

Supplementary Table S1. Potentially deleterious variants identified in candidate genes in HNPGLs and association with clinical-pathological characteristics of the patients.

Gene	Protein	Variant type	Variant description	Status	VA F	Maximum population frequency	Tumor Id	Clin Var	ACMG /AMP 2015 (Inter Var)	VarS ome	Variants in susept ibility genes	Tumor localiz ation	S ex	A ge	Clinical features	Arteria l hypert ension	IH C SD HB
ACO 1	Aconitase 1	Misse nce	NM_002197 : c.A622G, p.T208A (chr9: 32418473, rs61753543)	Somatic	0.44	0.005	127 tv	NA	US	US	No	Vagal	F	49	No	No	-
				NA	0.68		169 tj				No	Middle ear	F	50	NA	NA	+
				NA	0.44		171 tj				No	Middle ear	F	57	No	NA	+
		Misse nce	NM_002197 : c.T1708G, p.F570V (chr9: 32430554, rs769809176)	NA	0.68	0	152 tc	NA	US	US	SDHC somatic	Carotid	M	63	No	NA	*
ARNT	Aryl Hydrocarbon Receptor Nuclear Translocator	Misse nce	NM_001668 : c.A868G, p.R290G (chr1: 150804811, rs763732376)	NA	0.53	0.00001	131 tc	NA	US	LP	No	Carotid	F	28	No	No	NA
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase	Misse nce	NM_004333 : c.G533A, p.R178Q (chr7: 140508767,	NA	0.39	0.00006	025 tc	US	US	US	No	Carotid	F	52	No	NA	+

			rs746348396)														
DLA T	Dihydrolipoamide S-acetyltransferase	Mis-sense	NM_001931 : c.C1114T, p.L372F (chr11: 111910106, rs782124389)	NA	0.27	6.5E-06	075tc	NA	US	US	No	Carotid	F	61	No	Yes	NA
CFA P126	Cilia And Flagella Associated Protein 126	Mis-sense	NM_001013625: c.C155T, p.S52F (chr1: 161336004)	NA	0.25	0	057tc	NA	US	US	No	Carotid	F	42	No	No	+
EGL N1	Egl-9 Family Hypoxia Inducible Factor 1	Mis-sense	NM_022051 : c.A994G, p.K332E (chr1: 231509743)	NA	0.48	0	119tv	NA	US	US	No	Vagal	F	38	Craniome-ningioma	Yes	+
EGL N3	Egl-9 Family Hypoxia Inducible Factor 3	Mis-sense	NM_022073 : c.G421A, p.G141S (chr14: 34400358, rs759224695)	NA	0.47	0.0001	011tc	NA	US	US	<i>SDHB</i>	Carotid	F	70	No	Yes	-
		Mis-sense	NM_022073 : c.A515T, p.K172I (chr14: 34398381)	Germline	0.54	0	089bc	NA	US	US	No	Carotid	F	42	Multifocal	NA	-

GAD 1	Glutamate Decarboxylase 1	Missequence	NM_000817 : c.C623T, p.T208M (chr1: 171693378, rs754891860)	NA	0.425	0.0008	031tc	NA	US	US	SDHB somatic	Carotid	F	58	No	Yes	+
GLUD2	Glutamate Dehydrogenase 2	Missequence	NM_012084 : c.A715G, p.T239A (chrX: 120182253)	NA	0.47	0	171tj	NA	US	US	No	Middle ear	F	57	No	NA	+
GOT 2	Glutamic-Oxaloacetic Transaminase 2	Missequence	NM_002080 : c.C233T, p.P78L (chr16: 58757663, rs765537389)	NA	0.51	0.0004	171tj	US	US	US	No	Middle ear	F	57	No	NA	+
GPT 2	Glutamic--Pyruvic Transaminase 2	Missequence	NM_133443 : c.C634T, p.P212S (chr16: 46943653)	NA	0.73	0	014tc	NA	US	US	No	Carotid	M	68	No	Yes	+
		Missequence	NM_133443 : c.G971A, p.G324E (chr16: 46952603, rs201383826)	Germline	0.36	0.003	161bc	NA	US	US	SDHD germline	Carotid	M	38	No	NA	+

