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Case Report

A novel leucine zipper-like transcriptional regulator 1 variant identified in a pair of siblings with familial schwannomatosis

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ABSTRACT

Background: Schwannomatosis is a rare genetic disorder marked by the emergence or predisposition to developing multiple schwannomas. Patients typically present with chronic pain or a mass in the second or third decade of life. Schwannomatosis is characterized by its associated gene, or if the specific gene is not known, then a descriptor is used. Here, we report a new Leucine zipper-like transcriptional regulator 1 (LZTR1) pathogenic variant identified in a pair of siblings with familial LZTR1-related schwannomatosis.

Case Descriptions: A 35-year-old male presented for evaluation of the left lower extremity pain. Magnetic resonance imaging (MRI) demonstrated multiple lesions throughout his body, highly likely for schwannomatosis. He underwent surgical resection of two of these lesions, located in the left femoral nerve and distal shin. Pathology confirmed that the resected lesions were schwannomas. Six months later, his 34-year-old sister was referred and evaluated for a right ankle mass, previously diagnosed as a ganglion cyst. MRI of her right ankle demonstrated a one-centimeter subcutaneous tumor. She underwent surgical resection, and pathology confirmed that the tumor was a schwannoma. Both siblings elected to undergo genetic analysis for pathogenic variants associated with schwannomatosis. Both results were positive for the c.263del pathogenic variant of the LZTR1 gene associated with LZTR1-related schwannomatosis. Additionally, genetic analysis also determined the mother of the siblings also carried the same c.263del pathogenic variant.

Conclusion: There are still schwannomatosis cases with novel switch/sucrose non-fermentable-related matrix-associated actin-dependent regulators of chromatin subfamily B member 1 or LZTR1 mutations to be reported. We report the first three cases of the c.263+1del LZTR1 pathogenic variant causing LZTR1-related schwannomatosis initially found in the two siblings. Identifying further LZTR1 pathogenic variants can give more insight into the pathogenicity of each variant.

Keywords: Genetic analysis, Leucine zipper-like transcriptional regulator 1-related schwannomatosis, Pathogenic variant, Schwannoma, Schwannomatosis

INTRODUCTION

Schwannomatosis is a rare genetic disorder marked by the emergence or predisposition to developing multiple schwannomas.[9] With an estimated incidence of 1:40,000–1:70,000,[9]

patients with schwannomatosis develop schwannomas commonly affecting the spine (74%) and peripheral nerves (89%), whereas cranial nerve schwannomas (mostly trigeminal) are uncommon (8%).[5,16] Patients typically present with chronic pain or a mass in the second or third decade of life.[16] Historically, schwannomatosis referred to patients with multiple schwannomas confirmed through biopsy without radiographic evidence or clinical signs of multiple vestibular nerve tumors or other stigmata of Neurofibromatosis 1 (NF1) or Neurofibromatosis 2 (NF2) at an age >18.[11] Germline mutations in the tumor suppressor genes, Switch/Sucrose non-fermentable-related matrix associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) or Leucine zipper-like transcriptional regulator 1 (LZTR1), on chromosome 22 were identified in patients with schwannomatosis.[16] In addition, these patients would often also have independent somatic mutations of the NF2 allele, causing inactivation on the remaining chromosome 22.[16] This finding gave insight into the potential role that the NF2 gene had in the development of schwannomatosis.[16]

In recent years, advances in molecular genetics, neuroimaging, and clinical management have shed new light on the intricacies of schwannomatosis, providing an enhanced understanding of its pathogenesis and diagnostics. Due to the common predisposition for schwannomas and phenotypic similarities seen in both NF2 and schwannomatosis, revised criteria developed from the existing literature by disease experts in 2022 combined NF2 and schwannomatosis into one broad category of schwannomatosis characterized by its associated gene.[6] Due to the revised criteria, schwannomatosis is now recognized as NF2-related schwannomatosis, SMARCB1-related schwannomatosis, LZTR1-related schwannomatosis, or if the specific gene is not known, then a descriptor is used.[6] Here, we report a novel LZTR1 pathogenic variant identified in a pair of siblings with familial LZTR1-related schwannomatosis to further contribute to our genetic understanding of schwannomatosis.

CASE PRESENTATIONS

Brother

A 35-year-old right-handed male presented for evaluation of the left lower extremity pain. He reported a 5–9/10 intermittent stabbing and shooting pain in the medial aspect of the left lower leg that had worsened over the past 6 years with no family history of peripheral nerve tumors or NF1. The patient also reported numbness in the same region. The patient denied any bowel/bladder dysfunction, balance difficulties, or gait abnormalities. Recent pelvic magnetic resonance imaging (MRI) demonstrated a left femoral mass and left sciatic nerve lesion [Figure 1a].

