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Original Article

Acquired uniparental disomy of chromosome 7 in a patient with MIRAGE syndrome that veiled a pathogenic *SAMD9* variant

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Abstract. Gain-of-function variants in *SAMD9*, which resides on chromosome 7, cause MIRAGE syndrome that is associated with congenital adrenal insufficiency and gonadal dysgenesis. We previously reported a Japanese patient with MIRAGE syndrome carrying a *de novo* heterozygous *SAMD9* variant (p.Ala1479Ser). In this study, we confirmed the pathogenicity of Ala1479Ser-SAMD9 *in vitro*. Genetic study results revealed an atypically low variant allele frequency (26%) and we suspected of genomic rearrangement(s) involving chromosome 7. Single nucleotide polymorphism (SNP) array and short tandem repeat analysis showed presence of mosaic maternal isodisomic uniparental disomy 7 (UPD7). Deep sequencing using DNA samples obtained at 0, 6, 10, and 25 mo of age revealed that the percentage of cells with UPD7 increased constantly from 6% to 82% over 25 mo, and this increase coincided with a decrease in the percentage of cells with p.Ala1479Ser from 94% to nearly undetectable levels. We further screened for low-allele-frequency and rare *SAMD9* variants in eight patients with Silver-Russel syndrome and maternal UPD7; however, none of the patients harbored such a variant. In conclusion, our case demonstrates that genetic findings can vary considerably in patients with MIRAGE syndrome and that a comprehensive diagnostic approach, including SNP array and deep sequencing, is important in such cases.

Key words: MIRAGE syndrome, uniparental disomy, Silver-Russell syndrome

Introduction

MIRAGE syndrome (OMIM #617053) is a multisystem disorder characterized by myelodysplasia, recurrent infections, restriction of growth, adrenal hypoplasia, genital abnormalities, and enteropathy (1). With its increasing recognition, several patients with atypical presentations, such as those lacking myelodysplasia (2, 3) or adrenal hypoplasia (4, 5) have been reported. MIRAGE syndrome is caused by germline heterozygous gain-of-function variants in *SAMD9*, which resides on the long arm of chromosome 7 (7q21.2). The SAMD9 protein has a mild antiproliferative capacity *in vitro* (6), and mutant SAMD9 proteins have an exaggerated antiproliferative capacity (1).

To date, three types of somatic genetic alterations have been reported to alleviate the excessive antiproliferative capacity of the mutant SAMD9 proteins: (i) loss of whole chromosome 7 or its long arm (monosomy 7/7q) (1), (ii) second-site loss-of-function variants in *SAMD9* (i.e., second-site reversion variants) (2), and (iii) uniparental disomy (UPD) for the long arm of chromosome 7 (UPD7q) (7). Monosomy 7/7q, which removes chromosome 7 harboring the mutant *SAMD9*, has been reported in 16 patients (1-3, 7–12). Second-site reversion variants, which occur in a *cis* configuration with germline variants, have been reported in seven patients (2, 5, 13). UPD7q has been reported in one patient who also had mosaic monosomy 7 (7). Monosomy 7/7q is vigorously searched by clinicians in patients with hematological abnormalities because of the risk of developing myelodysplastic syndrome. Second-site reversion variants and UPD7 are not associated with specific complications and may remain undiagnosed.

Silver-Russell syndrome (SRS) is a well-known congenital disorder (14) with clinical and genetic features

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overlapping with those of the MIRAGE syndrome. Shared clinical features include intrauterine growth restriction, postnatal growth failure, and feeding difficulties (1, 15). Maternal UPD7 is detected in up to 10% of patients with SRS (16) and is considered diagnostic.

Here, we report the results of detailed genetic analyses of a Japanese patient with MIRAGE syndrome who acquired maternal UPD7q. The acquisition and expansion of UPD7q cells caused a drastic decrease in the percentage of cells with a pathogenic *SAMD9* variant to undetectable levels. We also screened for low-allele-frequency and rare *SAMD9* variants in eight SRS patients with maternal UPD7. We emphasize the importance of analyzing UPD7 in a patient with clinically suspected MIRAGE syndrome yet negative *SAMD9* gene testing.

Patient and Methods

Ethical approval

The study was approved by the ethics committee of the National Center for Child Health and Development, Tokyo, Japan. Written informed consent for genetic analysis was obtained from the patient's parents.

