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Ibrahim A. Ahmed  
*Children's Mercy Hospital*

Midhat S. Farooqi  
*Children's Mercy Hospital*

Mark T. Vander Lugt

Jessica Boklan

Melissa Rose

*See next page for additional authors*

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Outcomes of Hematopoietic Cell Transplantation in Patients with Germline SAMD9/SAMD9L Mutations

Ibrahim A. Ahmed1, Midhat S. Farooqi2, Mark T. Vander Lugt3, Jessica Boklan4, Melissa Rose5, Erika D. Friehling6, Brandon Triplett7, Kenneth Lieuw8, Blachy Davila Saldana9, Christine M. Smith10, Jason R. Schwartz11, Rakesh K. Goyal12,*

1 Division of Pediatric Hematology, Oncology and Blood and Marrow Transplantation, Department of Pediatrics, Children’s Mercy Kansas City, Kansas City, Missouri
2 Department of Pathology and Laboratory Medicine, Children’s Mercy Kansas City, Kansas City, Missouri
3 Division of Pediatric Hematology/Oncology, Department of Pediatrics, C. S. Mott Children’s Hospital, University of Michigan, Ann Arbor, Michigan
4 Department of Oncology, Phoenix Children’s Hospital, Phoenix, Arizona
5 Hematology & Oncology, Nationwide Children’s Hospital, Columbus, Ohio
6 Division of Pediatric Hematology/Oncology, Department of Pediatrics, UPMC Children’s Hospital of Pittsburgh, Pittsburgh, Pennsylvania
7 Department of Bone Marrow Transplant, St. Jude Children’s Research Hospital, Memphis, Tennessee
8 Department of Pediatrics, Walker Reed National Military Medical Center, Bethesda, Maryland
9 Division of Blood and Marrow Transplantation, Children’s National Medical Center, Washington, DC
10 Division of Hematology-Oncology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee
11 Hematology Department, St. Jude Children’s Research Hospital, Memphis, Tennessee
12 Division of Pediatric Hematology, Oncology and Blood and Marrow Transplantation, Department of Pediatrics, Children’s Mercy Kansas City, Kansas City, Missouri

ABSTRACT

Germline mutations in SAMD9 and SAMD9L genes cause MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy) (OMIM: *610456) and ataxia-pancytopenia (OMIM: *611170) syndromes, respectively, and are associated with chromosome 7 deletions, myelodysplastic syndrome (MDS), and bone marrow failure. In this retrospective series, we report outcomes of allogeneic hematopoietic cell transplantation (HCT) in patients with hematologic disorders associated with SAMD9/SAMD9L mutations. Twelve patients underwent allogeneic HCT for MDS (n = 10), congenital amegakaryocytic thrombocytopenia (n = 1), and dyskeratosis congenita (n = 1). Exome sequencing revealed heterozygous mutations in SAMD9/SAMD9L genes in MIRAGE syndrome cases. Median age at HCT was 2.8 years (range, 1.2 to 12.8 years). Conditioning was myeloablative in 9 cases and reduced intensity in 3 cases. Syndrome-related comorbidities (diarrhea, infections, adrenal insufficiency, malnutrition, and electrolyte imbalance) were present in MIRAGE syndrome cases. One patient with a familial SAMD9L mutation, MDS, and morbid obesity failed to engraft and died of refractory acute myeloid leukemia. The other 11 patients achieved neutrophil engraftment. Acute post-transplant course was complicated by syndrome-related comorbidities in MIRAGE cases. A patient with SAMD9L-associated MDS died of diffuse alveolar hemorrhage. The other 10 patients had resolution of hematologic disorder and sustained peripheral blood donor chimerism. Ten of 12 patients were alive with a median follow-up of 3.1 years (range, 0.1 to 14.7 years). More data are needed to refine transplant approaches in SAMD9/SAMD9L patients with significant comorbidities and to develop guidelines for their long-term follow-up.

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INTRODUCTION

In recent years, advances in genetic interrogation of patient samples have led to discovery of several novel genes that underlie inherited bone marrow failure and myelodysplastic syndrome (MDS) [1]. These include SAMD9 (sterile α-motif domain-containing protein 9) and SAMD9L (SAMD9-like) genes, located head to tail on chromosome 7q21.2 in a region that is frequently deleted in myeloid malignancies [2,3].

Germline mutations in SAMD9 and SAMD9L cause the multisystem disorders, MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy) and ataxia-pancytopenia syndromes, respectively [4-6]. Recent studies in children reported a rate of SAMD9 and SAMD9L mutations in 18.6% and 17% cases with suspected inherited bone marrow failure syndromes and those with primary MDS, respectively [7,8].

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* Correspondence and reprint requests: Rakesh K, Goyal, MD, Division of Hematology/Oncology/BMT, Children’s Mercy Kansas City, 2401 Gillham Road, Kansas City, MO 64108.
E-mail address: rkgoyal@cmh.edu (R.K. Goyal).

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SAMD9 and SAMD9L proteins are involved in endosomal trafficking and negatively regulate cell proliferation [9]. Gain-of-function heterozygous mutations in these genes lead to cellular growth restriction and hypoplasia, resulting in cytopenias, bone marrow failure, and immunodeficiency. Interestingly, in many cases, there is a nonrandom loss of the mutated allele via full or partial deletion of chromosome 7 [4,10-12]. The resultant monosomy 7 or deletion 7q can result in the development of MDS and acute myeloid leukemia (AML) [8,11,12]. Conversely, other “genetic correction” events such as in cis misense, nonsense, or loss of heterozygosity through uniparental disomy can result in normal hematopoiesis.

