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Genetics of Carney Triad: Recurrent Losses at Chromosome 1 but Lack of Germline Mutations in Genes Associated with Paragangliomas and Gastrointestinal Stromal Tumors

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Context: Carney triad (CT) describes the association of paragangliomas (PGLs) with gastrointestinal stromal tumors (GISTs) and pulmonary chondromas. Inactivating mutations of the mitochondrial complex II succinate dehydrogenase (SDH) enzyme subunits SDHB, SDHC, and SDHD are found in PGLs, gain-of-function mutations of c-*kit* (*KIT*), and platelet-derived growth factor receptor A (*PDGFRA*) in GISTs.

Objective: Our objective was to investigate the possibility that patients with CT and/or their tumors may harbor mutations of the *SDHB*, *SDHC*, *SDHD*, *KIT*, and *PDGFRA* genes and identify any other genetic alterations in CT tumors.

Design: Three males and 34 females with CT were studied retrospectively. We sequenced the stated genes and performed comparative genomic hybridization on a total of 41 tumors.

Results: No patient had coding sequence mutations of the investigated genes. Comparative genomic hybridization revealed a number of DNA copy number changes: losses dominated among benign lesions, there were an equal number of gains and losses in malignant lesions, and the average number of alterations in malignant tumors was higher compared with benign lesions. The most frequent and greatest contiguous change was 1q12-q21 deletion, a region that harbors the *SDHC* gene. Another frequent change was loss of 1p. Allelic losses of 1p and 1q were confirmed by fluorescent *in situ* hybridization and loss-of-heterozygosity studies.

Conclusions: We conclude that CT is not due to SDH-inactivating or *KIT*- and *PDGFRA*-activating mutations. GISTs and PGLs in CT are associated with chromosome 1 and other changes that appear to participate in tumor progression and point to their common genetic cause. **(*J Clin Endocrinol Metab* 92: 2938–2943, 2007)**

CARNEY TRIAD (CT) describes the association of paragangliomas (PGLs) with gastrointestinal stromal tumors (GISTs) and pulmonary chondromas (PCH) [Online Mendelian Inheritance in Man (OMIM) no. 604287; http://www.ncbi.nlm.nih.gov/omim/]. The condition was first described as the "triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma" (1). Initially, the gastric sarcomas were thought to arise from the smooth muscle (1, 2), but later, their origin was linked to the interstitial cells of Cajal (3), as in other GISTs (4–6). The condition was called the Carney triad (5); it is in essence a multiple neoplasia syndrome affecting mostly females and predisposing to a variety of tumors including cortisol-producing tumors and other nonfunctioning bilateral or unilateral adrenocortical adenomas (ACA) (3).

Although a few familial cases had been identified within

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Abbreviations: ACA, Adrenocortical adenoma; BAC, bacterial artificial chromosome; CGH, comparative genomic hybridization; CSS, Carney-Stratakis syndrome; CT, Carney triad; FISH, fluorescence *in situ* hybridization; GIST, gastrointestinal stromal tumor; IHC, immunohistochemistry; LOH, loss of heterozygosity; OMIM, Online Mendelian Inheritance in Man; PCH, pulmonary chondroma; PGL, paraganglioma; SDH, succinate dehydrogenase.

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the original cohort of patients with CT (3), it was recently recognized (7) that autosomal dominant inheritance of the dyad of paraganglioma and gastric stromal sarcoma or the Carney-Stratakis syndrome (CSS) (8) is a separate condition, which affects both males and females and is not associated with PCH; the syndrome is listed in OMIM as a separate entity (OMIM no. 606864) (9). Mutations of the genes coding for the succinate dehydrogenase (SDH) subunits that are associated with familial PGLs appear to be the most likely molecular cause of CSS (10).

Once cases of CSS are removed, there appear to be no inherited cases of the triad. In the latest series (3), 77 patients with CT were reported: 66 female and 11 male. One fifth of the patients had the three tumors; the remainder had two of the three, usually gastric GIST and PCH. ACAs were identified in one eighth of the patients, and esophageal leiomyoma was also suggested as a probable component (3).

