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Single Case – General Neurology

A Patient with Noonan Syndrome with a *KRAS* Mutation Who Presented Severe Nerve Root Hypertrophy

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Keywords
Noonan syndrome · Nerve root hypertrophy · *KRAS* gene mutation · Ras/MAPK pathway · RASopathy

Abstract
We report a 45-year-old female with clinical features resembling Noonan syndrome (NS) who presented with significant nerve root hypertrophy. She was initially diagnosed with Charcot-Marie-Tooth disease because her gait disturbance gradually deteriorated and nerve conduction velocity was reduced. However, she did not carry a *PMP22* gene mutation. RASopathies are a group of phenotypically overlapping developmental syndromes caused by germline mutations that encode components of the Ras/MAPK signaling pathway. These disorders include NS, cardiofaciocutaneous (CFC) syndrome, and Costello syndrome and are associated with molecular abnormalities in the Ras/MAPK pathway. The patient was suspected to have NS and related disorders because of pulmonary artery stenosis, lymphedema, distinctive facial

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appearance, and intellectual disability. Genetic analysis identified a heterozygous de novo mutation in *KRAS* (c.211T>G, p.Tyr71Asp), which is usually observed in patients with NS or CFC syndrome. Although our patient was diagnosed with NS, she revealed clinical manifestations that were typical to CFC syndrome, including intellectual disability. It has been reported that some patients diagnosed with RASopathies with mutations in *PTPN11*, *SOS1*, or *KRAS* developed nerve root hypertrophy. These results suggest that nerve root hypertrophy may be associated with RASopathy, although the onset mechanisms of nerve root hypertrophy are unknown.

Introduction

Noonan syndrome (NS) is a congenital malformation syndrome characterized by short stature, intellectual disability, distinctive facial appearance, congenital heart defects, hypertrophic cardiomyopathy, pectus deformity, and lymphatic malformation. In the majority of patients NS is a congenital malformation syndrome, characterized by short stature, clinically diagnosed, but molecular genetic testing is performed in 70% of cases. Nine gene mutations (*PTPN11*, 50%; *SO1S*, 10–13%; *RAF1*, 5%; *RIT1*, 5%; *KRAS*, <5%; *NRAS*, 8 individuals and 4 families; *BRAF*, <2%; *MAP2K1*, <2%; and *LZTR1*, unknown) related to this disease have been reported [1, 2].

The Ras/mitogen-activated protein kinase (Ras/MAPK) pathway is a signal transduction pathway that controls cellular proliferation, differentiation, and death. "Ras/MAPK syndrome" or "RASopathy" has been proposed to describe characteristic congenital disorders that have been associated with gene mutations encoding members of the Ras/MAPK pathway. The RASopathies include NS, Costello syndrome, cardiofaciocutaneous (CFC) syndrome, NS with multiple lentigines (formerly called LEOPARD [lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitals, retarded growth, deafness syndrome]), NS-like syndrome, and neurofibromatosis type 1 (NF1). These syndromes frequently overlap and coexist with malignant tumors [3].

We report the case of a 45-year-old female who was suspected to have NS or related disorders accompanied by severe peripheral nerve hypertrophy. We identified a *KRAS* mutation in this case.

Case Presentation

The patient was a 45-year-old female, with no similar cases or consanguineous marriages in her family line.

Past History

The patient underwent surgery for pulmonary artery stenosis at the age of 1 year and lymphatic duct bypass surgery for lymphedema of the left leg at the age of 15 years.

Illness

The patient could not walk until the age of 14 months and was slender since childhood. She could walk slowly, but not for long distances. Her lower limb strength, particularly in the distal part, gradually weakened, starting at the age of 34 years. She was unable to walk and maintain a standing position at the age of 37 years. She presented with intermittent severe pain in the left abdomen at the age of 44 years. A retroperitoneal tumor was revealed by abdominal computed tomography (CT). This tumor was believed to originate from the lumbar neural plexus, as indicated by abdominal magnetic resonance imaging (MRI). She could sit in a wheelchair for only a short time and was almost bedridden at admission.

Intelligence Examination

The patient's verbal, performance, and total intelligence quotient scores were 60, 53, and 59, respectively, as assessed by the Wechsler Adult Intelligence Scale – revised, which was equivalent to a mental age of 9 years 8 months according to the Tanaka-Binet Intelligence Scale.

