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BRIEF COMMUNICATION

A postzygotic *KRAS* mutation in a patient with Schimmelpenning syndrome presenting with lipomatosis, renovascular hypertension, and diabetes mellitus

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Abstract

Schimmelpenning syndrome is a rare neurocutaneous disorder categorized as a mosaic RASopathy due to postzygotic *HRAS* or *KRAS* mutations. We report a 6-year-old girl diagnosed with Schimmelpenning syndrome due to a postzygotic *KRAS* G12D mutation. The patient had three atypical symptoms of Schimmelpenning syndrome: renovascular hypertension, congenital lipomatosis, and diabetes mellitus. The first two symptoms may overlap with phenotypes of other neurocutaneous syndromes or congenital lipomatous overgrowth syndrome due to mosaic RASopathies or other somatic mosaic mutations. We propose that impaired glucose tolerance was caused by *KRAS* mutation and a novel clinical phenotype of Schimmelpenning syndrome. Our study indicated that clinical diagnosis of Schimmelpenning syndrome or related conditions should be reorganized with genetic diagnosis of postzygotic mutation. Moreover, further accumulation of genetically proven cases with mosaic RASopathies should be used to more accurately characterize phenotypic presentations of this syndrome and develop a future therapeutic strategy, such as molecular-targeted therapy.

Introduction

Schimmelpenning syndrome (MIM 163200) is a rare neurocutaneous disorder characterized by a classical triad of symptoms, including craniofacial nevus sebaceous (NS), seizures, and intellectual disability [1]. In addition, a broad spectrum of ipsilateral neurological, ophthalmological, and skeletal symptoms are frequently encountered [2]. Schimmelpenning syndrome was recently categorized as a mosaic RASopathy due to postzygotic *HRAS* or *KRAS* mutations [3]. Because HRAS and KRAS are associated with cellular proliferation and ubiquitously expressed, in Schimmelpenning syndrome, somatic *HRAS*- and *KRAS*-activating mutations might be associated with various manifestations involving multiple organs [4]. Here, we report a patient with rare manifestations of Schimmelpenning syndrome, including lipomatosis, renovascular hypertension, and impaired glucose tolerance.

Case report

A 6-year-old Japanese girl clinically diagnosed with Schimmelpenning syndrome in infancy was referred to our hospital because of a positive urine glucose test. A casual plasma glucose level was elevated (11.2 mmol/L). An HbA1c level of 5.8% [40 mmol/mol] was within normal ranges. Her father developed diabetes mellitus (DM) treated with exercise and dietary therapy in young adulthood. Hypertension (systolic blood pressure 130–150 mmHg) was coincidentally discovered. Thus, she was admitted to our hospital for further examination.

At birth, she had multiple craniofacial NS that were predominantly on the right side of her head. Brain magnetic

