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The triad of paragangliomas, gastric stromal tumours and pulmonary chondromas (Carney triad), and the dyad of paragangliomas and gastric stromal sarcomas (Carney–Stratakis syndrome): molecular genetics and clinical implications

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Abstract

Carney triad (CT) describes the association of paragangliomas (PGLs) with gastrointestinal stromal tumours (GISTs) and pulmonary chondromas (PCH). A number of other lesions have been described in the condition including pheochromocytomas, oesophageal leiomyomas and adrenocortical adenomas; CT is a novel form of multiple endocrine neoplasia (MEN), a genetic condition with a female predilection. Inactivating mutations of the mitochondrial complex II succinate dehydrogenase (SDH) enzyme subunits SDHB, SDHC and SDHD have been found in familial and sporadic PGLs, and gain-of-function mutations of the oncogenes c-kit (*KIT*) and platelet-derived growth factor receptor A (*PDGFRA*) cause sporadic and familial GISTs. We recently reported an international series of patients with CT, 34 females and three males (median age of presentation 21 years) who did not carry *SDHA*, *SDHB*, *SDHC*, *SDHD*, *KIT* or *PDGFRA* gene mutations. Comparative genomic hybridization revealed a number of DNA copy number changes. The most frequent and greatest contiguous change was a deletion within the 1pcen13-q21 region, which harbours the *SDHC* gene. Another frequent change was loss of 1p. Although GISTs showed more frequent losses of 1p than PGLs, the pattern of chromosomal changes was similar in the two tumours despite their different tissue origin and histology; the findings were consistent with a common genetic aetiology of these two tumours in CT. In a separate condition, in which the association (or dyad) of GISTs with PGLs is inherited in an autosomal dominant manner (Carney–Stratakis syndrome, CSS), germline mutations of the *SDHB*, *SDHC* and *SDHD* genes (but not *KIT* or *PDFGRA*) were found; GISTs in this condition were caused by SDH deficiency. We conclude that CT is a novel MEN syndrome whose genetic defect remains elusive. CSS is caused by SDH defects, suggesting that sarcomas (GISTs) can be caused by defective mitochondrial oxidation, consistent with recent data implicating this enzyme in a variety of endocrine and other tumours. The above have clinical implications (i) for patients with GISTs that are *cKIT*- and *PDGFRA*-mutation negative: these tumours are usually resistant to treatment with currently available tyrosine kinase inhibitors and may be part of a syndrome such as CT or CSS; and (ii) for patients with an inherited PGL syndrome, family history should be explored to identify any other tumours in the family, and in particular other endocrine lesions and GISTs.

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Introduction: Carney triad

Carney triad (CT) describes the association of paragangliomas (PGLs) with gastrointestinal stromal tumours (GISTs) and pulmonary chondromas (PCH) (Online Mendelian Inheritance in Man, OMIM, catalogue number 604287) [1]. The condition was first described as the 'triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma' [2]. Initially, GISTs were thought to arise from the smooth muscle [2, 3] (hence the term 'leiomyosarcoma') but, later, they were shown to originate from the interstitial cells of Cajal (ICCs) [4, 5]. The condition was called 'Carney triad' [6], but it is in fact a multiple neoplasia syndrome affecting mostly females and predisposing to a variety of tumours including bilateral or unilateral adrenocortical adenomas (ACA) that are usually nonfunctioning [4, 7].

Although a few cases with family history of PGLs and GISTs were included within the original cohort patients with CT [4], it was recently recognized [8] that the dyad of 'paraganglioma and gastric stromal sarcoma' or the 'Carney–Stratakis syndrome' (CSS) which affects both males and females and is not associated with PCH [9] is a separate condition that is transmitted by autosomal dominant inheritance. The syndrome is listed in OMIM as a separate entity (OMIM#606864) and has been since reported in a number of kindreds [10] (see below).