Physical Findings

The patient had short stature, emaciation (body height 145 cm (1st centile), body weight 31 kg (1st centile), body mass index 14.7 kg/m^2), and a characteristic facial appearance (low-set hairline, hypertelorism, exophthalmos, flat root of the nose, wide wings of the nose, thick lower lips, high palate, wide interdentium, malocclusion, and macroglossia) (Fig. 1). The left eye showed exotropia, but she had no complaints of diplopia. Similarly, she presented with no hearing difficulties or face and neck muscle weakness. Slight anemia was observed in the palpebral conjunctiva, with no abnormality in the iris, including Lisch nodule. Tumor and swelling of the thyroid gland were not observed. A cardiac systolic murmur, Levine IV/VI grade, could be heard in the right sternum margin area. The abdominal wall was soft and flat, bowel sounds were normal, and no tumors were detected. The vulva showed red-brown pigmentation, eczema, and marginal swelling. Flexion contractures were observed in the metacarpophalangeal and interphalangeal joints of both hands. Significant bilateral leg swelling, talipes equinus contracture, and hallux valgus were observed. Hypertrophic peripheral nerve bundles were detected in the supraclavicular and popliteal fossa.

Neurological Findings

There was muscular weakness, with severer amyotrophy and hypotonicity in the distal limbs than in the proximal regions. The results of manual muscle testing were as follows: upper limb, good; hand, poor; proximal lower limb, trace; and distal lower limb, zero. Deep tendon reflexes were not evident, and pathological reflexes were not observed. Vibration sense was deteriorated in the distal lower limbs, and the perception of temperature, touch, and position had disappeared in the distal lower limb, starting at the knee joint.

Blood and Cerebrospinal Fluid Test Findings

There were no abnormalities in major biochemical measures, thyroid hormone, or immunoglobulins, except for iron deficiency (red blood cells, 592 × 10^4/μL; hemoglobin, 9.6 g/dL; hematocrit, 31.8%; mean corpuscular volume, 53 fL; Fe, 9 μg/dL; unsaturated iron-binding capacity, 375 μg/dL; and ferritin, <1.0 ng/mL). A fecal occult blood test was negative. Proteinuria and urinary occult blood were observed. The cerebrospinal fluid test findings were as follows: cell count, 12/μL (only mononuclear cells); protein, 790 mg/dL; glucose, 60 mg/dL; Cl, 121 mEq/L; myelin basic protein, 504 pg/mL (<102); and no oligoclonal band.

Imaging Examinations

Brain MRI showed slight brain atrophy and several high-intensity lesions in deep white matter on T2-weighted images. Vertebral MRI showed hypertrophy of the brachial plexus (Fig. 2a), intercostal nerve, and lumbar plexus (Fig. 2b). Abdominal MRI showed a poorly enhanced tumor lesion (14 × 48 mm) around the abdominal aorta, celiac artery, superior mesenteric artery, and inferior vena cava (Fig. 2c). Lower limb, pelvis, and thigh MRI (Fig. 2d–f) showed severe thickening of the sciatic (diameter 25 mm) and tibial nerves. However, clear thickening of the sural nerve was not confirmed on MRI image. Echocardiography showed bilateral ventricular outlet stenosis, with normal left ventricle function.

Electrophysiological Examinations

Electrocardiography showed sinus rhythm, incomplete right bundle branch block, and pulmonary artery hypertension pattern. Nerve conduction studies showed deteriorated compound muscle action potentials in both median nerves, and conduction velocities were 18.8 m/s on the left side and 18 m/s on the right side. Compound muscle action potentials of both ulnar nerves, common peroneal nerves, and posterior tibial nerves were absent. The sensory nerve action potential was deteriorated in the right median nerve, and conduction velocity was decreased by 26 m/s. Sensory nerve action potentials of both ulnar nerves, sural nerves, and left median nerve were absent. Conduction blocking was not clear, but temporal dispersion was observed in the right common peroneal nerve.

Pathological Findings

A sural nerve biopsy found very few large, myelinated fibers, some onion bulb lesions, and no inflammatory cells (Fig. 3).

