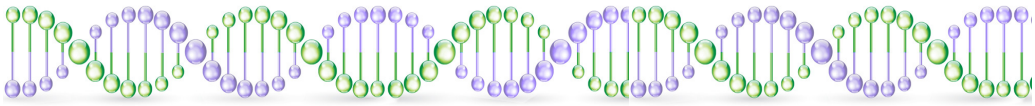
Information Sheet



Hereditary Paraganglioma Pheochromocytoma syndrome and the SDH genes

Hereditary Paraganglioma Pheochromocytoma syndrome is rare, affecting perhaps 1:5000 to 1:10,000 individuals (the exact number is not known). It is caused by mutations affecting the SDH family of genes (SHDA, SDHB, SDHC, SDHD and SDHAF2).

What are Paraganglioma and Pheochromocytomas?
Paragangliomas and Pheochromocytomas are very rare. They are diagnosed in 1 to 10 people per million people each year.

Paragangliomas are cells of the peripheral nervous system (i.e. the nerves outside the brain and spinal cord) that are growing when they shouldn't. When a paraganglioma arises within the adrenal gland is called a pheochromocytoma. Pheochromocytoma and paraganglioma cause problems by local effects, such as pain or nerve compression, by secreting the "flight or fight" hormones such as adrenalin or, rarely, by spreading (metastasising) to distant sites.

Are Paraganglioma and Pheochromocytoma Inherited?
One third of paragangliomas and pheochromocytomas are causes by hereditary mutations. This is important as there may be an increased risk of more paragangliomas occurring as well as other tumours and cancers.

Who should be tested for SDHB and other SDH mutations?
All people diagnosed with a paraganglioma or pheochromocytoma should consider genetic testing.

The clinical history gives a clue. This includes:

- diagnosis under 50 years
- more than one paraganglioma or pheochromocytoma
- malignant transformation
- loss of SDHB on IHC testing
- other tumours (eg kidney cancer, GIST, neuroendocrine tumours)
- other signs (multiple cysts, skin lesions)

In addition to the SDH genes, more information is available on our website about other hereditary causes including:

- VHL gene and Von Hippel Lindau syndrome
- RET gene and Multiple Neuroendocrine syndrome Type 2 (MEN2)
- NF1 gene and Neurofibromatosis type 1
- the TMEM127 and MAX genes

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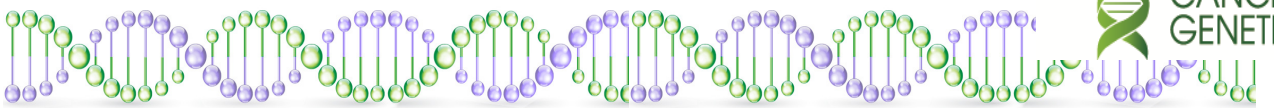

What does loss of staining or loss of expression of SDHB mean?
It is a strong clue that it was caused by a hereditary mutation. Using immunohistochemical staining, the paraganglioma or pheochromocytoma tissues is tested to see if the SDH proteins are present. Loss of SDHB indicates that the SDHB gene (or one of the other SDH genes) has been damaged. The pathology report may state either loss of staining or loss of expression.

Kidney (renal cell carcinoma) and GIST (gastrointestinal stromal tumours) may also show loss of staining for SDB on IHC testing.

Who should have genetic testing for SDHB, SDHC or SDHD?
All people with loss of staining of SDHB on IHC testing of a tumour should have genetic testing. All people with a personal or family history of paraganglioma or pheochromocytoma, especially if malignant, should consider genetic testing.

This testing is not yet Medicare funded. Testing for mutations in the SDHB gene costs around $600 and usually includes a panel of genes such as FH, MAX, NF1, NF2, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127 and VHL.

Management of individuals with SDHB, SDHC and SDHD mutations.
Individuals with SDH mutations have a 30 to 60% lifetime risk of developing a pheochromocytoma or paraganglioma and around one third of these will become cancerous if not detected early. The likelihood depends on the gene affected.

There is a 3% to 5% lifetime risk of kidney cancers. Kidney cancers caused by SDH mutations can be aggressive (grow fast and/or spread to other organs). Also, there is a 1% lifetime risk of a gastrointestinal stromal tumour (GIST). The GIST usually occur in the stomach and are not associated with somatic KIT or PDGFRA mutations.

Surveillance, to allow early detection and treatment, includes:

- blood pressure testing from age 5
- annual catecholamine screening (via a blood or urine test) from age 5
- An MRI from base of skull to coccyx and including kidneys and adrenals every 2 years from age 10
- Blood pressure and catecholamine screening should be considered before any surgery.

As the SDH genes are involved in oxygen sensing pathways, there is evidence that individuals with an SDH gene mutation should not live for long periods at high altitudes and should not smoke. In addition, other long term exposures to hypoxia, such as obstructive sleep apnoea, should be treated and/or avoided.

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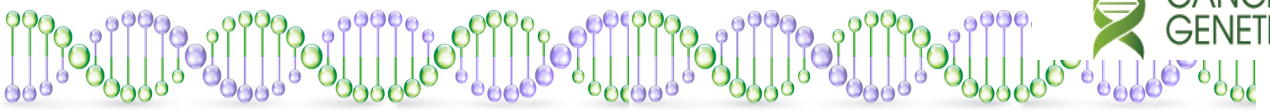

Is Hereditary Paraganglioma Pheochromocytoma syndrome inherited?
Yes. Hereditary Paraganglioma Pheochromocytoma syndrome is a hereditary cancer syndrome causes by mutations affected the SDH genes SHDA, SDHB, SDHC, SDHD and SDHAF2. Genetic testing is available.

There is a 50% chance of a person who carries a germline SDH mutation, whether male or female, passing the mutation to their son or daughter. If a mutation were identified, then predictive testing would be available for adult blood relatives. This allows screening of at-risk relatives to start early.

SDHD and Parent-of-Origin Effect.
The SDHD gene is unusual: the mutation almost never causes problems if it is inherited from the mother. That means, a woman can pass the mutation on to her children but they are very unlikely to develop SDH-related problems.

Does this sound like you or your family?
Have you or a relative had a pheochromocytoma or paraganglioma? Has an SDHA, SDHB, SDHC or SDHB mutation been detected in a blood relative? Genetic testing is available.

Make an appointment with Dr Hilda High at Sydney Cancer Genetics. It is a confidential opportunity to discuss your personal and family history of cancer and genetic testing can be organised, if needed.

More information is available on our website, including links to the following:

- The Pheo Para Troopers support group is for individuals and families affected by Hereditary Paraganglioma Pheochromocytoma syndrome, Paraganglioma and/or Pheochromocytoma. They are based in the USA but have members around the world.
- The Cancer Genetics section of the Cancer Institute's eviQ website provides up-to-date Australian-based management guidelines
- The US National Library of Medicine website has more information about this syndrome.

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