Supplementary information: Clinical progression and metachronous paragangliomas in a large cohort of SDHD germline variant carriers

Table 1
SDHD variants as observed in the study population. All variants are considered pathogenic or likely pathogenic, except the last one (c.299C>T) which has not been described previously and classified as variant of unknown significance (VUS).

SDHD variant	**Number (%)**	**LOVD_ID[2]**
c.274G>T p.(Asp92Tyr)	177 (80%)	SDHD_000004
c.416T>C p.(Leu139Pro)	27 (12%)	SDHD_000016
c.284T>C p.(Leu95Pro)	6 (3%)	SDHD_000039
c.-8828_169+442 del	4 (2%)	SDHD_000121
c.169_169+9 del TGTATGTTCT	2 (1%)	SDHD_000074
c.337_340 del GACT p.(Asp113Metfs*21)	2 (1%)	SDHD_000022
c.242C>T p.(Pro81Leu)	1 (0.5%)	SDHD_000003
c.3G>C p.(Met1lle)	1 (0.5%)	SDHD_000015
c.284T>G p.(Leu95Arg)	1 (0.5%)	SDHD_000172
c.299C>T p.(Thr100Ile)	1 (0.5%)	SDHD_000171

Note 1: reference sequence: NT_033899.7 NM_003002.2
Note 2: data was submitted to the Leiden Open Variation Database (LOVD):
http://databases.lovd.nl/shared/references/DOI:10.1038/s41431-018-0016-4

Table 2
Multivariate recurrent event analysis predicting development of new head and neck paragangliomas.

	Hazard ratio (95%CI)	**p-value**
Gender (ref = Female)	1.63 (1.10-2.40)	p = 0.01
Symptomatic versus asymptomatic at baseline (ref = asymptomatic)	1.61 (1.01-2.55)	p = 0.04
No. of head and neck paragangliomas present at baseline	0.68 (0.56-0.82)	p < 0.001
Year follow-up started (1990-2015)	1.04 (1.00-1.08)	p = 0.06

Table 3
Logistic regression predicting the development of new symptoms at any point between the start of follow-up and the last PGL-related visit. For 215 *SDHD* variant carriers it was known if they developed new symptoms during a median time of 8 years (IQR: 5 - 13), these patients were included in the analysis.

	Odds ratio (95%CI)	**p-value**
Gender (ref = Male)	1.92 (1.06-3.53)	p = 0.03
Symptomatic versus asymptomatic at baseline (ref = asymptomatic)	1.55 (0.82-2.98)	p = 0.18
Age at the start of follow-up of follow-up[1]	0.76 (0.60-0.95)	p = 0.02
No. of HNPGLs at start of follow-up	1.53 (1.13-2.10)	p = 0.01
No. of HNPGLs developed during follow-up	1.90 (1.26-2.99)	p = 0.003
Follow-up time	1.03 (0.98-1.09)	p = 0.25

Note 1: Odds ratio for a ten year increase in age.

Table 4
Treatment related cranial nerve paralysis/ paresis. In total, treatment for 22 (20%) carotid body tumors, 5 (28%) vagal body tumors, 7 (23%) jugulotympanic paragangliomas caused cranial nerve injury. Five vagal body tumors were treated surgically, in all cases there was postoperative vocal cord paralysis.

Nerve	**Patients**	**Carotid body tumors**	**Vagal body tumors**	**Jugulotympanic tumors**[1]
	Total (Recovered)	Total (Recovered)	Total (Recovered)	Total (Recovered)
NV	1 (0)	1 (0)	0 (0)	0 (0)
NVII	10 (7)	5 (5)	0 (0)	5 (2)
NVIII	1 (0)	0 (0)	0 (0)	1 (0)
NIX	4 (2)	1 (0)	1 (0)	2 (2)
NX	24 (4)	15 (3)	5[2] (0)	4 (1)
NXI	5 (4)	4 (4)	1 (0)	0 (0)
NXII	15 (7)	8 (6)	5[2] (0)	2 (1)
Cranial nerve dysfunction	33 (9)	22 (7)	5 (0)	7 (1)

Note 1: 6 Jugular paragangliomas, 1 tympanic and 1 jugulotympanic paraganglioma
Note 2: Combined surgery for a carotid and vagal body tumor in 4 cases.