Patient description

Detailed clinical descriptions of the patient have been previously reported (17). In brief, the patient was delivered premature by emergency cesarean section due to fetal distress and was small for gestational age. He had ambiguous genitalia with a 46,XY karyotype. Generalized skin pigmentation was noted soon after birth, which led to the diagnosis of primary adrenal insufficiency due to adrenal hypoplasia. He also had transient thrombocytopenia and leukopenia with spontaneous recovery after two months of age. He had severe diarrhea and could not tolerate enteral feeding. He suffered from recurrent infections that were often accompanied by adrenal crises. Based on these characteristic features, MIRAGE syndrome was suspected. To confirm the diagnosis, genetic analysis was performed at 6 mo of age, which showed a *de novo* heterozygous variant in the *SAMD9* gene [NM_017654.4:c.4435G> T, p.(Ala1479Ser)].

Functional analyses

We established stable HEK293 cell lines expressing wild-type or Ala1479Ser variant SAMD9 protein in a doxycycline-dependent manner, as previously described (13). The Ala1479Ser variant was introduced using the Gibson assembly technique (NEBuilder HiFi DNA Assembly Master Mix; New England Biolabs, Ipswich, MA, USA). Cell growth was analyzed using an IncuCyte ZOOM time-lapse microscope (Sartorius, Göttingen, Germany), as previously described (13).

Detailed genetic analyses

Deep sequencing and variant allele frequency (VAF) estimation

Genomic DNA samples were obtained from the patient at 0, 6, 10, and 25 mo of age. Except for the sample obtained at 0 mo of age, DNA was extracted from peripheral leukocytes using a standard technique. The DNA samples were subjected to long-range PCR with PrimeSTAR GXL DNA Polymerase (Takara Bio, Shiga, Japan) to amplify the entire coding region of *SAMD9* using the primer set 5'-ACT GGC AAT AGT CAC ATT CTC TCA-3' and 5'-CTG TAT CTA TAA CCT TGC CGG TTT-3'. For the 0-mo sample, a 1-mm square of the stored dried blood spot, which was originally obtained for newborn screening tests, was used for direct PCR amplification. We amplified 839-bp fragments containing the Ala1479 residue with the primer set 5'-CAA GTT TTC TGG GCT CTT GGA AT-3' and 5'-CTG TAT CTA TAA CCT TGC CGG TTT-3' and 850-bp fragments containing the Arg824 residue with the primer set 5'-CCA CAC ATA TTT CAG GGA TGG AAA-3' and 5'-CTG TTC TTT GGG AGA GAG TTG CTG-3' using Ampdirect Plus (Shimadzu, Kyoto, Japan). Sequencing libraries were prepared using the Nextera XT DNA Library Prep Kit (Illumina, San Diego, CA, USA) according to the manufacturer's protocol. The libraries were sequenced on an Illumina MiSeq System (2×250-bp) to generate more than 500× mean depth of coverage. Reads were aligned to the human reference genome (NCBI build 37; hg19) using BWA v.0.7.17 (18). The obtained SAM files were converted to BAM files using SAM tools v1.8, and the reads were visualized using Integrative Genomics Viewer (IGV) (19). Subsequently, we calculated VAF by dividing the visualized variant read counts by the total read counts at each nucleotide of interest, namely c.4435 (corresponding to Ala1473) and c.2470 (corresponding to Arg824). Using the VAF data, we estimated the fraction of the three cell types: cells with maternal UPD7q, cells harboring only p.Ala1479Ser, and cells with both p.Ala1479Ser and p.Arg824Ter.

Copy number variation analysis and loss of heterozygosity (LOH) analysis

Chromosome 7 deletion was screened with oligonucleotide array comparative genomic hybridization (array CGH) (SurePrint G3 Human CGH 4× 180 K, catalog #5190-4370; Agilent Technologies, Santa Clara, CA, USA) using the sample obtained at 6 mo of age. LOH in chromosome 7 was screened with a single nucleotide polymorphism (SNP) array (SurePrint G3 Human CGH+SNP 4× 180 K; Agilent Technologies) using the sample obtained at 10 mo of age. The data were analyzed using the default settings of the Genomic Workbench software (Version 6.5, Agilent Technologies).