Since the initial report of MIRAGE syndrome in 2016, a series of studies has described clinical and genetic findings in patients and families with SAMD9/SAMD9L mutations [7,11,13]. Hematopoietic cell transplantation (HCT) therapy has been included in some reports, but transplant details are lacking. A recent article by Sarthy et al. [14] documented 2 children with MIRAGE syndrome who succumbed to posttransplant complications due to syndrome-related comorbidities. We aimed to obtain a more complete assessment of transplant outcomes and the challenges and complications encountered in these patients.

METHODS

After management of 2 cases with MIRAGE syndrome, additional cases were identified by literature search and peer consultations. For inclusion, patients were required to have a confirmed heterozygous mutation in the SAMD9 or SAMD9L gene and a minimum of 1-year follow-up post-transplant. Deidentified data for each case were collected by using a standardized questionnaire. All studies involving human subjects were performed in accordance with site-specific protocols approved by the institutional review board and in accordance with Declaration of Helsinki guidelines.

The primary study endpoints were overall survival and event-free survival. Safety and tolerability of HCT and impact of pretransplant comorbidities were evaluated by occurrence and severity of post-transplant complications, need for life support measures, and risk of transplant-related mortality. Transplant outcomes were defined using Center for International Blood and Marrow Transplant Research criteria [15]. Grading of acute graft-vs-host disease (GVHD) and diagnosis of chronic GVHD were based on standard criteria [16]. Surviving patients were censored at last follow-up. Continuous variables were summarized as median and range of values and analyzed using the Mann-Whitney test.

RESULTS

Twelve patients underwent allogeneic HCT for hematologic disorders associated with germline SAMD9 (n = 6) or SAMD9L (n = 6) mutations (Table 1). Patients 3, 4, 6, 11, and 12 (Table 1) were included in previous reports [11,13,17]. Indication for transplant was MDS in 10 of 12 (83%) cases. One SAMD9 patient with markedly reduced megakaryocytic precursors in marrow underwent transplantation for a presumed diagnosis of congenital amegakaryocytic thrombocytopenia, and 1 patient with SAMD9L mutation and shortened telomeres underwent transplantation on a presumed diagnosis of dyskeratosis congenita.

Median age at presentation for patients with SAMD9 mutations (1.65 years; range, 0.17 to 4.8 years) was similar to those with SAMD9L mutations (1.43 years; range, 0.67 to 12.6 years). Six patients had pancytopenia, including 5 with thrombocytopenia and 1 with anemia. Bone marrow was hypocellular in 11 (92%) cases and showed dysplasia most prominently in the megakaryocytic lineage in most cases. Chromosome 7 abnormalities, including monosomy 7 and chromosome 7q deletions, were present in all cases. All except 1 case showed somatic mosaicism for chromosome 7 abnormalities (ie, detection of a monosomy 7 or chromosome 7 deletion clone in only a fraction of hematopoietic cells in bone marrow).

Exome sequencing revealed 5 different missense heterozygous mutations in the 6 SAMD9 cases and 4 different missense mutations in the 6 SAMD9L cases. Their genomic details and pathogenicity assessment of variants are summarized in Table 2 and cross-referenced [5,7,8,12,13,17-20]. Six of 12 cases were familial. Four SAMD9 patients had phenotypic features of MIRAGE syndrome (patients 1, 2, 5, and 6; Tables 1 and 2); unique findings included panhypopituitarism, laryngeal cleft, and glomerulosclerosis. Two other cases with a SAMD9 mutation had milder phenotypes with growth restriction in 1 and hypospadias and a bifid scrotum in another. The remaining patients had no phenotypic abnormalities.

Transplant details of individual cases are summarized in Table 3. Median age at HCT was 2.8 years (range, 1.16 to 12.8 years). Median age at HCT tended to be higher in SAMD9 patients versus SAMD9L patients at 4.15 years versus 2.2 years, respectively (P = .81). Median time from initial presentation to transplant was 0.45 years (range, 0.2 to 6.53 years). There was an interval of 5.5 and 6.53 years from initial diagnosis to HCT in 2 cases of MIRAGE syndrome because in these cases, blood counts seemed to show improvement before patients developed sustained marrow failure. Stem cell sources included bone marrow (matched unrelated, n = 7; HLA identical sibling, n = 2; and haploidentical parent, n = 1) and unrelated cord blood (n = 2). Nine patients received myeloablative conditioning (busulfan based, n = 7, or total-body irradiation based, n = 2). Three patients received reduced-intensity conditioning with fludarabine, cyclophosphamide, or melphalan, with rabbit antithymocyte globulin or alemtuzumab.

Clinically significant pretransplant comorbidities were present in SAMD9 cases with MIRAGE syndrome (Table 3). These included chronic diarrhea, electrolyte imbalance, infections, adrenal insufficiency, failure to thrive, lung disease, and renal dysfunction. One patient with SAMD9L mutation (patient 10, Table 2 and Table 3) had been treated for hemophagocytic lymphohistiocytosis, disseminated sepsis, invasive fungal infections before transplant.

