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SCAN ME

Dominant-Negative Pathogenic Variants in *LZTR1*-Related Schwannomatosis

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BACKGROUND

Loss-of-function (LoF) and dominant-negative (DN) pathogenic variants in the *LZTR1* gene cause autosomal recessive and autosomal dominant Noonan syndrome (NS), respectively.

LoF pathogenic variants are also associated with *LZTR1*-related schwannomatosis, which is inherited in an autosomal dominant manner.

However, an association between DN pathogenic variants and schwannomatosis remains unknown, primarily due to a paucity of affected individuals with DN pathogenic variants.

- Only one presumably DN variant (p.S247N) has been identified in a patient who had both NS and schwannomas[1]
- Another DN variant (p.R284C) has been reported in autosomal dominant NS[1,2] and schwannomatosis[3] separately

METHODS

To delineate a relationship between DN pathogenic variants and schwannomatosis, we reviewed clinical details of two different cohorts with DN (likely) pathogenic variants for the presence of schwannomas.

- The first cohort included children with clinical features consistent with autosomal dominant NS (age 0-17 years).
- The second cohort consisted of adults who underwent routine multi-gene cancer panel testing (mean age 55 years).

In addition, the frequency of schwannomas was compared between the DN and five most common LoF variants in the cancer cohort.

Mechanism	Classification	Variant
DN	(Likely) Pathogenic	p.G248R, p.P281L, p.R284C, p.R412C
Suspected DN	VUS	p.Y119H, p.Y136H, p.R283Q, p.G286R, p.H287Y
LoF	Pathogenic	p.Q10Afs*24, p.Q10Rfs*15, p.R210*, p.F258Lfs*93, and p.R362*

RESULTS

None of the children with NS were reported to have schwannomas.

In the cancer cohort, a personal history of schwannomas was reported at higher frequency with DN (likely) pathogenic variants, compared with LoF pathogenic variants.

There was statistically significant difference in the frequency of schwannomas between DN and LoF variants.

Even when suspected DN VUS were combined with (likely) pathogenic variants, the results were similar.

Association of schwannomas with DN *LZTR1* variants

Children with AD NS

Variant	Classification	Patients with schwannoma
c.742G>A (p.G248R)	Pathogenic	0/3
c.842C>T (p.P281L)	Likely Pathogenic	0/3

Adults tested on multi-gene cancer panels

Variant	Classification	Patients with schwannoma
c.742G>A (p.G248R)	Pathogenic	1/15
c.842C>T (p.P281L)	Likely Pathogenic	1/10
c.850C>T (p.R284C)	Pathogenic	0/8
c.1234C>T (p.R412C)	Pathogenic	1/9

Comparison between DN and LoF variants in the cancer cohort

Variant Type	Frequency of schwannoma reports	P value*
DN (Likely) Pathogenic	3/42 (7.14%)	0.013
DN (Likely) Pathogenic & Suspected DN VUS	4/59 (6.78%)	0.007
LoF Pathogenic	2/311 (0.64%)	N/A

*Compared to LoF variants (Fisher's exact test)

TAKE-HOME POINTS

- To our knowledge, this is the first study to investigate an association between DN pathogenic variants and *LZTR1*-related schwannomatosis
- It remains unknown whether patients with autosomal dominant NS develop schwannomas
- DN pathogenic variants can cause schwannomas in some individuals
- Our data suggests that DN variants may confer a higher risk of schwannomatosis, compared to LoF variants

REFERENCES

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