**CASE REPORT**

**LZTR1** molecular genetic overlap with clinical implications for Noonan syndrome and schwannomatosis

Kirsten M. Farncombe1, Emily Thain2, Carolina Barnett-Tapia3,4, Hamid Sadeghian3,4 and Raymond H. Kim5,6*

**Abstract**

**Background:** Noonan syndrome (NS) is a genetic disorder characterized by developmental delays, typical facial gestalt and cardiovascular defects. *LZTR1* variants have been recently described in patients with NS and schwannomatosis, but the association, inheritance pattern and management strategy has not been fully elucidated. Here, we review the contribution of *LZTR1* in NS and describe a patient with a novel, likely pathogenic variant in *LZTR1*.

**Case presentation:** A female patient was diagnosed with clinical NS at 8 months of age. She presented in adulthood when a brain and spine MRI identified plexiform neurofibromas; however, she did not meet the clinical criteria for Neurofibromatosis type 1. No pathogenic variants were identified through molecular genetic analysis of *NF1*, *SPRED1* and a multigene NS panel. Whole exome sequencing at age 23 identified a novel de novo likely pathogenic heterozygous variant in the *LZTR1* gene denoted as c.743G>A (p.Gly248Glu). Serial MRIs have shown stable imaging findings and the patient is being followed clinically by cardiology, neurology and medical genetics.

**Conclusions:** We identified a novel mutation in the *LZTR1* gene, not previously reported in association with NS. This report provides additional evidence to support for the assessment of schwannomatosis in patients with *LZTR1*-NS and may have overlap with Neurofibromatosis type 1.

**Keywords:** Noonan syndrome, Neurofibromas, Whole exome sequencing, *LZTR1*

**Background**

Noonan syndrome (NS) is a genetic multisystem disorder with a prevalence of 1 in 1000–2500 live births (1). This condition is characterised by varying developmental delays, distinctive facial features, congenital heart defects and short stature; clinical diagnosis is often based on these features (2). NS is part of a group of phenotypically similar developmental disorders (RASopathies), caused by germline variants in the genes within the RAS/MAPK signalling pathway (3).

There are multiple genes that cause NS, all linked to the RAS/MAPK signalling pathway (4, 5). Fifty percent of individuals with NS have a germline pathogenic variant (PV) in *PTPN11* (2). Other reported genes include *SOS1, RAF1, ROT1* and *KRAS*, occurring in 13%, 5%, 5% and <5% of cases, respectively (2). PVs in other genes, including *BRAF, MAP2K1* and *NRAS*, have been identified in less than 1% of affected individuals (2). Another gene, *LZTR1*, has been recently identified as a causative gene in RASopathies (6); however, its precise role in the RAS/MAPK signalling pathway is less defined. Additionally, germline pathogenic variants in *LZTR1* have been identified in patients with schwannomatosis and is thought to be a distinct entity as schwannomas are not frequently seen in NS (7, 8). There is a paucity of cases...
to address this genetic and phenotypic heterogeneity in LZTR1 carriers.

LZTR1 (OMIM 600574), encoding leucine zipper-like transcription regulator 1 (LZTR1), was proposed as a tumor suppressor gene belonging to the BTB-Kelch superfamily (9). LZTR1 is a Golgi protein and belongs to the BTB-Kelch superfamily (7, 9), where it is reported to be involved in apoptosis (9) and acts as a substrate-specific adaptor for the Cullin-3 (Cul3) ubiquitin ligase (10, 11). Using a computational platform, LZTR1 was identified as a tumor suppressor gene, with somatic mutations in this gene driving glioblastoma (10). Somatic mutations in LZTR1 have also been associated with liver cancer (12).

Recent investigations have provided more insight into its potential role in the RAS/MAPK signalling pathway. LZTR1 binds to the RAF1/SHOC2/PP1CB complex and promotes RAF1 Ser259 phosphorylation, leading to MAPK signalling pathway inactivation (13). Additional data reports that LZTR1 enables the polyubiquitination and degradation of endogenous RAS, which ultimately inhibits RAS/MAPK signalling (14). Two other studies suggest that LZTR1 mediates RAS ubiquitination and MAPK pathway activation, contributing to the development of human disease (15, 16). Examination of LZTR1 variants associated with NS suggest this gene is functionally-linked to the RAS/MAPK pathway by negatively controlling RAS protein levels and MAPK signalling (17). In addition, a biological relationship has been proposed between LZTR1 and RIT1, whereby pathogenic mutations affecting RIT1 or LZTR1 leads to RIT1 accumulation and contributes to hyperactivation of MAPK signalling (18).

While the association of germline LZTR1 variants with human disease is still being elucidated, germline loss-of-function mutations in LZTR1 predispose to schwannomatosis (7, 19, 20) and NS (2). NS has wide genetic heterogeneity and clinical variability (21). Inheritance most frequently occurs in an autosomal dominant (AD) manner, however, PVs in LZTR1 leading to NS can also be inherited in an autosomal recessive (AR) manner (2). Expression experiments suggest that LZTR1 variants that cause AD NS may not be gain-of-function, whereas variants in patients with AR NS may have a loss-of-function effect (13). Loss-of-function mutations in biallelic LZTR1 variants include splice site, frameshift, nonsense and missense modifications (17). Experiments assessing the functionality of missense LZTR1 mutations suggests that schwannomatosis-associated LZTR1 mutations act heterogeneously in modifying RAS-MAPK signalling, similar to variants causing dominant NS (17). The pleotropic function of LZTR1 may explain the multiple inheritance patterns (AR, AD) of LZTR1-associated NS.