Carney triad and CSS have been reported in all races and in several countries; there appears to be no specific ethnic or geographical predilection. The prevalence of the two syndromes is unknown; CSS is probably more frequent than CT (see below). Once the familial cases of CSS are removed from the original cohort of patients with CT, there appear to be no inherited cases of the triad. In the latest report [4], 77 nonfamilial cases of CT were reported; 66 female and 11 male. One-fifth of the patients had the three tumours; the remainder had two of the three, usually gastric GIST and PCH. ACAs were identified in one-eighth of the patients. Oesophageal leiomyoma was also suggested as an additional, probable component [4].

In the absence of patients with similarly affected relatives, can one consider CT a genetic disorder? The rarity of the individual components of this condition in the general population, their coexistence in affected individuals and the multiplicity and young age of tumour occurrence, all suggest a specific genetic defect. Positional cloning of the responsible gene(s), however, is hampered by the absence of inherited cases. We recently analysed DNA from 37 CT patients and/or their tumours for the coding sequence of the *SDHB*, *SDHC*, *SDHD*, *KIT*, and *PDGFRA* genes that have been involved in the pathogenesis of familial PGLs [10]. We also sequenced the gene coding for the SDH subunit A (*SDHA*), because polymorphisms of this gene had been potentially implicated in predisposition to PGLs [11]. In addition, we employed comparative genomic hybridization (CGH) to identify chromosomal loci associated with CT by comparing DNA extracted from peripheral blood cells to tumour DNA, or in the absence of the former, genetic material obtained from different tumours from the same patient [10].

There were no coding sequence mutations in any of the screened genes [10]. The most frequent and greatest contiguous change detected by tumour CGH studies was deletion of the 1cen-q21 chromosomal region involving the *SDHC* gene. Other alterations were also detected, including loss of the 1p region. Significantly, PGLs and GISTs in CT shared the same genetic alterations despite their different tissue origin. These data excluded known genes as the cause of CT and point to a common genetic aetiology for its component tumours.

Patients and candidate gene sequencing

We studied an international series of patients with CT; 34 females and three males, with a median age at presentation of 21 years (Table 1). CTRS2 and CTR04.01 were cases 3 and 1, respectively, in the reports by Carney *et al.* [2] and Carney [3]. CTR04.01 had a peripheral blood karyotype 46,XX, inv(9)(p11:q13), a variant found in the general population at a frequency of up to 1.5% and only rarely associated with phenotypic abnormalities [12]. CTR04.01 was developmentally normal but was born with complete and partial agenesis of the left and right external ear; she underwent left adrenalectomy for an ACA and subclinical Cushing syndrome at the age of 47 years. CTRS2 had multiple GIST metastases to the liver and elsewhere. CTR05.01, CTRS5T, CTR06.01, CTRS.13, CTRS21 and CTR08.03 are described in detail by Sigmund *et al.* [13], Cameron *et al.* (second case in that report) [14], Wintermark *et al.* [15], McLaughlin *et al.* [16], Grace *et al.* [6] and Convery *et al.* [17]. CTR06.01 had also ACA [15]. Patients CTRS21, CTRS23, CTRS42 and CTR07.03 and the archived specimens CT.1 to CT.24 were included in the last series on CT by Carney [4]; sample B177/B178 was from the proband with CT, parotid gland tumours and breast cancer; the patient also had a brother with Hirschprung disease. The family was reported by Scopsi *et al.* [18]. Finally, samples CTRS19 and CTRS41 were newly identified patients with CT that have not been reported. As mentioned above, there were no coding sequence mutations of the *KIT*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD* and *PDGFRA* genes in the germline and tumour DNA samples. A number of *SDHA* sequence variants were identified but they were relatively common polymorphisms (Table 2). There were no major deletions or other chromosomal rearrangements detected in any of the samples for the chromosomal loci of the candidate genes.

Tumour culture chromosome analysis and CGH results

Carney triad tumours, histological diagnoses, karyotypes and DNA copy number changes are reported elsewhere [10]. CGH was performed on a total of 41 tumours: 31 GIST, six PGL, three PCH and one ACA. For six of the tumours (five GIST, one PCH), primary culture karyotypes were obtained; with the exception of a polyclonal *46,XX, t(5;7)(q31:q11.2)* abnormality detected in 2 of 30 cells from GIST CTRS9, there were no other abnormalities. Overall, 21 specimens showed no significant CGH changes; four were PGLs. Of the 41 GISTs, 17 (41.5%) showed no changes, a surprisingly large number given that almost 90% of sporadic GISTs have detectable chromosomal imbalances [10].

