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 paucity of affected individuals with DN pathogenic variants. Only one presumably DN variant (p.S247N) has been identified in a patient who had NS and schwannoma[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 one of three DN (likely) pathogenic variants (p.P281L, p.R284C, and p.G248R) 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 was adults who underwent routine multi-gene cancer panel testing (mean age 55 years). In addition, a frequency of schwannoma was compared between the three DN and five common LoF variants (p.Q10Afs*24, p.R210*, p.F258Lfs*93, p.Q10Rfs*15, and p.R362*) in the cancer cohort.

Results: None of the children with NS was reported to have schwannoma. In the cancer cohort, a personal history of schwannoma was reported in two of 33 patients (6.06%) with a DN (likely) pathogenic variant, whereas only two of 311 patients (0.64%) with LoF pathogenic variants reported schwannomas. There was borderline statistical significance in the frequency of schwannomas between DN and LoF variants (Fisher's exact test p = 0.047). Five variants of unknown significance have evidence of autosomal dominant inheritance in the literature or unpublished data. When these variants were combined with (likely) pathogenic variants, the results were similar – three of 55 patients with schwannoma (5.45%, p = 0.026 compared to LoF).

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

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