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

**SDHA2** – 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 paragangiomas 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, SDHA2, 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