BC CANCER HEREDITARY CANCER
Provincial Health Services Authority

Incidental *LZTR1* Gene Variants

Overview

Pathogenic variants in *LZTR1* have been associated with schwannomatosis, and less commonly, Noonan syndrome.

For people with an incidentally identified pathogenic *LZTR1* variant on genetic testing that was done for another reason and who have no personal or family history of schwannomas, neurofibromas or meningiomas, the clinical significance is limited.

LZTR1-associated Schwannomatosis

LZTR1 is associated with autosomal dominant schwannomatosis, characterized most commonly by multiple schwannomas (peripheral, sometimes vestibular) and more rarely, meningiomas or neurofibromas. Penetrance of *LZTR1*-associated schwannomatosis is incomplete and appears to be substantially lower in people who have an *LZTR1* variant found incidentally through multi-gene panel genetic testing than in families with known schwannomatosis. **In the absence of a personal or family history of schwannomas or related tumours, the risk for schwannomatosis associated with an *LZTR1* variant may be as low as 1%.**

Noonan Syndrome

Noonan syndrome (NS) is characterized by characteristic facies, short stature, congenital heart defects, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape, cryptorchidism, coagulation abnormalities, lymphatic dysplasia, and ocular abnormalities.

Missense variants in the *LZTR1* gene Kelch domains have occasionally been reported in patients with autosomal dominant Noonan syndrome. Most incidentally identified loss-of-function *LZTR1* variants are not known to confer a significant risk; however, inheriting two pathogenic *LZTR1* variants (one from each parent) can cause autosomal recessive Noonan syndrome.

Cancer Screening and Management

LZTR1-associted Schwannomatosis

In the absence of a personal or family history of schwannoma, meningiomas or neurofibromas, no tumour surveillance is typically recommended.

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in the absence of clinical features suggestive of Noonan syndrome, no specific investigations are typically recommended based solely on an incidental pathogenic variant in *LZTR1*.

Some clinicians may consider obtaining a baseline echocardiogram and electrocardiogram to rule out valvular dysplasia, cardiomyopathy or conduction defects.

Referral to the Hereditary Cancer Program

Referral or re-referral may be considered if:

- A schwannoma, meningioma, or neurofibroma or features of Noonan syndrome are identified in the person with the *LZTR1* pathogenic variant or a close relative.
- There is a personal or family history suggestive of schwannomatosis.
- Additional information becomes available that changes interpretation of the variant or associated risks.

Family and Reproductive Considerations

Each child of a person with an *LZTR1* pathogenic variant has a 50% chance of inheriting the variant. Rarely, inheriting pathogenic *LZTR1* variants from both parents can cause autosomal recessive Noonan syndrome. If both parents carry a pathogenic *LZTR1* variant, the chance of having an affected child is 25%.

The Hereditary Cancer Program does not currently offer familial variant testing for *LZTR1* in the absence of a personal or family history suggestive of schwannomatosis, as identification of additional carriers would not be expected to alter their clinical management.

Individuals with an *LZTR1* pathogenic variant who are planning a family and have questions about reproductive risks may benefit from referral to the Provincial Medical Genetics Program (tel: 604.875.2157; fax: 875.2825) [or Vancouver Island Medical Genetics (tel: 250.727.4461; fax: 250.727.4295)].