On the other hand, 10 of 15 benign tumours (75%) and five of six (83%) metastatic lesions showed chromosomal changes. Information was not available on the nature of tumour (benign versus metastatic) in the remaining lesions. There were more gains than losses in benign tumours (16 versus 12). The average number of alterations in benign tumours was 2.1 (range: 0–5). Amongst metastatic lesions, the average number of CGH changes was 3.8 (range, 0–6); gains were more frequent than losses (14 versus 12).

In total, 15 chromosomal regions showed gains in benign tumours. However, 11 were represented in only one sample each. Three chromosomal regions, 6 (6p and 6q), 15q and 17q, were involved in two cases (13%). Losses were identified on chromosomes 1p and 1q (61%) and 11p. In metastatic tumours, 15 chromosomal regions were involved in gains but only two regions, 15q and chromosome 4, showed gains in more than one sample.

Gains of five chromosomal regions that were present in at least one sample were identified in both benign and metastatic tumours. The latter showed more losses than the former; chromosome 1 losses were the most frequent (66%). The minimal region of losses harboured the *SDHC* locus; 1p33–36.4 also showed losses in both benign and malignant tumours (15%). Some other regions on chromosomes 3q, 11q, 16q and 17p had losses but

those on 3q, 11q and 17p were detected in only one sample each. Loss of 16q was present in two metastatic lesions.

CGH, fluorescent *in situ* hybridization (FISH) and loss-of-heterozygosity (LOH) studies

Tumours that showed losses of 1q region by CGH (samples CTRS9, CTRS5T, CTRS6, CTRS7, CTRS10, CTRS13, CTRS19, CTRS21 and CTRS36) were subjected to interphase FISH, using the bacterial artificial chromosome (BAC) RP11 0338-B-10 containing the *SDHC* gene. FISH detected loss of the region in seven of the samples [10]. In these samples, 38–70% of cells showed only one signal of the probe used. In addition to these tumours, we also analysed three GISTs that were not included in the CGH analysis, but belonged to patients CTR07.07.03, CTR08.03 and CTR09.01; two also showed the loss of 1q21 region. Finally, LOH studies confirmed losses of the 1q21 region in these samples [10].

Array CGH was performed on a sample that showed minimal or no abnormalities in the previous analysis (CTRS2). The data are shown in Table 3. This sample was also selected because of the good quality of its DNA and the fact that it was obtained from a GIST excised from case 3 of the original reports of the syndrome by Carney *et al.* [2] and Carney [3] (Fig. 1). Although minimal changes were shown (confirming the lack of significant abnormalities upon the first CGH analysis), most of the single BAC changes were seen on chromosomal regions that were identified in other tumours (Table 2); chromosome 1 involvement included the 1p and 1q regions.

Tumour type and CGH abnormalities

There were small differences between GISTs and PGLs in chromosomal involvement: 17q gains were detected only in PGLs (CTRS7 and CTRS19). There was only one PCH (out of the three investigated) that had CGH abnormalities (CTRS13); it demonstrated chromosome 6 gains, gains that were also detected in one adrenal tumour that was studied, a benign ACA (CTRS14). 1q losses were present in both the PCH and ACA tumours, as well as in three of the six PGLs; 1p losses were seen in two PGLs and five of the GISTs.

Summary of the findings in CT

This genetic investigation of 37 patients and 41 CT tumours is the most comprehensive ever performed in this disease. A total of five patients with CT who underwent genetic analysis has recently been reported in three case studies [19–21]. GISTs in these patients were negative for *KIT* or *PDGFRA* mutations [19–21]; one case (with multiple extra-adrenal paragangliomas) was also screened for *SDHB, SDHC* and *SDHD* mutations and none was found [19]. Three more cases of CT were included in another series; none had mutations in the screened genes and the CGH abnormalities were similar to those reported here [22]. Thus, to date, more than half of the known cases of CT worldwide have been screened for the genes that are linked with the sporadic or genetic forms of two of the individual tumours that comprise the syndrome (GIST and PGL) and no mutations have been found.