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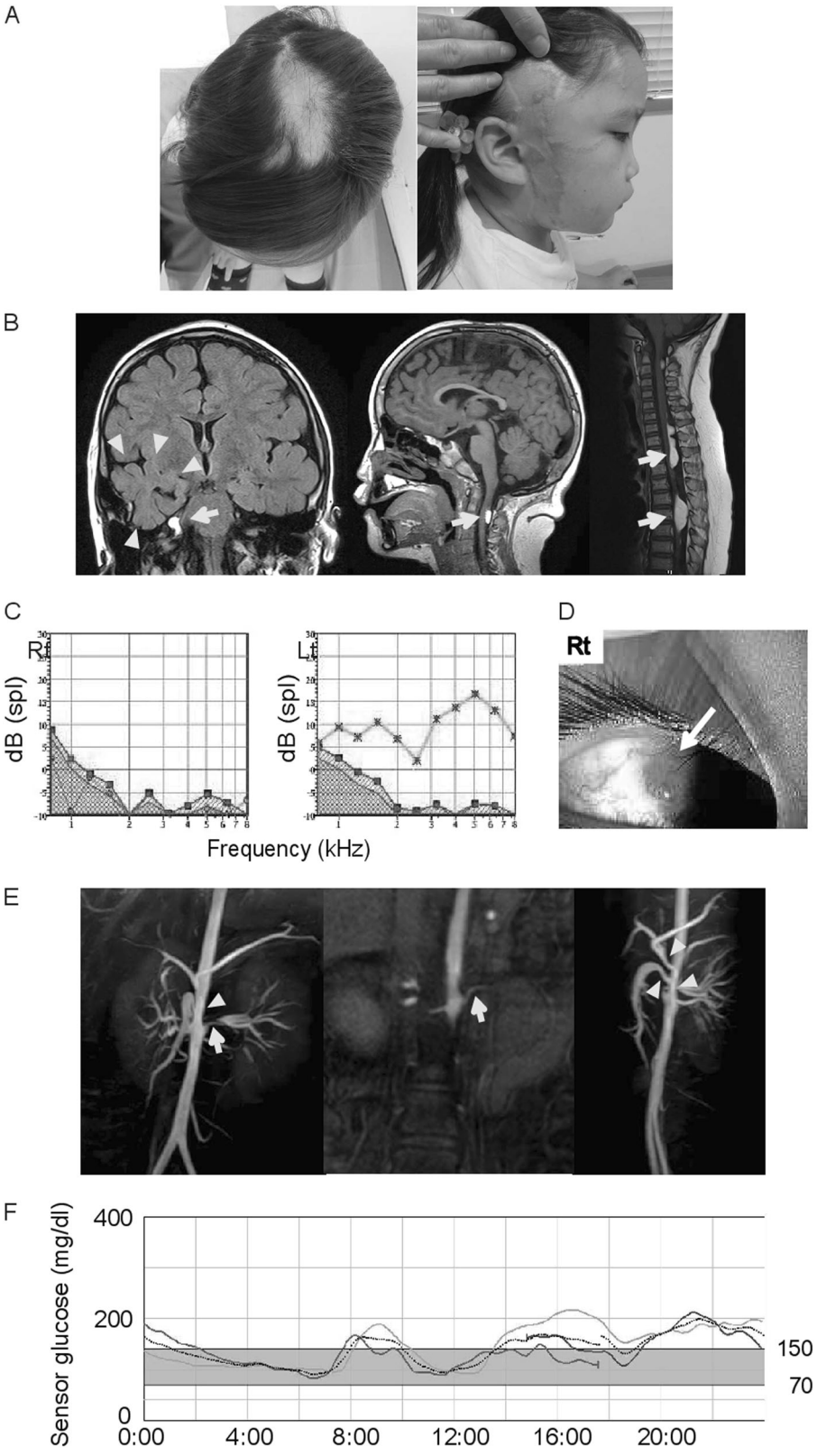

Fig. 1 Patient symptoms and test results upon admission. **a** Photograph of the patient at 5 years of age. Linear nevus sebaceous of the skin on the right side of the face and scalp with surgical scars. **b** Brain and spinal magnetic resonance imaging revealed cortical dysplasia in the right temporal lobe (yellow arrowheads) and hyperostosis in the right temporal bone with multiple intradural lipoma in the right cerebellopontine angle cistern and dorsal spinal cord (yellow arrows). **c** Distortion-product otoacoustic emission test revealed deafness in the right ear in all range of frequencies. **d** Ocular examination showed limbal dermoid in the right eye conjunctiva. **e** Magnetic resonance angiography of the celiac, superior, and inferior mesenteric arteries showed left renal artery stenosis (yellow arrows) and multiple mild stenoses in the abdominal aorta upstream of the renal arterial branch, celiac artery, and superior mesenteric artery (yellow arrowheads). **f** Glucose profile produced using a continuous glucose monitoring system showed postprandial hyperglycemia. Lines in colors including, blue, orange, red, and black (dashed) indicated day 1, 2, 3 and the average of monitoring, respectively

resonance imaging (MRI) showed dysplasia of the right temporal lobe and multiple lipomatosis in the intracerebral space. Punched-out lesions in the right temporal and parietal bones were revealed and turned into hyperostosis with age. She developed epilepsia nutans at eight months of age and thus received chronic anticonvulsant therapy. She had a