The parental origin of LOH and the degree of LOH mosaicism were evaluated with short tandem repeat analysis using the DNA samples obtained from the patient at 0, 6, 10, and 25 mo of age and his parents.

The DNA was PCR-amplified with AmpliTaq Gold 360 DNA Polymerase (Thermo Fisher Scientific, Waltham, MA, USA) using a fluorescently labeled forward primer and an unlabeled reverse primer for the microsatellite marker D7S515 at the 7q22.1 locus. The obtained PCR fragments were analyzed with an ABI3500xl sequencer and GeneMapper V.3.7, (Thermo Fisher Scientific).

Patients with SRS and maternal UPD7

Eight patients with SRS and maternal UPD7 were included in this study. All patients were clinically suspected to have SRS and confirmed to have maternal UPD7 using short tandem repeat analysis, as described previously (20). Genomic DNA was extracted from blood samples obtained at the age of 1–11 years (median 4.5 yr) using standard methods. The DNA was subjected to long-range PCR of the coding region of *SAMD9* and analyzed using the Nextera XT DNA Library Prep Kit (Illumina) and MiSeq (Illumina) as described above to generate 1000× mean depth of coverage. We searched for variants with VAF >2%.

Results

Confirmation of the pathogenicity of Ala1479Ser-SAMD9

We first conducted a functional analysis to verify the pathogenicity of Ala1479Ser-SAMD9. Induced expression of wild-type SAMD9 resulted in mild growth suppression, whereas expression of Ala1479Ser-SAMD9 caused exaggerated growth suppression (**Fig. 1**), as typically seen with MIRAGE syndrome-causing pathogenic variants (1).

Detailed genetic analysis

We performed detailed genetic analyses, including VAF estimation, copy number analysis, and LOH analysis. In the DNA sample obtained at 6 mo of age, deep sequencing revealed that the VAF of the p.Ala1479Ser variant was 26%, suggesting a loss of the chromosome harboring p.Ala1479Ser. We also detected a nonsense variant, c.2470C>T, p.Arg824Ter, with 7% VAF. We performed array CGH, but monosomy 7 was not detected (data not shown). We then suspected UPD7 and performed SNP array analysis using the DNA obtained at the age of 10 mo, showing copy-neutral LOH on chromosome 7q (*i.e.,* isodisomic UPD7q) (**Fig. 2A**). To determine the parental origin of UPD7q, we analyzed a short tandem repeat marker on 7q22.1. We found that the signal derived from the paternal allele was detectable yet relatively low compared to the signal derived from the maternal allele. This indicated the mixed status of the cells with biparental chromosome 7 and the cells with maternal isodisomic UPD7q (mosaic maternal isodisomic UPD7q) (**Fig. 2B**). This finding, together with the decrease in the VAF of the p.Ala1479Ser variant, led us to hypothesize that p.Ala1479Ser was on paternal chromosome 7. We assumed that the three types of cells existed in the patient's hematopoietic system: cells with p.Ala1479Ser only, cells with p.Ala1479Ser and p.Arg824Ter, and cells with maternal UPD7q harboring two non-mutated *SAMD9* alleles.

Chronological evaluation of the cell-type fraction

Next, we investigated age-dependent changes in VAF (p.Ala1479Ser and p.Arg824Ter) using samples obtained at 0, 10, and 25 mo of age. The VAF of p.Ala1479Ser was nearly 50% at 0 mo but constantly decreased to 9% over 25 mo (**Fig. 3A**). The VAF of p.Arg824Ter increased from 0% to 14% over 10 mo, but

