / PGL / HNPGL	**5**	neg	neg	**3 (60%)**	**0**	**1 (20%)**	**4 (80%)**	Astuti D et al. 2003 [51] (English)
Familial PHEO / PGL / HNPGL	**5**	nd	nd	**5 (100%)**	**0**	**nd**	**5 (100%)**	Bayley JP et al. 2006 [54] (Dutch and other countries)
Familial PHEO / PGL / HNPGL	**3**	**0**	**1 (33.3%)**	**1 (33.3%)**	**0**	**1 (33.3%)**	**2 (66.6%)**	Castellano M. et al. 2006 [66] (Italian)

Table 4

***SDH* germline mutations in series of cases with head and neck paragangliomas (HNPGL)**

Data on the prevalence of *SDH* germline mutations in series of cases with HNPGL either sporadic (unique tumours), multiple or familial are derived from 8 studies analysing different populations outside the area of Low Countries. The last paper (marked with #) has been excluded from calculation of the general prevalence because data were not presented according with different phenotypes.

Phenotype	N° of cases	SDHB	SDHC	SDHD	Tot SDH	References (population)
HNPGL	**47**	**3 (6.4%)**	**2[#] (4.3%)**	**7 (14.9%)**	**12 (25.5%)**	Baysal BE et al. 2002, # Baysal BE et al. 2004 [55, 56] (US, Pittsburg and Los Angeles)
- familial (10)		2 (20%)	1 (10%)	5 (50%)	8 (80%)	
- multiple (5)		0	0	2 (40%)	2 (40%)	
- sporadic (32)		1 (3.1%)	1 (3.1%)	0	2 (6.3%)	
HNPGL	**17**	**1 (5.9%)**	**0**	**1 (5.9%)**	**2 (11.8%)**	Mhatre AN et al. 2004 [101] (US)
- familial (3)		1 (33.3%)		1 (33.3%)	2 (66.7%)	
- sporadic (14)		0		0	0	
HNPGL	**34**	**0**	**0**	**4 (11.8%)**	**4 (11.8%)**	Astuti D et al. 2003 [51] (English)
- familial (1)				1 (100%)	1 (100%)	
- multiple (3)				3 (100%)	3 (100%)	
- sporadic (30)				0	0	
HNPGL	**34**	**3 (8.8%)**	**0**	**11 (32.3%)**	**14 (41.2%)**	Badenhop RF et al. 2004 [52] (Australian)
- familial (10)		1 (10%)		8 (80%)	9 (90%)	
- multiple (1)		0		1 (100%)	1 (100%)	
- sporadic (23)		2 (8.7%)		2 (8.7%)	4 (17.4%)	
HNPGL	**23**	**1 (4.3%)**	**1 (4.3%)**	**6 (26%)**	**8 (34.8%)**	Fakhry N et al. 2008 [74] (French, Caucasian and Maghreb)
- familial (4)		0	0	4 (100%)	4 (100%)	
- multiple (3)		0	1 (33.3%)	2 (66.6%)	3 (100%)	
- sporadic (16)		1 (6.3%)	0	0	1 (6.3%)	
HNPGL	**40**	**7 (17.5%)**	**0**	**5 (12.5%)**	**12 (30%)**	Lima J et al. 2007 [92] (Spanish, Portuguese)
- familial (4)		1 (25%)		3 (75%)	4 (100%)	
- sporadic (36)		6 (16.7%)		2 (5.5%)	8 (22.2%)	

Phenotype	N° of cases	SDHB	SDHC	SDHD	Tot SDH	References (population)
HNPGL		**1 (5%)**	**1 (5%)**	**2 (10%)**	**4 (20%)**	
- familial (1)	**20**	0	1 (100%)	0	1 (100%)	Schiavi F et al. 2006 [121] (Italian)
- multiple (2)		0	0	2 (100%)	2 (100%)	
- sporadic (17)		1 (5.8%)	0	0	1 (5.8%)	
HNPGL familial, multiple and sporadic (data no specified)	**121**	**8 (6.6%)**	**5 (4.1%)**	**20 (16.5%)**	**33 (27.3%)**	# Schiavi F et al. 2005 [120] (77% German, 23% other countries)
Sporadic HNPGL	**168**	11/168 **6.5%**	1/168 **0.6%**	4/168 **2.4%**	**9.5%**	combined data
Multiple HNPGL	**14**	0/14 **0%**	0/14 **0%**	10/14 **71.4%**	**71.4%**	
Familial HNPGL	**33**	5/33 **15%**	2/33 **6%**	22/33 **66.6%**	**87.8%**	