NS has been associated with Neurofibromatosis type 1 (NF1) [Neurofibromatosis-Noonan syndrome (NFNS)], a rare disorder where individuals present with phenotypic characteristics of these two autosomal dominant conditions (22). While there was an earlier debate about whether NFNS is a separate genetic condition, more recent reports illustrated clinical findings of both disorders, providing support that this is a new syndrome (23). NFNS is mainly caused due to mutations in NF1 (24–28), however, there has occasionally been a PTPN11 mutation reported in addition to the NF1 gene mutation (29, 30). The involvement of other genes within the RAS-MAPK signalling pathway that cause NS have not yet been explored in NFNS (31). As such, NS should be considered part of the differential diagnosis in NF1 patients.

In this report, we describe a patient with clinically diagnosed NS who presented with sacral plexiform nerve sheath tumors, suggestive of neurofibromas or schwannomas. Whole exome sequencing (WES) revealed a de novo likely pathogenic heterozygous variant in the LZTR1 gene. Here we demonstrate the clinical overlap of NS, schwannomatosis and NF1 and support the inclusion of LZTR1 in gene panels for NS. In addition, we have reviewed the published literature on NS patients and variants in the LZTR1 gene, noting zygosity, inheritance pattern and clinical characteristics, to inform the management of individuals with a heterozygous LZTR1 mutation.

Case presentation
Case description
A Caucasian female received a clinical diagnosis of NS at 8 months of age, prompted by an extra nuchal skin fold (Fig. 1). Facial features were consistent with NS (large eyes, low-set cupped ears and prominent lips) and she was also found to have congenital heart defects (subaortic ridge with mild left ventricular outflow tract obstruction, mitral valve prolapse with mild mitral regurgitation and tricuspid aortic valve with mild aortic insufficiency), recurrent migraines, pectus excavatum and a history of learning disability.

The patient received daily growth hormone (GH) injections as a child between ages 9–16 to address short stature. Her pre-growth hormone height was 118.6 cm (<5th percentile according to CDC growth charts and 50th percentile in Noonan Syndrome growth charts) (32). No significant adverse effects were reported. Her height at adulthood (~17 years of age) was 158.4 cm, placing her in the 25th percentile on the CDC Growth Charts and 90th percentile on Noonan Syndrome growth charts. Due to delayed puberty, the patient had a trial of transdermal estradiol at the age of 14. This was
transitioned to Premarin with good gonadotropic effect, and she has been on oral contraceptives since 16 years of age.

At 20 years of age, a magnetic resonance imaging (MRI) brain and intracranial magnetic resonance angiography (MRA) was performed for chronic frontal headaches. MRA was normal. MRI of the brain and subsequent MRIs of the whole spine revealed a cerebellar ectopia related to a Chiari type 1 malformation and sequested syringomelia extending from C1-T6 with no evidence of an underlying mass. There were multiple plexiform neurofibromas in the sacral spine, prompting a referral to neurosurgery for suspicion of NF1. At 23 years of age, a discontinuous expansile syrinx present from C6-T6 was noted, with enlargement of the dorsal root ganglia in the cervical spine.

The plexiform neurofibromas involved all nerve roots and caused marked expansion of the sacral foramina. As a biopsy was unlikely to change management, these lesions were not biopsied and thus imaging findings were not pathologically confirmed (Fig. 2A–B). Serial MRIs have shown stable imaging findings. Upon clinical examination, the patient did not present with café-au-lait macules (CALMs), skinfold freckling, or cutaneous or subcutaneous neurofibromas. Due to the initial question of NF1, genetic testing was conducted in a step wise fashion to establish a molecular genetic diagnosis.

**Next generation sequencing**

Exon-level germline analysis of *NF1* [NCBI RefSeq NM_000267.3], *SPRED1* [NM_152594.2] and a multigene NS panel (*BRAF* [NM_004333.4], *CBL* [NM_005188.3],...
was not yet included in the laboratory's NS gene panel. Exon 8 of the gene [NM_006767.3]. Variants at pathogenic heterozygous c.743G>A (p.Gly248Glu) in the gene did not reveal any PVs in the genes tested. A single nucleotide polymorphism (SNP) microarray at the same laboratory was in-keeping with a normal female, arr(1-22,X)×2. As schwannomas and neurofibromas are not typically reported in patients with NS, the molecular genetic approach in patients with nerve sheath tumors often begins with NF1. For this patient, multi-gene panel testing for NS, NF1 and Legius syndrome were negative—there is a degree of phenotypic overlap and uncertainty between other similar conditions; therefore, the focus of genetic testing may be on this rare manifestation with a misdiagnosis of NF1, NF2 or schwannomatosis, rather than NS. A recent study performed an extensive literature review to estimate the number of conditions that may mimic NF1, as well as examining data from 40 pediatric patients with NF1-like syndromes (50). Phenotypic overlap, particularly with skin manifestations or tissue overgrowth, was observed between NS,}

