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Mastocytosis in a Case of Noonan Syndrome Caused by a De Novo Pathogenic *CBL* Variant

Tatsuya Kawaguchi,* Tohru Okanishi,* Tetsuya Okazaki,† Chisako Aoki,† Noriko Kasagi,†‡ Kaori Adachi,†§ Yuichi Yoshida,‖ Noriko Miyake,¶ Naomichi Matsumoto** and Yoshihiro Maegaki*†**

**Division of Child Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago 683-8504, Japan, †Division of Clinical Genetics, Tottori University Hospital, Yonago 683-8504, Japan, ‡Department of Fundamental Nursing, School of Health Science, Faculty of Medicine Tottori University, Yonago 683-8504, Japan, §Research Initiative Center, Organization for Research Initiative and Promotion, Tottori University, Yonago 683-8503, Japan, ‖Division of Dermatology, Department of Sensory and Motor Organs, Faculty of Medicine, Tottori University, Yonago 683-8503, Japan, ¶Department of Human Genetics, Research Institute, National Center for Global Health and Medicine, Tokyo 162-8655, Japan, and **Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan*

ABSTRACT

Noonan syndrome is an autosomal dominant disease characterized by multi-organ disorders caused by variants of genes involved in the RAS/MAPK signaling pathway. The nine causative genes including *PTPN11* and *CBL* have been identified. Mastocytosis is a disease characterized by mast cell proliferation in skin, bone marrow, and other organs. To date, no previous cases of Noonan syndrome with mastocytosis caused by a pathogenic *CBL* variant have been reported. A boy was diagnosed with Noonan syndrome at 8 months of age with facial features and minor anomaly of his body. He presented with brown nodules of 5–10 mm on his body since the age of 2 months. The patient was diagnosed with mastocytosis by a biopsy specimen from brown nodules, which showed infiltration of mast cells. Whole-exome sequencing of the parent–patient trio revealed a de novo pathogenic *CBL* variant. The occurrence of mastocytosis may be a cue for the analysis of the *CBL* gene in Noonan syndrome. The *CBL* gene is involved in mastocytosis and various cancers. In the case of the pathogenic variant, long-term follow-up for the risk of cancers related to the *CBL* variant is necessary.

Key words *CBL* gene; mastocytosis; Noonan syndrome; RAS/MAPK signaling pathway

Noonan syndrome is an autosomal dominant disease characterized by postnatal growth retardation, distinctive facial features, developmental delay, and congenital heart disease.[1] The causative genes *BRAF*, *KRAS*, *LZTR1*, *MAP2K1*, *MEK1*, *MRAS*, *NRAS*, *PTPN11*, *RAF1*, *RASA2*, *RRAS2*, *RIT1*, *SHOC2*, *SOS1*, *SOS2*, and *CBL* have been identified, and they commonly encode the components or regulators of the RAS/MAPK signal transduction pathway. Variants in these genes cause hyperactivity or dysregulation of the RAS/MAPK signaling pathway.[1]

Mastocytosis is a disease characterized by mast cell proliferation in skin, bone marrow, and other organs.[2] Isolated skin involvement is termed cutaneous mastocytosis, whereas systemic mastocytosis is characterized by multi-organ mast cell proliferation, including bone marrow, skin, liver, and spleen.[3] Although pediatric mastocytosis is mainly cutaneous mastocytosis, systematic mastocytosis can also develop. While a variant of the *C-KIT* gene, an oncogene, is most commonly found in mastocytosis, the *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, *RAS, and CBL* genes have also been identified as pathogenic genes.[3]

In this report, we describe a patient with Noonan syndrome caused by a pathogenic *CBL* variant, who presented with mastocytosis.

PATIENT REPORT

Clinical course

A boy with a fetal history of hydramnios, pleural/ascitic effusion, and enlarged lateral ventricles from 27 weeks of gestation was born at 39 weeks of gestation with a weight of 3,043 g (34 percentile) and head circumference of 34.3 cm (77 percentile). He was diagnosed with Noonan syndrome at 8 months of age with facial features of hypertelorism, blepharoptosis, down-slanted palpebral fissures, divergent strabismus, low-set/cupped ears, high palate, pectus carinatum/excavatum, multiple black nevi, brown nodules on his body, webbed neck, hypotonia, and right cryptorchidism.