Post-transplant complications included pericardial effusions (n = 3), veno-occlusive disease of liver (n = 3), thrombotic microangiopathy (n = 2), and diffuse alveolar hemorrhage (n = 1). Unique complications in several MIRAGE syndrome cases included large volume stool losses with dehydration and electrolyte imbalance, temperature and blood pressure instability, and hypoxia. Eight patients required transfer to intensive care for management of respiratory failure (n = 5), sepsis (n = 1), and severe hypertension (n = 1) and VOD of liver (n = 1).

One patient with a familial SAMD9L mutation, MDS, (patient 7, Table 3) and morbid obesity failed to engraft following reduced-intensity conditioning with double unrelated cord blood transplantation. All other patients achieved neutrophil and platelet engraftment at a median of 16 days (range, 12 to 19; n = 11) and 17 days (range, 12 to 40; n = 10) post-HCT, respectively. Two patients developed grade II to III acute GVHD, which resolved with treatment. Two patients developed mild skin chronic GVHD. Two patients have chronic lung disease, and 2 other patients have chronic kidney disease. One patient with SAMD9L mutation and MDS (patient 7, Table 3) with failed engraftment subsequently developed AML and died of its treatment complications. A second patient, with SAMD9L mutation and MDS (patient 10, Table 3), died of diffuse alveolar hemorrhage while receiving defibrotide for treatment of veno-occlusive disease of liver. Immune reconstitution data are summarized in Table 4.

Ten of 12 patients were alive with a median follow-up of 3.1 years (range, 0.1 to 14.7 years). All surviving patients (n = 10) at time of last follow-up had resolution of hematologic disorder,
| Patient No. | 1 | 2 | 3 | 4 | 5 |
|-------------|---|---|---|---|---|
| Age at initial presentation, years | 0.17 | 1 | 3.1 | 4.8 | 0.8 |
| Gender | M | M | F | M | F |
| Race/Ethnicity | Hispanic | Caucasian | Caucasian | Caucasian | African American |
| Gene mutation | SAMD9 c.2471G>A; p.R824Q | SAMD9 c.4690G>A; p.G1564S | SAMD9 c.3406G>C; p.E1136Q | SAMD9 c.3406G>C; p.E1136Q | SAMD9 c.2407G>C; p.E803Q |
| Family member with same gene mutation | Parents negative | Parents negative | Patient no. 3 and 4 in this report, a younger sibling and their mother positive | Patient no. 3 and 4 in this report, a younger sibling and their mother positive | Parents negative |
| MIRAGE syndrome features (SAMD9 cases) | Infections, restriction of growth, adrenal, genital, enteropathy | MDS, infections, restriction of growth, adrenal, enteropathy | MDS | MDS, genital | MDS, infections, restriction of growth, enteropathy |
| Other clinical findings | Newborn Period: Born at 29 weeks, birth weight 982 grams, mechanical ventilation. Chronic lung disease of prematurity. Microcephaly, developmental delay, panhypopituitarism, laryngeal cleft, intussusception, FSGS | Newborn Period: Born at 34 weeks, birth weight 1425 grams, no mechanical ventilation. Achalasia of esophagus, developmental delay | – | – | Newborn Period: Born at 36 weeks, birth weight 1895 grams, no mechanical ventilation. Staphylococcal sepsis with respiratory failure. Developmental delay |
| Hematology | Thrombocytopenia followed by pancytopenia. Hypoplastic marrow, megalakaryocytic hypoplasia | Pancytopenia. Hypocellular marrow, reduced megalakaryocytes and dysplasia | Thrombocytopenia. Hypocellular marrow, trilineage dysplasia | Hypocellular marrow, trilineage dysplasia, refractory cytopenia of childhood | Pancytopenia. Normocellular marrow, megalakaryocytic dysplasia |
| Chromosome 7 | Somatic mosaic monosomy 7, somatic mosaic chr. 7q deletion, UPD chr. 7 | Somatic mosaic monosomy 7, somatic mosaic 7q31 deletion, UPD chr. 7 | Monosomy 7 | Somatic mosaic monosomy 7 | Somatic mosaic monosomy 7 |
| Patient No. | 6 | 7 | 8 | 9 | 10 |
| Age at initial presentation, years | 2.3 | 12.6 | 0.9 | 8.1 | 0.7 |
| Gender | M | F | M | F | M |
| Race/Ethnicity | Caucasian | Hispanic | Caucasian | African American |
| Gene mutation | SAMD9 c.2318T>C; p.I773T | SAMD9L c.1877C>T; p.S626L | SAMD9L c.1877C>T; p.S626L | SAMD9L c.3538T>C; p.W1180R | SAMD9L c.4651G>C; p.V1551L |
| Family member with same gene mutation | Mother negative, father unavailable | Patients no. 7 and 8 in this report are nephews. Parents not tested. A maternal aunt is positive | Patients no. 7 and 8 in this report are nephews. Parents not tested. A maternal aunt is positive | Parents not tested | Parents negative |
| MIRAGE syndrome features (SAMD9 cases) | MDS, infections, restriction of growth, adrenal, genital, enteropathy | N.A. | N.A. | N.A. | N.A. |
| Other clinical findings | Newborn Period: Born at 34 weeks, birth weight 1853 grams, no mechanical ventilation. FSGS, short telomeres. Microcephaly, hypotelorism, strabismus, healed nose, reactive airway disease, warts | – | – | Hypogammaglobulinemia | HLH. Sepsis |
| Hematology | Thrombocytopenia. Hypocellular marrow, dysplastic megalakaryocytes | Hypocellular marrow, dyserythropoiesis | Hypocellular marrow, dyserythropoiesis and dysmegakaryopoiesis | Hypocellular marrow, atypical megalakaryocytes | Pancytopenia. Hypocellular marrow, dyserythropoiesis, dysgranulopoiesis |
| Chromosome 7 | Mosaic chr. 7q deletion | Absence of heterozygosity chr. 7q (myeloid) | Mosaic monosomy 7 | Mosaic monosomy 7 | Mosaic monosomy 7 |