Genetic Analysis

G-band karyotyping showed a normal female karyotype, 46 XX. No *PMP22* gene domain duplication or deletion was identified by fluorescence in situ hybridization. Genomic DNA was isolated from the patient's leukocytes after receiving informed consent. All coding exons and flanking introns in *PTPN11*, exons 1, 2, and 5 in *KRAS*, exon 1 in *HRAS*, exons 6 and 11–16 in *BRAF*, exon 7 in *RAF1*, and exons 2 and 3 in *MAP2K1/2* were amplified by polymerase chain reaction. After amplification, the polymerase chain reaction products were gel-purified and sequenced on the ABI 3130 automated DNA sequencer (Applied Biosystems, Carlsbad, CA,

USA). A heterozygous missense variant (c.211T>G, p.Tyr71Asp) was identified in exon 2 of *KRAS* in the patient's DNA. The variant was not detected in the parental samples.

Discussion and Conclusion

The most particular points of this case were severe nerve root hypertrophy, from the cervical spinal nerves to the sacral plexus, and retroperitoneal plexus swelling, which caused intense pain. Since our case did not have café-au-lait spot, Lisch nodule, or neurofibroma, we determined that peripheral nerve hypertrophy was not caused by NF1 and did not perform gene analysis of NF1. However, a subtype of NF1 called spinal NF1 that lacks skin symptoms, which are the core of diagnostic criteria, has been reported [4]. The spinal magnetic resonance image and progressive symptoms of peripheral neuropathy such as walking disorders are very similar to the findings of our patients. Our patient has NS based on physical examination and genetic analysis. Judging by its clinical course, we considered the possibility of Charcot-Marie-Tooth disease type 1A, but we could not detect *PMP22* (17p11.2) duplication or mutation. Our patient has distinctive facial appearance, pulmonic stenosis, lymphedema, and intellectual disability, suggesting NS and related disorders. We examined hot spot mutations in *PTPN11*, *RAF1*, *HRAS*, *KRAS*, *BRAF*, and *MAP2K1/2*, the causative genes for Ras/MAPK syndrome. A heterozygous *KRAS* gene mutation (c.211T>G, p.Tyr71Asp) has been identified in patients. KRAS mutations have been identified in patients with NS or CFC syndrome. Our patient was diagnosed with NS based on the physical findings and the presence of *KRAS* gene mutation (c.211T>G, p.Tyr71Asp). Alternatively, the patient may be diagnosed with CFC syndrome because of intellectual disability.

Silburn et al. [5] reported 5 patients with NS, with nerve root hypertrophy, in one family. On the basis of our literature search, this report represents the earliest report of NS with nerve root hypertrophy. The diagnosis of NS was based on clinical features, and 4 of the 5 patients had *PMP22* duplication based on a DNA dosage test, and nerve conduction studies revealed abnormalities. The authors described a proband in detail. The 37-year-old female patient with NS, with *PMP22* duplication, presented progressive muscle weakness and sensory disturbance of the extremities. MRI showed thickening of cervical and lumbar nerve roots and revealed an 8- to 10-cm tumor in the pelvic cavity. Biopsies of the sural nerve and the intrapelvic tumor showed myelinated fiber loss, demyelination, and onion bulb formation in both. The clinical course, the image views, and the pathological findings of this described patient greatly resemble those of our patient. Moreover, the proband's daughter was diagnosed with NS, without *PMP22* duplication. She presented significant thickening of the lumbosacral nerve roots on MRI. Although she presented a café-au-lait spot, she did not fulfill the other criteria for NF1. Therefore, the authors concluded that the nerve root hypertrophy observed in this family was not caused by *PMP22* but may, instead, represent a rare phenotype of NS [5]. We believe that our patient has a similar disease to that described for their patients, supporting their conclusion that peripheral nerve hypertrophy may be a phenotype of NS.

After the report by Silburn et al. [5], additional RASopathy cases associated with peripheral nerve hypertrophy were reported (Table 1). Some patients with CFC syndrome with

peripheral nerve disorders have been reported. Manci et al. [6] reported an autopsy case of a 7-year-old boy with peripheral nerve hypertrophy and onion bulb formation. DeRoos et al. [7] reported the case of a 27-year-old man with marginal demyelination and axonopathy, diagnosed by nerve conduction studies. In these two reports, gene analysis was not performed. Stark et al. [8] reported 3 patients with CFC syndrome in two families. The child showed gait developmental abnormalities. He did not carry any *PMP22* mutations but was found to carry the same *KRAS* point mutation (c.211T>C, p.Tyr71His) observed in our patient. Unfortunately, as the MRI images were not shown, whether nerve root hypertrophy existed is not clear. A sporadic patient in another family presented with a different *KRAS* gene mutation (c.439A>G, p.Lys147Glu). Stark et al. [8] concluded that peripheral nerve disorder is not an accidental complication but is, instead, a phenotype of CFC syndrome.