**Discussion and conclusions**

Monoallelic and biallelic LZTR1 variants in NS are not well described, however, previous studies have reported germline variants causative for NS (Table 1) in either an autosomal recessive or autosomal dominant manner (6, 8, 13, 37, 38, 41–47). Of note, a different missense mutation at the same protein residue as our patient (p.Gly248Arg) was reported as pathogenic or likely pathogenic in other individuals with NS (6, 13, 38, 47), with the same designations on ClinVar. In silico analysis of variants (p.Ala116Val, p.Arg284Cys, p.Arg688Cys, p.Gly248Arg, p.His287Tyr, p.Pro520Leu, p.Ser247Asn, p.Ser122Leu, p.Tyr119Cys and p.Val456Gly) found in the LZTR1 gene support a deleterious effect (6, 7, 42).

Our patient’s phenotype is unique, as not many patients with NS present with plexiform nerve sheath tumors. These are typically benign tumors, with neurofibromas characteristic of NF1 (48) and schwannomas often occurring in patients with NF2 or schwannomatosis (49). This case highlights one of the main issues in identifying NS patients—there is a degree of phenotypic overlap and uncertainty between other similar conditions; therefore, the focus of genetic testing may be on this rare manifestation with a misdiagnosis of NF1, NF2 or schwannomatosis, rather than NS. A recent study performed an extensive literature review to estimate the number of conditions that may mimic NF1, as well as examining data from 40 pediatric patients with NF1-like syndromes (50). Phenotypic overlap, particularly with skin manifestations or tissue overgrowth, was observed between NS,
Table 1: Previous published reports of Noonan syndrome and LZTR1 variants