This suggests that other as yet unidentified gene(s) are responsible for CT. Further support to this notion is provided by the clinical and molecular analysis of *KIT* mutation-negative GISTs: *KIT* mutations are rare in childhood GISTs, tumours that occur predominantly in females, mostly during the second decade of life and with a gastric predilection [23] – all features of GISTs associated with CT [3, 4]. More recent studies show that *KIT*- and *PPDFGRA* mutation-negative GISTs have a distinct pattern of gene expression [24, 25].

The CGH results are consistent with the different genetic background of CT-associated GISTs and PGLs: In sporadic GISTs, the most common alterations are 14q, 22q and 1p losses, seen in 70%, 60% and 50% of the tumours respectively [24]. In the CT tumours we

studied, 1p loss was seen relatively frequently (two PGLs and five GISTs) but 14q and 22q losses occurred in only one GIST each. 1q loss was by far the most frequent genetic abnormality in CT-associated GISTs and PGLs and was present in the single adrenal adenoma and one of three lung chondromas we studied.

In conclusion, the triad of PGL, GIST and PCH, a multiple neoplasia syndrome that includes adrenocortical and other endocrine tumours, is not due to SDH-inactivating or *KIT* and *PDGFRA*-activating mutations. Chromosome 1 and other copy number changes distinguished these tumours from their sporadic and other familial counterparts and point to a common, yet elusive, genetic cause of CT.

The dyad of ‘paraganglioma and gastric stromal sarcoma’ (CSS)

In 2002, we described a total of 12 patients, seven males and five females, in five unrelated families in which the PGL and GIST were inherited in an apparently autosomal dominant manner, with incomplete penetrance [8]. Paragangliomas were multicentric and gastric stromal sarcomas multifocal in all patients, supporting the inherited nature of this predisposition. The condition has been referred to as the dyad of ‘paraganglioma and gastric stromal sarcoma’ or the CSS (OMIM#606864) [1, 9].

We recently reported germline mutations of the *SDHB*, *SDHC* and *SDHD* genes in patients with the dyad and in their tumours [26, 27]: GISTs from the patients showed allelic losses around the *SDHB* and *SDHC* chromosomal loci pointing to a tumour-suppressor function of SDH subunits in these neoplasms. None of the patients had mutations of the *PDGFRA* or *KIT* genes.

GISTS and SDH deficiency: a new molecular pathway (and therapeutic target?) for GISTs

Although rare, GISTs are the most common mesenchymal tumours (5000 new cases per year in the United States) of the gastrointestinal tract with frequent occurrence in the muscular wall of the stomach (70%), small bowel (10–20%) and, at lower frequencies, in the oesophagus, omentum and mesentery [5, 28, 29]. The median age at diagnosis is around 60 years. The 5-year survival in patients with large tumour size and high mitotic index is less than 40%, indicating poor prognosis [29].

GISTs originate from stem cells with characteristics of the ICCs [5], the pacemaker cells which regulate peristalsis in the digestive tract. Similar to ICCs, up to 95% of GISTs express the receptor tyrosine kinase KIT whose immuno-histochemical detection (CD117) and that of the marker CD34 (haematopoietic progenitor cell antigen) is typical of the lesion [18]. In recent years it has been established that 75–80% of sporadic GISTs harbour somatic gain-of-function mutations in the *KIT* gene encoding the c-KIT protein; an additional 7% of sporadic GISTs harbour mutations in the functionally related *PDGFRA* gene [5, 27–29]. In both cases germline missense mutations or small in frame deletions generate constitutively activated tyrosine kinase receptors with ligand-independent autophosphorylation and downstream signalling. To date, germline *KIT* and *PDGFRA* mutations have also been identified in several families with familial GIST [5, 27–29]. Polyclonal diffuse hyperplasia of ICCs within the myenteric plexus is considered the primary effect of c-KIT constitutive activation [5]. Mutations in *KIT* and *PDGFRA*, either somatic or germline, are mutually exclusive events.

