Hereditary Paraganglioma-Pheochromocytoma Panels

Disease Overview

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are familial cancer syndromes characterized by benign or malignant neuroendocrine tumors. PGL/PCC tumors can affect both the sympathetic nervous system and the parasympathetic nervous system. Pathogenic germline variants in multiple genes have been implicated in hereditary PGL/PCC syndromes. PGL/PCC syndromes are characterized by the presence of paragangliomas (neuroendocrine tissue-derived tumors) and pheochromocytomas (paragangliomas confined to the adrenal medulla). Hereditary PGL/PCC is often characterized by an early age of disease onset, the presence of multiple (or recurrent) paragangliomas/pheochromocytomas, and family history.

Clinical presentation varies but may include:

- Hypertension
- Paroxysmal tachycardia
- Heart palpitations
- Pallor/weight loss
- Hyperglycemia
- Metastatic disease

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to the ARUP Hereditary Cancer Panel Comparison table.

Hereditary Paraganglioma-Pheochromocytoma Expanded Panel, Sequencing and Deletion/Duplication 3005912

Method: Massively Parallel Sequencing

Preferred initial test when hereditary PGL/PCC is suspected with no clear biochemical findings

Hereditary Paraganglioma-Pheochromocytoma (SDHA, SDHB, SDHC, and SDHD) Sequencing and Deletion/Duplication 3004480

Method: Massively Parallel Sequencing/Multiplex Ligation-Dependent Probe Amplification (MLPA)

Preferred initial test when hereditary PGL/PCC is suspected and characteristic biochemical findings are present

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Testing Strategy

Biochemical Testing

Biochemical testing is often utilized in conjunction with computed tomography (CT) radiography and aids in characterizing the clinical and phenotypic features of PGL and PCC. Initial biochemical testing for hereditary PGL/PCC syndromes includes measurement of plasma-free metanephrines and/or urine metanephrines, dopamine (in plasma or urine), homovanillic acid, methoxytyramine, and fractionated catecholamines.

The following biochemical phenotypes are observed in the presence of pathogenic variants in the associated genes[1,2]:

- *MAX*: mixed
- *SDHA*: mixed
- *SDHAF2*: unclear
- *SDHB*: norepinephrine/normetanephrine
- *SDHC*: norepinephrine/normetanephrine
- *SDHD*: norepinephrine/normetanephrine, often silent
- *TMEM127*: mixed

Genetic Testing

Genetic testing should be considered in individuals who have either PGL/PCC tumors or a relative with a hereditary PGL/PCC syndrome, and in individuals who meet any of the following criteria[2,3,4]:

- Clinical evidence of a PGL/PCC syndrome
- Confirmed family history of PGL/PCC tumors
- Multiple, multifocal, or extra-adrenal tumors
- Malignancy associated with a PGL/PCC tumor
- Onset occurs at <45 years of age

Offer targeted testing for a known familial variant. If no familial variant has been previously identified, order a multigene sequencing panel that includes a deletion/duplication analysis.

For detailed information on the testing strategy for PGL/PCC tumors, refer to the ARUP Consult Pheochromocytoma - Paraganglioma topic.

Genetics

Genes

For more detailed information about the genes included on these panels, refer to the Genes Tested table.

Genes Included in ARUP's Hereditary Paraganglioma-Pheochromocytoma Tests		
Genes Included	Hereditary Paraganglioma-Pheochromocytoma (*SDHA*, *SDHB*, *SDHC*, and *SDHD*) Sequencing and Deletion/Duplication 3004480	Hereditary Paraganglioma-Pheochromocytoma Expanded Panel, Sequencing and Deletion/Duplication 3005912
FH		✓
MAX		✓
MEN1		✓
NF1		✓
RET		✓
SDHA	✓	✓
SDHAF2		✓
SDHB	✓	✓
SDHC	✓	✓
SDHD	✓	✓
TMEM127		✓
VHL		✓

Inheritance

- Autosomal dominant (AD); some genes may show a parent-of-origin effect.