| Variant(s)                        | Zygosity         | Mode of inheritance | Clinical diagnosis/Features                                                                                                                                                                                                 | PMID        |
|-----------------------------------|------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| c.742G>A (p.Gly248Arg)            | Heterozygous     | Maternal            | **Proband**: typical facial features, short/webbed neck, pectus deformity, pulmonary valve stenosis/atrial septal defect, ophthalmological abnormality (prominent corneal nerves), lacrimal duct obstruction  
**Mother**: typical facial features, short/webbed neck, pectus deformity, mitral valve prolapse, height -2.5 SDS  
**Grandfather**: typical facial features, short/webbed neck, pectus deformity, mitral valve prolapse, abnormal hemostasis (Factor XI deficiency), height -2.9 SDS | 25795793    |
| c.850C>T (p.Arg284Cys)            | Heterozygous     | Maternal            | **Proband**: typical facial features, abnormal hemostasis (prolonged ATTP)  
**Mother**: typical facial features, nevi  
**Sibling 1**: typical facial features, ectodermal findings (curly hair, sparse eyebrows, hyperkeratosis pilaris), nevi  
**Sibling 2**: typical facial features, short/webbed neck, ectodermal findings (curly hair), hemangioma  
**Half Sibling 1**: typical facial features  
**Half Sibling 2**: typical facial features, height -3.8 SDS | 25795793    |
| c.859C>T (p.His287Tyr)            | Heterozygous     | De novo             | **Proband**: typical facial features, pulmonary valve stenosis/atrial septal defect, cryptorchidism, abnormal hemostasis (prolonged ATTP), ophthalmological abnormality (prominent corneal nerves), developmental delay, learning disability | 25795793    |
| c.356A>G (p.Tyr119Cys)            | Heterozygous     | De novo             | **Proband**: typical facial features, left ventricular hypertrophy, lymphedema, varicose veins                                                                                                                               | 25795793    |
| c.740C>A (p.Ser247Asn)            | Heterozygous     | Maternal            | **Proband**: typical facial features, short/webbed neck, pectus deformity, mitral valve insufficiency, ectodermal findings (curly hair), developmental delay, learning disability  
**Mother**: typical facial features, short/webbed neck, aorta coarctation, hyperopia, tumors (neurinomas of right hand and forearm, lipoma of thorax = schwannomas) | 25795793    |
| c.881G>T (p.Arg294Leu)/c.2212C>T (p.Gln738*) | Compound heterozygous | Maternal/paternal | **Proband**: typical NS facial features, pectus excavatum, short stature treated with growth hormone, growth hormone deficiency, thickening of the left side of the optic chiasm suggestive of glioma, Senning correction surgery for transposition of the great vessels, pulmonary stenosis, interventricular and interatrial communication | 29959388    |
| c.509G>C (p.Arg170Pro)/c.2374T>G (p.Cys792Gly) | Compound heterozygous | Maternal/paternal | **Proband**: NS clinical phenotype, short stature, left ventricular outflow tract obstruction, atrial septal defect                                                                                                        | 30732632    |
| Variant(s) | Zygosity | Mode of inheritance | Clinical diagnosis/Features                                                                                                                                                                                                 | PMID          |
|-----------|----------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| c.850C>T (p.Arg284Cys) | Heterozygous | Maternal Dominant | Proband: Typical NS dysmorphism, Charcot-Marie-Tooth syndrome, manual dyspraxia and distal muscular weakness, short stature treated with growth hormone, scoliosis and lumbar scoliosis, partial complex seizures leading to identification of a right fonto-temporo-insular tumor, severe kyphoscoliosis with a gibbus, pectus excavatum, generalized amyotrophy, mild defect in factor XI, grade IV glioblastoma | 30664951     |
| c.1149+1G>T | Heterozygous | Maternal Autosomal dominant | Proband: typical NS appearance, short stature, delayed psychomotor development, frequent premature ventricular beats, hemivertebra deformity, scoliosis, refractive errors, growth hormone deficiency, pectus excavatum, café au lait spots, mild hypertrichosis  
Sibling: typical NS appearance, pectus carinatum, short stature  
Mother: mild typical NS appearance | 33407364     |
| c.1084C>T (p.Arg362*)/c.1149+1G>T | Compound heterozygous | Maternal/paternal Autosomal recessive | Proband: severe hypertrophic cardiomyopathy, mild pulmonary valve stenosis, characteristic NS facies, broad QRS complexes, right bundle branch block, left axis deviation, striking negative pattern in the left precordial leads  
Sibling: typical craniofacial dysmorphology, pulmonary valve stenosis/branch pulmonary arterystenosis, slight asymmetric hypertrophy of interventricular sept, café au lait spots, nevi or lentigines, permanence of fetal finger and toepads, narrow palate | 31182298     |
| c.2070-2A>G/c.1735G>A (p.Val579Met) | Compound heterozygous | Paternal/maternal Autosomal recessive | Proband: severe hypertrophic cardiomyopathy without obstruction, left axis deviation, negative pattern in the left precordial leads, severe feeding problems | 31182298     |
| c.355T>C (p.Tyr119His) | Not provided | De novo | Proband: typical craniofacial dysmorphology, pulmonary valve stenosis/branch pulmonary arterystenosis, slight asymmetric hypertrophy of interventricular sept, café au lait spots, nevi or lentigines, permanence of fetal finger and toepads, narrow palate | 32514133     |
| c.1430C>T (p.Ala477Val)/three LRPI variants | Heterozygous | Paternal/maternal | Proband: delayed development, height -498 SD, typical craniofacial dysmorphology, broad thorax with wide-spaced nipples, cubitus valgus, clinobrachydactyly, cryptorchidism, GH deficiency, previous epilepsy (rolandic type, absences), thoracolumbar scoliosis, generalized hirsutism | 32514133     |
| c.347C>T (p.Ala116Val) | Heterozygous | De novo | Proband: typical facial dysmorphology, height -43 SD, short webbed neck with low posterior hairline, pectus deformity, heart murmur, hypertrophic cardiomyopathy, cryptorchidism, ostium secundum atrial septal defect, mitral anomaly, ectodermal findings, sparse eyebrows, ulcer-hema ophriogenes, developmental delay | https://doi.org/10.4172/0974-8369.1000414 |
| Variant(s) | Zygosity               | Mode of inheritance | Clinical diagnosis/Features | PMID |
|------------|------------------------|---------------------|-----------------------------|------|
| c.628C>T (p.Arg210*)/c.2220-17C>A (p.Tyr741His*89) | Compound heterozygous | Paternal/maternal Autosomal recessive | Sibling 1: typical facial dysmorphism, broad/short neck, low posterior hairline, pectus carinatum or excavatum, congenital heart defect or valvarlur disease, Sibling 2: prenatal hydrops, nuchal transl or cardiac findings, typical facial dysmorphism, broad/short neck, low posterior hairline, pectus carinatum or excavatum, congenital heart defect or valvarlur disease, curly hair, developmental delay, Sibling 3: typical facial dysmorphism, broad/short neck, low posterior hairline, pectus carinatum or excavatum, wide-spaced nipples/broad chest, congenital heart defect or valvarlur disease, height < 3rd centile, Several individuals in this family had suggestive schwannomas. | 29469822 |
| c.2178C>A (p.Tyr726*)/ c.1943-256C > T | Heterozygous | Paternal/maternal Autosomal recessive | Sibling 1: prenatal hydrops, nuchal transl or cardiac findings, typical facial dysmorphism, broad/short neck, low posterior hairline, wide-spaced nipples/broad chest, pectus carinatum or excavatum, cardiomyopathy, congenital heart defect or valvarlur disease, cryptorchidism, developmental delay/intellectual disability, height < 3rd centile, Sibling 2: prenatal hydrops, nuchal transl or cardiac findings, typical facial dysmorphism, broad/short neck, cardiomyopathy, congenital heart defect or valvarlur disease, height < 3rd centile | 29469822 |
| c.1943-256C>T, *70G>A/ c.1943-256C>T, *70G>A | Homozygous | Paternal/maternal Autosomal recessive | Sibling 1: prenatal hydrops, nuchal transl or cardiac findings, depressed or wide bridge, low set ears, broad/short neck, low posterior hairline, wide-spaced nipples/broad chest, cardiomyopathy, height < 3rd centile, Sibling 2: prenatal hydrops, nuchal transl or cardiac findings, ptosis, downslanted palpebral fissures, low set ears, cardiomyopathy, congenital heart defect or valvarlur disease, height < 5-10th centile | 29469822 |
| c.1687G>C (p.Glu563Gln) | Homozygous | Paternal/maternal Autosomal recessive | Sibling 1: typical facial dysmorphism, broad/short neck, low posterior hairline, pectus carinatum or excavatum, cardiomyopathy, congenital heart defect or valvarlur disease, developmental delay/intellectual disability, height < 3rd centile, Sibling 2: prenatal hydrops, nuchal transl or cardiac findings, broad/short neck, cardiomyopathy, congenital heart defect or valvarlur disease, cryptorchidism | 29469822 |
Table 1 (continued)