The existence of GISTs that lack detectable somatic mutations in either *KIT* or *PDGFRA* suggests that a different signalling pathway of tumourigenesis is likely to be involved in the pathogenesis of these neoplasms [24, 30]. The identification of germline loss-of-function mutation in the *SDHB*, *SDHC* and *SDHD* genes in the majority of the patients reported worldwide with the familial syndrome of ‘paraganglioma and gastric stromal sarcoma’ led

to the uncovering of a new molecular aetiology for GISTs. These GISTs displayed clear losses of the wild type allele indicating a tumour suppressor role for the SDH enzyme in GISTs that are negative for *KIT* and *PDGFRA* mutations. These findings link mesenchymal tumours to the mitochondrial tumour suppressor gene pathway opening a new field of research and potentially identifying a new molecular target for GISTs that are not responsive to treatment with tyrosine kinase inhibitors [24, 30].

Conclusions – clinical implications

In summary, two new syndromes, CT and CSS, have entered the realm of multiple endocrine neoplasias in the last 5 years [31]. Both are linked to predisposition to PGLs and pheochromocytomas, and one is due to *SDHB*, *SDHC* and *SDHD* mutations that are becoming amongst the most frequently encountered genetic defects in a variety of endocrine tumours [32].

Although both CT and CSS are rare conditions, CSS is probably quite more frequent than what the current numbers indicate (so far, about 20 kindreds are known to us with the dyad or CSS). CSS may be particularly prevalent amongst young patients with GISTs that are negative for *KIT* and *PDGFRA* mutations.

Doctors who take care of patients with apparently ‘sporadic’ PGLs or GISTs should always obtain detailed medical and family histories as often these conditions have decreased penetrance and variable expression. A search for CT or CSS should always follow the detection of a *KIT*- or *PDFGRA*-mutation-negative GIST, especially in the younger patient.

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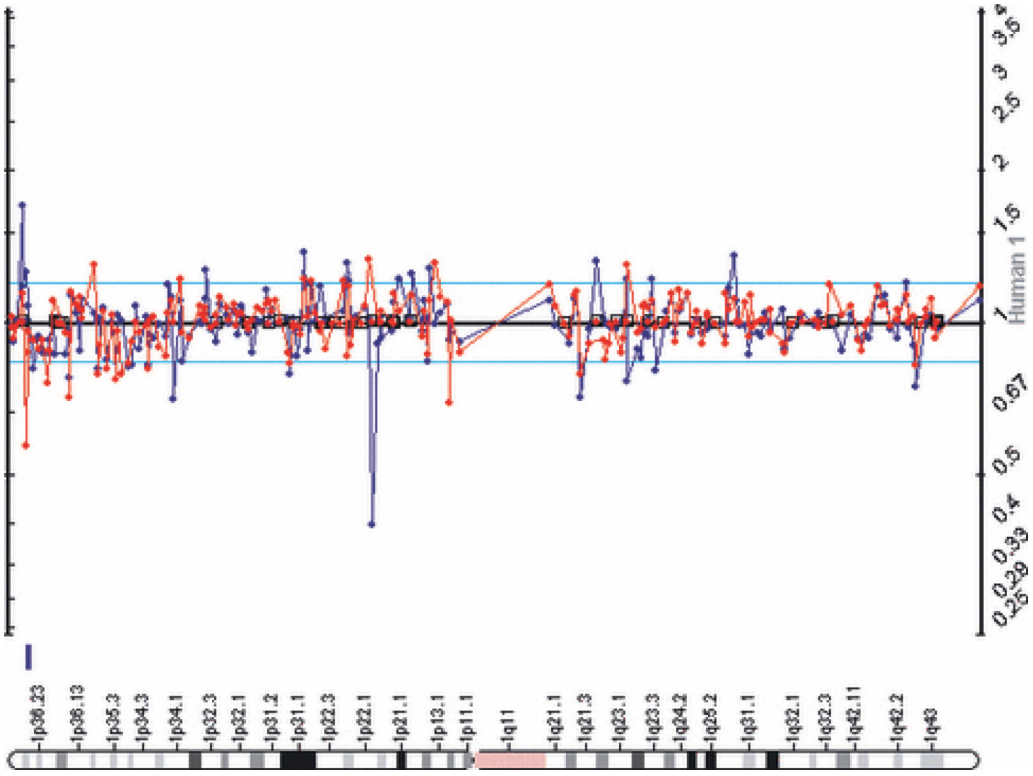

Figure 1.