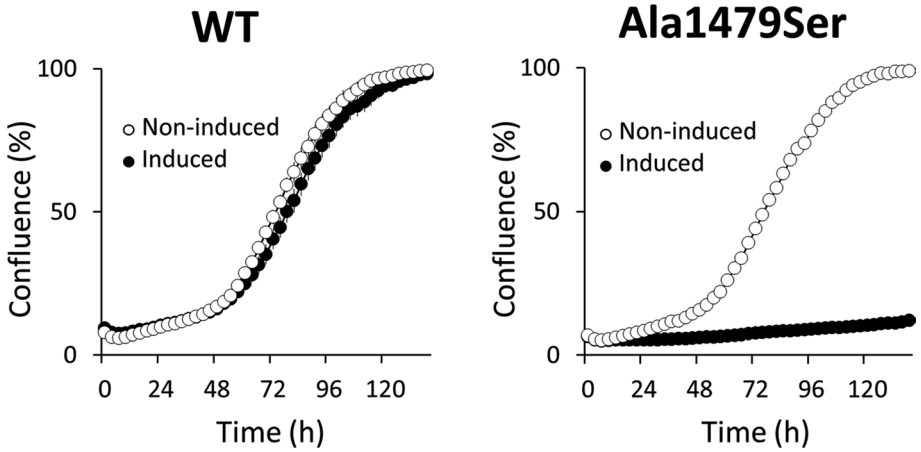

Fig. 1. Functional analysis of Ala1479Ser-SAMD9. Growth of HEK293 cells that overexpressed SAMD9 [wildtype (WT) or Ala1479Ser] was monitored with a time-lapse microscope for 144 h. Note that expression of Ala1479Ser-SAMD9 caused profound growth restriction, which is a characteristic of MIRAGE syndrome-associated variants. Values represent the mean ± SEM (n = 3).

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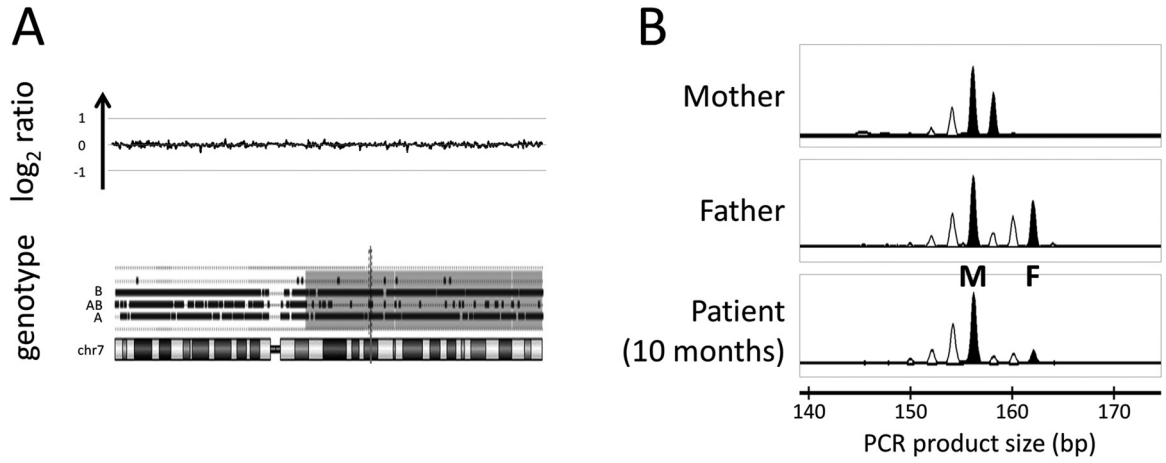

Fig. 2. Copy number variation analysis and loss of heterozygosity (LOH) analysis. (A) Single nucleotide polymorphism (SNP) array analysis using the DNA obtained at the age of 10 mo showed copy-neutral LOH on chromosome 7q (i.e., isodisomic UPD7q). The shaded area represents LOH. A vertical bar denotes 7q21.2, where SAMD9 resides. (B) Evaluation of the short tandem repeat marker D7S515 indicated the presence of mosaic maternal isodisomic UPD7. The signal derived from the paternal allele (highlighted as "F") was detectable yet relatively low as compared with the signal derived from the maternal allele (highlighted as "M").