Table 1 Glycometabolism profile

OGTT[†]		0 min	30 min	60 min	90 min	120 min
BG	mmol/L	4.6	12.2	12.3	NA	15.1
IRI	μU/mL	3.9	15.1	15.5	NA	19.5
UG	nmol/L	1.3	NA	5.9	NA	246
		Insulinogenic index	: 0.08			
		HOMA-IR	: 0.79		HOMA-β	: 73.9 %
Glucagon stimulation test[‡]		0 min	3 min	6 min	19 min	15 min
BG	mmol/L	4.1	4.7	5.6	5.9	7.1
IRI	μU/mL	4.2	21.7	17.6	12.0	7.7
CPR	ng/mL	0.8	2.1	2.2	1.8	1.7
		Urine-CPR	: 27.7 μg/day		ΔCPR (6 min)	: 1.4 ng/mL

BG blood glucose, *IRI* immunoreactive insulin, *UG* urinary glucose, *CPR* C-peptide immunoreactivity, *NA* not assessed

HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β cell function

ΔCPR, change in C-peptide immunoreactivity (ΔCPR) by subtracting fasting CPR from CPR 6 min after glucagon injection

[†]1.75 g/kg oral glucose tolerance test

[‡]0.03 mg/kg intravenous injection

mild intellectual disability (a developmental quotient score of 60 at 3 years of age).

On admission, her weight was 26.6 kg (+ 1.26 SD), height was 113.6 cm (−0.76 SD). There were NS on the right side of her face and neck (Fig. 1a). Brain and spinal MRI revealed dysplasia of the right temporal lobe and multiple lipomas (Fig. 1b). Otolaryngological and ophthalmological examination revealed right-sided unilateral hearing loss (Fig. 1c), amblyopia, and limbal dermoid (Fig. 1d). Abdominal magnetic resonance angiography revealed multiple artery stenoses (Fig. 1e), which could cause renovascular hypertension.

Continuous glucose monitoring showed postprandial hyperglycemia (Fig. 1f). HOMA-R score of 0.79, and HOMA-β score of 73.9% were within normal ranges. A low insulinogenic index of 0.08 (> 0.4) indicated impaired early insulin secretion. A glucagon stimulation test revealed a relatively low level of change in C-peptide immunoreactivity, 1.4 ng/mL (> 2.0 ng/mL), and a low C-peptide immunoreactivity index, 1.08 (> 1.2), which indicated impaired β-cell function (Table 1). Islet-associated autoantibodies were negative. Abdominal ultrasound and MRI revealed no abnormal findings in the pancreas and the feeding arteries.

Excisional skin surgery of NS lesions was performed. Histological findings of a lesion from the patient's scalp and face were consistent with NS, but did not indicate neoplastic transformation (Fig. 2a).

Genomic DNA was separately extracted from the multiple NS lesions, blood, non-lesional skin, hair, and oral mucosa of the patient. Each exon of *HRAS*, *KRAS*, and *NRAS* was amplified by polymerase chain reaction using specific primer pairs, and direct sequencing revealed a missense mutation of *KRAS* c.35G>A (p.Gly12Asp, rs121913529) which was previously reported to be pathogenic [3] in all NS lesions but not in other tissue samples (Fig. 2b). These clinical and histopathological findings led to the diagnosis of Schimmelpenning syndrome due to a postzygotic *KRAS* Gly12Asp mutation.

Discussion

In addition to the classical triad of Schimmelpenning syndrome, the patient had eye symptoms and skeletal deformity which were reported to be frequent [1]. The limbal dermoid and focal osteosclerosis of the temporal bone of the patient could be consistent with the clinical diagnosis of Schimmelpenning syndrome, as previously reported [1, 5].