Array CGH was performed on a sample that showed minimal or no abnormalities in the previous analysis, CTRS2 from case 3 of the original reports of the syndrome by Carney *et al.* [2] and Carney [3]. Table 3 lists the genome-wide changes; in this figure, chromosome 1 data showed involvement of the 1p and 1q regions.

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Table 1

Patients with the triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma (Carney triad)

Patient	Id	Sex	Age	Tumours	Other	Reference
CTRS2	1	F	15	GIST, PGL	Chest X-ray normal; metastatic GIST; multiple PGLs (mediastinal)	Case 3, Carney et al. [2] and Carney [3]
CTR04.01	2	F	12	GIST, PGL, PCH	Peripheral blood karyotype is 46,XX,inv(9) (p11:q13); born with complete and partial agenesis of the left and right external ear, respectively; she has had multiple PGLs (neck) and PCHs and recurrent GIST; left adrenocortical adenomas (subclinical Cushing)	Case 1, Carney *et al.* [2] and Carney [3]
CTR05.01	3	F	17	GIST, PGL, PCH	Multiple GISTs (one malignant); multiple PCH; one PGL (retroperitoneal)	Sigmund et al. [13]
CTRS.5T	4	F	29	GIST, PGL, PCH	Multiple GIST (metastatic); multiple PCH; one PGL (gastric); left adrenocortical tumour (nonfunctional)	Case 2, Cameron et al. [14]
CTRS.6	5	F	14	GIST, PGL, PCH	Multiple GIST (metastatic)	
CTR06.01	6	F	18	GIST, PGL, PCH	Multiple GIST (metastatic); PGL (neck and abdominal); left adrenocortical adenoma	Wintermark et al. [15]
CTRS.13	7	F	26	GIST, PCH	GIST (malignant); multiple PCH	McLaughlin et al. [16]
CTRS.19	8	F	23	GIST, PCH	GIST (multiple); multiple PCH	
CTRS.21	9	F	21	GIST, PGL	GIST (multiple); PGL (cardiac)	Grace et al. [6]
CTRS.23	10	F	25	GIST, PGL	GIST (metastatic); adrenocortical tumour	
CTRS.27	11	F	26	GIST, PCH	GIST (multiple, gastric); lymphoma	
CTRS.41	12	F	12	GIST, PGL	GIST (multiple, metastatic); PGL (para-aortic)	
CTRS.42	13	F	28	GIST, PGL, PCH	GIST (multiple, metastatic); PGL; adrenocortical adenoma	Carney et al. [4]
CTR07.03	14	F	17	GIST, PGL, PCH	GIST (multiple, metastatic); PGL; PCH (mutliple)	Carney et al. [4]
CTR08.03	15	F	21	GIST, PGL, PCH	GIST (multiple, metastatic); PGL; PCH (mutliple)	Convey et al. [17]
CTR09.01	16	F	26	GIST, PGL, PCH	GIST (multiple, metastatic); PGL (metastatic); PCH (mutliple)	
CTR10.01	17	F	21	GIST, PGL	GIST (multiple, metastatic); PGL (nonfunctioning, abdominal); adrenocortical adenoma	
B177/B178	18	F	25	GIST, PGL, PCH	GIST (metastatic), multiple PGLs (mediastinal) and PCHs; right ductal breast cancer at age 50 years	Scopsi et al. [18]
CT.1	19	F	19	GIST, PGL, PCH*		
CT.2	20	F	22	GIST, PCH*		
CT.3	21	F	21	GIST, PCH*		
CT.4	22	F	13	GIST, PCH*		
CT.6	23	M	21	GIST, PCH*		

Patient	Id	Sex	Age	Tumours	Other	Reference
CT.11	24	F	11	GIST, PCH*		
CT.12	25	F	26	GIST, PCH*		
CT.13	26	F	44	GIST, PCH*		
CT.14	27	F	19	GIST, PCH*		
CT.15	28	M	36	GIST, PCH*		
CT.16	29	F	17	GIST, PCH*		
CT.17	30	F	16	GIST, PCH*		
CT.18	31	F	9	GIST, PCH*		
CT.19	32	F	13	GIST, PCH*		
CT.20	33	F	7	GIST, PGL*		
CT.21	34	F	11	GIST, PGL*		
CT.22	35	F	11	GIST, PCH*		
CT.23	36	F	19	GIST, PCH*		
CT.24	37	M	30	GIST, PGL*		

GIST, gastrointestinal stromal tumour (initially referred to as gastric leiomyosarcoma); PCH, pulmonary chondroma; PGL, paraganglioma.