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Table 5

***SDH* germline mutations in series of cases with head and neck paragangliomas (HNPGL) from the Netherlands and Belgium**

Data on the prevalence of *SDH* germline mutations in series of cases with HNPGL either sporadic (unique tumours), multiple or familial belonging from the Netherlands and Belgium are derived from 5 studies. When the same research group published an increasing series of cases over the time, only the last publication has been considered for the calculation of the general prevalence (marked with #). "nd" = analysis not done.

Phenotype	N° of cases	SDHB	SDHC	SDHD	Tot SDH	References (population)
HNPGL				**52 (59.7%)**		
- familial (32)	**87**	nd	nd	31* (96.9%)		Taschner P et al. 2001 [126] (Dutch) * the only negative family is linked to PGL2 locus
- multiple (10)				8 (80%)		
- sporadic (45)#				13 (28.9%)		
HNPGL sporadic (no further specified)	**95 #**	**2 (2.1%)**	**1 (1%)**	**24 (25.3%)**	**27 (28.4%)**	Bayley JP et al. 2006 Taschner P et al. 2001 [54, 126] (Dutch)
HNPGL				**32 (56.1%)**		
- familial (19)	**57**	nd	nd	19 (100%)		Dannenberg H et al. 2002 [69] (Dutch)
- multiple (10)				7 (70%)		
- sporadic (28)				6 (21.4%)		
HNPGL		**1 (4.8%)**		**11 (52.4%)**	**12 (57.1%)**	
- familial (12)	**21**	0	nd	11* (91.7%)	11 (91.7%)	Douwes Dekker PB et al. 2003 [71] (Dutch) * the only negative family is linked to PGL2 locus
- multiple (3)		0		0	0	
- sporadic (6)		1 (16.7%)		0	1 (16.7%)	
HNPGL		**7 (19.4%)**		**9 (25%)**	**16 (44.4%)**	
- familial (6)	**36**	0	**0**	6 (100%)	6 (100%)	Persu A et al. 2008 [115] (Belgian)
- sporadic (30)		7 (23.3%)		3 (10%)	10 (33.3%)	
Sporadic HNPGL	**159**	10/131 **7.6%**	1/125 **0.8%**	33/159 **20.7%**	**29.1%**	combined data
Familial HNPGL	**69**	**0%**	**0%**	67/69 **97%**	**97%**	

Table 6

Clinical manifestations of *SDHB* mutation carriers

Clinical manifestations of *SDHB*, *SDHD* and *SDHC* affected carriers. The first column shows the number of cases reported in each study and the selection criteria. When patients have been selected for PHEOs/PGL head and neck tumours were absent or not specified ("ns") as it was true for series of HNPGL cases where adrenal and extra-adrenal PGLs were absent or not specified ("ns"). With respect to HNPGL, the percentage reported for each paraganglia refers to the involvement of the organ with respect to the total number of tumours recorded. Carotid b. = carotid body. nos = no otherwise specified.