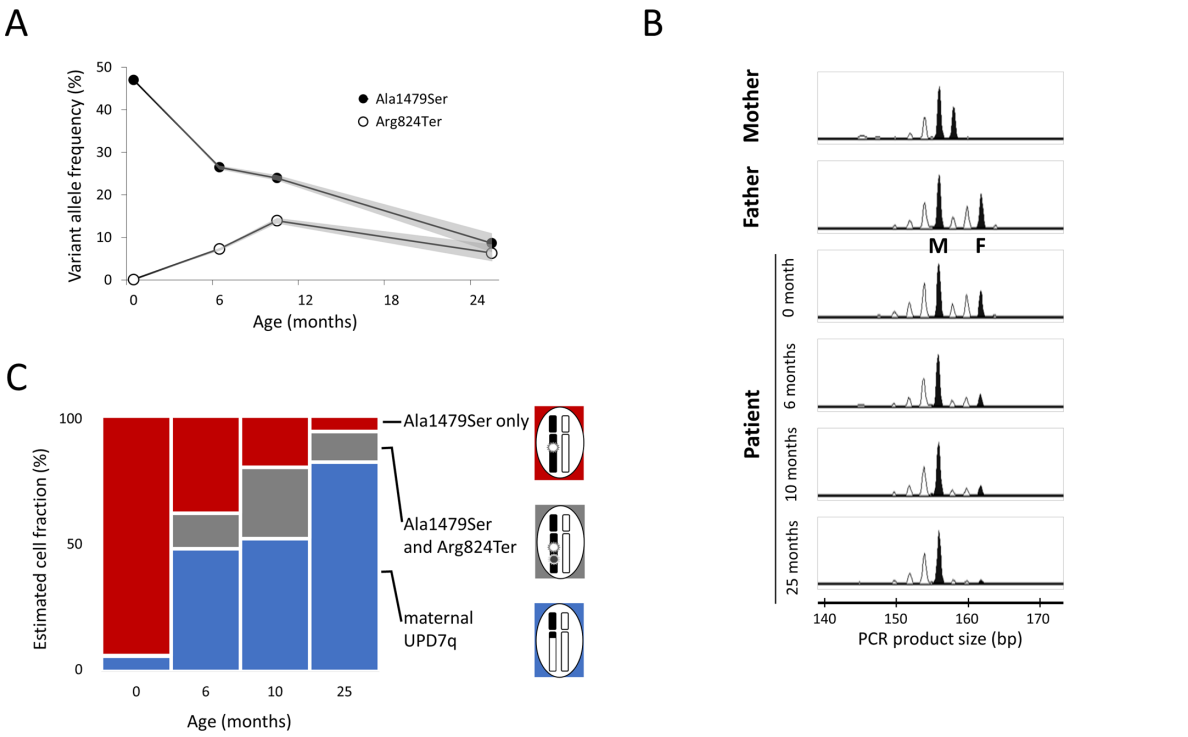

Fig. 3. Chronological evaluation of the three cell types in the patient's hematopoietic system. (A) A line graph showing variant allele frequencies (VAFs) of Ala1479Ser (solid circles) and Arg824Ter (open circles) analyzed by deep sequencing. Shaded areas represent 95% confidence intervals. (B) Chronological changes of short tandem repeat analysis at locus D7S515. The signal derived from the paternal allele (highlighted as "F") showed constant decrease over time compared to the signal derived from the maternal allele (highlighted as "M"). (C) Fraction of the three types of cells estimated from VAFs of Ala1479Ser and Arg824Ter. The data corresponding to cells with Ala1479Ser only, those with Ala1479Ser and Arg824Ter, and those with maternal UPD7q are shown in red, grey and blue, respectively.

no further increase was observed (**Fig. 3A**). Analyses of a short tandem repeat marker on 7q22.1, with the same genetic materials, showed a constant decrease in the fluorescence signal derived from the paternal allele (**Fig. 3B**). The estimated fraction of the cells based on VAF data showed that the percentage of cells with maternal UPD7q increased from 6% to 82% over 25 mo, while the fraction of cells harboring only p.Ala1479Ser

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decreased from 94% to 6% (**Fig. 3C**). The fraction of cells with p.Ala1479Ser and p.Arg824Ter expanded up to 28% and subsequently dropped to 12%.

SAMD9 analysis in SRS patients with maternal UPD7

We hypothesized that a patient with MIRAGE syndrome who acquired UPD7 could be misdiagnosed as SRS with maternal UPD7, because the VAF of the pathogenic *SAMD9* variant could be too low to be detected with standard sequencing techniques. In view of this hypothesis, we conducted deep sequencing of *SAMD9* in eight patients who were diagnosed with SRS with maternal UPD7. We found that none of the eight patients harbored a rare *SAMD9* variant with more than 2% VAF (data not shown).