The p.Tyr71Asp, p.Tyr71His mutation in *KRAS* may be closely related to the peripheral nerve disorders observed in RASopathy, including NS and CFC syndrome. However, patients with LEOPARD syndrome [9], NS with multiple lentigines [10, 11], and nerve root hypertrophy, associated with *PTPN11* mutations, have also been reported. Bertola et al. [12] found a *KRAS* mutation in a patient who also presented with nerve root hypertrophy. Santoro et al. [13] reported an *SOS1* gene mutation in a case that was clinically diagnosed with NF1 and exhibited an intermediate NS phenotype. The MRI images of this case resemble those of our case, and the authors summarized comparisons between previous detailed reports of RASopathies with nerve root hypertrophy. The following mutations have been reported: *SOS1* (p.Ser548Arg), *KRAS* (p.Lys147Glu, p.Lys5Glu), and *PTPN11* (p.Thr468Met, p.Thr279Cys) [13].

Vizcaino et al. [14] reported an 11-year-old boy with thickening from the nerve root to the peripheral nerve. The patient did not present any specific RASopathy features other than the café-au-lait spot. The patient had a *KRAS* alteration in the peripheral nerve and cutaneous melanocyte specimens, although the mutation was not observed in the blood sample, supporting a mosaic presentation of RASopathy. Furthermore, the authors confirmed the accumulation of phospho-extracellular signal-regulated kinase in peripheral nerve specimens and concluded that the activation of the local Ras/MAPK system may cause Schwann cells to grow, resulting in neurothickening [14]. There are many overlapping phenotypes among the various RASopathies. Moreover, the phenotypes among individual cases with the same gene mutation can vary widely. The diagnosis of RASopathy by phenotype may be meaningless through the development of genetic analyses.

In recent reviews of NS, neurological problems included delayed mental development and co-occurrence of tumors; however, no description of a neurological form was included [1, 2]. Since MRI and CT scans are regularly performed in patients with RASopathies, the occult phenotype of a neurological form, such as nerve root hypertrophy, will likely become more obvious.

At present, mutations associated with nerve root hypertrophy have been reported in three genes – *PTPN11*, *SOS1*, and *KRAS* – which are relatively frequent genes identified in NS and constitute a series of cascades in the Ras/MAPK pathway [3]. The reason why mutations in these different genes result in similar abnormalities is not currently understood. Moreover, why cases with point mutations in the same gene can differ between the presentations of

nerve root hypertrophy is also not clear. There may be a common mechanism underlying nerve root thickening because spinal NF1 is a type of RASopathy. Further investigation and case report data remain necessary to determine which point mutations are specifically associated with the underlying mechanisms that result in nerve root hypertrophy.

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Statement of Ethics

The patient died at the age of 47 years, and we received written informed consent for the publication of the case including the use of facial images from the patient's father and sister.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Inpatient medical examination: Y. Ando, M. Sawada, M. Morita. Outpatient medical examination: T. Kawakami. Manuscript – writing of the first draft: Y. Ando. Manuscript – review and critique: M. Sawada, T. Kawakami, M. Morita, Y. Aoki. Gene analysis (RASopathy): Y. Aoki.

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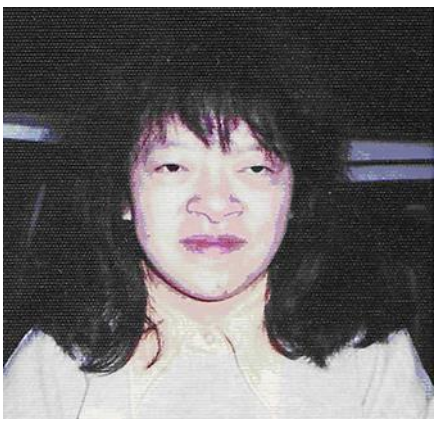

Fig. 1. Characteristic facial appearance. The patient showed a low-set hairline, hypertelorism, exophthalmos, flat root of the nose, wide wings of the nose, and thick lower lips.