(continued)
had no chromosome 7 abnormalities, and sustained peripheral blood donor chimerism (90% to 100%). All patients were thriving. SAMD9 cases had varying degrees of developmental delays (n = 6) and chronic kidney disease (n = 3). All patients with clinical characteristics of MIRAGE syndrome (n = 4) were short for age, required supplemental feeds, and had persistent adrenal insufficiency. In SAMD9L cases (n = 4), no clinical neurologic manifestations have been observed so far.

### DISCUSSION

In this report, we describe transplant details and outcomes in a series of patients with hematologic diseases associated with SAMD9/SAMD9L germline mutations. We found that most patients underwent transplantation for MDS with chromosome 7 abnormalities and received myeloablative conditioning with HCT from nonsibling donor graft sources. Allogeneic HCT led to successful resolution of MDS or marrow failure, with sustained donor chimerism and excellent survival.

On review of literature, we found 10 other cases with SAMD9 mutation who underwent HCT. A 4-year-old child with MIRAGE syndrome and monosomy 7 MDS underwent transplantation with active AML and died of Epstein-Barr virus-related lymphoproliferative disorder a year later [4]. Wilson and colleagues [21] reported a patient with MIRAGE syndrome who underwent reduced-intensity conditioning and unrelated donor HCT that led to resolution of monosomy 7 MDS. Sarthy et al. [14] described a patient with marrow failure and another patient with MDS who had severe MIRAGE phenotypes and underwent HCT after reduced-intensity conditioning. Comorbidities, including enteropathy, electrolyte imbalances, adrenal crises, bacteremia, and lung disease, significantly led to a complicated transplant course and ultimately death in both cases. Although transplant details in 6 other cases are limited, 1 patient without the MIRAGE phenotype died of unknown cause, and 5 were surviving following HCT [7,10]. There were 4 cases of MIRAGE syndrome in our series. Before transplant, 3 of 4 cases had chronic diarrhea, malnutrition, and adrenal insufficiency. Post-HCT, we observed severe gastrointestinal fluid losses, electrolyte imbalance, and acute dehydration in these 3 cases. Whether such dramatic stool losses without an infectious etiology were secretory and whether autonomic instability could have contributed are unknown. Patients also experienced temperature and blood pressure instability, respiratory distress, and acute renal dysfunction.

Several of these medical issues are similar to those reported in the report by Sarthy et al. [14]. Despite a complicated acute transplant course, all 4 patients with MIRAGE syndrome in our series survived.

We observed a high rate of ongoing medical issues in MIRAGE syndrome transplant survivors. These include adrenocortical insufficiency, diarrhea, need for supplemental nutrition, and developmental delays. Patients with pre-existing lung disease and nephropathy continue to have these issues following HCT. Most of these issues are related to pre-existing MIRAGE syndrome manifestations. The transplant survivor reported by Wilson et al. [21] had ongoing medical issues of adrenocortical insufficiency, growth and developmental delays, and chronic lung and chronic kidney diseases.

In this series, all 6 SAMD9L patients had cytopenias and MDS with chromosome 7 abnormalities. We did not observe ataxia, incoordination, or other neurologic manifestations before or following transplant. On review of the literature, we found 11 additional cases of patients with SAMD9L mutations who had undergone HCT [5,7,11]. Although transplant details are limited, 2 patients died of complications (cerebral

| Patient No. | Age at initial presentation, years | Gender | Race/Ethnicity | Gene mutation | Family member with same gene mutation | Other clinical findings | Chromosome 7 abnormalities | Hematology | Affected organ system(s) |
|-------------|----------------------------------|--------|---------------|---------------|--------------------------------------|------------------------|------------------------|------------|-------------------------|
| 11          | 1.6                              | F      | Caucasian     | SAMD9L c.2957G>A; p.R986H | Patients no. 11 and 12 in this report are siblings. Father positive. Mother negative | Eczema, N/A | Mosaic monosomy 7 | Mosaic monosomy 7 | N/A         |
| 12          | 1.3                              | M      | Caucasian     | SAMD9L c.2957G>A; p.R986H | Patients no. 11 and 12 in this report are siblings. Father positive. Mother negative | Eczema, N/A | Mosaic monosomy 7 | Mosaic monosomy 7 | N/A         |