IDH2	Isocitrate Dehydrogenase (NADP(+)) 2	Missequence	NM_002168 : c.T1154C, p.L385P (chr15: 90628257)	Germline	0.47	0	040tv	NA	US	US	SDHB germline	Vagal	F	56	No	NA	-
		Missequence	NM_002168 : c.G515A, p.R172K (chr15: 90631838, rs121913503)	Somatic	0.33	6.5E-06	080tv	P/LP	LP	P	No	Vagal	F	39	No	No	+
IDH3A	Isocitrate Dehydrogenase (NAD(+)) 3 Catalytic Subunit Alpha	Missequence	NM_005530 : c.G893A, p.G298D (chr15: 78458520, rs368666636)	NA	0.53	7.7E-05	154tc	US	NA	US	No	Carotid	M	60	Prostate adenoma	Yes	+
KIT	KIT Proto-Oncogene, Receptor Tyrosine Kinase	Missequence	NM_000222 : c.G793A, p.G265S (chr4: 55569926, rs1060502570)	NA	0.5	0.0002	170tj	US	US	US	No	Middle ear	F	67	No	NA	+
		Missequence	NM_000222 : c.G2926A, p.V976I (chr4: 55604718, rs773955363)	NA	0.395	0.00001	171tj	US	US	US	No	Middle ear	F	57	No	NA	+

KMT 2D	Lysine Methyltrans ferase 2D	Misse nce	NM_003482 : c.A7687C, p.N2563H (chr12: 49433866)	Ger mlin e	0. 54	0	149 tc	NA	US	US	<i>SDHD</i> somati c	Caroti d	F	1 9	Metastasi s	No	*
L2H GDH	L-2- Hydroxyglut arate Dehydrogen ase	Fram eshift	NM_024884 : c.853delT, p.Y285Tfs*4 (chr14: 50735933, rs74891038 2)	Ger mlin e	0. 41	0.000 3	118 tv	P	NA	P	No	Vagal	F	5 6	No	Yes	+
LDH AL6 A	Lactate Dehydrogen ase A Like 6A	Fram eshift	NM_144972 : c.605delG, p.S202Mfs* 3 (chr11: 18497942)	NA	0. 73	0	130 tc	NA	US	US	No	Caroti d	F	4 4	No	Yes	NA
		Splici ng	NM_144972 : c.592+1G>A (chr11: 18497187, rs14583320 1)	NA	0. 46	0.004	171 tj	NA	NA	US	No	Middl e ear	F	5 7	No	NA	+
LDH B	Lactate Dehydrogen ase B	Misse nce	NM_002300 : c.G299A, p.R100H (chr12: 21796991, rs77701973 9)	NA	0. 76	0.000 02	039 tc	NA	US	US	No	Caroti d	F	6 8	No	Yes	+

LDH C	Lactate Dehydrogenase C	Missequence	NM_002301 : c.T841G, p.Y281D (chr11: 18472516)	NA	0.62	0	036 tc	NA	US	US	SDHD somatic	Carotid	M	59	No	NA	*
LDH D	Lactate dehydrogenase D	Missequence	NM_153486 : c.T548C, p.M183T (chr16: 75148505)	NA	0.57	0	109 tc	NA	US	US	No	Carotid	F	39	No	NA	*
LRFN 4	Leucine Rich Repeat And Fibronectin Type III Domain Containing 4	Missequence	NM_024036 : c.C739T, p.R247W (chr11: 66625954)	Germline	0.36	0	143 tc	NA	US	US	SDHD germline	Carotid	F	38	No	No	+
ME1	Malic Enzyme 1	Stopgain	NM_002395 : c.G679T, p.E227X (chr6: 84025054)	NA	0.42	0	032 tc	NA	US	US	No	Carotid	F	62	No	Yes	+
MET	MET Proto-Oncogene, Receptor Tyrosine Kinase	Missequence	NM_000245 : c.G1789T, p.D597Y (chr7: 116395496)	Somatic	0.35	0	019 tc	NA	US	US	No	Carotid	M	35	No	No	*
		Missequence	NM_000245 : c.T682C, p.F228L (chr7: 116339820,	Germline	0.43	0.0002	063 tc	US	US	US	No	Carotid	F	63	No	Yes	NA

			rs921083171)														
MERTK	MER Proto-Oncogene, Tyrosine Kinase	Missequence	NM_006343 : c.G2467C, p.E823Q (chr2: 112779952, rs55924349)	Germline	0.47	0.003	019tc	US	US	US	No	Carotid	M	35	No	No	*
MYH3	Myosin Heavy Chain 3	Missequence	NM_002470 : c.T791C, p.I264T (chr17: 10550688, rs763347751)	NA	0.5	0.0007	035tc	US	US	LP	SDHD germline, RET	Carotid	F	30	No	No	-
		Missequence	NM_002470 : c.C1325T, p.T442I (chr17: 10547753, rs769788909)	NA	0.48	0.0008	009tc	US	US	US	No	Carotid	F	51	NA	NA	+
		Missequence	NM_002470 : c.A2392G, p.M798V (chr17: 10543684)	Germline	0.52	0	018tv	US	US	US	No	Carotid	F	64	No	NA	+
OGDH	Oxoglutarate Dehydrogenase	Missequence	NM_002541 : c.A1483C, p.S495R (chr7: 44733571, rs2230446)	Germline	0.2	0.0025	128tc	US	US	US	SDHD germline	Carotid	M	54	Multifocal	Yes	NA
					0.73		128tv					Vagal					