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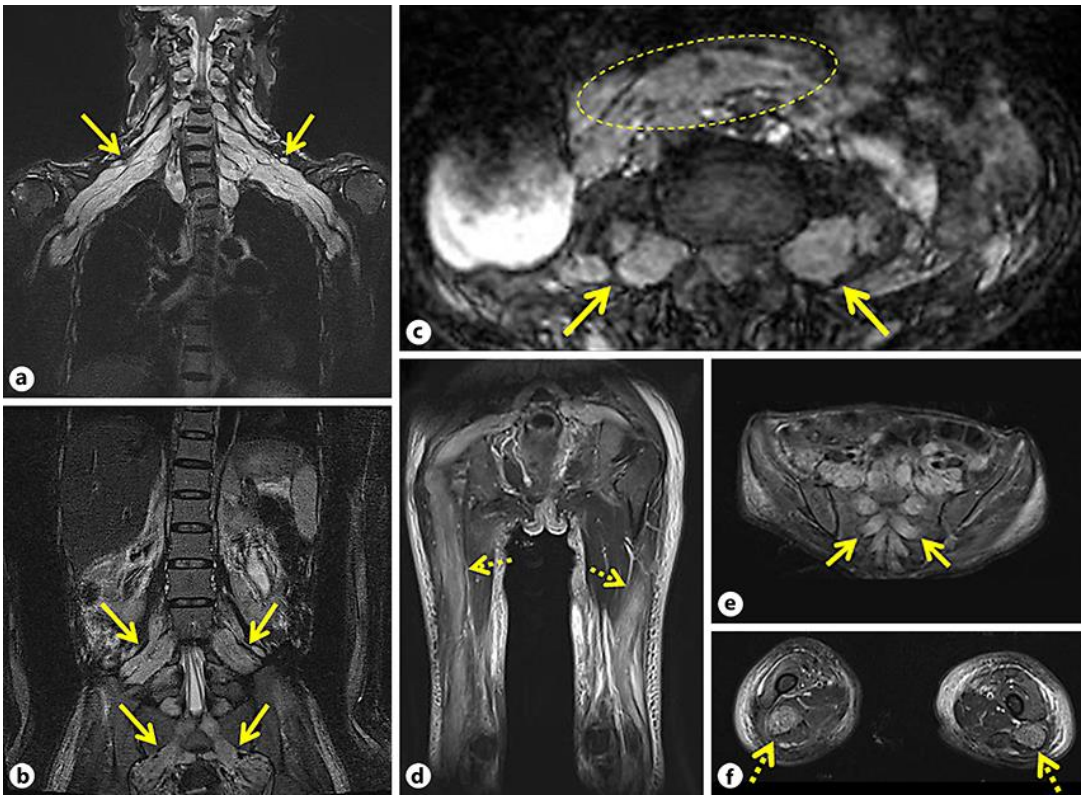

Fig. 2. Magnetic resonance images. Cervical plexus (**a**), lumbar plexus (STIR TR 2850 TE 89) (**b**), abdomen (Tfisp MPR TR 272.89 TE 2.15) (**c**), lower limbs (**d**), pelvis (**e**), and thighs (STIR TR 4200 TE 68) (**f**). These images show hypertrophy of the cervical, lumbar, and sacral plexus (solid arrows), a retroperitoneal tumor around the abdominal aorta and celiac artery (dashed circle), and hypertrophy of the sciatic nerve (dashed arrows).

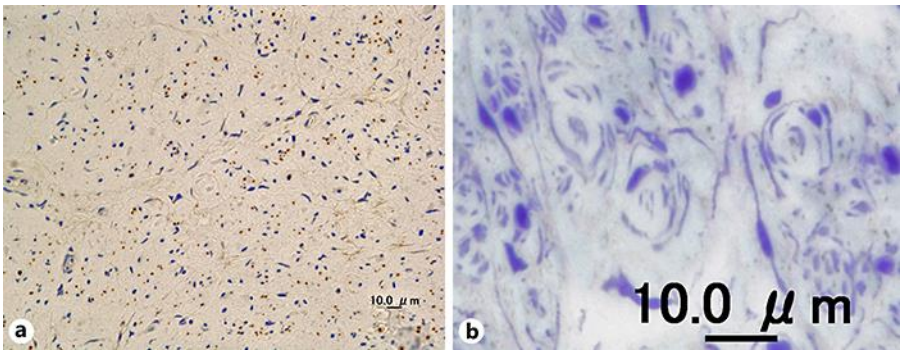

Fig. 3. Pathological findings of a sural nerve biopsy. Neurofilament antibody staining (**a**) and toluidine blue staining (**b**). We observed very few large, myelinated fibers, some onion bulb lesions, and no inflammatory cells.