**Abbreviations:** Chr. 7 (chromosome 7); FSGS (Focal sclerosing glomerulosclerosis); HCT (hematopoietic cell transplantation); HLH (hemophagocytic lymphohistiocytosis); MDS (myelodysplastic syndrome); MIRAGE syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy); and, UPD (uniparental disomy).
Table 2  
Pathogenicity Assessment of Observed SAMD9 and SAMD9L Variants

| Patient No. | Gene and Variant | Method of genetic diagnosis | SAMD9 / SAMD9L variant: De novo status | Germline source | Family tested for the same variant | ACMG* classification | How pathogenicity was ascribed | References |
|-------------|------------------|-----------------------------|----------------------------------------|-----------------|-----------------------------------|--------------------|-----------------------------|----------|
| 1           | SAMD9. Heterozygous c.2471G>A (p.Arg824Gln) | WES confirmed by Sanger sequencing | SAMD9L. Heterozygous c.3406G>C (p.E1136Q) | Kidney | Sibling donor was not tested prior to BMT since the SAMD9 variant was discovered in the recipient afterwards. Parents subsequently tested and were negative. | Pathogenic | 

PM2 – absent from controls 
PM6 – assumed de novo 
PP3 – in silico prediction: deleterious 
PP4 – UPD7 together with MIRAGE features | Not found via literature search | Perisa et al. [17] |
| 2           | SAMD9. Heterozygous c.4690G>A | WES confirmed by Sanger sequencing | SAMD9L. Heterozygous c.3406G>C (p.E1136Q) | Sorted lymphocytes | Parents negative | Likely Pathogenic | 

PS2 – de novo, parentage confirmed | Schwartz et al. [8] (Leukemia), Schwartz et al. [13] (Nat Comm) |
| 3           | SAMD9. Heterozygous c.3406G>C (p.E1136Q) | WES and WGS, targeted Sanger sequencing of parent | SAMD9L. Heterozygous c.3538T>C (p.W1180R) | Sorted lymphocytes | Patient no. 3 and 4 in this report, a younger sibling and their mother positive. The younger sibling had transient thrombocytopenia at birth requiring platelet transfusion. | VUS (Potentially Pathogenic) | 

PS3 – functional study supports damaging effect 
PM2 – absent from controls 
BS4 – lack of segregation in family members | Schwartz et al. [8] (Leukemia), Schwartz et al. [13] (Nat Comm) |
| 4           | SAMD9. Heterozygous c.3406G>C (p.E1136Q) | WES confirmed by Sanger sequencing | SAMD9L. Heterozygous c.3538T>C (p.W1180R) | – | Patient no. 3 and 4 in this report, a younger sibling and their mother positive. The younger sibling had transient thrombocytopenia at birth requiring platelet transfusion. | VUS (Potentially Pathogenic) | 

PS3 – functional study supports damaging effect 
PM2 – absent from controls 
BS4 – lack of segregation in family members | Schwartz et al. [8] (Leukemia), Schwartz et al. [13] (Nat Comm) |
| 5           | SAMD9L. Heterozygous c.2407G>C (p.E803Q) | WES confirmed by Sanger sequencing | SAMD9L. Heterozygous c.3538T>C (p.W1180R) | – | Parents negative | Likely Pathogenic | 

PS3 – functional study supports damaging effect 
PM2 – absent from controls | Ortolano et al. [19] |

(continued)
| Patient No. | 11 | 12 |
|------------|----|----|
| **Gene and Variant** | SAMD9L, Heterozygous c.2957G→A (p.R986H) | SAMD9L, Heterozygous c.2957G→A (p.R986H) |
| **Method of genetic diagnosis** | Sanger sequencing of peripheral blood. Confirmed by Sanger sequencing of hair follicles | Targeted NGS. Confirmed by Sanger sequencing of hair follicles |
| **SAMD9 / SAMD9L variant:** | Not de novo | Not de novo |
| **Germline source** | Hair follicles | Hair follicles |
| **Family tested for the same variant** | Patients no. 11 and 12 in this report are siblings. Father positive. Mother negative. | Patients no. 11 and 12 in this report are siblings. Father positive. Mother negative. |
| **ACMG* classification** | Likely Pathogenic | Likely Pathogenic |
| **How pathogenicity was ascribed** | PS3 – functional study supports damaging effect PM5 – another variant (p.R986C) at the same position is pathogenic | PS3 – functional study supports damaging effect PM5 – another variant (p.R986C) at the same position is pathogenic |
| **References** | Tesi et al. [5]; Bluteau et al. [7]; Wong et al. [12] | Tesi et al. [5]; Bluteau et al. [7]; Wong et al. [12] |

Abbreviations: WES indicates whole exome sequencing; WGS, whole genome sequencing; BMT, blood and marrow transplantation; ACMG, American College of Medical Genetics, and VUS, variant of unknown significance; NGS, Next generation sequencing.

* Each pathogenic criterion was weighted as very strong (PVS1), strong (PS1–4); moderate (PM1–6) or supporting (PP1–5) and each benign criterion was weighted as stand-alone (BA1), strong (BS1–4) or supporting (BP1–6). From Richards et al. [20].