The patient's phenotype might overlap with clinical diagnostic criteria of Schimmelpenning syndrome and other neurocutaneous syndromes, such as encephalocraniocutaneous lipomatosis (ECCL [MIM 613001]) or CLOVES syndrome (MIM 612918). The patient had three atypical symptoms of Schimmelpenning syndrome, including renovascular hypertension, congenital intracerebrospinal lipomatosis, and DM. The first two symptoms are extremely rare in Schimmelpenning syndrome but common in ECCL and CLOVES syndrome [6–10]. Clinical overlap of symptoms might confound the diagnosis of neurocutaneous syndromes.

Recently, the term "mosaic RASopathy" has been proposed for syndromes caused by mosaic mutations of the Ras/MAPK

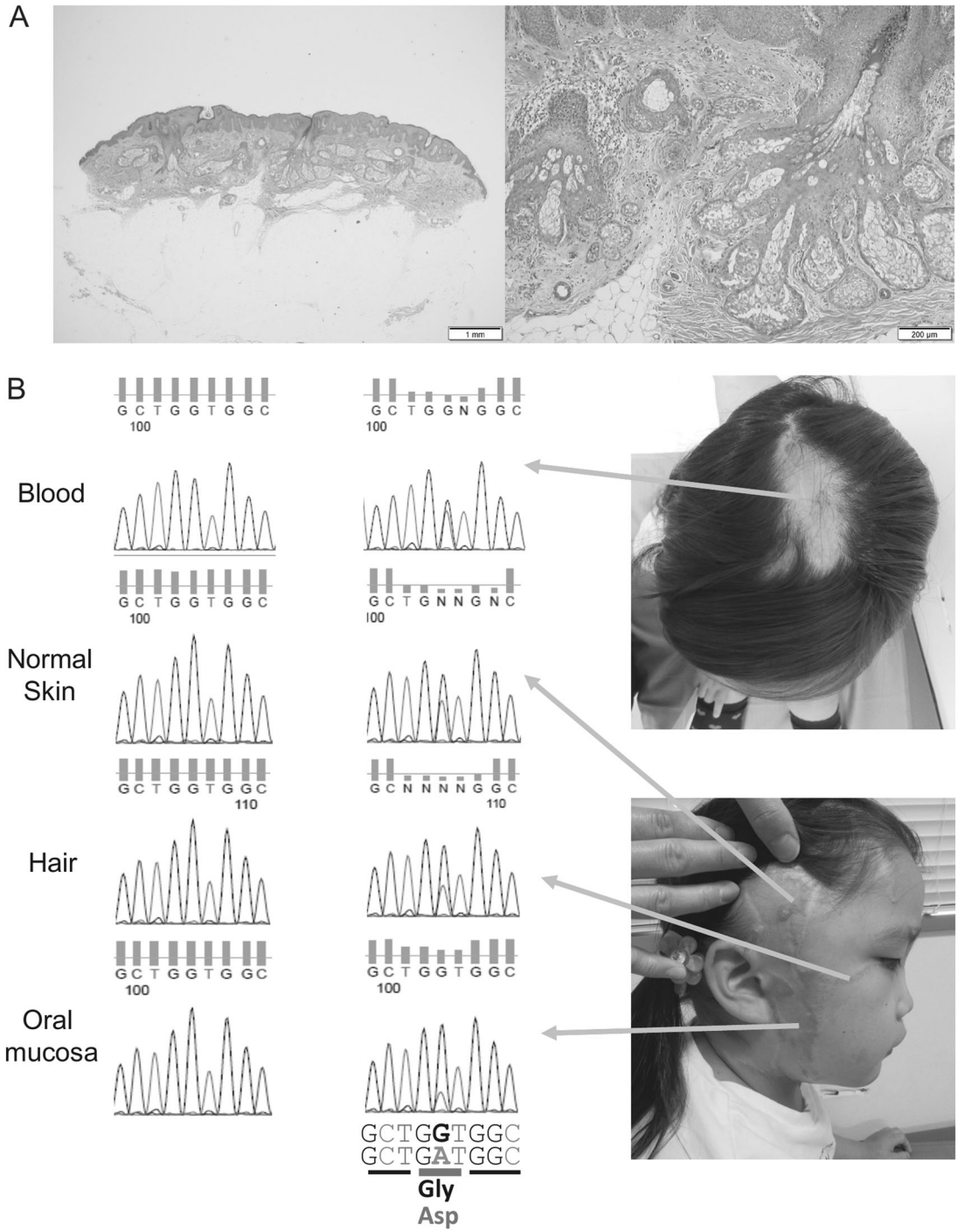

Fig. 2 Histopathological and sequencing findings of the patient with Schimmelpenning syndrome. **a** Histopathological findings of a nevus sebaceous from the patient's scalp. Hematoxylin and eosin staining showed epidermal acanthosis, papillomatosis, prominent sebaceous, and absent hair follicles (left panel, × 40; right panel, × 200). **b** Sequence electropherograms of *KRAS* for each sample. A *KRAS* c.35G>A (p.Gly12Asp) point mutation was found in the multiple nevus sebaceous from the face and scalp. Peripheral blood leukocytes, non-lesional skin, hair, and oral mucosa showed wild-type sequences

signaling pathway [4]. Besides *HRAS* and *KRAS*, mosaicism of *NRAS* and *BRAF* mutations were also detected in Schimmelpenning syndrome [2, 11]. Although ECCL was thought to be caused by mosaic-activating mutations in *FGFR1* [12], it was reported that postzygotic *KRAS* mutations might be associated with ECCL [8]. Mosaic-activating *RAS* mutations could produce a pleiotropic phenotype with the severity and extent of disease dependent on mutation onset [13]. Genetic diagnosis of postzygotic mutations might be able to account for the clinical overlap of neurocutaneous syndromes.