Number of cases	Age at first tumour	Adrenal pheo	Abdominal pgl	Thoracic pgl	Head and neck pgl	Multiple tumours	Malignant tumours	References (population)
32	**31.3** (10–65)	**9 (28.1%)**	**16 (50%)**	**3 (9.3%)**	**10 (31.2%)**	**9 (28.1%)**	**11 (34.4%)**	Neumann H et al. 2004 [106] (German, Polish)
51	**47** (7–68)	**9 (17.6%)**	**34 (66.7%)**	**9 (17.6%)**	**14 (27.4%)**	**6 / 49 (12.2%)**	**18 / 48 (37.5%)**	Benn D et al. 2006 [58] (Australian, French, US, English, German)
18*	**28** (10–48)	**6 (33.3%)**	**13 (72.2%)**	**2 (11.1%)**	**2 (11.1%)**	**3 (16.6%)**	**6 (33.3%)**	Srirangalingam U et al. 2008 [123] (English) * including 2 relatives and 3 genetic variants
21 PHEO-PGL	**33.6** (10–58)	**7 (33.3%)**	**17 (80.9%)**		ns	**3 (14.3%)**	**15 (71.4%)**	Amar L et al. 2005 [46] (French)
15 HNPGL only	**39** (21–66)	ns	ns	ns	67% carotid b. 13% jugular 0% tympanic 13% vagal	**4 (27%)**	**6 (40%)**	Schiavi F et al. 2005 [120] (German, Polish and other countries)
3 HNPGL	**27** (22–32)	**0**	ns	ns	0% carotid b. 67% jugular 0% tympanic 33% vagal	**0**	**0**	Badenhop RF et al. 2004 [52] (Australian)
264	**33.3** (7–76)	**12%**	**66%** (abdominal in 45% of cases, thoracic in 5%, both in 4%, nos in 11% of cases)		**25%**	**33%**	**41%**	present work

Table 7

Clinical manifestations of *SDHD* mutation carriers

Clinical manifestations of *SDHB*, *SDHD* and *SDHC* affected carriers. The first column shows the number of cases reported in each study and the selection criteria. When patients have been selected for PHEOs/PGL head and neck tumours were absent or not specified ("ns") as it was true for series of HNPGL cases where adrenal and extra-adrenal PGLs were absent or not specified ("ns"). With respect to HNPGL, the percentage reported for each paraganglia refers to the involvement of the organ with respect to the total number of tumours recorded. Carotid b. = carotid body. nos = no otherwise specified.

Number of cases	Age at first tumour	Adrenal Pheo	Abdominal pgl	Thoracic pgl	Head and neck pgl	Multiple tumours	Malignant tumours	References (population)
34	**32.4** (5–60)	**18 (52.9%)**	**7 (20.6%)**	**6 (17.6%)**	**27 (79.4%)**	**25 (73.5%)**	**0**	Neumann H et al. 2004 [106] (German, Polish)
28	**31** (7–73)	**2 (7.1%)**	**5 (17.8%)**	**3 (10.7%)**	**25 (89.3%)**	**8 / 27 (29.6%)**	**2 / 26 (7.7%)**	Benn D et al. 2006 [58] (Australian, French, US, English, Canadian)
18	**39** (14–69)	**3 (16.6%)**	**3 (16.6%)**	**2 (11.1%)**	**16 (88.9%)** 79% carotid b. 9% jugular 12% vagal	**15 (83.3%)**	**0**	Simi L et al. 2005 [122] (Italian carriers of the fouder mut p.Gln109X)
11 PHEO-PGL	**31.2** (17–59)	**5 (45.4%)**	**7 (63.6%)**		ns	**4 (36.3%)**	**0**	Amar L et al. 2005 [46] (French)
57 HNPGL	**34.2** (8–60)	**6 (10.5%)**	ns	ns	84.5% carotid body unilateral or bilateral	**32 (56.1%)**	**4 (7%)**	Astrom CK et al. 2003 [49] (21 from US, 1 from Canada, 1 from Turkey)
42 HNPGL only	**36** (13–67)	ns	ns	ns	83% carotid b. 19% jugular 10% tympanic 2% vagal	**24 (57%)**	**0**	Schiavi F et al. 2005 [120] (German, Polish and other countries)
40 HNPGL	**45.8**	**7 (17.5%)**	**1 (2.5%)**	**0**	85% carotid b. 32.5% jugulo-tympanic 47.5% vagal	**20 (50%)**	**0**	van Houtum WH et al. 2005 [130] (Dutch)
19 HNPGL Fam, only	**37.3**	ns	ns	**1 (5.3%)**	66% carotid b. 12% jugular 6% tympanic 16% vagal	**17 (89.5)**	**0**	Dannenberg H et al. 2002 [69] (Dutch)
13 HNPGL	**37.6** (18–69)	**1 (7.7%)**	**1 (7.7%)**	**2 (15.4%)**	74% carotid b. 7% jugular 7% vagal 11% other pgls	**10 (76.9%)**	**0**	Fish JH et al. 2007 [75] (Austrian)
11 HNPGL	**36.4** (14–65)	**1 (9%)**	ns	ns	82% carotid b. 18% jugular 0% tympanic 27% vagal	**4 (36.3%)**	**0**	Badenhop RF et al. 2004 [52] (Australian)
395	**35** (5–73)	**14–16%**	**12–14%**		**91%**	**79%**	**5%**	present work

