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Hereditary Paraganglioma-Pheochromocytoma (PGL/PCC) Syndromes

What You Should Know About Hereditary PGL/PCC Syndromes

Individuals with hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome have an increased risk for paragangliomas, which are tumors that arise from neuroendocrine tissue (a type of nerve tissue), and pheochromocytomas, which are paragangliomas that arise from the adrenal glands. PCCs secrete hormones that can cause symptoms such as high blood pressure, headaches, and heart palpitations. PGLs/PCCs are typically benign, but have the potential to become cancerous. Individuals with hereditary PGL/PCC syndrome may also be at risk for gastrointestinal stromal tumors (GISTs; tumors of the digestive tract), and cancers of the breast, kidney, and thyroid.

Hereditary PGL/PCC syndrome is frequently caused by mutations in one of five genes: *SDHA*, *SDHB*, *SDHC*, *SDHD* and *SDHAF2A*. These are collectively known as the *SDHx* genes. Mutations in other genes can also cause increased risks for PGLs/PCCs.

Cancer Risks Associated with *SDHx* mutations

The risk for PGLs/PCCs for individuals with an *SDHx* mutation varies widely by gene and among individuals. The estimated risk for PGLs/PCCs (to age 50) is up to 86% for individuals with an *SDHD* mutation, and <50%-77% for individuals with an *SDHB* mutation. Risk estimates for individuals with mutations in the other *SDHx* genes are unknown.

The risk for a PGL/PCC to become cancerous is highest for individuals with an *SDHB* mutation, with estimates ranging from 34%-97%. This risk appears to be low for an individual with a *SDHC* and *SDHD* mutation, and is unknown for the other *SDHx* genes.

Risks to Family Members

SDHx gene mutations are inherited in an autosomal dominant manner. This means that children, brothers, sisters, and parents of individuals with an *SDHx* mutation have a 50% (1 in 2) chance of having the mutation as well. Individuals with an *SDHx* mutation may develop one or more PGL or PCC, or no tumors at all.

Mutations in the *SDHD* gene (and possibly the *SDHAF2* gene) have different PGL/PCC risks depending from which parent the mutation is inherited. Mutations in these genes inherited from an individual's father are associated with much higher risks to develop PGLs/PCCs than maternally inherited mutations.

Managing Cancer Risks

The Endocrine Society has published PCC and PGL Clinical Practice Guidelines. Routine screening is recommended to begin between the ages of 6 to 8 years.

- Annual physical exam (including blood pressure and evaluation for arrhythmia and/or palpable abdominal masses)
- Annual 24-hour urine fractionated metanephrines and catecholamines and/or plasma free fractionated metanephrines. Annual plasma methoxytyramine. Follow-up imaging for abnormal biochemical screening results.
- Periodic MRI/CT imaging (e.g., 2-4 years) of the abdomen, chest, pelvis, base of the skull, and neck

- Periodic imaging (e.g., 2-4 years) using a specialized technique known as 123I-MIBG (metaiodobenzylguanidine) scintigraphy
- Consider evaluation for GISTs in individuals with unexplained gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting, difficulty swallowing), internal obstruction, or anemia
- Consider kidney cancer screening, which can include urinalysis (urine test) to screen for small amounts of blood in the urine or imaging tests (ultrasound, CT, MRI)

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