In the absence of inherited cases, can one consider CT a genetic disorder? The rarity of the individual components of this condition in the general population, their unusual coexistence in affected individuals, and their multiplicity and young age of tumor occurrence all suggest a specific genetic defect.

In the present study, we first analyzed 37 CT patients (Table 1) and/or their tumors for the coding sequence of the *SDHB*, *SDHC*, *SDHD*, *KIT*, and *PDGFRA* genes (11). The gene coding for the SDH subunit A (*SDHA*) was also sequenced (12). We then employed comparative genomic hybridization (CGH) comparing, in most cases, tumor DNAs from various samples from the same patient. In total, we studied 41 tissue samples.

There were no coding sequence mutations in any of the screened genes. The most frequent and greatest contiguous change detected by tumor CGH studies was deletion of the 1q12-q23.3 chromosomal region harboring the *SDHC* gene. Other alterations included loss of the 1p region. The PGLs and GISTs shared genetic alterations despite their variable tissue origin and clinical course.

Subjects and Methods

Subjects and tissues

These investigations have been approved by the institutional review boards of the participating institutions. Tissue was collected at surgery and processed for routine histopathology and immunohistochemistry (IHC). DNA was extracted from blood, frozen and/or archived tissue samples, or cell lines.

DNA studies

Mutation analysis for the *KIT*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *PDGFRA* genes was performed following standard methods (10–14). Tumor DNA was also subjected to loss-of-heterozygosity (LOH) analysis using markers surrounding the *SDHB* and *SDHC* genes and normal tissue (or peripheral blood)-derived samples.

All sequence variants identified in the patients were also searched for in more than 100 ethnically matched control DNA samples. Numerous polymorphisms were identified in the samples of the patients for all six genes, but these were also present in the control samples (data not shown). We also searched for microdeletions of *SDHB*, *SDHC*, *SDHD*, and other loci; tumor DNA was tested by Southern blotting for the respective loci (13).

CGH and fluorescence *in situ* hybridization (FISH) were performed as described previously (15).

Results

Clinical findings and IHC

Despite multiple metastases and/or recurrences, GISTs in patients with CT had a relatively better prognosis than what is known in the literature about such metastatic tumors (11, 16).

We were able to obtain IHC for c-KIT for 28 of the 31 GISTs (Table 2); three were negative, 24 were positive, and one (CTRS.27; Id 11 in Table 2) was read as negative by one pathologist and weakly positive by the referring pathologists. Overall, however, c-KIT immunoreactivity was lower than that seen in c-KIT-mutation-positive tumors and did not correlate with outcome (data not shown).

Sequencing of candidate genes

There were no major deletions or other chromosomal rearrangements or coding sequence mutations of the *KIT*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *PDGFRA* genes in any of the germline or tumor DNA samples. A number of *SDHA* sequence variants were identified, but all were present in the normal population (data not shown).

Tumor culture chromosome analysis and CGH results

CT tumors, their karyotypes, and DNA copy number changes are summarized in Table 2. CGH was performed on a total of 41 tumors: 31 GIST, six PGL, three PCH, and one ACA.

For six of the tumors (five GIST, one PCH), primary culture karyotypes were obtained; with the exception of a *46, XX, t(5, 7)(q31:q11.2)* abnormality detected in two of 30 cells from GIST CTRS9, there were no other abnormalities. Two tumors from patient CTR06.01 (a PGL and an ACA) had also been cultured and reported to be of normal chromosomal constitution *46, XX*.

Overall, 21 specimens showed no significant CGH changes; four were PGLs. Of the 41 GISTs, 17 (57%) showed no changes, which is a surprisingly large number given that almost 90% of sporadic GISTs have detectable chromosomal imbalances (11, 14).