We suspect that the impaired glucose tolerance was caused by a gain-of-function *KRAS* mutation, and could be a novel clinical phenotype of Schimmelpenning syndrome. It was recently reported that children with multiple congenital melanocytic nevi, a mosaic RASopathy, might tend to have insulin insensitivity or impaired glucose tolerance [14]. Indeed, in vivo and in vitro research revealed that KRAS is associated with pancreatic β cell function and insulin sensitivity; activating KRAS or RAS signalling pathway induces suppression of pancreatic endocrine cell growth as well as insulin resistance [15, 16]. To clarify the correlation between mosaic RASopathy and DM, further accumulation of cases and long-term evaluation of glycometabolism are required.

Clinical diagnosis of Schimmelpenning syndrome or related conditions should be reorganized with genetic diagnosis as mosaic RASopathies, as is done with germline RASopathies or "PIK3CA-Related Overgrowth Spectrum (PROS)". PROS encompasses CLOVES syndrome and related megalencephalic conditions with somatic mosaic *PIK3CA*-activating mutations [17]. A few studies on molecular-targeted therapy for somatic mosaic syndromes including PROS and linear syringocystadenoma papilliferum syndrome due to *BRAF* mutation revealed to be effective [11, 18, 19]. Genetic diagnosis is necessary for molecular-targeted therapy, which might be a potential therapeutic strategy for mosaic RASopathies.

In conclusion, our study provides novel insights into clinical overlap between mosaic RASopathy and other congenital lipomatous overgrowth syndromes, and the possible correlation between KRAS and glycometabolism. Further accumulation of genetically proven cases with mosaic RASopathies should be acquired to more accurately characterize phenotypic variability and develop a future therapeutic strategy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement We obtained written informed consent from the patient's parents in accordance with the ethic committee of the Institutional Review Board of Tokyo Medical and Dental University (article#: 2015-39) and in adherence to the principles of the Declaration of Helsinki.

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