Supplementary Online Content

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eTable 2. Characteristics of Patients With Pheochromocytomas and Paragangliomas With Germline Mutations in the *SDHA*, *TMEM127*, *MAX*, and *SDHAF2* Genes

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Germline Mutations in the *SDHA, TMEM127, MAX*, and *SDHAF2* Genes and Corresponding Phenotypes in 64 Unrelated Index Cases

Case Nationality	Age /Sex	Family History	Paraganglionic Phenotype	Clinical Predictors Suggesting Heritability	Nucleotide Change	Amino Acid Change	ACMG Variant Class
***SDHA* Germline Mutations (NCBI Reference Sequence: NM_004168.2)**							
1 GER	66 / M	-	Extraadrenal, thoracic	1	c.1A>C	p.Met1?	5
2 GER	30 / M	-	Adrenal, unilateral	1	c.1A>T	p. Met1?	5
3 GER	27 / F	-	Carotid	2	c.2T>G	p.Met1?	5
4 GER	34 / M	-	Adrenal, unilateral	1	c.3G>C	p.Met1?	5
5 GER	15 / M	-	Adrenal, unilateral	1	c.91C>T	p.Arg31*	5
6 GER	36 / M	+	Extraadrenal, retroperitoneal	3	c.91C>T	p.Arg31*	5
7 GER	20 / F	-	Carotid	2	c.91C>T	p.Arg31*	5
8 GER	37 / F	-	Carotid	2	c.91C>T	p.Arg31*	5
9 GER	34 / F	-	Jugular	2	c.91C>T	p.Arg31*	5
10 SWE	20 / F	-	Extraadrenal, retroperitoneal	2	c.223C>T	p.Arg75*	5
11 SWE	47 / M	-	Adrenal, unilateral	0	c.223C>T	p.Arg75*	5
12 GER	47 / F	-	Jugular	1	c.296A>G	p.His99Arg	5

13 GER	26 / F	-	Jugular	2	c.457-1G>A	p.?	5
14 TUR	17 / M	-	Extraadrenal, retroperitoneal	2	c.566G>A	p.Cys189Tyr	4
15 GER	43 / M	-	Carotid	1	c.622T>C	p.Ser208Pro	4
16 SWE	64 / M	-	Adrenal, unilateral	0	c.629G>A	p.Arg210Gln	3
17 GER	53 / M	-	Jugular	1	c.778G>A	p.Gly260Arg	4
18 USA	33 / M	-	Extraadrenal, pelvic	2	c.820G>A	p.Gly274Ser	5
19 POL	27 / F	-	Adrenal, unilateral	1	c.830C>T	p.Thr277Met	3
20 GER	46 / F	-	Jugular	1	c.940G>A	p.GLu314Lys	4
21 GER	24 / M	-	Adrenal, unilateral	1	c.1115C>G	p.Pro372Arg	3
22 GER	63 / F	-	Carotid	1	c.1177G>A	p.Val393Met	3
23 GER	58 / M	-	Adrenal, bilateral	2	c.1283_1298del	p.Gln428Profs*37	5
24 USA	30 / F	-	Extraadrenal, pelvic	2	c.1316G>A	p.Gly439Glu	4
25 GER	20 / F	-	Jugular	2	c.1334C>T	p.Ser445Leu	5
26 GER	48 / M	-	Carotid, bilateral	1	C.1340A>G	p.His447Arg	5
27 GER	49 / M	-	Jugular	1	c.1361C>A	p.Ala454Glu	4
28 USA	28 / M	-	Adrenal, unilateral, maligne	3	c.1361C>A	p.Ala454Glu	4
29 GER	44 / M	-	Extraadrenal, retroperitoneal	1	c.1432_1432+1del	p.?	5
30 GER	50 / F	-	Jugular	1	c.1766G>A	p.Arg589Gln	5