On the other hand, 10 of 16 benign tumors (75%) and five of five metastatic lesions showed CGH changes; a representative result from sample CTRS12, a GIST from one of the three originally reported patients by Carney *et al.* (1, 2) is shown in Fig. 1A. There was no information on the nature of tumor (benign *vs.* metastatic) in the remaining lesions. There were more gains than losses in benign tumors (15 *vs.* 12). The average number of alterations in benign tumors was 1.6 (range, 0–4). Among metastatic lesions, the average number of CGH changes was 1.4 (range, 1–2); gains were less frequent than losses (1 *vs.* 5). In these metastatic tumors, only one chromosomal region was involved in gains that were also present in a benign GIST.

In total, 13 chromosomal regions showed gains in benign tumors. However, 11 of these were represented in only one sample. Two chromosome regions, 6q and 17q, were involved in three and two cases, respectively. Losses were identified on chromosomes 1p and 1q (43%); 10q and 11p losses were identified in two tumors each.

Metastatic tumors showed more losses compared with benign lesions; chromosome 1 losses were by far the most

TABLE 1. Patients with the triad of gastric stromal sarcoma, functioning extraadrenal PGL, and PCH (CT)

Patient	Id	Sex	Age (yr)	Tumors	Other	Ref.
CTRS2	1	F	15	GIST, PGL	X-rays of the lungs are normal; metastatic GIST; multiple PGLs (mediastinal)	Case 3, Carney *et al.* (1, 2)
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 adenomatosis (subclinical Cushing's)	Case 1, Carney *et al.* (1, 2)
CTR05.01	3	F	17	GIST, PGL, PCH	Multiple GISTs (one malignant); multiple PCH; one PGL (retroperitoneal)	
CTRS.5T	4	F	29	GIST, PGL, PCH	Multiple GIST (metastatic); multiple PCH; one PGL (gastric); left adrenocortical tumor (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 GISTs; PGL (neck and abdominal); pheochromocytoma left adrenocortical adenoma	
CTRS.13	7	F	26	GIST, PCH	GIST (malignant); multiple PCH	
CTRS.19	8	F	23	GIST, PCH	GIST (multiple); multiple PCH	
CTRS.21	9	F	21	GIST, PGL	GIST (multiple); PGL (cardiac)	
CTRS.23	10	F	25	GIST, PGL	GIST (metastatic); adrenocortical tumor	
CTRS.27	11	F	26	GIST, PCH	GIST (multiple, gastric); adrenocortical tumor	
CTRS.41	12	F	12	GIST, PGL	GIST (multiple, metastatic); PGL (paraaortic)	
CTRS.42	13	F	28	GIST, PGL, PCH	GIST (multiple, metastatic); PGL; adrenocortical adenoma	Carney (3)
CTR07.03	14	F	17	GIST, PGL, PCH	GIST (multiple, metastatic); PGL; PCH (multiple)	Carney (3)
CTR08.03	15	F	21	GIST, PGL, PCH	GIST (multiple, metastatic); PGL; PCH (multiple)	
CTR09.01	16	F	26	GIST, PGL, PCH	GIST (multiple, metastatic); PGL; (metastatic) PCH (multiple)	
CTR10.01	17	F	21	GIST, PGL	GIST (multiple, metastatic); PGL; (non-functioning, 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 yr	Scopsi *et al.* (16)
CT1	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		
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		

DNA from samples CT.1–CT.24 (patients 19–37) was obtained from archival material; these patients were included in Carney (3). F, Female; Id, identification number; M, male.

frequent (60%). The minimal region of losses on chromosome 1q harbored the *SDHC* locus (1q21–q23.3) (Fig. 1A); 1p33–36.4 also showed losses in both benign and malignant tumors (15%). Some other regions on chromosomes 3q, 11q, 16q, 17p, and 17q also demonstrated losses but they were detected in only one sample.