| Variant(s) | Zygosity       | Mode of inheritance         | Clinical diagnosis/Features                                                                 | PMID     |
|------------|----------------|-----------------------------|---------------------------------------------------------------------------------------------|----------|
| c.2407-2A>G/ c.2090G>A (p.Arg697Gln) | Compound heterozygous Paternal/maternal Autosomal recessive | Sibling 1: prenatal hydrops, nuchal transl or cardiac findings, typical facial dysmorphism, broad/short neck, wide-spaced nipples/broad chest, curly hair, cardiomyopathy, congenital heart defect or valvular disease, height 3rd centile Sibling 2 (twins): prenatal hydrops, nuchal transl or cardiac findings, broad/short neck, wide-spaced nipples/broad chest, congenital heart defect or valvular disease | 29469822 |
| c.27delG (p.Gln10fs*15)/ c.1149+1G>A | Compound heterozygous Paternal/maternal Autosomal recessive | Proband: typical facial dysmorphism, broad/short neck, wide-spaced nipples/broad chest, height < 5th centile | 29469822 |
| c.361C>G (p.His121Asp)/ c.2264G>A (p.Arg755Gln) | Compound heterozygous Paternal/maternal Autosomal recessive | Proband: prenatal hydrops, nuchal transl or cardiac findings, typical facial dysmorphism, broad/short neck, low posterior hairline, wide-spaced nipples/broad chest, pectus carinatum or excavatum, curly hair, cardiomyopathy, congenital heart defect or valvular disease, developmental delay/intellectual disability, height < 3rd centile | 29469822 |
| c.508C>T (p.Arg170Trp); c.614T>C (p.Ile205Thr)/ c.508C>T (p.Arg170Trp); c.614T>C (p.Ile205Thr) | Compound homozygous Paternal/maternal Autosomal recessive | Proband: typical facial dysmorphism, broad/short neck, curly hair, cardiomyopathy, congenital heart defect or valvular disease, cryptorchidism developmental delay/intellectual disability, height < 3rd centile | 29469822 |
| c.650A>C (p.Glu217Ala)/ c.650A>C (p.Glu217Ala) | Homozygous Paternal/maternal Autosomal recessive | Proband: typical facial dysmorphism, broad/short neck, cardiomyopathy, congenital heart defect or valvular disease, developmental delay/intellectual disability, height 3rd centile | 29469822 |
| c.2062C>G (p.Arg688Gly)/ c.1943-256C>T | Heterozygous Paternal/maternal Autosomal recessive | Sibling 1: prenatal hydrops, nuchal transl or cardiac findings, typical facial dysmorphism, broad/short neck, wide-spaced nipples/broad chest, pectus carinatum or excavatum, cardiomyopathy, developmental delay/intellectual disability, height < 3rd centile | 29469822 |
| c.232S+1G>A/ c.1943-256C>T | Not provided Paternal/maternal Autosomal recessive | Sibling 1: prenatal hydrops, nuchal transl or cardiac findings, typical facial dysmorphism, broad/short neck, wide-spaced nipples/broad chest, pectus carinatum or excavatum, cardiomyopathy, congenital heart defect or valvular disease | 29469822 |
| Variant(s) | Zygosity | Mode of inheritance | Clinical diagnosis/Features | PMID |
|------------|----------|---------------------|-----------------------------|------|
| c.2462T>C (p.Ile821Thr)/c.2462T>C (p.Ile821Thr) | Homozygous | Paternal/maternal Autosomal recessive | **Sibling 1**: typical facial dysmorphism, low posterior hairline, wide-spaced nipples/broad chest, pectus carinatum or excavatum, curly hair, cardiomyopathy, congenital heart defect or valvular disease, developmental delay/intellectual disability<br>**Sibling 2**: low set ears, post angulated ears, midface retrusion, low posterior hairline, wide-spaced nipples/broad chest, pectus carinatum or excavatum, cardiomyopathy, congenital heart defect or valvular disease, developmental delay/intellectual disability, height < 3rd centile | 29469822 |
| c.406T>C (p.Tyr136His) | Heterozygous | De novo Autosomal dominant | **Proband**: abnormalities of the abdomen, atrioventricular valves, heart values and spatial orientation of the cardiac segments, coarctation of the aorta, heptomegaly, large for gestational age, malrotation of small bowel, malformations of the heart and great vessels, height 2-9th centile, mild typical facial dysmorphism | 30859559 |
| c.434A > T (p.Asn145Ile) | Heterozygous | Maternal Autosomal dominant | **Proband**: short stature, characteristic NS facial features, mild pulmonary stenosis, mild learning difficulties, mild right bundle branch block with mild left ventricular dilation with a normal pulmonary valve, low posterior hairline, widely spaced nipples, mild pectus excavatum, café-au-lait macule, platelet dysfunction disorder<br>**Mother**: mild clotting disorder, type 1 von Willebrand's disease, mild learning difficulties, mild NS-like facial features<br>**Cousin**: Cerebral Palsy, characteristic NS facial features, periventricular leukomalacia, global developmental delay, abnormal gait with increased limb tone, moderate learning difficulties, behavioural issues within the autistic spectrum disorders<br>**Aunt**: childhood growth delay, delayed puberty, hypothryroidism, underweight<br>**Half Aunt**: heart murmur, mitral valve prolapse, small spina bifida, subtle facial features of NS | 30859559 |
| c.290G > T (p.Arg97Leu) | Not provided | De novo Autosomal dominant | **Proband**: prenatal cardiac findings (absent ductus venosus), atrial septal defect, typical NS facial features, downslanted palpebral fissures, epicanthus, wide spaced nipples/broad chest, curly hair hypertrophic cardiomyopathy, short stature, ventricular septal defect, foot abnormalities, delayed walking, scoliosis, impaired clotting, respiratory problems | 30859559 |