31 USA	65 / F	-	Carotid	1	c.1799G>A	p.Arg600Gln	4
32 GER	49 / M	-	Extraadrenal, retroperitoneal, multiple	2	c.1799G>A	p.Arg600Gln	4
33 TUR	42 / F	-	Vagal	1	c.1799G>A	p.Arg600Gln	4
34 POL	39 / M	-	Adrenal, unilateral	1	c.1979C>G	p.Ala660Gly	3
***TMEM127* Germline Mutations (NCBI Reference Sequence: NM_017849.3)**							
35 USA	35 / F	-	Adrenal, unilateral	1	c.3G>A	p.Met1?	5
36 USA	36 / M	-	Adrenal, unilateral	1	c.3G>A	p.Met1?	5
37 USA	58 / F	-	Adrenal, unilateral	0	c.3G>A	p.Met1?	5
38 GER	52 / F	+	Adrenal, unilateral	1	c.3G>A	p.Met1?	5
39 GER	68 / M	-	Adrenal, unilateral	0	c.73A>T	p.Lys25*	5
40 POL	43 / F	-	Adrenal, bilateral	1	c.131T>G	p.Leu44Arg	4
41 GER	58 / F	-	Adrenal, unilateral	0	c.215T>A	p.Leu72*	5
42 GER	34 / F	-	Carotid	2	c.325T>C	p.Ser109Pro	4
43 GER	45 / M	-	Adrenal, bilateral	1	c.410-1G>C	p.?	5
44 GER	66 / M	-	Extraadrenal, retroperitoneal	1	c.413T>G	p.Leu138Pro	4
45 HUN	22 / F	-	Adrenal, bilateral	2	c.419G>A	p.Cys140Tyr	5
46 GER	76 / M	-	Adrenal, unilateral	0	c.462C>G	p.Ile154Met	4
47 HUN	51 / F	-	Adrenal, bilateral,	3	c.464T>A	p.Leu155*	5

			Carotid, maligne				
48 GER	26 / F	-	Adrenal, unilateral	1	c.518T>C	p.Phe173Ser	4
49 POL	25 / F	-	Adrenal, unilateral	1	c.532dup	p. Tyr178Leufs*48	5
50 ISR	33 / F	+	Adrenal, bilateral	3	c.543_555dup	p. Ala186Argfs*44	5
51 TUR	51 / F	-	Adrenal, bilateral Extraadrenal, retroperitoneal	2	c.553G>A	p.Gly185Arg	4
52 GER	50 / F	-	Tympanic	1	c.568G>A	p.Ala190Tyr	4
53 TUR	26 / F	-	Adrenal, unilateral	1	c.572del	p.Thr191Argfs*16	5
54 HUN	47 / F	-	Adrenal, bilateral	1	c.572del	p.Thr191Argfs*16	5
55 SWE	55 / F	-	Adrenal, unilateral	0	c.665C>T	p.Ala222Val	3
***MAX* Germline Mutations (NCBI Reference Sequence: NM_002382.4)**							
56 GER	36 / F	-	Adrenal, unilateral	1	c.73C>T	p.Arg25Trp	5
57 GER	23 / F	-	Adrenal, unilateral	1	c.146C>G	p.Ser49*	5
58 GER	38 / M	-	Adrenal, bilateral	2	c.223C>T	p.Arg75*	5
59 POL	32 / F	-	Adrenal, unilateral	1	c.223C>T	p.Arg75*	5
60 POL	36 / M	+	Adrenal, bilateral	3	c.223C>T	p.Arg75*	5
61 GER	50 / F	+	Adrenal, bilateral	2	c.242_243del	p.His81Profs*5	5

62 GER	21 / M	-	Adrenal, unilateral	1	c.292dup	p.Gln98Profs*48	5
63 GER	26 / M	-	Adrenal, bilateral	2	c.307G>T	p.Glu103*	5
***SDHAF2* Germline Mutation (NCBI Reference Sequence: NM_017841.2)**							
64 USA	25 / F	+	Carotid, vagal	3	c.232G>A	p.Gly78Arg	5

The information of the table represents the status before clinical surveillance imaging. Mutations are classified according to the variant classification system of the American College of Medical Genetics and Genomics (ACMG): class 3: variant of unknown clinical significance; class 4: likely pathogenic; class 5 certainly pathogenic. 58 index cases had certain (class 5) or likely pathogenic (class 4) mutations and six index cases DNA variants of unknown significance (class 3). The six cases (five *SDHA* and one *TMEM127*) with DNA variants of unknown clinical significance were not included in further analyses.