1 The SAMD9 variant c.3406G→C (p.E1136Q) was classified as a VUS using strict ACMG criteria. We believe this variant is pathogenic based on well-established functional data from two separate experimental studies showing that it has a deleterious effect on cells. The younger sibling of the patients above also carries the variant and had transient neonatal thrombocytopenia requiring transfusion. However, the mother of these patients carries the variant as well and presently lacks an apparent phenotype. Whether she was transiently affected in the past is unknown, but this is possible as somatic revertant mosaicism is a known associated phenomenon with SAMD9/SAMD9L variants. Other potential mechanisms that could account for the lack of phenotypic segregation include monoallelic gene expression, incomplete penetrance, or variable expressivity. We feel this is important to note for clinical reasons in case this variant is observed in another patient.
| Patient No. | 1 | 2 | 3 | 4 | 5 |
|-------------|---|---|---|---|---|
| Gene involved | SAMD9 (MIRAGE syndrome) | SAMD9 (MIRAGE syndrome) | SAMD9 | SAMD9 | SAMD9 (MIRAGE syndrome) |
| Age at HCT, years | 6.7 | 1.4 | 3.3 | 5 | 1.2 |
| Interval from diagnosis to HCT, years | 6.5 | 0.4 | 0.2 | 0.2 | 0.4 |
| Indication for HCT | Presumed congenital amegakaryocytic thrombocytopenia | MDS | MDS | MDS | MDS |
| Significant pretransplant issues | Secretory diarrhea, adrenocortical insufficiency, lung disease, CKD, failure to thrive | Esophageal achalasia, gastroesophageal reflux, diarrhea, failure to thrive | — | — | Diarrhea, Failure to thrive. |
| Donor type | HLA-identical sibling, female, bone marrow | Unrelated, 10/10 allele match, male, bone marrow | Unrelated, 8/8 allele match, female, bone marrow | Unrelated, 8/8 allele match, male, bone marrow | Father, 5/10 allele match, bone marrow |
| Conditioning regimen; GVHD prophylaxis | Flu/Cy/ATG; Tac/MMF | Bu/Flu/ATG; Tac/Mtx | Bu/Cy/ATG; CsA/Mtx | Bu/Cy/ATG; CsA/Mtx | Bu/Flu; posttransplant Cy, Tac/MMF |
| Conditioning intensity (MA / RIC) | RIC | MA | MA | MA | MA |
| Neutrophil engraftment, days+ | 13 | 12 | 16 | 19 | 14 |
| Platelet engraftment, days+ | 16 | 30 | 14 | 15 | 40 |
| Posttransplant course | Temperature & blood pressure instability, electrolyte imbalance, dehydration, hypoxia | TMA, recurrent pericardial effusions, hypoxia | VOD of liver | Pericardial effusion | TMA, pericardial effusion, VOD of liver |
| Intensive care | Severe hypertension | No | Respiratory distress, did not require intubation | Respiratory distress, required intubation | Respiratory failure, did not require intubation |
| Acute GVHD / Chronic GVHD | No / No | No / Yes | No / No | No / No | No / No |
| Chimerism | 99% donor | 100% donor | 100% donor | 99% donor | 100% donor |
| Post-HCT hematologic outcome | Normal blood counts, no monosomy 7 | Normal blood counts, no monosomy 7, resolution of MDS | Resolution of MDS, no chr. 7 finding | Resolution of MDS, no chr. 7 findings | Normal blood counts, no monosomy 7, resolution of MDS |
| Survival status | Alive; 2.4 y post-HCT | Alive; 3.8 y post-HCT | Alive; 3.2 y post-HCT | Alive; 3 y post-HCT | Alive; 1.4 y post-HCT |
| Current health status | Secretory diarrhea, enteral feeds, low weight and height, thriving, developmental delay, CKD, hypertension, adrenal insufficiency | Recurrent aspiration pneumonias, chronic lung disease, malnutrition, diarrhea, developmental delay, thriving, adrenal insufficiency | School performance issues | Learning disabilities | Supplemental feeds, hypoglycemia episodes, diarrhea, low weight and height, thriving, developmentally delay |
| Patient No. | 6 | 7 | 8 | 9 | 10 |
|------------|---|---|---|---|----|
| Gene involved | SAMD9 (MIRAGE syndrome) | SAMD9L | SAMD9L | SAMD9L | SAMD9L |
| Age at HCT, years | 7.8 | 12.8 | 2.3 | 8.3 | 2 |
| Interval from diagnosis to HCT, years | 5.5 | 0.2 | 1.4 | 0.2 | 1.3 |
| Indication for HCT | MDS | Presumed dyskeratosis congenita | MDS | MDS | MDS |
| Significant pretransplant issues | Hypertension, chronic kidney disease, asthma | Obesity (BMI 34, >97th percentile for age) | Obesity (BMI 27, >97th percentile for age) | – | HLH therapy, E. coli sepsis, punculitis, eplemy gangrenosum, aspergilus and candida sepsis |
| Donor type | Unrelated, 10/10 allele match, male, bone marrow | Unrelated double cord blood, male (5/6 allele match), female (5/6 allele match) | Unrelated cord blood, 6/6 allele match, female | HLA-identical sibling, female, bone marrow | Unrelated, 9/10 allele match, bone marrow |
| Conditioning regimen; GVHD prophylaxis | Flu/Mel/Alemtuzumab; Tac/MMF | Flu/Mel/Alemtuzumab; Tac/MMF | Flu/Cy/TBI; CsA/MMF | Cy/TBI/Ara-C | Bu/Cy/ATG |
| Conditioning intensity (MA / RIC) | RIC | RIC | MA | MA | MA |
| Neutrophil engraftment, days* | 19 | No | 13 | 17 | 18 |
| Platelet engraftment, days* | 19 | No | 12 | 31 | No |
| Posttransplant course | Blood pressure instability, electrolyte imbalance, fever, hypoxia | Restrictive lung disease | Parainfluenza with respiratory failure, renal dysfunction | Culture negative sepsis, bleeding gastric ulcer, hemorragic cystitis | Coronavirus respiratory tract infection, VOD of liver with respiratory failure, defbrilatation, diffuse alveolar hemorrhage |
| Intensive care | No | No | Respiratory failure | Systemic inflammatory response syndrome | Respiratory failure, required intubation |
| Acute GVHD / Chronic GVHD | No / No | No / No | Yes (Grade II, GI, resolved) // No | No / No | Not evaluable / Not evaluable |
| Chimerism | 98% donor | 0% donor | 90% donor | 100% donor | Not done |
| Post-HCT hematologic outcome | Normal blood counts | Graft failure | Resolution of MDS, no chr. 7 finding | Resolution of MDS, no chr. 7 finding | Neutrophil engraftment. Bone marrow not assessed |
| Survival status | Alive; 4.1 y post-HCT | Died of refractory AML; 1.1 y post-HCT | Alive; 2.3 y post-HCT | Alive; 14.7 y post-HCT | Died at day +23 post-HCT from complications related to VOD of liver |
| Current health status | Adrenal insufficiency, diarrhea, hypotension, CKD, urethrocuffaneous fistula, developmental delay, thriving | N.A. | CXD | Doing well | N.A. |

