Cleveland Clinic
Genomic Medicine Institute

Hereditary Paraganglioma-Pheochromocytoma Syndrome (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *MAX*, *TMEM127* genes)

There are three genes that are commonly associated with Hereditary Paraganglioma-Pheochromocytoma Syndrome: *SDHB*, *SDHC*, and *SDHD*. Each gene confers slightly different risks for pheochromocytoma (PC) and paraganglioma (PGL). Individuals with *SDHB* mutations tend to have extra-adrenal PC, which are malignant about 30% of the time. In a few cases, early-onset kidney and thyroid cancers have been diagnosed in individuals with *SDHB* mutations. *SDHC* mutations are relatively rare and predispose to primarily head and neck paraganglioma (HNPGL). Men and women with *SDHD* mutations are likely to develop multiple HNPGL and have an approximate 30% lifetime risk of developing a PC. Three other genes – *SDHAF2*, *TMEM127*, and MAX – have also been recently discovered and are associated with an increased risk of paraganglioma and pheochromocytoma.

The genes noted above are all passed on in families by autosomal dominant transmission, whereby each child of a carrier has a 50% (1 in 2) chance of inheriting the abnormal copy from the carrier parent. A maternal imprinting effect has been observed in families with *SDHD* and *SDHAF2* mutations. Since *SDHD* and *SDHAF2* are regulated by imprinting, the children of a woman with an *SDHD* or *SDHAF2* mutation will not be at increased risk to develop PC/PGL even if they inherit the mutation. While not clearly delineated, the *MAX* gene may have a similar pattern of inheritance as *SDHD* and *SDHAF2*.

The Center for Personalized Genetic Healthcare