GER = Germany, SWE = Sweden, TUR = Turkey, USA = United States, POL = Poland, HUN = Hungary, ISR = Israel; Age = age at diagnosis; M = male, F = female; FH = family history for pheochromocytoma or paraganglioma. Clinical predictors suggesting heritability were a family history of pheochromocytomas and paragangliomas, age at diagnosis <40 years, more than one pheochromocytoma or paraganglioma, tumor location outside the adrenal glands, and malignant tumors; in case of more than two mutation carries the lowest and highest age at diagnosis was indicated.

eTable 2. Characteristics of Patients With Pheochromocytomas and Paragangliomas With Germline Mutations in the *SDHA*, *TMEM127*, *MAX*, and *SDHAF2* Genes

Gene	*SDHA*	*SDHA* lit.[11,26-28,30,32,34]	*TMEM127*	*TMEM127* lit.[13,,22-26,31-33]	*MAX*	*MAX* lit.[12,21,32,35]	*SDHAF2*	*SDHAF2* lit.[10,25,29]
	(n=38)	(n=10)	(n=29)	(n=75)	(n=11)	(n=47)	(n=1)	(n=18)
Family history*	3% (1/29)	13% (1/8)	10% (2/20)	23% (7/31)	25% (2/8)	14% (6/42)	100% (1/1)	100% (2/2)
Age at diagnosis (median)	8-76 (28)	20-64 (46)	18-76 (47)	16-72 (43)	18-50 (36)	13-80 (29)	25	22-67 (32)
>1 Pheochromocytoma or paraganglioma	9% (3/33)	11% (1/9)	39% (11/28)	37% (19/51)	82% (9/11)	52% (24/46)	100% (1/1)	79% (15/18)
Adrenal	28% (8/29)	44% (4/9)	74% (20/27)	98% (51/52)	100% (11/11)	98% (46/47)	0% (0/1)	14% (2/14)
Bilateral adrenal	4% (1/26)	0% (0/8)	37% (10/27)	38% (20/52)	73% (8/11)	46% (21/46)	0% (0/1)	0% (0/2)
Extraadrenal-retroperitoneal or pelvic§	27% (7/26)	11% (1/9)	4% (1/27)	0% (0/52)	9% (1/11)	0% (0/46)	0% (0/1)	0% (0/2)
Head and Neck Paraganglioma	44% (15/34)	33% (3/9)	22% (6/27)	2% (1/47)	0% (0/11)	2% (1/47)	100% (1/1)	86% (12/24)
Malignant pheochromocytoma and paraganglioma	12% (4/34)	0% (0/10)	10% (3/29)	0% (0/52)	9% (1/11)	2% (1/47)	0% (0/1)	0% (0/14)

The grey columns represent the results of the current study in comparison to all cases published in the literature (lit.) summarized in the white columns.

The numbers (n=index cases + mutation positive relatives) and the denominators in the columns may be different, because the denominators represent the number of mutation carriers for whom imaging information was available.

*family history refers to index cases carrying a *SDHA,TMEM127*, *MAX* or *SDHAF2* germline mutation

§thoracic paraganglioma: only one patient of the current study (4%, 1/26) had an *SDHA* mutation and a thoracic paraganglioma. In the literature no *SDHA, TMEM127, MAX* and *SDHAF2* mutation carrier had a thoracic paraganglioma.