(continued)
| Patient No. | 11  | 12  |
|------------|-----|-----|
| Gene involved | SAMD9L | SAMD9L |
| Age at HCT, years | 2.1 | 1.8 |
| Interval from diagnosis to HCT, years | 0.5 | 0.5 |
| Indication for HCT | MDS | MDS |
| Significant pretransplant issues | Otitis media, croup, roseola | Alpha hemolytic streptococcal sepsis |
| Donor type | Unrelated, 10/10 allele match, female, bone marrow | Unrelated, 10/10 allele match, female, bone marrow |
| Conditioning regimen; GVHD prophylaxis | Bu/Cy; Tac/Mtx | Bu/Cy; Tac/Mtx |
| Conditioning intensity (MA / RIC) | MA | MA |
| Neutrophil engraftment, days* | 19 | 9 |
| Platelet engraftment, days* | 17 | 12 |
| Posttransplant course | Uneventful | VOD of liver, hemolysis, coagulopathy |
| Intensive care | No | VOD |
| Acute GVHD / Chronic GVHD | Yes (Grade II, skin, gut, resolved) / Yes skin, mild | No / No |
| Chimerism | 100% donor | 100% donor |
| Post-HCT hematologic outcome | Normal blood counts, no monosomy 7, resolution of MDS | Normal blood counts, no monosomy 7, resolution of MDS |
| Survival status | Alive; 5.3 y post-HCT | Alive; 1.3 y post-HCT |
| Current health status | Doing well | Doing well |

Abbreviations: ATG (anti-thymocyte globulin); Ara-C (cytosine arabinoside); BU (busulfan); BMI (body mass index); Chr. 7 (chromosome 7); CKD (chronic kidney disease); Cy (cyclophosphamide); CsA (cyclosporine A); GI (gastrointestinal); Flu (fludarabine); HLH (hemophagocytic lymphohistiocytosis); MA (myeloablative); MDS (myelodysplastic syndrome); Mel (melphalan); MIRAGE syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy); MMF (mycophenolate mofetil); Mtx (methotrexate); N.E. (not evaluable); RIC (reduced intensity conditioning); Tac (tacrolimus); TBI (total body irradiation); TMA (thrombotic microangiopathy); and VOD (veno-occlusive disease)
hemorrhage and infection, 1 each), 1 had unknown survival status, and 8 were alive. Of the surviving patients, 1 had pulmonary fibrosis, and 3 had neurologic issues.

Mutations in \textit{SAMD9} and \textit{SAMD9L} add to a growing list of recently described heritable conditions associated with cytopenias, marrow failure, MDS, and AML \cite{1,7,8}. Although these patients can be managed symptomatically with transfusions and treatment of infections, the only curative treatment is with allogeneic HCT.

Indications and timing of HCT in these patients are not straightforward because marrow cells can undergo somatic genetic correction events and spontaneous blood count recovery \cite{4,8,12,22}. In our series, there was an interval of several years from initial presentation to development of bone marrow failure or MDS in 2 cases. Most patients in our series underwent transplant conditioning, with a high rate of engraftment and resolution of MDS or marrow failure. Clinically significant comorbidities were common in \textsc{MIRAGE} syndrome cases and contributed to unique adverse events in the acute post-transplant phase. These patients continue to require ongoing management and multispecialty care for syndrome-related nonhematologic manifestations.