On physical examination, very tender palpable masses were found in the left trapezius, right mid back, left femoral region and left lower leg with a positive Tinel's sign. The sciatic lesion was unable to be palpated. In addition, he had decreased sensation to light touch in the left shin and foot, bilateral sacroiliac joint, and sciatic and left gluteal tenderness. Strength was 5/5 bilaterally in the upper and lower extremities. No other clinical evidence of vestibular schwannoma or other stigmata of NF1 or NF2 were seen on physical exam.

Given the patient's history, symptoms, physical examination, and imaging findings, he was suspected to have schwannomatosis likely. He underwent exploration and resection of the left proximal femoral nerve sheath tumor and resection of the left distal shin subcutaneous nerve tumor without complications. Histopathology confirmed the resected masses as schwannomas. On a follow-up visit 1 week later, the patient had greatly improved left leg pain; however, he had increased numbness in the medial aspect of his left lower extremity. The patient then presented again for 1 year follow-up, in which he was doing well; however, he had developed new symptomatic lesions. Physical examination demonstrated a palpable right parasagittal superficial thoracic lesion and a left-sided superficial brachial plexus lesion. MRI revealed a stable left sciatic nerve lesion, a new right-sided thoracic lesion, and a new left-sided brachial plexus lesion [Figure 1b]. He then underwent resection of the left brachial plexus and multiple posterior back lesions [Figure 2a and b]. Pathology confirmed that all these lesions were schwannomas [Figure 2c and d], and genetic analysis was positive for a pathogenic variant of the LZTR1 gene associated with LZTR1-related schwannomatosis. The analysis specifically identified the NM_006767.3:c.263del (also known as NM_006767.3:c.263 + 1del) variant in the LZTR1 gene.

Sister

Six months after the brother's initial visit and schwannoma resections, his 34-year-old right-hand dominant sister was referred and evaluated for a right ankle mass that had been diagnosed as a ganglion cyst 7 years prior. The patient stated that the mass was originally asymptomatic, except for a burning sensation when running. However, over the past few years, she noticed a gradual enlargement of the mass, and 6 months ago, she started experiencing an increasing frequency of burning pain in her right ankle. This pain often caused her to wake up from her sleep. She reported no gait abnormalities. MRI of her right ankle demonstrated a one-centimeter subcutaneous tumor lateral

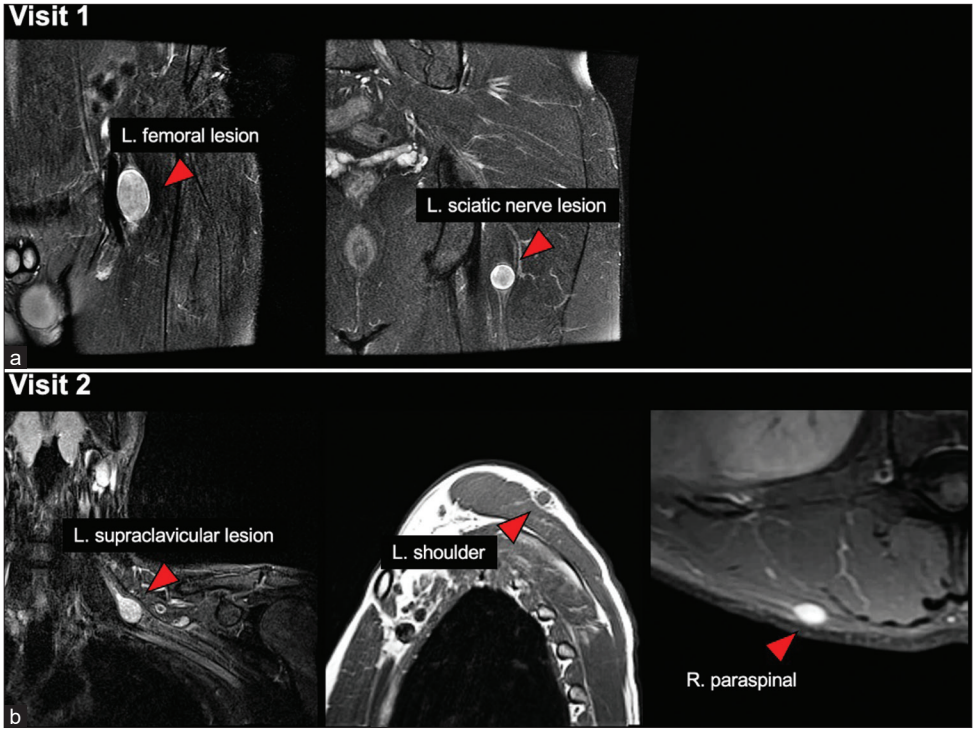

Figure 1: Peripheral lesions of brother sibling on (a) first visit showing lesions (red triangles) in the left femoral (left, T2-weighted coronal magnetic resonance imaging [MRI]) and left sciatic nerve (right, T2-weighted coronal MRI) regions which histology showed to be consistent with schwannoma, followed by (b) second visit showing lesions (red triangles) in the left supraclavicular (left, T2-weighted coronal MRI), left shoulder (middle, T1-weighted no contrast MRI), and right paraspinal (right, T1-weighted with contrast MRI) regions which histology showed to be consistent with schwannoma.

