SickKids | Genome Diagnostics

Rhabdoid tumour predisposition syndrome/ schwannomatosis

Rhabdoid tumour predisposition syndrome 1 (RTPS-1) is a cancer syndrome that predisposes an individual to rhabdoid tumours. These tumours are referred to as atypical teratoid/rhabdoid tumours (AT/RT) when arising in the central nervous system, and as malignant rhabdoid tumours (MRTs) if found in other sites (i.e. renal, liver, lung, skin, heart). Most of these tumours are characterized by loss of function of the *SMARCB1* gene. Germline mutations in *SMARCB1* can predispose an individual to developing these tumours. Rhabdoid tumours are highly malignant and usually occur in children less than 2 years of age, and may present in multiple sites.

Schwannomatosis is a genetic condition characterized by multiple schwannomas. Schwannomas can arise wherever Schwann cells occur, in the spinal cord and along peripheral and cranial nerves. The most common presentation of non-vestibular nerve schwannomas is painful lumps along the skin and/or neurological deficits.

Genetics

RTPS-1 and schwannomatosis are caused by heterozygous germline mutations in the *SMARCB1* gene, located on chromosome 22 (22q11.2). These conditions are inherited in an autosomal dominant manner, meaning that the disease will be present when a person has one mutated copy of the *SMARCB1* gene. Both conditions show variability in ages of onset, sites of tumour development, and severity. However, most patients with RTPS-1 due to germline *SMARCB1* mutations are very young (median age 5 months) and present more often with multi-site disease compared with 18 months for sporadic mutations.

Cases of gonadal mosaicism (multiple affected children of an unaffected parent) have been reported. Germline *SMARCB1* mutations may show variable penetrance, where parents of affected children that have *SMARCB1* mutations may develop schwannomatosis later in life or may stay asymptomatic. RTPS-1 and schwannomatosis can both be *de novo* (caused by new mutations that are not inherited). The risk of developing tumors or schwannomatosis when a germline mutation is found is unknown.

Before molecular testing

Immunohistochemical staining for the SMARCB1 protein in tumour cells is required. If the results are negative (no protein found) molecular testing is warranted.

Who Should be Tested?

- Individuals with a rhabdoid tumour or clinically suspected of being affected with schwannomatosis,
- Unaffected relatives of individuals with a rhabdoid tumour or schwannomatosis
- Pregnancies at risk due to a family history of rhabdoid tumours or schwannomatosis, if familial mutation is known.

Test Methods

- Complete sequencing of the 9 exon coding regions and flanking exon/intron boundaries of the *SMARCB1* gene to identify point mutations on genomic DNA
- Quantitative testing of the *SMARCB1* to test for deletions or duplications, using Multiplex Ligation-dependent Probe Amplification (MLPA) on genomic DNA

Test sensitivity

- Germline mutations in *SMARCB1* are found in 35 –50% of children diagnosed with rhabdoid tumours but is seen at higher frequency (up to 60%) in younger children affected with rhabdoid tumours (< 6months at diagnosis)
- Germline mutations in SMARCB1 are estimated to contribute to ~10% of sporadic and ~85% of familial schwannomatosis.

For More Information

Online Mendelian Inheritance In Man:

- http://www.ncbi.nlm.nih.gov/omim/609322
- http://www.ncbi.nlm.nih.gov/omim/162091
- http://www.ncbi.nlm.nih.gov/omim/601607

Children's Tumor Foundation: http://www.ctf.org/Living-with-NF/schwannomatosis.html

Malignant Rhabdoid Tumors: http://emedicine.medscape.com/article/993084-overview

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of inherited form of rhabdoid tumour predisposition syndrome.

2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

4. This test was developed and its performance characteris-tics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Ad-ministration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical pur-poses.