Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital problems, and enteropathy (MIRAGE) syndrome is a genetic disorder caused by gain-of-function SAMD9 mutations, which lead to a multisystemic growth restriction disorder. Recently, several cases of patients with MIRAGE syndrome presenting with dysautonomia have been reported. Familial dysautonomia (FD) is a rare genetic disease caused by a founder variant in the ELP1 gene. FD involves impaired development of sensory and afferent autonomic nerves, which leads to widespread organ dysfunction and mortality. Early signs and symptoms include hypotonia, feeding difficulties, growth restriction, a lack of tears, and frequent lung infections. Most of these symptoms are also observed in patients with MIRAGE syndrome. In several patients with FD-like symptoms, no ELP1 mutation was identified. This study describes the case of a patient who presented with FD-like symptoms and myelodysplastic syndrome (MDS) with monosomy 7 and was posthumously diagnosed as having MIRAGE syndrome due to a rare SAMD9 variant.

The patient was born with severe asphyxia at 37.3 weeks of gestation (birth weight: 2.002 g [-2.1 SD]; birth length: 44 cm [-1.6 SD]). The newborn had dysphagia, repeated apneic attacks, thrombocytopenia, and anemia. Additionally, dysautonomic conditions such as hyperhidrosis, paresthesia, and lacrimal deficiency were observed. External features included a flat upper lip and tongue mushroom papilla loss (Fig. 1A). The results of array comparative genomic hybridization were normal, and the patient was discharged at 4 months. At 8 months, the patient was diagnosed with MDS associated with monosomy 7. At 16 months, the patient experienced irritative contractions after the methacholine eye drop test, with increased levels of catecholamine metabolites (plasma norepinephrine: 1.79 ng/mL [range: 0.15–0.57], urine homovanillic acid: 14.4 mg/g creatinine [range: 2.1–8.2], urine vanillylmandelic acid: 2.93 mg/g creatinine [range: 2.4–8.3], ratio of homovanillic acid to vanillylmandelic acid: 2.93 [range < 1.5]) and a negative histamine intradermal reaction (Fig. 1B). On the basis of these findings, we suspected FD. However, the analysis of the ELP1 gene revealed no mutations; therefore, the patient was considered to have an FD-like disease. Growth retardation continued (Fig. 1C). The patient experienced intermittent pneumonia and vomiting episodes with colonic dilation despite undergoing Nissen surgery and gastrostomy at 17 months of age. There was no adrenal insufficiency. Mental retardation was noted at 32 months. At 5.5 years, with progressing pancytopenia, bone marrow tests showed the progression of MDS to refractory anemia, with excess type 2 blasts (RAEB-2). Allogeneic bone marrow transplantation was performed at 5.75 years. Despite achieving complete remission, RAEB-2 recurred at 6.33 years, leading to the patient’s death.

The genetic profile of the patient remained unclear even after her death in 2013. MIRAGE syndrome was suspected when the condition was first reported in 2016. Genomic DNA and RNA were extracted from leukocytes, saliva, and fibroblasts obtained from the patient’s right anterior chest skin. ELP1 expression was evaluated, and SAMD9 was sequenced from genomic DNA isolated from fibroblasts, as previously described. Genomic analysis revealed a heterozygous de novo missense SAMD9 mutation (NM_017654.4: c.1310T>C, p.F437S) (Fig. 2A). This mutation has not been reported in the gnomAD database, the 1000 Genomes database, or the Human Gene Mutation Database. The phenylalanine at position 437 (F437) is conserved across several species.

The effect of the F437S mutation on cell growth was evaluated in HEK293 cells expressing the native or mutated SAMD9 protein (Wild type (WT) and F437S, respectively) upon induction, which were established and analyzed to measure the growth rate, as previously described. WT-SAMD9 expression induced mild
growth suppression, as previously reported, whereas F437S-SAMD9 inhibited cell growth (Fig. 2C). LAMP-1 visualization showed a remarkable increase in the lysosome number in the patient’s fibroblasts (Fig. 2D), which is a characteristic of MIRAGE syndrome1,4. Thus, the patient was posthumously diagnosed with this syndrome.

Written informed consent for genetic analysis and the use of patient photos for publication was obtained from the patient’s parents. This study was approved by the Ethical Review Board of the Tottori University School of Medicine, Japan (No. 19A066G), and conducted according to the principles of the Declaration of Helsinki.

Dysautonomia, including insensitivity and anhidrosis, has been reported in several MIRAGE syndrome cases2–4. Conversely, dysautonomia at birth, feeding difficulties, poor growth, and frequent lung infections are observed only in FD and not in any other form of dysautonomia9. Interestingly, our patient also tested positive for laboratory test results common to FD, such as irritable

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**Fig. 1** Clinical findings. A The patient at 16 months of age, showing the flat upper lip and loss of tongue mushroom papillae. B Image 15 min after the histamine intradermal reaction test. Swelling and flare were not identified. C Patient cell growth curve.

**Fig. 2** Analysis of the SAMD9 variant in the patient. A Patient and parent polymerase chain reaction-amplified SAMD9 electropherograms; a heterozygous mutation was identified in the patient (arrow). B Alignment (Clustal software) showing the conserved F437 residue. C Growth curves of HEK293 cells transfected without (empty circles) or with (solid circles) wild-type (WT)-SAMD9 (left panel) and F437S-SAMD9 (right panel) plasmids. D Confocal image of patient-derived fibroblasts showing lysosomes and nuclei stained with anti-LAMP-1 antibody (green) and DAPI (blue), respectively.
contractions with the methacholine eye drop test, increased catecholamine metabolite levels, and a negative histamine intradermal reaction. Further studies are warranted to determine whether ELP1 interacts with SAMD9. In conclusion, the new SAMD9 variant (p.F437S) also causes MIRAGE syndrome, and dysautonomia is considered a symptom that indicates the possibility of MIRAGE syndrome.

**HGV DATABASE**
The relevant data from this Data Report are hosted at the Human Genome Variation Database at https://doi.org/10.6084/m9.figshare.hgv.3042.

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**COMPETING INTERESTS**
The authors declare no competing interests.

**ADDITIONAL INFORMATION**
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