Table 8

Clinical manifestations of *SDHC* mutation carriers

Clinical manifestations of *SDHB*, *SDHD* and *SDHC* affected carriers. The first column shows the number of cases reported in each study and the selection criteria. When patients have been selected for PHEOs/PGL head and neck tumours were absent or not specified ("ns") as it was true for series of HNPGL cases where adrenal and extra-adrenal PGLs were absent or not specified ("ns"). With respect to HNPGL, the percentage reported for each paraganglia refers to the involvement of the organ with respect to the total number of tumours recorded. Carotid b. = carotid body. nos = no otherwise specified.

Number of cases	Age at first tumour	Adrenal Pheo	Abdominal pgl	Thoracic pgl	Head and neck pgl	Multiple tumours	Malignant tumours	References (population)
22	**46** (13–73)	**0**	**0**	**0**	**22 (100%)** 59% carotid b. 27% jugular 9% tympanic 9% vagal	**2 (9%)**	**0**	Schiavi F et al. 2005 [120] (German, Polish and other countries)
30	**39** (13–73)	**1 (33%)**	**3 (10%)**	**0**	**26 (87%)**	**8 (27%)**	**1 (3%)**	present work

Table 9

***SDH* somatic point mutations and deletions (LOH) in pheochromocytomas (PHEO) and paragangliomas (PGL). When possible, samples from carriers of *SDH* germline mutations have been removed**

Results of 17 studies dealing with the search for somatic mutations and/or deletions (mainly loss-of-heterozygosity = LOH at microsatellite analysis) at *SDH* loci in HNPGLs, adrenal PHEOs and extra-adrenal PGLs. “nd” = analysis not done.

Tumour type	N° of samples	SDHB		SDHC		SDHD		Notes	References
		mut	LOH	mut	LOH	mut	LOH		
CNS-PGL	**22**	nd	nd	nd	nd	**0**	nd	Apparently sporadic pgls of the cauda equina	Masuoka J et al. 2001 [146]
HNPGL	**78**	nd	nd	nd	nd	**0**	nd	Tumours from 57 cases (32 with germline *SDHD* mut)	Dannenberg H et al. 2002 [69]
HNPGL	**30**	**0**	nd	**0**	nd	**0**	nd	Tumours from cases negative for germline *SDHB-D* mut	Astuti D et al. 2003 [51]
HNPGL	**14**	**0**	nd	**0**	nd	**0**	nd	Tumours from cases negative for germline *SDHB-C-D* mut	Mhatre AN et al. 2004 [101]
HNPGL	**17**	**1/17**	nd	**0**	nd	**1/17**	**17 (100%)**	Apparently sporadic hnpgls 3 of which malignant	Braun S et al. 2005 [147]
PHEO - PGL	**134**	nd	nd	nd	nd	**0**	nd	Tumours from 126 cases (2 with germline *SDHD* mut)	Dannenberg H et al. 2005 [70]
PHEO	**30**	**0**	nd	nd	nd	**0**	nd	Tumours from cases negative for germline *SDHB-C-D RET* and *VHL* mut (*SDHB-D* promoter methylation was also negative)	Cascòn A et al. 2004 [33]
PHEO	**24**	**0**	**21/36* (58%)**	**0**	nd	**0**	**33%**	Tumours from 24 sporadic cases (1 with a germline *SDHB* mut) *36 further analysed in 2004	Astuti D et al. 2001 [12, 50]
PHEO	**20**	nd	nd	nd	nd	**0**	nd	Tumours from cases negative for germline *SDHD* mut	Aguiar R et al. 2001 [148]
PHEO - PGL	**16**	nd	nd	nd	nd	**1/16 (6%)**	**11 (69%)**	Tumours from cases negative for germline *SDHD* mut	Gimm O et al. 2000 [81]
PHEO - PGL	**18**	nd	nd	nd	nd	**0**	**1/3 (33.3%)** **1/3 (33.3%)0/2**	Pheochromocytomas (9) Sympathic PGLs (4) Para-sympathic PGLs (4)	Perren A et al. 2002 [149]
PHEO - PGL	**44**	nd	nd	nd	nd	**0/18** **0/3**	**9/30** **(30%) 1/6 (17%)**	37 sporadic pheos 7 sporadic abdominal pgls	Kytölä S et al. 2002 [150]
PHEO - PGL	**26**	nd	**9 (35%)**	nd	nd	nd	**7 (27%)** all benign adrenal	Tumours from cases negative for germline *SDHB-D* mut	Gimenez-Roqueplo AP et al. 2003 [80]
PHEO - PGL	**35**	nd	nd	nd	nd	**0**	**6/19 (31.6%)** **2/6 (33.3%)**	25 sporadic pheos 10 sporadic extra-adrenal pgls	Sun HY et al. 2006 [151]