Discussion

This study reports three novel findings. First, we demonstrated the pathogenicity of the previously reported Ala1479Ser-SAMD9 *in vitro*. Second, we conducted a chronological evaluation of VAFs for the two *SAMD9* variants (a germline pathogenic variant Ala1479Ser and a second-site reversion variant Arg824Ter) and LOH using DNA samples taken at four different time points: 0, 6, 10, and 25 mo of age. This led us to conclude that the percentage of cells with a germline pathogenic *SAMD9* variant could decrease to as low as 6% when coexisting with acquired UPD7 cells. This was the most marked decrease compared to the previously reported two MIRAGE syndrome patients with VAF decrease either due to monosomy 7 (2) or UPD7q (7). Third, this finding prompted us to investigate a novel hypothesis that a low fraction of *SAMD9* variant-positive cells might be veiled and missed in SRS patients with maternal UPD7. We screened for low-allele-frequency and rare *SAMD9* variants in eight SRS patients with maternal UPD7, but none of them harbored one.

To date, three types of somatic alterations in hematopoietic cells of patients with MIRAGE syndrome have been reported: monosomy 7/7q, second-site reversion variants, and UPD7q. All three types of alterations allow cells to grow faster than cells without such alterations by mitigating the antiproliferative effect of gain-of-function *SAMD9* variants. Acquisition of a second-site reversion variant does not reduce the VAF of the germline *SAMD9* variant. In contrast, monosomy 7/7q and UPD7 result in reduction of VAF (2, 7) and may lead to false-negative *SAMD9* gene testing. Of the three somatic alterations, only monosomy 7/7q was associated with myelodysplastic syndrome. Indeed, monosomy 7/7q is one of the most frequent chromosomal aberrations related to pediatric myeloid disorders (21), and gain-of-function *SAMD9* variants are predisposing factors for monosomy 7-associated pediatric myeloid disorders (22, 23). Thus, monosomy 7 and *SAMD9* variants have been actively searched in pediatric patients with myelodysplastic syndrome. In contrast, UPD7 has no specific hematological complications to suspect its existence and thus may be overlooked.

One of the most widely used clinical diagnostic criteria for SRS is the Netchine-Harbison clinical scoring system, which consists of six criteria (24). Three of the six criteria, small for gestational age, postnatal growth failure, and feeding difficulties and/or low body mass index, are commonly seen in patients with MIRAGE syndrome (1). Another criterion, protruding forehead, which is considered specific to SRS, was also observed in three patients with MIRAGE syndrome (8, 11, 25). In addition, patients with MIRAGE syndrome may lack some of the core features such as hematological abnormalities (13), adrenal failure (26), or enteropathy (3). Meeting three or more of the six criteria together with a molecular finding of maternal UPD7 is considered sufficient to confirm the diagnosis of SRS (15). Involved UPD7q region found in two patients with MIRAGE syndrome (current case, (7)) ranged from the upstream of *SAMD9* localization (7q21.2) to the terminus of the long arm region. The region includes two candidate SRS-imprinted clusters, PEG10 (7q21.3) and MEST (7q32) (27), making UPD7q found in MIRAGE syndrome compatible as maternal UPD7q seen in SRS. Taken together, we hypothesized that a patient harboring a germline *SAMD9* variant with decreased VAF due to acquired maternal UPD7 and clinically lacking several core features of MIRAGE syndrome could be diagnosed with SRS. However, of the eight patients analyzed, none were positive for a rare *SAMD9* variant. This suggests that undiagnosed MIRAGE syndrome is not a frequent etiology of SRS with maternal UPD7.

This study has two limitations. First, the limited number of patients with SRS included in this study made it difficult to draw a firm conclusion on the prevalence of underlying MIRAGE syndrome in SRS with maternal UPD7. Further investigation of SRS patients with maternal UPD7, especially those with an atypical presentation for SRS, such as cytopenia, chronic diarrhea, or recurrent infection, is warranted. The second is the relatively high age of patients with SRS (median 4.5 yr) at DNA sampling. If the cells with maternal UPD7 completely replaced the cells with a germline *SAMD9* variant in the hematopoietic system, it would be impossible to detect the variant unless we analyzed the DNA derived from non-hematopoietic tissues.

In summary, we described a patient with MIRAGE syndrome who showed a drastic decrease in VAF of a germline pathogenic *SAMD9* variant down to undetectable levels, which was due to acquired maternal UPD7q. Our case demonstrates that genetic findings can change considerably in patients with MIRAGE syndrome. In a patient with clinically suspected MIRAGE syndrome with negative *SAMD9* gene testing, it is important to conduct SNP arrays to diagnose UPD7/7q, and deep sequencing using DNA samples collected at the earliest time.

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