THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Hereditary Pheochromocytoma and Paraganglioma Panel

Clinical Features:
A pheochromocytoma (PCC) is a tumor arising from adrenomedullary chromaffin cells that commonly produces one or more catecholamines. A paraganglioma (PGL) is a tumor derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis. PGLs also arise from parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull; these do not produce catecholamines [1]. Most of the PCC/PGL hypersecrete catecholamines, and if left untreated have high cardiovascular morbidity and mortality [1]. PCC/PGLs enlarge with time and may cause mass-effect symptoms by encroaching upon or extending into adjacent tissues and organs. Some PCC/PGLs also have the potential to become malignant.

Hereditary PCC/PGLs represent 30-50% of all PCC/PGLs, for which prevalence is around 1/500,000 for PCC and 1/1,000,000 for PGL. The prevalence of PCC/PGL in patients with hypertension in general outpatient clinics varies between 0.2 and 0.6% [1]. PGLs can occur at any age but have the highest incidence between the ages of 40 and 50 years [2, 3]. Patients with hereditary PCC/PGLs typically present with multifocal disease and at a younger age than those with sporadic neoplasms [4, 5]. Prevalence of germline mutations is also high among patients with bilateral or multifocal PCC/PGLs [1]. The inheritance pattern of PCC/PGL depends on the gene involved. While most families show traditional autosomal dominant inheritance, those with mutations in *SDHAF2* and *SDHD* show almost exclusive paternal transmission of the phenotype [6, 7]. PCC/PGL can be seen as part of several well-described tumor susceptibility syndromes including von Hippel-Lindau, multiple endocrine neoplasia type 2, neurofibromatosis type 1, Carney Triad, Carney-Stratakis syndrome, and renal cell carcinoma with *SDHB* mutation[1]. Detection of a tumor in the proband may result in earlier diagnosis and treatment in other family members.

Our Hereditary Pheochromocytoma and Paraganglioma Panel includes mutation analysis of all 14 genes listed below.

EGLN1 (PDH2)	EPAS1 (HIF2A)	KIF1B	MEN1	MAX
NF1	RET	SDHA	SDHAF2/SDH5	SDHB
SDHC	SDHD	TMEM127	VHL	

Hereditary Pheochromocytoma and Paraganglioma Panel genes and associated cancers

Gene	Life time risk of PCC/PGL	Frequency of germline mutations in PCC/PGL	Paraganglial features	Cancer Syndrome	Non PCC/PGL tumors	References
EGLN1 (PDH2)	Unknown	rare	Single case reported (family segregation unclear)	Undetermined familial PCC and/or PGL syndrome (EGLN1-related)	Erythrocytosis	[1, 8]
EPAS1 (HIF2A)	Unknown	rare	Associated with polycythemia	Undetermined familial PCC and/or PGL syndrome (EPAS1-related)	None recurrently observed	[1]
KIF1B	Unknown	rare	Predominant adrenal Disease. Other malignancies are rare.	Undetermined familial PCC and/or PGL syndrome (KIF1β-related)	Neuroblastoma, medulloblastoma	[1, 8]
MEN1	Unknown	rare	The reported tumors were unilateral in all cases and malignant in one case (14%).	Multiple endocrine neoplasia type 1 (MEN1)	Parathyroid, pituitary, pancreatic islet cell, and medullary thyroid cancer; facial angiofibroma; meningioma; leiomyoma; collagenoma;	[9]

					ependymoma	
MAX	Low, paternal transmission	rare	Predominant adrenal disease, moderate rate of malignancy, moderate positive family history	Undetermined familial PCC and/or PGL syndrome (MAX-related)	None recurrently observed	[1, 8, 10, 11]
NF1	0.1-5.7%	3.3%	Predominant adrenal, family history common.	Neurofibromatosis type 1	Neurofibromas; malignant peripheral nerve sheath tumors; gliomas, leukemia	[1, 8, 9, 12]
RET	50%	6.3%	Predominant adrenal disease, occasional bilaterality, benign, family history common.	Multiple endocrine neoplasia type 2	Medullary thyroid carcinoma; para-thyroid hyperplasia or adenoma	[1, 8, 9, 13]
SDHA	low	rare	Predominant extraadrenal disease	PCC/PGL	Gastrointestinal stromal tumors	[1, 8]
SDHAF2 (SDH5)	100% of paternal transmission	<1%	Multiple head and neck paraganglioma, moderate rate of family history, no malignancy described.	Familial PGL2; PCC/PGL	None recurrently observed	[1, 8, 9, 14]
SDHB	77%	6-10.3%	Single paraganglioma, occasional adrenal, frequent malignancy.	Familial PGL4; Carney-Stratakis syndrome	Renal cell carcinoma; gastrointestinal stromal tumors.	[1, 8, 9]
SDHC	Unknown	1%	Multiple paraganglioma, low rate of family history, rare malignancy.	Familial PGL3; Carney-Stratakis syndrome	Gastrointestinal stromal tumors	[1, 8, 9]
SDHD	86% of paternal transmission; 0 for maternal transmission	5-8.9%	Multiple head and neck paraganglioma, less frequent adrenal, moderate rate of family history.	Familial PGL1; Carney-Stratakis syndrome	Gastrointestinal stromal tumors, thyroid tumors.	[1, 8, 9]
TMEM127	low	1.7-2%	Predominant adrenal disease, relatively late onset, moderate rate of family history.	Familial pheochromocytoma 2q	None recurrently observed	[1, 15]
VHL	10-26%	9-12%	Predominant adrenal disease, early onset, family history common	von Hippel-Lindau	Clear cell RCC; CNS hemangioblastomas	[1, 8, 9]

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Hereditary Pheochromocytoma and Paraganglioma Panel (14 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $3000
CPT codes: 81437
Turn-around time: 6 weeks

Results:
Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Hereditary Pheochromocytoma and Paraganglioma panel. All abnormal results are reported by telephone or email.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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