Hereditary Paraganglioma/Pheochromocytoma Syndromes

Indications for Ordering

- Individuals with paraganglioma/pheochromocytoma (PGL/PCC) tumors who have
  - Clinical evidence of PGL/PCC syndrome
  - Confirmed family history of PGL/PCC tumors
  - Multiple, multifocal, or extra-adrenal tumors
  - Malignancy associated with PGL/PCC tumor
  - Age of onset <45 years
- Presymptomatic testing for relatives of an individual with hereditary PGL/PCC syndrome

Test Description

- Bidirectional sequencing of the coding regions and intron/exon boundaries of the *SDHA*, *SDHB, SDHC, SDHD* genes
- *SDHA* sequencing primers are specifically selected to target the functional *SDHA* gene
- Multiplex ligation-dependent probe amplification to identify large exonic deletions/duplications in *SDHB*, *SDHC*, *SDHD*

Tests to Consider

Primary tests

Hereditary Paraganglioma-Pheochromocytoma (*SDHB, SDHC,* and *SDHD*) Sequencing and Deletion/Duplication Panel 2007167
- Preferred initial test when hereditary PGL/PCC is suspected

Hereditary Paraganglioma-Pheochromocytoma (*SDHA*) Sequencing 2011461
- Confirm a suspected diagnosis of hereditary PGL/PCC when *SDHB*, *SDHC,* and *SDHD* testing is negative

Hereditary Paraganglioma-Pheochromocytoma (*SDHB*) Sequencing and Deletion/Duplication 2007108
- Use when *SDHB*-related hereditary PGL/PCC is suspected

Hereditary Paraganglioma-Pheochromocytoma (*SDHC*) Sequencing and Deletion/Duplication 2007117
- Use when *SDHC*-related hereditary PGL/PCC is suspected

Hereditary Paraganglioma-Pheochromocytoma (*SDHD*) Sequencing and Deletion/Duplication 2007122
- Use when *SDHD*-related hereditary PGL/PCC is suspected

Related tests

Familial Mutation Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

SDHB with Interpretation by Immunohistochemistry 2006948
- May be beneficial in directing testing algorithms
- Weak diffuse staining for SDHB correlates well with the presence of a germline variant in the genes of the succinate dehydrogenase complex – *SDHB*, *SDHC*, *SDHD*

Disease Overview

Incidence – ~1/300,000/year

Clinical presentation
- Paragangliomas – neuroendocrine tumors of the autonomic nervous system
- Sympathetic nervous system tumors
  - Secrete catecholamines
  - Usually in retroperitoneal space, abdomen, or thorax
  - Paroxysmal tachycardia/palpitations
  - Hypertension
  - Headache
  - Hyperglycemia
  - Pallor/weight loss
- Parasympathetic nervous system tumors
  - Usually in head and neck region, or aortic root
  - Tumors are usually nonsecreting
  - Symptoms are due to compression or infiltration of adjacent structures (including cranial nerves)
- Pheochromocytomas – PGLs of the adrenal medulla
- Tumors can be benign or malignant
  - Rate of malignancy varies by gene
    - *SDHB* – 31-71% of individuals
    - *SDHD* – 2.5-7% of individuals
    - *SDHC* – very low
    - *SDHA* – unknown

Syndromes

Variants in specific genes are associated with specific syndromes

SDHD – hereditary PGL/PCC type I
- Age of onset
  - Mean – 35 years
  - Range – 10-96 years
- Multiple tumors – especially head and neck

SDHAF2 – hereditary PGL/PCC type 2
- Mean age of onset – 32 years
- Multiple head and neck tumors

SDHC – hereditary PGL/PCC type 3
- Age of onset
  - Mean – 38 years
  - Range – 17-70 years
- Tumors
  - Typically paragangliomas of the head or neck
  - Rarely adrenal or extra-adrenal PGL tumors
  - Gastrointestinal stromal tumors (GISTs) have been reported

SDHB – hereditary PGL/PCC type 4
- Age of onset
  - Mean – ~30 years
  - Range – 6-77 years
- Tumors
  - Extra-adrenal chest, abdominal, pelvic sympathetic PGL tumors most common
  - Often appear sporadic and isolated
  - High risk of malignant transformation
- Increased risk for GISTs, papillary thyroid cancer, neuroblastoma, and renal cell carcinoma

SDHA – hereditary PGL/PCC type 5
- Tumors
  - PGL and PCC tumors have been reported
  - GISTs have been reported

TMEM127
- Mean age of onset – ~40 years
- Tumors
  - Primarily PCC tumors – often bilateral
  - Some PGL tumors – especially head, neck, and extra-adrenal abdominal sites
    - Malignancy reported in one individual
  - Bilateral or unilateral adrenal tumors

MAX
- Tumors
  - PCC tumors – often bilateral
    - High risk of malignant transformation

Genetics

Genes – *SDHA, SDHB, SDHC*, *SDHD*
- *MAX, SDHAF2, TMEM127,* and other genes yet to be identified are also predicted to be causative for hereditary PGL/PCC

Inheritance – autosomal dominant
- *SDHD* gene variants exhibit a parent-of-origin effect
  - Tumor predisposition generally occurs only when variants are inherited paternally
- ~30% of individuals diagnosed with PGL/PCC have a detectable germline variant in one of the genes associated with PGL/PCC susceptibility
- Autosomal recessive variants in *SDHA* have been associated with Leigh syndrome

Penetrance – age dependent, incomplete, and varies by gene
- *SDHD* – high
- *SDHB* and *SDHA* – lower
- *SDHC* – unknown

Variants
- 90% of detectable variants are sequence variants
- ≤10% of variants are large deletions
- Founder variants exist
  - Dutch – *SDHD* p.Asp92Tyr, p.Leu95Pro, p.Leu139Pro
  - Spaniards – *SDHB* exon 1 deletion
  - Chinese – *SDHD* p.Met1

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity
  - Combined sequencing and deletion/duplication analysis for familial or apparently sporadic PGL or PCC
    - *SDHD* – 15% (Buffet, 2012; Kirmani, 2014)
    - *SDHB* – 7-11% (Buffet, 2012; Kirmani, 2014)
    - *SDHC* – 4% (Kirmani, 2014; Lefebvre, 2014)
    - *SDHA* – <3% (Kirmani, 2014; Korpershoek, 2011; Lefebvre, 2014)
- Analytical sensitivity/specificity – 99%

Results
- Positive – one copy of pathogenic variant detected
  - Predicts hereditary PGL/PCC syndrome
- Negative – no variants detected
  - Hereditary PGL/PCC syndrome is unlikely but not excluded
- Inconclusive – variants of unknown clinical significance may be identified

Limitations
- Not detected or evaluated
  - Variants in genes other than those listed
  - Deep intronic and regulatory region variants
- Breakpoints of large deletions/duplications will not be determined
- Diagnostic errors can occur due to rare sequence variations
- *SDHA* – in some cases, results may be uninterpretable due to technical limitations in the presence of pseudogenes

References

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- Kirmani S, Young WF. Hereditary Paraganglioma-Pheochromocytoma Syndromes. 2008 May 21 [Updated 2014 Nov 6]. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015 (www.ncbi.nlm.nih.gov/books/NBK1548/)
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