Table 1. Reported RASopathies with nerve root hypertrophy

Reference (first author)	Relationship of cases	Patient age/sex	Clinical diagnosis	Gene	Mutation	Psychological/neurological features	Imaging findings	Pathology
Silburn [5]	case 1	37/F	NS	*PMP22* duplication +		progressive gait disturbance, NCV reduction	SR hypertrophy, intrapelvic tumor	PN and tumor biopsy: onion bulb formation, demyelination
	daughter of case 1	16/F	NS	*PMP22* duplication –		NCV normal	SR hypertrophy	NA
Manci [6]		7/M	CFC syndrome	NA		intellectual disability	skin PN hypertrophy	skin biopsy: onion bulb formation, axonal atrophy
DeRoos [7]		27/M	CFC syndrome	NA		progressive gait disturbance, NCV reduction	chronic hydrocephalus	NA
Bertola [12]		23/F	Costello syndrome	*KRAS*	p.Lys5Glu	difficulty in relaxation of hand muscle, abdominal pain, nausea	SR hypertrophy	PN biopsy: schwannoma
Stark [8]	case 1	4/M	CFC syndrome	*KRAS*	p.Tyr71His	intellectual disability, gait development disability	NA	NA
	case 2	3/F	CFC syndrome	*KRAS*	p.Lys147Glu	sensorimotor disorder of extremities	SR hypertrophy	NA
Spatola [9]		41/F	NSML	*PTPN11*	p.Thr468Met	patchy sensorimotor disorder of extremities	SR hypertrophy	NA
Maridet [10]		43/F	NSML	*PTPN11*	p.Thr468Met	skin tumor	SR hypertrophy	NA
Conboy [11]	case 1	28/M	NSML	*PTPN11*	p.Thr468Met	skin tumor, NCV reduction	SR hypertrophy	NA
	case 2	50/M	NSML	*PTPN11*	p.Thr468Met	autism spectrum disorder, back pain, skin tumor, NCV reduction	SR hypertrophy	PN and intrapelvic nerve biopsy: onion bulb formation
	case 3	16/F	NSML	*PTPN11*	p.Thr279Cys	chest pain, hearing loss, pain and weakness of lower limb (operation)	paraspinal tumor, lumbar root hypertrophy	radial nerve operation (past history): schwannoma
	mother of case 3	60/F	NSML	*PTPN11*	p.Thr279Cys	intellectual disability, convulsion, hearing loss, abdominal pain, pain and weakness of lower limb	paraspinal tumor, cerebellar tumor, brain stem tumor, lumbar root hypertrophy	NA
Santoro [13]	case 1	15/M	NSML	*SOS1*	p.Ser548Arg	intellectual disability	no SR hypertrophy	NA
	mother of case 1	40/F	NSML	*SOS1*	p.Ser548Arg	epilepsy, depression, insomnia, behavior and attention disorder, sensorimotor disorder of extremities	SR hypertrophy	NA
Vizcaino [14]		11/M	*KRAS*-mediated RASopathy	*KRAS*	C38_40dupGCG	no detailed mention	SR hypertrophy, PN hypertrophy	PN biopsy: onion bulb formation, Schwann cell processes, axonal loss
Our report		45/F	NS	*KRAS*	p.Tyr71Asp	intellectual disability, progressive gait disturbance, NCV reduction	SR hypertrophy, retroperitoneal tumor, PN hypertrophy	PN biopsy: onion bulb formation

CFC, cardiofaciocutaneous; F, female; M, male; NA, not available; NCV, nerve conduction velocity; NS, Noonan syndrome; NSML, Noonan syndrome with multiple lentigines; PN, peripheral nerve; SR, spinal root.