Tumour type	N° of samples	SDHB		SDHC		SDHD		Notes	References
		mut	LOH	mut	LOH	mut	LOH		
PGL	**23**	**1/23 (4%)**	nd	nd	nd	**0**	nd	Tumours from cases negative for germline *SDHB-D* mut	Korpershoek E et al. 2007 [85]

Table 10

***SDH* somatic point mutations and deletions (LOH) in tumour samples other than pheochromocytomas and paragangliomas**

Results of 11 studies dealing with the search for somatic mutations and/or deletions (mainly loss-of-heterozygosity = LOH at microsatellite analysis) at *SDH* loci in a variety of tumours known to be characterized by 1p or 11q LOH or related to the "paraganglioma-pheochromocytoma syndrome" such as renal cell cancers.

Tumour type	N° of samples	SDHB		SDHC		SDHD		Notes	References
		mut	LOH	mut	LOH	mut	LOH		
Neuroendocrine tumours	**25**	nd	nd	nd	nd	**0/18** **0/7**	**5/8 (62.5%)** nd	Midgut carcinoids (18) Merkel cell skin carcinomas (7)	Kytölä S et al. 2002 [150]
Neuroendocrine tumours	**35**	nd	nd	nd	nd	**0/8** **0/6** **0/21**	**3/4 (75%)** **1/3 (33%)** **4/14 (29%)**	Nets lung (8) Nets gastro-intestinal (6) Nets pancreas (21)	Perren A et al. 2002 [149]
Medullary thyroid ca.	**35**	**0**	**8/30 (27%)**	**0**	nd	**0**	**1/24 (4.2%)**	22 sporadic 13 from MEN2A patients	Montani M et al. 2005 [154]
Parathyroid adenomas	**10**	nd	nd	nd	nd	**0**	**0**		Perren A et al. 2002 [149]
Neuroblastomas	**98**	nd	nd	nd	nd	**0/67** **2/31 (6.4%)**	**20/67 (30%)** **8/31 (26%)**	67 primary tumours 31 cell lines	De Preter K et al. 2004 [32]
Neuroblastomas	**46**	**0**	**unk**	nd	nd	nd	nd	46 primary tumours	Astuti D et al. 2004 [153]
Nasopharyngeal carcinomas	**50**	nd	nd	nd	nd	**0**	**22/43**	43 primary tumours 4 cell lines 3 xenografts	Hui AB et al. 2002 [155]
Burkitt's lymphomas	**9**	nd	nd	nd	nd	**0**	**unk**	5 primary tumours 4 cell lines	Hui AB et al. 2002 [155]
Gastrointestinal cancers	**111**	nd	nd	nd	nd	**unk**	**5/35 (14%)** **5/40 (13%)**	Colorectal cancers (52) Gastric cancers (59) Full paper not available	Habano W et al. 2003 [156]
Renal cell tumours	**95**	**0**	nd	nd	nd	**0**	nd	65 clear cell (35 < 50 yrs), 14 oncocytoma, 9 oncocytic -papillary, 3 papillary, 2 granular cell, 2 mixed	Vanharanta S et al. 2004 [129]
Renal cell tumours	**29**	**0**	**1/18 (5.5%)**	nd	nd	nd	nd	25 clear cell, 4 oncocytoma	Morris MR et al. 2004 [157]