| Variant(s) | Zygosity | Mode of inheritance | Clinical diagnosis/Features                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | PMID  |
|------------|-----------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| c.407A>G (p.Tyr136Cys) | Not provided | De novo Autosomal dominant | Proband: 2–3 toe syndactyly, typical NS facial features, barrel-shaped chest, cryptorchidism, delayed speech and language development, depressed nasal bridge, wide spaced nipples/broad chest, curly hair, generalised hypotonia, low-set posteriorly rotated ears, motor delay, unilateral ptosis, wide intermammillary distance, GH deficiency, mild pulmonary valve stenosis, short stature | 30859559 |
| c.731C > G (p.Ser244Cys) | Not provided | De novo Autosomal dominant | Proband: café-au-lait spots, hypermetropia, typical NS facial features, low-set posteriorly rotated ears, wide spaced nipples/broad chest, pectus carinatum, webbed neck, short stature, single transverse palmar crease, strabismus, webbed neck | 30859559 |
| c.742G>A (p.Gly248Arg) | Not provided | De novo Autosomal dominant | Proband: prenatal hydrops, depressed nasal bridge, epicanthus, microcephaly, preauricular pit, prominent metopic ridge, severe global developmental delay, perinatal asphyxia, seizures, underweight, height 1st centile, marked micrognathia and feeding problems, facial features now atypical for NS, cubitus valgus, pectus excavatum, renal abnormalities, valvular heart disease | 30859559 |
| c.1591G>A (p.Asp531Asn)/ c.628C > T (p.Arg210*) | Compound heterozygous Autosomal recessive | | Proband: autistic behaviour, global developmental delay, hypertrophic cardiomyopathy, long palpebral fissure, mitral valve prolapse, pes plantus, prominent fingertip pads, tonic–clonic seizures, facial features suggestive of Kabuki syndrome, height 3rd centile, cryptorchidism | 30859559 |
| c.1149+1G > T/ c.2062C > T (p.Arg688Cys) | Compound heterozygous Autosomal recessive | | Proband: bilateral ptosis, typical NS facial features, blue irides, downslanted palpebral fissures, hyperacusis, hypertelorism, joint hypermobility, square thumb, low-set posteriorly rotated ears, pectus carinatum, broad/short neck, wide spaced nipples/broad chest, proportionate short stature, mild developmental delay, delayed speech and language development | 30859559 |
| c.628C > T (p.Arg210*)/ c.1735G>A (p.Val579Met) | Compound heterozygous Autosomal recessive | | Proband: rare biallelic variants in NEB lead to a “blended” phenotype, nuchal translucency abnormalities, typical NS facial features, bifid uvula, bilateral ptosis, downslanted palpebral fissures, generalised joint laxity, hearing impairment, high palate, hypertelorism, long face, macrodactyly, myopathy, pectus excavatum, pointed chin, renal duplication, retrognathia, mitral valve regurgitation, duplex kidney, mild developmental delay, delayed speech and language development, delayed walking, hypotonia, feeding problems, easy bruising | 30859559 |
| Variant(s) | Zygosity | Mode of inheritance | Clinical diagnosis/Features | PMID |
|------------|----------|---------------------|-----------------------------|------|
| c.1311G>A (p.Trp437*)/c.‑38T>A | Compound heterozygous | Suspected autosomal recessive | *Proband*: typical NS facial features, prenatal hydrops, nuchal translucency abnormalities, broad/short neck, webbed neck, low posterior hairline, wide spaced nipples/broad chest, left ventricle hypertrophy, foot abnormalities, delayed walking, hypotonia, joint laxity/hypermobility | 30859559 |
| c.1407G>A (p.Trp469*)/c.2246A>G (p.Tyr749Cys) | Compound heterozygous | Suspected autosomal recessive | *Proband*: typical NS facial features, severe hypertrophic cardiomyopathy, broad/short neck, webbed neck, low posterior hairline, wide spaced nipples/broad chest, pes planus, mild developmental delay, impaired vision | 30859559 |
| c.1382C>A (p.Ala461Asp)/c.1385T>C (p.Ile462Thr) | Compound heterozygous | Maternal/paternal | Suspected autosomal recessive | 30859559 |
| c.848G>A (p.Arg283Gln) | Heterozygous | De novo | *Proband*: dysmorphic features, short stature, short neck, webbed neck, scoliosis, hyperelastic skin, hyperkeratosis, wrinkled palms and soles, café au lait spots, atrial septal defect, ventricular septal defect, pulmonary stenosis, patent ductus arteriosus, severe intellectual disability | 30368668 |
| c.742G>A (p.Gly248Arg) | Heterozygous | Maternal | Suspected autosomal dominant | 30368668 |
| c.2102C>A (p.Pro701His)/c.2069+2T>C | Compound heterozygous | Paternal/maternal | Suspected autosomal recessive | 30368668 |
| c.428A>G (p.Asn143Ser) | Heterozygous | Paternal | *Proband*: hypertelorism, low-set ears, sparse eyebrows, short stature, short neck, scoliosis, pectus excavatum, hyperpigmentation, hypertrophic cardiomyopathy, mild intellectual disability, squint, amblyopia, 5th brachymetapody | 30368668 |
| c.606_650del (p.Met202fs) | Heterozygous | Paternal | *Proband*: pleural effusion, relative macrocephaly, typical NS facial features, short stature, short neck, webbing of neck, hypertrophic cardiomyopathy, atrial septal defect, pulmonary stenosis, arrhythmia | 30368668 |
Table 1 (continued)