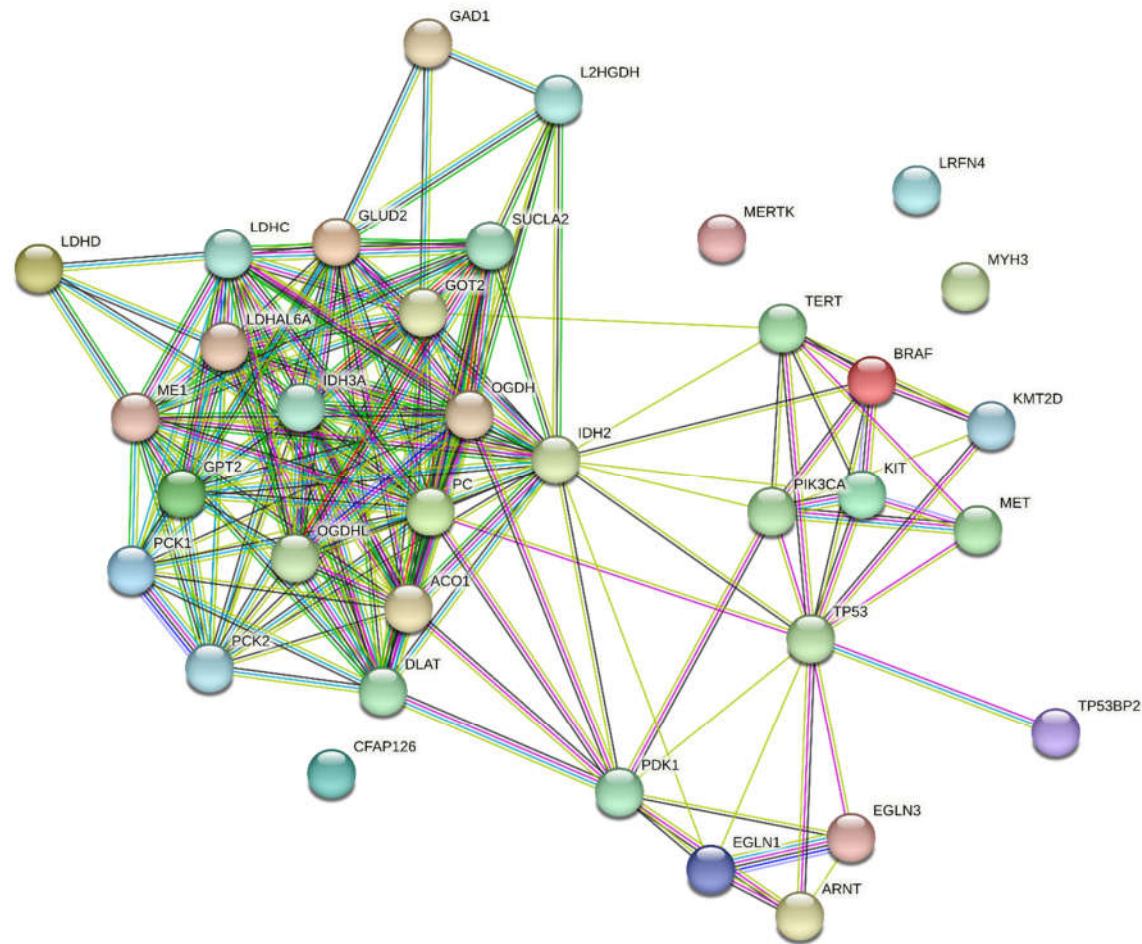
OGD HL	2-oxoglutarate Dehydrogenase-Like	Missequence	NM_018245 : c.G660C, p.W220C (chr10: 50959962, rs138462834)	NA	0.52	0.002	170 tj	NA	US	US	No	Middle ear	F	67	No	NA	+
		Missequence	NM_018245 : c.A541T, p.I181F (chr10: 50960232, rs201458076)	NA	0.4	0.0009	015 tv	NA	US	US	No	Vagal	F	52	No	Yes	*
		Missequence	NM_018245 : c.G587C, p.R196P (chr10: 50960186)	Germline	0.46	0	101 tv1	NA	US	US	SDHB germline	Vagal	F	46	Reccurrence	Yes	-
					0.46		101 tv2					Vagal (reccurrence)					+
		Missequence	NM_018245 : c.T542C, p.I181T (chr10: 50960231, rs147143536)	NA	0.78	0.0011	108 tc	NA	US	US	No	Carotid	M	48	No	Yes	-
PC	Pyruvate Carboxylase	Missequence	NM_000920 : c.G1003C, p.V335L (chr11: 66636336, rs768230282)	Germline	0.42	0.00001	106 tc	NA	US	US	SDHB germline	Carotid	F	38	Metastasis, recurrence	Yes	*
					0.61		106 mc					Metastasis					*