He started speaking at 4 years of age and walked at 5 years of age. He was admitted to Tottori University Hospital at 8 years of age. Routine blood tests, head MRI, electroencephalography, auditory brainstem response, short-latency somatosensory-evoked potentials, and flash visual-evoked potentials showed no

Corresponding author: Tatsuya Kawaguchi
t_kawaguchi@tottori-u.ac.jp
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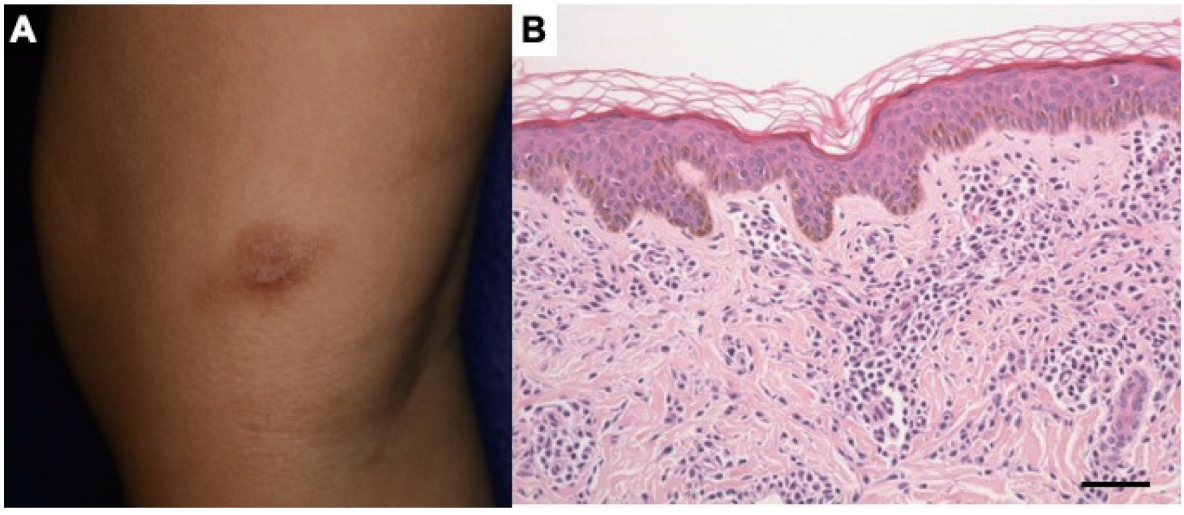

Fig. 1. (**A**) Brown nodule of 10 mm in diameter on the right leg. (**B**) Hematoxylin-eosin stain of the brown nodule. Deposition of melanin at stratum basal and infiltration of numerous mast cells at dermis are observed. Bar = 100 μm.

remarkable changes. His Intelligence Quotient was 33 on the Tanaka-Binet IQ scale V at 13 years of age.

History of mastocytosis

He presented with brown nodules of 5–10 mm on the abdomen, right upper leg, and left lower leg since the age of 2 months. Darier's sign was observed in the same lesions. A biopsy specimen from the macule on his right thigh (Fig. 1A) showed melanin deposition in the basal layer and infiltration of numerous mast cells in the dermis (Fig. 1B).

During the clinical course, no symptoms related to mastocytosis, other than repetitive urticaria, were observed, and the patient was diagnosed with cutaneous mastocytosis. No exacerbation of mastocytosis or malignant transformations were observed.

Genetic tests

G-band karyotyping revealed a normal male karyotype (46,XY). Array comparative genomic hybridization showed no deletions or duplications. Whole-exome sequencing of the parent–patient trio revealed a de novo pathogenic *CBL* variant (NM_005188.4: c.1100A>C:p.(Gln367Pro)), respectively.

Ethics

Written informed consent for publication and genetic analysis using whole-exome sequencing was obtained from the parents of the patient.

DISCUSSION

In the present case, Noonan syndrome with a *CBL* pathogenic variant presented with mastocytosis. Mastocytosis is a rare complication of Noonan syndrome and may be cause by the *CBL* variant.

The risk of childhood cancer increases 8.1-fold in patients with Noonan syndrome.[4] It has been reported that five (0.79%) of 632 patients with Noonan syndrome had blood tumors, including three patients with juvenile myelomonocytic leukemia and two patients with acute lymphoblastic leukemia.[5] Mastocytosis is a rare complication of Noonan syndrome and only two cases have been reported.[6, 7] One of which was caused by a variant in the *PTPN11* gene and causes systemic mastocytosis in adulthood.[6] There have been no reports of mastocytosis in Noonan syndrome caused by *CBL* variants.