*DNA from samples CT.1 to CT.24 (patients 19 to 37) was obtained from archival material; these patients were included in Carney *et al.* [4].

Table 2

SDHA polymorphic sequences

Genomic region	Sequence	Frequency in CT (37)	Frequency in controls (45)
Promoter	-82 ins. T hom	0	0
	-82 ins. T het	11	10
Intron 1	IVS1 +65 G>A*	8	13
	IVS1 +65 A	1	7
Intron 5	IVS5-12 ins.C het	1	1
	IVS5-12 ins.C hom	0	0
Exon 6	684 T>C*	11	8
	684 C	8	19
Exon 7	891 T>C	11	12
	891 C	16	23
Exon 15	1932 G>A + 1969 G>A	11	3
	1932 A + 1969 A	0	6

Het, heterozygous; hom, homozygous.

* In these two polymorphisms, IVS1+65 G>A and 684 T>C, Fisher's exact test shows statistically significant higher frequency of the ‘mutant’ alleles G and T in the control population. The significance of this finding is unclear; it probably reflects an error in the existing publicly available information concerning the *SDHA* sequence and the frequency of its polymorphisms.

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Table 3

Array CGH analysis in sample CTRS2.

Clone	Cyto Locn	Cy5 test log ratios	Cy3 test log ratios	DNA change	Comment
RP11-421C4	1p36.3–1p36.3	0.273	-0.257	Gain	Single BAC change
RP4-703E10	1p36.32–1p36.33	0.389	-0.745	Gain	Polymorphism
RP11-452O22	1q21.1–1q22	0.337	-0.676	Gain	Polymorphism
RP5-1016N21	1q42.13–1q43	0.225	-0.204	Gain	Single BAC change
RP11-91M15	3q11.2–3q11.2	0.209	-0.326	Gain	Single BAC change
RP5-963K6	4q35.2	0.432	-0.431	Gain	Single BAC change
RP11-90A9	5q14–5q14	0.414	-0.366	Gain	Single BAC change
RP1-304O5	6q12–6q13	0.455	-0.266	Gain	Single BAC change
RP11-89A20(E)	7q11.23	-0.288	0.239	Loss	Single BAC change
RP11-18-L2	8p23.1	0.52	-0.227	Gain	Polymorphism
RP11-89C6	9p21.3–9p22	0.18	-0.253	Gain	Single BAC change
RP11-80F13	9q31.3–9q31.3	-0.183	0.178	Loss	Single BAC change
RP11-88B18	10q21.1–10q21.1	-0.209	0.178	Loss	Single BAC change
RP1-137E24	10q26.3	0.26	-0.356	Gain	Possible gain
RP11-108K14	10q26.3–10q26.3	0.236	-0.274	Gain	Possible gain
RP1-44H16	11p15.5	0.217	-0.234	Gain	Single BAC change
RP5-908H22	11p15.5	0.216	-0.232	Gain	Single BAC change
c197-2	17p13.3	0.189	-0.196	Gain	Possible gain
c197-4	17p13.4	0.229	-0.302	Gain	Possible gain
c197-9	17p13.5	0.371	-0.424	Gain	Possible gain
RP11-79F15	19p13.2–19p13.2	-0.476	0.483	Loss	Single BAC change
RP4-788L20	20p11.21–20p11.23	0.294	-0.179	Gain	Single BAC change
RP3-355C18	22q13.3–22q13.3	0.207	-0.291	Gain	Single BAC change
CTD-3018K1	22q13.33	0.477	-0.392	Gain	Single BAC change