Test Interpretation

Sensitivity/Specificity

Clinical Sensitivity

Variable, based on phenotype.

Approximately 30% of individuals diagnosed with PGL/PCC have a detectable germline variant in one of the genes associated with PGL/PCC susceptibility.

Gene	Proportion of Hereditary PGL/PCC Syndromes Attributed to Pathogenic Variants in Gene	Proportion of Variants Detectable by Sequence Analysis	Proportion of Variants Detectable by Deletion/Duplication Analysis
SDHA	0.6-3.0%	~100%	None reported
SDHB	10-25%	~85-95%	~5-15%

HNPGL, head and neck paraganglioma

Sources: Else, 2018[1]; Bausch, 2017[7]; Baysal, 2002[8]; Berends, 2018[9]; Burnichon, 2009[10]

Gene	Proportion of Hereditary PGL/PCC Syndromes Attributed to Pathogenic Variants in Gene	Proportion of Variants Detectable by Sequence Analysis	Proportion of Variants Detectable by Deletion/Duplication Analysis
	12-20% of HNPGL 24-44% of chest, abdomen, and pelvic PGL/PCC		
SDHC	2-8%	~85%	~15%
SDHD	~8-9% ~40-50% of HNPGL ~15% of chest, abdomen, and pelvic PGL/PCC	~95%	~5%

HNPGL, head and neck paraganglioma

Sources: Else, 2018[1]; Bausch, 2017[7]; Baysal, 2002[8]; Berends, 2018[9]; Burnichon, 2009[10]

Analytic Sensitivity/Specificity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9
Exon-level deletions/duplications (MLPA)	>99	>99

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by MLPA unless otherwise indicated.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; MLPA, multiplex ligation-dependent probe amplification; MPS, massively parallel sequencing; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result As Reported in Chart	Variant(s) Detected	Clinical Significance
Positive	One pathogenic or likely pathogenic variant detected	Confirms or predicts a diagnosis of a hereditary PGL/PCC syndrome[a]
See note	One variant of uncertain significance detected	Unknown if the variant is disease-causing or benign
Negative	No pathogenic variants detected	Diagnosis of hereditary PGL/PCC is less likely, though not excluded

[a]For pathogenic and likely pathogenic *MAX*, *SDHAF2*, and *SDHD* variants, clinical manifestations generally only occur when inherited paternally.

Limitations

- A negative result does not exclude a diagnosis of hereditary PGL/PCC or another cancer syndrome.
- Diagnostic errors can occur due to rare sequence variations
- The interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
  - The following exons are not sequenced due to the technical limitations of the assay:

    - *MEN1* (NM_001370251) 8
    - *SDHA* (NM_004168) 14; (NM_001294332) 13; (NM_001330758) 12
    - *SDHC* (NM_001035511) partial exon 5 (Chr1:161332225-161332330); (NM_001278172) partial exon 4 (Chr1:161332225-161332330)
    - *SDHD* (NM_001276506) 4
    - *VHL* (NM_001354723) 2
- The following may not be detected:
    - Deletions/duplications/insertions of any size by MPS
    - Large duplications fewer than 3 exons in size
    - Noncoding transcripts
    - Single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement.
    - Some variants may not be detected due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions.
    - Low-level somatic variants
    - Deletions/duplications in the following exons:
        - *MEN1* (NM_001370251) 8
        - *SDHA* (NM_004168) 1,10-15; (NM_001294332) 1,9-14; (NM_001330758) 1,10-13
        - *VHL* (NM_001354723) 2

Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to the ARUP Hereditary Cancer Panel Comparison table.

