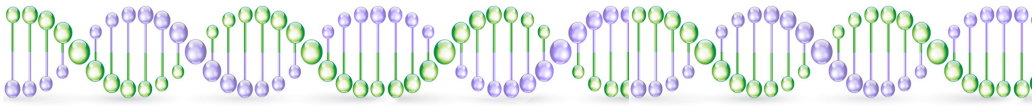
Information Sheet



Neurofibromatosis Type 1 and the NF1 gene

Neurofibromatosis Type 1, also known as von Recklinghausen Disease, is a hereditary cancer syndrome caused by germline mutations in the NF1 gene. It is not rare, affecting 1 in 3,000 to 1 in 4,000 people.

NF1 is characterised by growths affecting the covering of peripheral nerves (neurofibromas) that can be seen as lumps on the skin.

Although there are a broad range of health problems associated with NF1, not everyone is affected, even within the same family.

Did the "Elephant Man" Joseph Merrick have Neurofibromatosis Type 1?
Neurofibromatosis Type 1 does NOT cause "elephant man" syndrome. Although Joseph Merrick, the person who was known as the Elephant Man, died in 1890, in 1986, geneticists Tibbles and Cohen published a paper in the British Medical Journal diagnosing Merrick with Proteus syndrome. This is a much rarer condition. Proteus syndrome results from a mutation in the AKT1 gene that occurs early on in the growing baby, after fertilisation of the egg by the sperm. This genetic change is not inherited and is not passed on. (Inherited mistakes in the AKT1 gene are, in fact, lethal and the baby doesn't grow).

How is Neurofibromatosis Type 1 diagnosed?
Unlike many hereditary cancer syndromes, in which a mistake in a gene has been passed down over many generations, in NF1 around half of the cases are caused by a new mistake (a "de novo" mutation) that occurred just in that particular sperm or egg or in the first few divisions are fertilisation.

NF1 is usually diagnosed clinically at a young age. Almost all children will meet the clinical criteria by age 8 and 50% by age 1. The clinical criteria include two or more of the following:

- six or more café-au-lait macules (each measuring 5 mm if prepuberty and 15 mm post puberty).
- two or more neurofibromas.
- one plexiform neurofibroma.
- freckling in the armpits or groin.
- optic glioma.
- two or more Lisch nodules (benign growths in the eye).
- an osseous lesion such as sphenoid dysplasia or tibial pseudoarthrosis.

How is Neurofibromatosis Type 1 managed?
Neurofibromatosis Type 1 is associated with growths that can cause problems by compressing other structures. The growths can also become cancers and this may happen at a young age. Most children and adults with NF1 are seen via special clinics to manage the screening and deal with any problems that may arise promptly. Individuals with NF1 should avoid unnecessary radiation, including unnecessary CT scans. The Royal North Shore Hospital's Clinical Genetics department has put together a checklist of what screening should be performed. You can download a copy from our website.

Some features of NF1 are characteristic but don't cause problems. Almost all people with neurofibromatosis type 1 have multiple café-au-lait spots (often called birth marks, although they can appear after birth and after puberty).

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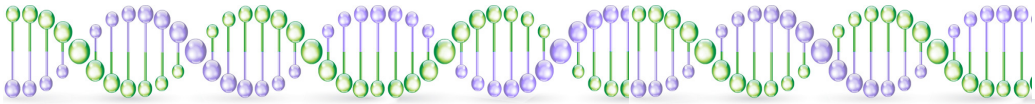

What are Lisch nodules?
During childhood, benign growths called Lisch nodules often appear in the coloured part of the eyes (the iris) in individuals with NF1. Lisch nodules are not normally visible to the naked eye but can be seen by an optometrist or ophthalmologist using a slit lamp as part of a standard eye examination. Lisch nodules do not interfere with vision and do not need treatment.

What is an optic nerve glioma?
Optic nerve gliomas are growths that arise in or around the optic nerve. Optic nerve gliomas occur in 15% of individuals with Neurofibromatosis Type 1 and mainly occur between ages 3 and 5. They do not usually require any intervention. However, because optic nerve gliomas can compress the optic nerve affecting sight, screening by an ophthalmologist is done every 6 months to age 4 and then annually to age 16.

Is breast cancer risk increased in NF1?
Yes. Women with Neurofibromatosis Type 1 are at higher risk for breast cancer than the average woman. This risk is "moderate" (15 to 30% lifetime compared to the average risk of 10 to 15%). Risk reducing mastectomies are not usually recommended at this level of risk.
Screening usually starts at age 35 and includes annual breast MRIs to age 50. After age 50 the risk is similar to the average woman and breast screening is then done every 2 years usually with mammograms.

What are malignant peripheral nerve sheath tumours?
Malignant peripheral nerve sheath tumours (MPNST) are an aggressive cancer (a soft tissue sarcoma) that grow in the layer surrounding a nerve. They usually arise in a plexiform neurofibroma and may present with a hard lump felt under the skin. Because they are associated with a nerve, they can cause pain, weakness or numbness

Plexiform neurofibroma occur in 50% of people with NF1 and around 15% develop into a malignant peripheral nerve sheath tumour if not removed.

Screening starts at age 10 with an annual physical examination.

What are Pheochromocytoma?
Pheochromocytoma are rare. They are diagnosed in 1 to 10 people per million people each year. They are usually small growths in the adrenal glands, which sits above the kidneys. They cause problems by secreting the "fight or flight" hormone adrenalin. Pheochromocytoma are not common in Neurofibromatosis Type 1, affecting only 2% of individuals with an NF1 mutation. However, in 12% of cases, the pheochromocytoma becomes malignant (cancerous).

In addition to the NF1 gene, hereditary causes include:

- SDH genes including SDHB, SDHC and SDHD and Hereditary Paraganglioma and Pheochromocytoma 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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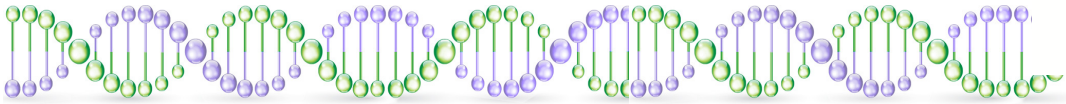

Screening for pheochromocytoma in individuals with Neurofibromatosis Type 1 starts at age 10, measuring blood pressure and checking the blood for breakdown products of adrenalin.

Who should have genetic testing for an NF1 mutation?
The diagnosis of Neurofibromatosis Type 1 is usually based on clinical diagnostic criteria and genetic testing does not alter the management.

Genetic testing could be considered in the following circumstances:

- Individuals who fulfil clinical criteria for Neurofibromatosis Type 1 and are considering prenatal or preimplantation genetic diagnosis.
- Children who do not yet meet clinical criteria for NF1 and a genetic diagnosis is considered important to inform management decisions.
- Adults who do not meet clinical criteria for NF1 and an atypical phenotype is suspected (e.g. spinal NF1).

Does this sound like you or your family?
Has an NF1 mutation been detected in a blood relative or has a clinical diagnosis of Neurofibromatosis Type 1 been made in you or your family? Genetic testing is available for NF1.

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 Children's Tumour Foundation Conquering NF is based in Australia and has information on research studies and support groups.
- The Cancer Genetics section of the Cancer Institute's eviQ website provides up-to-date Australian-based management guidelines as well as the lifetime risk of tumours for individuals with NF1.
- The US National Library of Medicine website has more information about this syndrome.

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