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

Kanako Tanase-Nakao1, Masanobu Kawai2, Kazuko Wada3, Masayo Kagami1, and Satoshi Narumi1
1Department of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo, Japan
2Department of Gastroenterology, Nutrition and Endocrinology, Osaka Women’s and Children’s Hospital, Osaka, Japan
3Department of Neonatology, Osaka Women’s and Children’s Hospital, Osaka, Japan

Abstract. Gain-of-function variants in \textit{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 \textit{de novo} heterozygous \textit{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 \textit{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 \textit{SAMD9}, which resides on the long arm of chromosome 7 (7q21.2). The \textit{SAMD9} protein has a mild antiproliferative capacity \textit{in vitro} (6), and mutant \textit{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 \textit{SAMD9} proteins: (i) loss of whole chromosome 7 or its long arm (monosomy 7/7q) (1), (ii) second-site loss-of-function variants in \textit{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 \textit{SAMD9}, has been reported in 16 patients (1-3, 7–12). Second-site reversion variants, which occur in a \textit{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-Russel syndrome (SRS) is a well-known congenital disorder (14) with clinical and genetic features...
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’-GCT GGA AGA GAT TTT-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 GTG AGA TCG TTC TTG TAT CTA TAA CCT TGC CGG TTT-3’ and 5’-CTG TTG GCT CTT GGA AT-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 CTC-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 \textit{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 (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 \textit{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

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 (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 \textit{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).
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 UPD7q increased from 4% to 18% over the same period.
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 UPD7q, and deep sequencing using DNA samples collected at the earliest time.
Acknowledgments

We thank the physicians for providing genetic materials and clinical information: Dr. Tomonobu Hasegawa (Keio University), Dr. Reiko Horikawa (National Center for Child Health and Development), Dr. Mika Inoue (National Hospital Organization Kanazawa Medical Center), Dr. Yuki Kiba (Komatsu Municipal Hospital), Dr. Rika Kosaki (National Center for Child Health and Development), Dr. Yumi Murayama (Nagaoka Red Cross Hospital), Dr. Keisuke Nagasaki (Niigata University), Dr. Masamichi Ogawa (Ogawa Clinic), and Dr. Atsuro Shiroti (St. Luke’s International Hospital). This work was supported by JSPS KAKENHI Grant Number 19H03627, a grant from the National Center for Child Health and Development (2020B-3), a grant from the Japan Intractable Diseases (Nanbyo) Research Foundation (2020A07), and a grant from the Takeda Science Foundation.