| Variant(s)                        | Zygosity          | Mode of inheritance | Clinical diagnosis/Features                                                                                                                                                                                                 | PMID  |
|-----------------------------------|-------------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| c.756_758del (p.Asn253del)        | Heterozygous      | De novo             | Proband: relative macrocephaly, typical NS facial features, short stature, short neck, webbing of neck, cubitus valgus, pectus carinatum, curly hair, hyperkeratosis, wrinkled palms and soles, hyperpigmentation, hypertropic cardiomyopathy, mild intellectual disability, visual field contraction, optic atrophy | 30368668 |
| c.1660G>C (p.Ala554Pro)           | Heterozygous      | Paternal            | Proband: relative macrocephaly, typical NS facial features, short neck, webbing of neck, cubitus valgus, curly hair, hyperelastic skin, hyperkeratosis, wrinkled palms and soles, hyperpigmentation, naevo, hypertropic cardiomyopathy, atrial septal defect, intellectual disability | 30368668 |
| c.742G>A (p.Gly248Arg)            | Heterozygous      | De novo             | Proband: cryptorchidism, choroid plexus cyst, mild pulmonary supravalvular stenosis, typical NS facial features, curly hair                                                                                                                                               | 31533111 |
| c.2074T>A (p.Phe692Leu)           | Homozygous        | Maternal/paternal   | Proband: short stature, mild pulmonary supravalvular stenosis, Von Willebrand disease, cryptorchidism, orthopexy, typical NS facial features, webbed neck                                                                                                                                 | 31533111 |
| c.730T>C (p.Ser244Pro)            | Heterozygous      | Maternal            | Proband: Chiari malformation type I, mild dorsal syringomyelia, hemangioma in the posterior cervical region, mastocytosis, high arched palate, crowded teeth, typical NS facial features, height lower end of the normal range, webbed neck, Mother: mild facial features, curly hair, height lower end of the normal range, pectum excavatum, webbed neck | 31533111 |
NF1-like syndromes, the RASopathies and other disorders associated with higher tumor development, including phosphatase and tensin homolog (PTEN) hamartoma tumor syndromes, constitutional mismatch repair deficiency (CMMRD) syndromes, chromosomal abnormalities and multiple endocrine neoplasia (MEN) syndromes (50). Furthermore, genotypic overlap can also be seen between NF1-like syndrome and other disorders, including NS (50).