The *CBL* gene encodes an E3 ubiquitin ligase involved in intercellular transport and protein ubiquitination and negatively regulates the RAS/MAPK signaling pathway,[8] which is involved in cell proliferation and contributes to oncogenesis (Fig. 2).[9, 10] The variant in this report is located within the adjacent linker connecting the RING finger domain to the N-terminal TKB domain. This variant was shown to cause impaired CBL-mediated degradation of cell-surface receptors in a dominant-negative fashion by *in vitro* functional expression studies.[9] While somatic *CBL* gene variants have been observed in lung cancer, teratoma, embryonal rhabdomyosarcoma, and myeloid malignancies, germline *CBL* gene variants have been demonstrated to induce a cancer-predisposing condition.[11] Although previous reports have indicated that 3.8–20.5% of patients have *CBL* variant-associated mastocytosis, no cases of Noonan syndrome have been reported.[12] The occurrence of mastocytosis may be a cue for the analysis of the *CBL* gene in Noonan syndrome. In the case of the

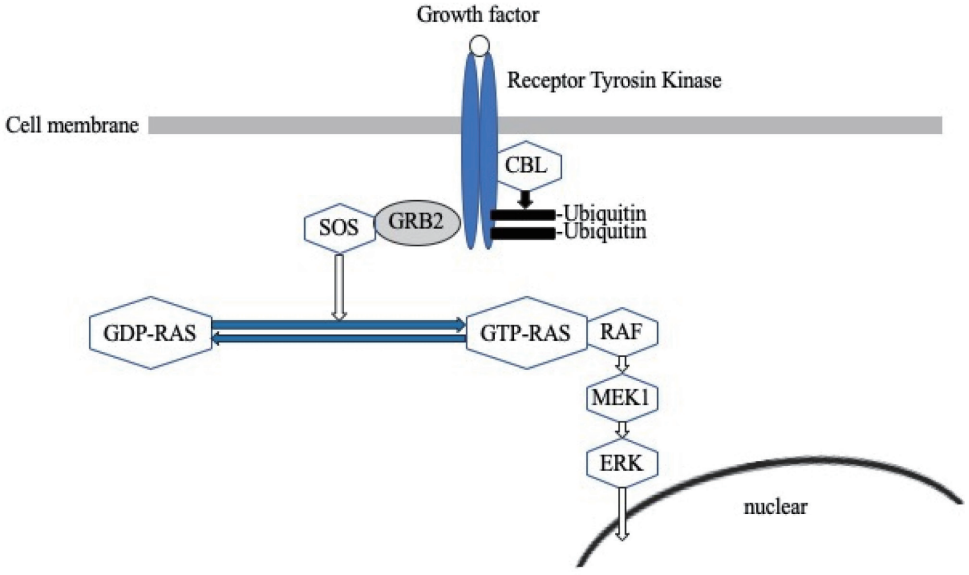

Fig. 2. RAS/MAPK signaling pathway and CBL correlation. Tyrosines are phosphorylated after growth factors bind to receptor tyrosine kinase. Phosphorylated tyrosines are bounded by adapter proteins, such as GRB2, and form constitutive complex with SOS. This reaction induces the dissociation of GDP-RAS and binding of GTP-RAS, activating the RAF–MEK–ERK cascade. Activated ERK enters the nucleus to alter gene transcription and modulate the activity of cytoplasmic targets. CBL acts as an E3 ubiquitin-protein ligase; it negatively regulates the RAS/MAPK pathway by transferring ubiquitin to substrates, thus promoting their degradation by the proteasome. *CBL* gene variants cause upregulation of the RAS/MAPK signaling pathway.

pathogenic variant, long-term follow-up for the risk of cancers related to the *CBL* variant is necessary. In this case, although the patient has no apparent tumors and takes no medication, we will perform blood tests and abdominal ultrasounds every 6-12 months as regular cancer screening.

Although pediatric cutaneous mastocytosis is considered to regress spontaneously during puberty in more than 80% of cases, 1% of patients can develop systemic mastocytosis.[13] Systemic mastocytosis infiltrates various organs, such as the bone marrow, spleen, liver, and gastrointestinal tract, and causes critical symptoms,[2, 3] Stem cell transplantation is necessary in cases of severe systemic mastocytosis.[3] Therefore, cutaneous mastocytosis should be carefully monitored for the systemic progression of Noonan syndrome caused by pathogenic *CBL* variants.

In conclusion, we have reported a case of Noonan syndrome complicated with mastocytosis. The *CBL* gene variant might be associated with both conditions. Regular cancer screening should be performed given the potential cancer risk.

The authors declare no conflict of interest.

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