to the lateral malleolus associated with the tibial sensory nerve, likely representing a schwannoma [Figure 3a-c]. She underwent resection of the right sensory tibial nerve tumor without complications, and pathology confirmed that the tumor was a schwannoma. At her 10-week postoperative visit, she was doing well with complete resolution of the right ankle pain.

Following tumor resection, she elected to undergo genetic analysis of the LZTR1, SMARCB1, and NF2 gene, genetic variants associated with schwannomatosis, to determine if there was a genetic cause of her nerve sheath tumor. At this time, she reported that her father had a neuroma of the neck resected at 37 years old, without further nerve sheath tumors or genetic testing performed. The results of the analysis were also positive for the NM_006767.3:c.263del variant in the LZTR1 gene.

Since both siblings had the same LZTR1 pathogenic variant identified, the mother of the siblings underwent genetic testing to determine if she was carrier of the variant. Interestingly, the genetic results revealed that she did in fact have the same variant as her children despite being asymptomatic. Currently, the mother does not have any imaging studies to review to assess for schwannomas, as she had no prior indications to have these imaging studies

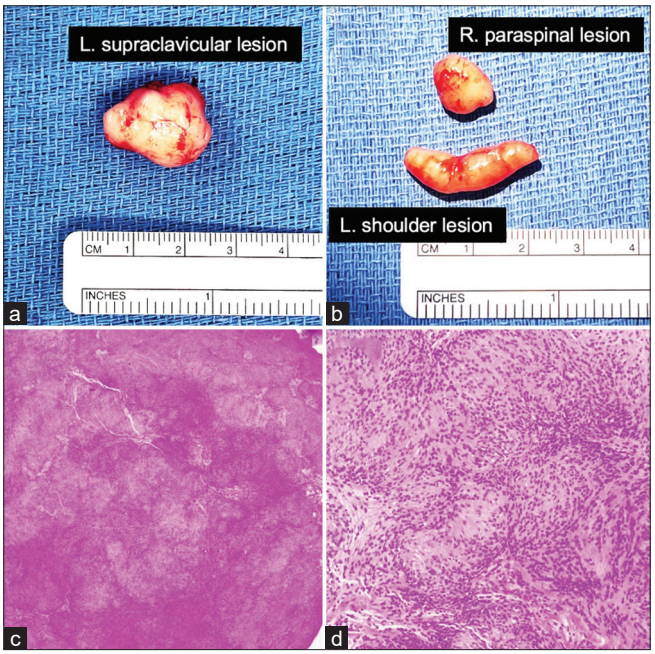

Figure 2: Surgical and histological results from visit 2 for the brother sibling showing surgical specimens for (a) the left supraclavicular lesion, (b) the right paraspinal and left shoulder lesions, as well as Hematoxylin and eosin (H&E) histology for the specimen demonstrating schwannoma at both (c) ×20 and (d) ×200 magnification.

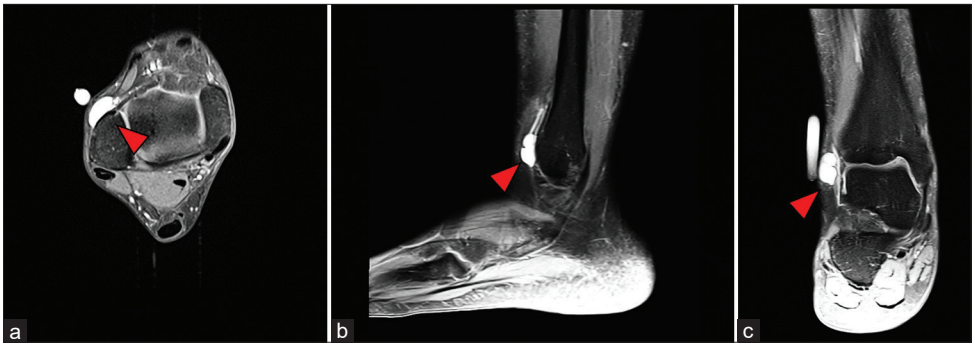

Figure 3: Peripheral lesion of sister sibling in the right ankle (red triangle) on T1-weighted magnetic resonance imaging with contrast on (a) axial, (b) sagittal, and (c) coronal axes initially thought to be a ganglion cyst, but histology proved to be schwannoma.

performed. However, per the 2022 schwannomatosis clinical practice guidelines published by Evans *et al.*[5], it is recommended that the mother and siblings have baseline brain MRI through the auditory canal and spine MRI and/or whole-body MRI for tumor surveillance. The future results of these imaging studies could give more insights into the manifestations of the NM_006767.3:c.263del pathogenic variant.