Besides our patient, there have been a few reports of neurofibromas/schwannomas in patients with a RASopathy phenotype. One patient presented with an overgrowth of peripheral nerve sheaths, suggestive of a schwannoma or neurofibroma (51). The final diagnosis was multiple diffuse schwannomas; although this is suggestive of NF2 or schwannomatosis, a germline KRAS variant (p.Lys5Glu) was identified (51). In one family with unaffected parents and four affected children with NS, a c.2220-17C>A (p.Tyr741Hisfs*89) maternally-inherited splice variant was found; several members of this family had suggestive signs of schwannomas on MRI analysis (37). Another individual with a c.740C>A (p.Ser247Asn) variant in LZTR1 developed multiple schwannomas in the right arm, however, no material from the schwannomas was available for molecular testing (6). This individual was the mother of a patient with NS (6).

Carriers of LZTR1 have phenotypic heterogeneity and management of LZTR1-NS patients has not been well described. Guidelines regarding the management of individuals with NS varies and is based on the clinical manifestations. Some common treatments include: treatment for cardiovascular anomalies, early intervention programs for developmental disabilities, treatment for serious bleeding conditions, GH treatment for short stature and further monitoring for abnormalities (2). In comparison, germline or mosaic mutations in the LZTR1 (7, 19, 20) and the SMARCB1 (52) genes have been associated with schwannomatosis, although the link between LZTR1 schwannomatosis and the development of other tumors has not been clearly defined. Current clinical management for schwannomatosis recommends that individuals have a baseline brain and spine MRI in late childhood/early adulthood to monitor the disease and management in adulthood should be performed by a neurologist or neurofibromatosis specialist to manage pain (53). Whole body MRI and increased surveillance can be considered if the patient is symptomatic (53). The guidelines on how to manage LZTR1-NS and LZTR1-schwannomatosis patients are not clear; therefore, a reasonable approach would be management of patients under both NS and schwannomatosis guidelines. Clarification of the genetic etiology of NS should be pursued early in the course of NS management as this may have implications on the use of GH therapy in a patient with LZTR1-NS. This includes consideration of tumor development and cardiac abnormalities, as individuals with NS are at increased risk, and there have been reports of tumors (54–57) and adverse cardiac reactions (58) following GH therapy.

Our proband’s likely PV in the LZTR1 gene was not detected on the original NF1, SPRED1 and multigene NS panel. Eventually, clinical exome sequencing analysis was able to identify the causative gene, which was later confirmed to be absent in her clinically unaffected parents. In 2018, the Clinical Genome Resource (ClinGen) RASopathy expert panel assessed 19 genes, including LZTR1, and found a strong association between LZTR1 and AD NS (59). As of 2020, the RASopathy expert panel definitively associates LZTR1 with AD NS and has stated there is strong evidence between LZTR1 and AR NS. Since then, LZTR1 has been a common new addition to many commercial and academic and laboratory NS panels. Based on our findings, inclusion of additional NS genes to schwannomatosis panels could also be considered. Due to the high de novo rate of variants causing NF1, NS and schwannomatosis, an alternative approach may be trio whole exome sequencing to aid in the interpretation of variants.

Based on previous reports and our findings, individuals with NS and a monoallelic or biallelic germline LZTR1 mutation may be at an increased risk of developing schwannomas and may meet the diagnostic criteria for schwannomatosis. Additional case reports of NS and variants in LZTR1, as well as functional studies showing the involvement of LZTR1 in the RAS/MAPK pathway would provide support for the creation of management guidelines for LZTR1-NS individuals. Due to the difficulties with overlapping phenotypes and genotypes, we believe that all NF1-like syndromes should be assessed in young individuals when identifying a causative gene and disorder. As clinical guidelines and gene panels change, clinicians should perform annual assessments of these patients to re-evaluate their original diagnosis and management. Due to the clinical implications for this patient presenting with schwannomas and NS, our patient will be followed as per NS and schwannomatosis surveillance guidelines to screen for nervous system tumors and monitor for tumor development.

**Abbreviations**

NS: Noonan syndrome; PV: Pathogenic variant; AD: Autosomal dominant; AR: Autosomal recessive; MRI: Magnetic resonance imaging; MRA: Magnetic resonance angiography; NF1: Neurofibromatosis type 1; NF2: Neurofibromatosis type 2; CALMs: Café-au-lait macules; SNP: Single nucleotide polymorphism; CNV: Copy number variant; NGS: Next generation sequencing.

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Author contributions
KMF was responsible for drafting the manuscript. ET was the genetic counselor. CBT and HS were the neurologists and RHK was the medical geneticist providing clinical care for the patient. Plexiform imaging was provided by CBT. ET, CBT, HS and RHK contributed to the interpretation of the findings and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study. The sequencing data that support the findings of this study will be made available on ClinVar under the following accession number: SCV002106410.

Declarations

Ethical approval and consent to participate
This study is in approval with the University Health Network Ethics Committee. Written informed consent was obtained from the patient.

Consent for publication
Written informed consent for publication of a case report was obtained from the patient.

Competing interests
CBT has been a consultant for Alexion, CSL, Takeda, Sanofi and has received research grants from Grifols and Octapharma, not related to this work. All other authors declare no competing interests.

Author details
1 Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada. 2 Bhalwani Familial Cancer Clinic, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. 3 Division of Neurology, Department of Medicine, University Health Network, University of Toronto, Toronto, ON, Canada. 4 Ellen and Martin Prosserman Centre for Neuromucous Diseases, Toronto General Hospital, University Health Network, Toronto, ON, Canada. 5 Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Sinai Health System, Toronto, ON, Canada. 6 Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Ontario Institute for Cancer Research, Department of Medicine, University of Toronto, Toronto, ON, Canada.

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