		Mis sion	NM_000920 : c.C875A, p.T292N (chr11: 66637801, rs74639760 0)	Ger mlin e	0. 47	6E-06	155 tc	NA	US	US	No	Caroti d	F	5 8	No	Yes	+
PCK1	Phosphoen olpyruvate Carboxykin ase 1	Mis sion	NM_002591 : c.C1211T, p.S404L (chr20: 56139562, rs14947297 2)	Ger mlin e	0. 55	0.003	072 tc	US	US	US	No	Caroti d	M	6 1	No	Yes	+
PCK2	Phosphoen olpyruvate Carboxykin ase 2	Mis sion	NM_004563 : c.C349T, p.R117W (chr14: 24567485, rs77812509 2)	NA	0. 37	0.000 1	169 tj	NA	US	US	No	Middl e ear	F	5 0	No	NA	+
PK1	Pyruvate Dehydrogen ase Kinase 1	Mis sion	NM_002610 : c.T226A, p.F76I (chr2: 173423465)	NA	0. 16	0	021 tc	NA	US	US	SDHD somati c	Caroti d	M	6 3	No	Yes	+
PIK3 CA	Phosphatid ylinositol- 4,5- Bisphospha te 3-Kinase Catalytic Subunit Alpha	Mis sion	NM_006218 : c.A3140G, p.H1047R (chr3: 178952085, rs12191327 9)	Som atic	0. 27	6E-06	018 tv	P	P	P	No	Caroti d	F	6 4	No	NA	+

SUCL A2	Succinate-CoA Ligase ADP-Forming Subunit Beta	Missequence	NM_003850 : c.T484A, p.Y162N (chr13: 48562726)	NA	0.2	0	119tv	NA	US	US	No	Vagal	F	38	Craniome ningioma	Yes	+
TERT	Telomerase Reverse Transcriptase	Missequence	NM_198253 : c.G355T, p.V119L (chr5: 1294646)	Germline	0.61	0	101tv1	NA	US	LP	SDHB germline	Vagal	F	46	Reccurrence	Yes	-
					0.55		101tv2					Vagal (reccurrence)					+
		Missequence	NG_055467.1: g.G586A (chr5: 1295228)	Somatic	0.34	NA	106tc	LP	NA	NA	SDHB germline	Carotid	F	38	Metastasis, reccurrence	Yes	*
					0.11		106mc					Metastasis					*
		Missequence	NM_198253 : c.A2158G, p.I720V (chr5: 1278884, rs373072850)	Germline	0.46	0.001	155tc	NA	US	US	No	Carotid	F	58	No	Yes	+
TP53	Tumor Protein P53	Missequence	NM_000546 : c.A170G, p.D57G (chr17: 7579517)	Somatic	0.26	0	001tc2	US	US	US	SDHD germline	Carotid	F	58	Multifocal	No	*
				NA	0.62		103tc				SDHD	Carotid	M	57	No	No	-
TP53 BP2	Tumor Protein P53 Binding Protein 2	Missequence	NM_005426 : c.C2932T6 p.R978C (chr1: 223971861,	NA	0.43	0.001	030tc	US	US	US	No	Carotid	M	40	No	No	-

			rs199572474)														
		Mis sion	NM_001031685: c.C247T, p.R83C (chr1: 224001984, rs200028775)	NA	0.39	0.0004	135tc	NA	US	US	SDHD	Carotid	F	50	No	No	NA
		Mis sion	NM_005426: c.G2680T, p.A894S (chr1: 223976806)	NA	0.53	0	021tc	NA	US	US	SDHD somatic	Carotid	M	63	No	Yes	+

IHC, immunohistochemistry. SDHB+, positive IHC staining. SDHB-, negative IHC staining. SDHB*, weak diffuse IHC staining. NA, data unavailable. VAF, variant allele frequency.



Supplementary Figure S1. Protein-protein interaction network made with STRING database for candidate genes in HNPGLs. Network nodes represent proteins that are coded by candidate genes. Edges represent protein-protein interactions (PPI), which are marked with the following colors: purple represents PPI that have been determined through experimental methods, turquoise represents PPI that have been sourced from curated databases, light green represents PPI that have been identified through text mining, black represents gene co-expression, light blue represents PPI that have been identified through protein homology, green represents PPI that have been identified through gene neighborhood analysis, and blue represents gene co-occurrence.