Comparison of CGH and FISH and LOH studies

Tumors that showed losses of 1q region by CGH were subjected to interphase FISH using the bacterial artificial chromosome (BAC) RP11 0338-B-10 containing the *SDHC* gene and the BAC 26N-13 from the 1q21–q23.3 region (Fig. 1B). FISH detected loss of the region in seven of the samples. In these samples, 38–70% of cells showed only one signal of the probe used. In addition to these tumors, we also analyzed three GISTs that were not included in the CGH analysis but belonged to patients CTR07.07.03, CTR08.03, and CTR09.01; two of them also showed the loss of 1q21–q23.3 region (data not shown). Finally, LOH studies confirmed losses of the 1q21–q23.3 region in these samples (data not shown).

TABLE 2. Genetic and IHC studies on gastric stromal sarcomas, PGLs, PCHs, and adrenal tumors from CT patients

Patient Id	Sample	Specimen	IHC (for c-KIT)	Cytogenetics	CGH (tumor)	
					Gains	Losses
1	CTRS2	GIST	POS	*46, XX*	None	None; possible 1q11-q21
2	CTR04.01	Blood		*46, XX, inv(9)(p11:q13)*		
	CTRS9	GIST	NEG	ND	None	None
	CTRS.12	GIST	NEG	*46, XX, t(5;7)(q31:q11.2)*	None	1p33–36.3; 1q11-q22; 17q
	CTRS.14	ACA	ND		6q	1q11
3	CTR05.01	Blood		*46, XX*		
	CTRS.4	PCH#1		*46, XX*	None	None
	CTRS.15	PCH#2		ND	None	None
	CTRS.22	GIST	POS	*46, XX*	None	None
4	CTRS.5T	GIST	POS	*46, XX*	8q23–24; 15q25-qter; 21q	1q11-q22
5	CTRS.6	GIST (met)	NA		15q25-qter	1q11-q21
6	CTRS.7	PGL#2 (abd)			13q; 17q; 18p	1q11-q21
	CTRS.10	PGL#3 (abd)			None	1p13-q23
	CTRS.11	PGL#1 (neck)			None	None
7	CTRS.13	PCH			6p;6q	1q11-q21
8	CTRS.19	PGL#1 (med)			6q; 17q22–24	1p32-ter; 1q11-q21
	CTRS.28	PGL#2 (right paraaortic)			7p; 7q; 16p; 16q	None
	CTRS.29	PGL#2 (left paraaortic)			None	None
	CTRS.36	GIST (met)	POS		None	1q21
9	CTRS.21	GIST (met)	NEG		None	1p, 1q21
10	CTRS.23	GIST	POS		None	None
	CTRS.24	GIST (met; LN)			None	1p
	CTRS.31	GIST (met; PA)			None	17p
11	CTRS.27	GIST (gastric)	POS/NEG		None	None
19	CT.1	GIST	POS		None	None
20	CT.2	GIST	POS		4, 12p11-p12; 12q13-q22	None
21	CT.3	GIST	POS		1p11; 5p11-q11	None
22	CT.4	GIST	POS		None	None
23	CT.6	GIST	POS		None	None
24	CT.11	GIST	POS		4p11-p15; 15q14-qter	10q22-qter; 16q; trend: 3q13-qter; 6q15-qter
25	CT.12	GIST	POS		None	None
26	CT.13	GIST	POS		None	None
27	CT.14	GIST	POS		None	None
28	CT.15	GIST	POS		None	None
29	CT.16	GIST	POS		None	None
30	CT.17	GIST	POS		None	None
31	CT.18	GIST	POS		None	None
32	CT.19	GIST	POS		None	None
33	CT.20	GIST	POS		None	1p31-pter; 22q; trend: 11p
34	CT.21	GIST	POS		None	1p; 10; 11p; trend: 14q23-qter
35	CT.22	GIST	POS		None	None
36	CT.23	GIST	POS		None	None
37	CT.24	GIST	POS		1q	1p

DNA from samples CT.1–CT.24 (patients 19–37) was obtained from archival material; these patients were included in Carney (3). abd, Abdominal; Id, identification number; LN, lymph node; med, mediastinal; met, metastatic; NA, not available; ND, not done; NEG, negative; PA, pancreas; POS, positive.