Gene Symbol	MIM #	Disorders	Inheritance
FH	136850	*FH* tumor predisposition syndrome/HLRCC Cutaneous and uterine leiomyomata, papillary type 2 renal cancer, paraganglioma, and pheochromocytoma	AD
		Fumarase deficiency	AR
MAX	154950	HPP syndromes Paraganglioma and pheochromocytoma	AD[a]
MEN1	613733	MEN type 1 Adrenocortical, carcinoid, GEP neuroendocrine tumors, meningioma, parathyroid, pituitary, and thyroid	AD
NF1	613113	NF1 Breast, GIST, gliomas, leukemia, malignant peripheral nerve sheath tumors, neurofibromas, and pheochromocytoma	AD
RET	164761	MEN2 Medullary thyroid carcinoma, parathyroid adenoma or hyperplasia, and pheochromocytoma	AD
SDHA	600857	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, and renal clear cell carcinoma	AD
SDHAF2	613019	HPP syndromes Paraganglioma	AD[b]
SDHB	185470	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, and renal clear cell carcinoma	AD
SDHC	602413	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, and renal clear cell carcinoma	AD
SDHD	602690	GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, and renal clear cell carcinoma	AD[b]
TMEM127	613403	HPP syndromes Paraganglioma, pheochromocytoma, and renal clear cell carcinoma	AD
VHL	608537	VHL syndrome	AD

[a]Possible paternal parent-of-origin effect.

[b]Paternal parent-of-origin effect.

AR, autosomal recessive; GEP, gastro-entero-pancreatic; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cell cancer; HPP, hereditary paraganglioma-pheochromocytoma; MEN, multiple endocrine neoplasia; NF1, neurofibromatosis type 1; VHL, Von Hippel-Lindau

Gene Symbol	MIM #	Disorders	Inheritance
		Endolymphatic sac tumors, epididymal and broad ligament cystadenomas, hemangioblastoma, neuroendocrine tumors, pheochromocytoma, renal cell carcinoma, and retinal angioma	

[a]Possible paternal parent-of-origin effect.

[b]Paternal parent-of-origin effect.

AR, autosomal recessive; GEP, gastro-entero-pancreatic; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cell cancer; HPP, hereditary paraganglioma-pheochromocytoma; MEN, multiple endocrine neoplasia; NF1, neurofibromatosis type 1; VHL, Von Hippel-Lindau

References

1. Else T, Greenberg S, Fishbein L. Hereditary paraganglioma-pheochromocytoma syndromes. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Oct 2018; Accessed: Feb 2020]

2. Lenders JWM, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(6):1915-1942.

3. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015;17(1):70-87. Reaffirmed with Addendum: *Genet Med*. 2019;21(12):2844.

4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: neuroendocrine and adrenal tumors. Version 3.2021. [Updated: Aug 2021; Accessed: Dec 2021]

5. van der Tuin K, Mensenkamp AR, Tops CMJ, et al. Clinical aspects of SDHA-related pheochromocytoma and paraganglioma: a nationwide study [published correction appears in *J Clin Endocrinol Metab*. 2018;103(5):2077]. *J Clin Endocrinol Metab*. 2018;103(2):438-445.

6. Jochmanova I, Wolf KI, King KS, et al. SDHB-related pheochromocytoma and paraganglioma penetrance and genotype-phenotype correlations. *J Cancer Res Clin Oncol*. 2017;143(8):1421-1435.

7. Bausch B, Schiavi F, Ni Y, et al. Clinical characterization of the pheochromocytoma and paraganglioma susceptibility genes SDHA, TMEM127, MAX, and SDHAF2 for gene-informed prevention. *JAMA Oncol*. 2017;3(9):1204-1212.

8. Baysal BE, Willett-Brozick JE, Lawrence EC, et al. Prevalence of SDHB, SDHC, and SDHD germline mutations in clinic patients with head and neck paragangliomas. *J Med Genet*. 2002;39(3):178-183.

9. Berends AMA, Buitenwerf E, de Krijger RR, et al. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. *Eur J Intern Med*. 2018;51:68-73.

10. Burnichon N, Rohmer V, Amar L, et al. The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. *J Clin Endocrinol Metab*. 2009;94(8):2817-2827.

Related Information

Pheochromocytoma - Paraganglioma
Paraganglioma - Pheochromocytoma Genetic Testing Algorithm
Pheochromocytoma Testing Algorithm

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review December 2022 | Last Update September 2023