DISCUSSION

Schwannomatosis was first reported by Nimura in 1973 and was characterized by multiple peripheral and spinal schwannomas without acoustic tumors or other signs of NF1 or NF2.[8] Multiple neurilemomas, multiple schwannomas, and congenital neurilemmomatosis have all been previously used to describe schwannomatosis.[4] SMARCB1 and LZTR1 on chromosome 22q, near the NF2 gene, were identified as the two genes that lead to the development of schwannomas through a 3-event, 4 hit mechanism that results in the complete inactivation of each gene and the NF2 gene.[5] The first hit of this mechanism is a germline mutation that results in the inactivation of LZTR1 or SMARCB1.[4] In the second hit, contiguous deletion on 22q occurs, resulting in the loss of heterozygosity.[4] In this hit, the wild-type SMARCB1, LZTR1, and NF2 alleles are lost.[4] In the third hit, a somatic mutation occurs that inactivates the remaining NF2 allele on the same chromosome, the LZTR1 or SMARCB1 germline inactivation from the first hit event occurs.[4] As a result, biallelic inactivation of SMARCB1 or LZTR1 occurs, leading to SMARCB1-related schwannomatosis or LZTR1-related schwannomatosis.[4] In addition, both NF2 alleles are inactivated, which is present in both SMARCB1- and LZTR1-related schwannomatosis.[4]

In 2022, Plotkin *et al.* published revised nomenclature for schwannomatosis, characterizing the condition by its pathogenic gene or descriptor.[15] About 70–80% of familial and 30% of sporadic schwannomatosis cases are caused by germline SMARCB1 and LZTR1 pathogenic variants and are diagnosed by molecular genetic testing.[4] Cases of schwannomatosis have been reported in the literature; however, cases including genetic analysis are far more limited. In 50–60% of sporadic cases and 15–30% of cases with a family history of schwannomatosis, no identifiable SMARCB1 or LZTR1 mutations have been found.[10] Therefore, Kehrer-Sawatzki *et al.* concluded that further schwannomatosis-causing genes may exist that have not been identified yet.[10] To the best of our knowledge, we report the first three cases of the NM_006767.3:c.263+1del LZTR1 pathogenic variant causing LZTR1-related schwannomatosis. The previous case reports have identified NM_006767.3:c.231delA and NM_006767.3:c.791+1G>A LZTR1 pathogenic variants,[7,12] and the previous studies have identified 16,[14] 18,[13] 19,[17] 7,[10] 3,[1] and 5[2] further LZTRI mutations, none of which include the NM_006767.3:c.263+1del variant we report.

Deng *et al.*, further reported that there are still many uncertainties regarding the pathogenicity of schwannomatosis-associated LZTR1 variants.[3] Incomplete penetrance has also been reported in schwannomatosis [3] and is likely an explanation for the different phenotypic manifestations seen in the disease. The identification of further LZTR1 pathogenic variants can give more insight into the incomplete penetrance associated with each identifiable variant. This clinical knowledge can help guide patients' expectations and understanding of schwannomatosis. In our cases of LZTR1-related schwannomatosis, the NM_006767.3:c.263+1del variant manifested as a single schwannoma in the sister's right ankle, while her brother presented with multiple schwannomas throughout his body. In addition, it was determined that the mother also carried the same pathogenic variant and reported to be asymptomatic. Genetic analysis determined that both siblings and the mother had the same pathogenic variant

causing LZTR1-related schwannomatosis, and the varying clinical manifestations among the family may be due to the increased penetrance of the NM_006767.3:c.263+1del LZTR1 variant.

In addition, by including the genetic results of our schwannomatosis patients, this information can be added to genetic databases. Further studies to understand schwannomatosis can then be conducted, such as investigating allele frequency or variant pathogenicity.[3] Our report aims to add to the current LZTR1 mutations that are known to cause schwannomatosis.

CONCLUSION

There are still schwannomatosis cases with novel SMARCB1 or LZTR1 mutations to be reported. We report the first three cases of the c.263+1del LZTR1 pathogenic variant causing LZTR1-related schwannomatosis. Identifying further LZTR1 pathogenic variants can give more insight into the pathogenicity of each variant.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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