Tumor 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 (of the three investigated) that had CGH abnormalities (CTRS13), chromosome 6 gains, which were also detected in the single adrenal tumor of the study, a benign ACA (CTRS14). 1q losses were present in both the PCH and ACA tumors, as well as in three of the six PGLs; 1p losses were seen in two PGLs and five of the GISTs.

Discussion

The present investigation of 37 patients and 41 tumors is the most comprehensive ever performed on the genetics of CT. Five patients with CT who underwent genetic analysis have recently been reported in case studies (16–19). GISTs in these patients were negative for *KIT* and *PDGFRA* mutations; one case (with multiple extraadrenal paragangliomas) was also screened for *SDHB*, *SDHC*, and *SDHD* mutations, and none was found (18). Thus, to date, 42 patients with CT, who constitute approximately half of the known cases worldwide, have been screened

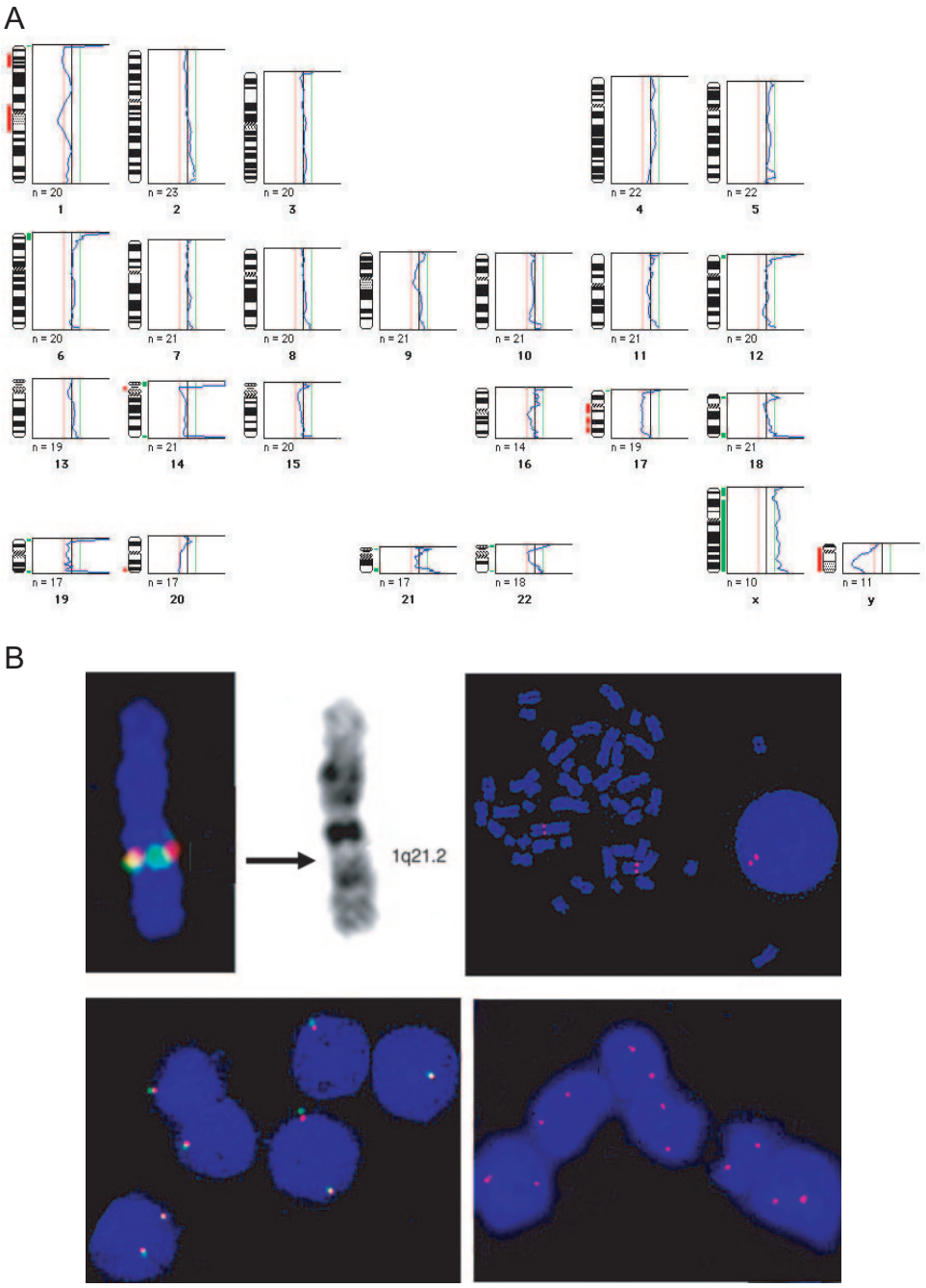

FIG. 1. A, A representative CGH result from sample CTRS12, a GIST from one of the three originally reported patients by Carney *et al.* (case 1 in Refs. 1 and 2). Losses of 1p and 1q were the most significant changes; other significant changes include losses of chromosome 17 (see text). B, Interphase FISH on a touch preparation from GIST CTRS21 with the BAC containing the *SDHC* gene detected loss of one copy of this 1q-located chromosomal region (*red* signal) and a diagram corresponding to the G-banding pattern of the chromosome 1 mapping the used BAC to the 1q region where the *SDHC* gene resides (1q21–q23.3). A control probe was used to show that the cells were euploid.