References

1. Narumi S, Amano N, Ishii T, Katsumata N, Muroya K, Adachi M, et al. SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. Nat Genet 2016;48: 792–7. [Medline] [CrossRef]
2. Buonocore F, Kühnen P, Suntharalingham JP, Del Valle I, Digweed M, Stachelscheid H, et al. Somatic mutations and progressive monosomy modify SAMD9-related phenotypes in humans. J Clin Invest 2017;127: 1700–13. [Medline] [CrossRef]
3. Jeffries L, Shima H, Ji W, Panisello-Manterola D, McGrath J, Bird LM, et al. A novel SAMD9 mutation causing MIRAGE syndrome: An expansion and review of phenotype, dysmorphology, and natural history. Am J Med Genet A 2018;176: 415–20. [Medline] [CrossRef]
4. Zhang Y, Zhang Y, Zhang VW, Zhang C, Ding H, Yin A. Mutations in both SAMD9 and SLC19A2 genes caused complex phenotypes characterized by recurrent infection, dysphagia and profound deafness - a case report for dual diagnosis. BMC Pediatr 2019;19: 364. [Medline] [CrossRef]
5. Roucher-Boulez F, Mallet D, Chatron N, Dijoud F, Gorduza DB, Bretones P, et al. De novo mutations in the SAMD9 gene cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. Nat Genet 2016;48: 792–7. [Medline] [CrossRef]
6. Li CF, MacDonald JR, Wei RY, Ray J, Lau K, Kandel C, et al. Human sterile alpha motif domain 9, a novel gene identified as down-regulated in aggressive fibromatosis, is absent in the mouse. BMC Genomics 2007;8: 92. [Medline] [CrossRef]
7. Csillag B, Ilenicikova D, Meissl M, Webersinke G, Laccone F, Narumi S, et al. Somatic mosaic monosomy 7 and UPD7q in a child with MIRAGE syndrome caused by a novel SAMD9 mutation. Pediatr Blood Cancer 2019;66: e27589. [Medline] [CrossRef]
8. Wilson DB, Bessler M, Ferkol TW, Shenoy S, Amano N, Ishii T, et al. Comment on: Acquired monosomy 7 myelodysplastic syndrome in a child with clinical features of dyskeratosis congenita and IMAGe association. Pediatr Blood Cancer 2018;65: 65. [Medline] [CrossRef]
9. Sarthy J, Zha J, Babushok D, Shenoy A, Fan JM, Wertheim G, et al. Poor outcome with hematopoietic stem cell transplantation for bone marrow failure and MDS with severe MIRAGE syndrome phenotype. Blood Adv 2018;2: 120–5. [Medline] [CrossRef]
10. Ahmed IA, Farooqi MS, Vander Lugt MT, Boklan J, Rose M, Friele HD, et al. Outcomes of hematopoietic cell transplantation in patients with germline SAMD9/SAMD9L mutations. Biol Blood Marrow Transplant 2019;25: 2186–96. [Medline] [CrossRef]
11. Mengen E, Kucukoguz Vayas A. A rare etiology of 46, XY disorder of sex development and adrenal insufficiency: A case of MIRAGE syndrome caused by mutations in SAMD9 gene. J Clin Res Pediatr Endocrinol 2020;12: 206–11. [Medline] [CrossRef]
12. Perisa MP, Rose MJ, Varga E, Kamboj MK, Spencer JD, Bajwa RPS. A novel SAMD9 variant identified in patient with MIRAGE syndrome: Further defining syndromic phenotype and review of previous cases. Pediatr Blood Cancer 2019;66: e27726. [Medline] [CrossRef]
13. Shima H, Koehler K, Nomura Y, Sugimoto K, Satoh A, Ogata T, et al. Two patients with MIRAGE syndrome lacking haematological features: role of somatic second-site reversion SAMD9 mutations. J Med Genet 2018;55: 81–5. [Medline] [CrossRef]
14. Silver HK, Kiyasu W, George J, Deamer WC. Syndrome of congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropins. Pediatrics 1953;12: 368–76. [Medline]
15. Wakeling EL, Brioude F, Lokulo-Sodipe O, O’Connell SM, Salem J, Blik J, et al. Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nat Rev Endocrinol 2017;13: 105–24. [Medline] [CrossRef]
16. Gicquel C, Rossignol S, Cabrol S, Houang M, Steunou V, Barbu V, et al. Epimutation of the telomeric imprinting center region on chromosome 11p15 in Silver-Russell syndrome. Nat Genet 2009;37: 1003–7. [Medline] [CrossRef]
17. Onuma S, Wada T, Araki R, Wada K, Tanase-Nakao K, Narumi S, et al. MIRAGE syndrome caused by a novel missense variant (p.Ala1479Ser) in the SAMD9 gene. Hum Genome Var 2020;7: 4. [Medline] [CrossRef]
18. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics 2009;25: 1754–60. [Medline] [CrossRef]
19. Robinson JT, Thorvaldsdóttir H, Winckler W, Guttman M, Lander ES, Getz G, et al. Integrative genomics viewer. Nat Biotechnol 2011;29: 24–6. [Medline] [CrossRef]

20. Fuke-Sato T, Yamazawa K, Nakabayashi K, Matsubara K, Matsuoka K, Hasegawa T, et al. Mosaic upd(7)mat in a patient with Silver-Russell syndrome. Am J Med Genet A 2012;158A: 465–8. [Medline] [CrossRef]

21. Inaba T, Honda H, Matsui H. The enigma of monosomy 7. Blood 2018;131: 2891–8. [Medline] [CrossRef]

22. Schwartz JR, Ma J, Lamprecht T, Walsh M, Wang S, Bryant V, et al. The genomic landscape of pediatric myelodysplastic syndromes. Nat Commun 2017;8: 1557. [Medline] [CrossRef]

23. Yoshida M, Tanase-Nakao K, Shima H, Shirai R, Yoshida K, Osumi T, et al. Prevalence of germline GATA2 and SAMD9/9L variants in paediatric haematological disorders with monosomy 7. Br J Haematol 2020;191: 835–43. [Medline] [CrossRef]

24. Azzi S, Salem J, Thibaud N, Chantot-Bastaraud S, Lieber E, Netchine I, et al. A prospective study validating a clinical scoring system and demonstrating phenotypical-genotypical correlations in Silver-Russell syndrome. J Med Genet 2015;52: 446–53. [Medline] [CrossRef]

25. Kim YM, Seo GH, Kim GH, Ko JM, Choi JH, Yoo HW. A case of an infant suspected as IMAGE syndrome who were finally diagnosed with MIRAGE syndrome by targeted Mendelian exome sequencing. BMC Med Genet 2018;19: 35. [Medline] [CrossRef]

26. Shima H, Hayashi M, Tachibana T, Oshiro M, Amano N, Ishii T, et al. MIRAGE syndrome is a rare cause of 46,XY DSD born SGA without adrenal insufficiency. PLoS One 2018;13: e0206184. [Medline] [CrossRef]

27. Ishida M. New developments in Silver-Russell syndrome and implications for clinical practice. Epigenomics 2016;8: 563–80. [Medline] [CrossRef]