### Table 4

Summary of Available Clinical Data on Immune Reconstitution

| Characteristic | 1 | 2 | 5 | 6 | 3 | 4 | 8 | 11 | 12 |
|----------------|---|---|---|---|---|---|---|-----|-----|
| Gene mutation  | SAMD9 | SAMD9 | SAMD9 | SAMD9 | SAMD9 | SAMD9 | SAMD9L | SAMD9L | SAMD9L |
| \textsc{MIRAGE} phenotype | Yes | Yes | Yes | Yes | No | No | No | No | No |

| Lymphocyte enumeration | 1 month post-HCT | 2 months post-HCT | 3 months post-HCT |
|------------------------|-----------------|-----------------|-----------------|
| ALC per cumm | 570 | 678 | 470 | 252 | 924 | 546 | 288 | 1512 |
| CD3 per cumm | 1970 | 1000 | 1320 | 864 | 2368 | 240 | 826 | NA |
| CD4 per cumm | 2080 | 1307 | 1650 | ND | ND | 1125 | 410 | NA |
| CD8 per cumm | 375 | 891 | ND | ND | ND | ND | ND | NA |
| NK cells per cumm | 250 | 369 | ND | ND | ND | ND | ND | NA |
| CD19 per cumm | 83 | 486 | ND | ND | ND | ND | ND | NA |
| CD19 per cumm | 520 | 167 | ND | ND | ND | ND | ND | NA |
| CD19 per cumm | 1145 | 249 | ND | ND | ND | ND | ND | NA |

### 6 months post-HCT

| ALC per cumm | 2500 | 840 | 4630 | 1254 | ND | 935 | 980 | 981 |
| CD3 per cumm | 1150 | 726 | 2224 | 390 | ND | ND | ND | 451 |
| CD4 per cumm | 600 | 308 | 1308 | 277 | ND | ND | ND | 216 |
| CD8 per cumm | 500 | 377 | 828 | ND | ND | ND | ND | 212 |
| NK cells per cumm | 900 | 114 | 916 | 193 | ND | ND | ND | 193 |
| CD19 per cumm | 450 | 0 | 1264 | 662 | ND | ND | ND | 337 |
| CD19 per cumm | 346 | 254 | 915 | 752 | 522 | 218 | ND | 521 |

### 12 months post-HCT

| ALC per cumm | 6100 | 1801 | 8200 | 1938 | ND | 770 | 2220 | 1400 |
| CD3 per cumm | 3841 | 999 | 6232 | 1212 | ND | ND | ND | 1356 |
| CD4 per cumm | 1829 | 495 | 3526 | 737 | ND | ND | ND | 1548 |
| CD8 per cumm | 1890 | 459 | 2460 | 362 | ND | ND | ND | 884 |
| NK cells per cumm | 549 | 185 | 656 | 178 | ND | ND | ND | 422 |
| CD19 per cumm | 1646 | 617 | 1148 | 502 | ND | ND | ND | 1271 |
| Serum IgG, mg/dL | 379 | 623 | 371 | ND | 300 | 841 | 351 | NA |

### 15 months post-HCT

| ALC per cumm | 6100 | 1801 | 8200 | 1938 | ND | 770 | 2220 | 1400 |
| CD3 per cumm | 3841 | 999 | 6232 | 1212 | ND | ND | ND | 1356 |
| CD4 per cumm | 1829 | 495 | 3526 | 737 | ND | ND | ND | 1548 |
| CD8 per cumm | 1890 | 459 | 2460 | 362 | ND | ND | ND | 884 |
| NK cells per cumm | 549 | 185 | 656 | 178 | ND | ND | ND | 422 |
| CD19 per cumm | 1646 | 617 | 1148 | 502 | ND | ND | ND | 1271 |
| Serum IgG, mg/dL | 379 | 623 | 371 | ND | 300 | 841 | 351 | NA |

Patient 1 (\textit{SAMD9} with \textsc{MIRAGE}): Protein-losing enteropathy. Intravenous immunoglobulin (IVIG) infusions. Patient 2 (\textit{SAMD9} with \textsc{MIRAGE}): Chronic diarrhea. Patient 3 (\textit{SAMD9} without \textsc{MIRAGE}): Lymphocyte enumeration 3 years post-HCT, ALC 4555, CD3 3160, CD4 3330, CD8 1610. NK cells 480, CD19 740, all in per cumm. Patient 4 (\textit{SAMD9} without \textsc{MIRAGE}): Lymphocyte enumeration 3 years post-HCT, ALC 3700, CD3 2530, CD4 1090, CD8 1140. NK cells 400, CD19 770, all in per cumm. Patient 5 (\textit{SAMD9} with \textsc{MIRAGE}): IVIG infusions monthly until 1 year post-HCT. Patient 6 (\textit{SAMD9} with \textsc{MIRAGE}): IVIG infusions monthly until 6 months post-HCT. Patient 7 (\textit{SAMD9L}): Not included in the table. ALC 286 on day +60. Graft failure. Patient 8 (\textit{SAMD9L}): Lymphocyte enumeration 5 years post-HCT, ALC 3600, CD3 2630, CD4 1220, CD8 1310, NK cells 120, CD19 810, all in per cumm. Patient 9 (\textit{SAMD9L}): No data. The patient died of transplant complications on day +23. Patient 10 (\textit{SAMD9L}): No data. The patient died of transplant complications on day +23. Patient 11 (\textit{SAMD9L}): Intermittent IVIG infusions. Patient 12 (\textit{SAMD9L}): Intermittent IVIG infusions.

ALC indicates absolute lymphocyte count; ND, not done; NK, natural killer; IgG, immunoglobulin G.
More data are needed to define timing of HCT in SAMD9/ SAMD9L patients and further refine conditioning regimens as well as management of patients with significant syndrome-related comorbidities. National and international transplant registries should be queried to examine reported outcomes in larger patient cohorts. Finally, long-term follow-up and care guidelines are needed for the survivors.

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