for the genes that are linked with the sporadic or genetic forms of two of the components of the syndrome (GIST and PGL), and no mutations have been found. The evidence suggests that other gene(s) are responsible for this condition. Additional support for this notion is provided by the clinical and molecular analysis of *KIT* mutation-negative GISTs: *KIT* mutations are rare in childhood-associated GISTs (11); the latter occur predominantly in females, mostly during the second decade of life and with a predilection for a gastric location (19), all features of GISTs associated with CT (2, 3).

Consistent with the different genetic background of CT tumors are the CGH results. In sporadic GISTs, the most common alterations are 14q, 22q, and 1p losses, which were seen in 70, 60, and 50%, respectively, of the studied tumors. In the CT tumors we studied, 1p loss was seen relatively frequently (two PGLs and five GISTs), but 14q and 22q losses were found in only one GIST each. 1q loss was by far the most frequent genetic abnormality in CT-associated GISTs and PGLs; it was also seen in the single adrenal tumor and one of three lung chondromas from CT patients that we studied.

What gene(s) in these regions are likely to be associated with progression of these GISTs? The *SDHB* and *SDHC* genes on 1p36.1–p35 and 1q21–q23.3, respectively, were obvious candidates and were recently identified to be responsible for the dyad of paraganglioma and gastric stromal sarcoma (10). The 1p region has also been implicated in a number of neu-

roendocrine tumors including neuroblastomas and pheochromocytomas (20). The region 11p shows losses in at least two tumors, interestingly those that also have 14q and 22q losses. Loss of the entire maternal chromosome 11 in SDHD-linked PGLs has recently been shown; finally, the 10q22-qter region also shows losses in two tumors and the 10q24 region harbors hypoxia-inducible factor-1α subunit inhibitor.

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References

1. **Carney JA, Sheps SG, Go VLW, Gordon H** 1977 The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med 296:1517–1518
2. **Carney JA** 1983 The triad of gastric epithelioid leiomyosarcoma, pulmonary chondroma, and functioning extra-adrenal paraganglioma: a five-year review. Medicine (Baltimore) 62:159–169
3. **Carney JA** 1999 Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney triad): natural history, adrenocortical component, and possible familial occurrence. Mayo Clin Proc 74:543–552
4. **Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM** 1998 Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 152:1259–1269
5. **Grace MP, Batist G, Grace WR, Gillooley JF** 1981 Aorticopulmonary paraganglioma and gastric leiomyoblastoma in a young woman. Am J Med 70: 1288–1292
6. **Perry CG, Young Jr WF, McWhinney SR, Bei T, Stergiopoulos S, Knudson RA, Ketterling RP, Eng C, Stratakis CA, Carney JA** 2006 Functioning paraganglioma and gastrointestinal stromal tumor of the jejunum in three women: syndrome or coincidence. Am J Surg Pathol 30:42–49
7. **Carney JA, Stratakis CA** 2002 Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 108:132–139
8. **Daum O, Vanecek T, Sima R, Michal M** 2006 Gastrointestinal stromal tumor: update. Klin Onkol 19:203–211 (Czech/Slovak)
9. **Boccon-Gibod L, Boman F, Boudjema S, Fabre M, Leverger G, Carney AJ** 2004 Separate occurrence of extra-adrenal stromal tumors in monozygotic twins: probable familial Carney syndrome. Pediatr Dev Pathol 7:380–384
10. **Passini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA, Ferrando B, Pacak K, Assie G, Baudin E, Chompret A, Ellison JW, Briere JJ, Rustin P, Gimenez-Roqueplo AP, Eng C, Carney JA, Stratakis CA,** Germline mutations of the genes encoding succinate dehydrogenase subunits (*SDHB, SDHC,* and *SDHD*) cause a familial form of gastrointestinal stromal tumors. [in press]
11. **Price VE, Zielenska M, Chilton-MacNeill S, Smith CR, Pappo AS** 2005 Clinical and molecular characteristics of pediatric gastrointestinal stromal tumors (GISTs). Pediatr Blood Cancer 45:20–24
12. **Baysal BE, Lawrence EC, Willett-Brozick JE, Ferrell RE** 2004 Sequence analysis of succinate dehydrogenase subunit A gene (*SDHA*) for paraganglioma tumor susceptibility. Am J Hum Genet 75(Suppl):91(384)
13. **McWhinney SR, Pilarski RT, Forrester SR, Schneider MC, Sarquis MM, Dias EP, Eng C** 2004 Large germline deletions of mitochondrial complex II subunits SDHB and SDHD in hereditary paraganglioma. J Clin Endocrinol Metab 89: 5694–5699
14. **Cameron S, Ramadori G, Fuzesi L, Sattler B, Gunawan B, Muller D, Ringe B, Lorf T** 2005 Successful liver transplantation in two cases of metastatic gastrointestinal stromal tumors. Transplantation 80:283–284
15. **Matyakhina L, Pack S, Kirschner LS, Pak E, Mannan P, Jaikumar J, Taymans SE, Sandrini F, Carney JA, Stratakis CA** 2003 Chromosome 2 (2p16) abnormalities in Carney complex tumours. J Med Genet 40:268–277
16. **Scopsi L, Collini P, Muscolino G** 1999 A new observation of the Carney's triad with long follow-up period and additional tumors. Cancer Detect Prev 23: 435–443
17. **Diment J, Tamborini E, Casali P, Gronchi A, Carney JA, Colecchia M** 2005 Carney triad: case report and molecular analysis of gastric tumor. Hum Pathol 36:112–116
18. **Colwell AS, D'Cunha J, Maddaus MA** 2001 Carney's triad paragangliomas. J Thorac Cardiovasc Surg 121:1011–1012
19. **Spatz A, Bressac-de-Paillerets B, Raymond E** 2004 Soft tissue sarcomas. Case 3. Gastrointestinal stromal tumor and Carney's triad. J Clin Oncol 22:2029–2031
20. **Benn DE, Dwight T, Richardson AL, Delbridge L, Bambach CP, Stowasser M, Gordon RD, Marsh DJ, Robinson BG** 2000 Sporadic and familial phcochromocytomas are associated with loss of at least two discrete intervals on chromosome 1p. Cancer Res 60:7048–7051

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