Spontaneous remission and loss of monosomy 7: a window of opportunity for young children with SAMD9L syndrome

Miriam Erlacher,[1,2*] Felicia Andresen,[1°*] Martina Sukova,[3] Jan Stary,[3] Barbara de Moerloose,[4] Jutte van der Werff Ten Bosch,[5] Michael Dworzak,[6,7] Markus G. Seidel,[8] Sophia Polychronopoulou,[9] Rita Beier,[10] Christian P. Kratz,[10] Michaela Nathrath,[11,12] Michael C. Frühwald,[13] Gudrun Göhring,[14] Anke K. Bergmann,[14] Christina Mayerhofer,[1] Dirk Lebrecht,[1] Senthilkumar Ramamoorthy,[1,15] Ayami Yoshimi,[1] Brigitte Strahm,[1] Marcin W. Wlodarski[1,16] and Charlotte M. Niemeyer[1,2]

[1]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [2]German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Partner Site Freiburg, Germany; [3]Department of Pediatric Hematology and Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic; [4]Department of Pediatric Hematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, Belgium; [5]Department of Pediatric Hematology-Oncology, University Hospital Brussel, Brussels, Belgium; [6]St. Anna Children's Hospital, Medical University of Vienna, Department of Pediatrics and Adolescent Medicine, Vienna, Austria; [7]St. Anna Children's Cancer Research Institute, Vienna, Austria; [8]Division of Pediatric Hematology-Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria; [9]Department of Pediatric Hematology-Oncology (T.A.O.), Aghia Sophia Children's Hospital, Athens, Greece; [10]Department of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany; [11]Department of Pediatric Hematology and Oncology, Klinikum Kassel, Kassel, Germany; [12]Department of Pediatrics and Children's Cancer Research Center, Klinikum rechts der Isar, Technical University of Munich, School of Medicine, Munich, Germany; [13]Pediatrics and Adolescent Medicine, University Medical Center Augsburg, Augsburg, Germany; [14]Department of Human Genetics, Hannover Medical School, Hannover, Germany; [15]Institute of Medical Bioinformatics and Systems Medicine, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany and [16]Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN, USA

ME and FA contributed equally as first authors.

°Current address: Division of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.

Correspondence: M. Erlacher
Miriam.erlacher@uniklinik-freiburg.de

Received: May 25, 2023.
Accepted: August 7, 2023.
Early view: August 17, 2023.

https://doi.org/10.3324/haematol.2023.283591

Abstract

Monosomy 7 is the most common cytogenetic abnormality in pediatric myelodysplastic syndrome (MDS) and associated with a high risk of disease progression. However, in young children, spontaneous loss of monosomy 7 with concomitant hematologic recovery has been described, especially in the presence of germline mutations in *SAMD9* and *SAMD9L* genes. Here, we report on our experience of close surveillance instead of upfront hematopoietic stem cell transplantation (HSCT) in seven patients diagnosed with SAMD9L syndrome and monosomy 7 at a median age of 0.6 years (range, 0.4-2.9). Within 14 months from diagnosis, three children experienced spontaneous hematological remission accompanied by a decrease in monosomy 7 clone size. Subclones with somatic *SAMD9L* mutations in *cis* were identified in five patients, three of whom attained hematological remission. Two patients acquired *RUNX1* and *EZH2* mutations during the observation period, of whom one progressed to myelodysplastic syndrome with excess of blasts (MDS-EB). Four patients underwent allogeneic HSCT at a median time of 26 months (range, 14-40) from diagnosis for MDS-EB, necrotizing granulomatous lymphadenitis, persistent monosomy 7, and severe neutropenia. At last follow-up, six patients were alive, while one passed away due to transplant-related causes. These data confirm previous observations that monosomy 7 can be transient in young children with SAMD9L syndrome. However, they also indicate that delaying HSCT poses a substantial risk of severe infection and disease progression. Finally, surveillance of patients with SAMD9L syndrome and monosomy 7 is critical to define the evolving genetic landscape and to determine the appropriate timing of HSCT (*clinicaltrials gov. Identifier: NCT00662090*).

Introduction

Loss of chromosome 7 and partial deletion of its long arm (i.e., monosomy 7 and del(7q)) are frequent non-random cytogenetic aberrations in pediatric patients with myeloid malignancies, including myelodysplastic syndrome (MDS).[1-3] Several tumor suppressors and regulators of myeloid differentiation have been identified on chromosome 7. Among them, deletion of *EZH2, MLL3/KMT2C, SAMD9L*, and *CUX1* has been shown to promote malignant transformation in mouse models.[4-8] The presence of monosomy 7 is generally associated with a high risk of disease progression and acquisition of oncogenic mutations, and timely allogeneic hematopoietic stem cell transplantation (HSCT) is warranted.[1,9-11] However, Scheurlen *et al*. first reported in 1994 on a 14-month-old boy with MDS and monosomy 7 who achieved spontaneous hematologic recovery within 2 years.[12] Subsequently, further case reports and series of transient monosomy 7 in infants and young children with MDS have been published demonstrating spontaneous hematologic recovery upon loss of monosomy 7.[13-17]

Chromosome 7 aberrations have been associated with several germline conditions predisposing to hematopoietic neoplasia, such as GATA2 deficiency syndrome and Fanconi anemia.[18-20] In GATA2 deficiency syndrome, 40% of pediatric patients with cytopenia carry monosomy 7, del(7q), or an unbalanced translocation der(1;7), with the highest prevalence in adolescence.[18,19] Recently, a growing body of research has highlighted the association of monosomy 7 and del(7q) with germline mutations in sterile α-motif domain-containing protein 9 (*SAMD9*) and SAMD9-like (*SAMD9L*).[19,21,22]

Gain of function (GOF) mutations in *SAMD9* and its paralogue *SAMD9L* were first reported in 2016 in children with MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotype, enteropathy) syndrome and ataxia pancytopenia syndrome (ATXPC), respectively.[19,23,24] Our recent analysis of pediatric patients with the histopathological phenotype of refractory cytopenia of childhood (RCC) and MDS enrolled in the registry of the European Working Group of MDS in Childhood (EWOG-MDS) revealed that patients with germline *SAMD9* and *SAMD9L* mutations presented with a broad and overlapping phenotypic spectrum. The majority of cases presented with RCC, whereas MDS with excess of blasts (MDS-EB) was diagnosed in only 7% of patients. Furthermore, chromosome 7 aberrations were observed in 55% of all *SAMD9*- and *SAMD9L*-mutated cases.[19]

SAMD9 and *SAMD9L* are located adjacent to each other on chromosome 7. Germline *SAMD9/9L* GOF mutations result in reduced proliferation and survival of hematopoietic stem and progenitor cells (HSPC).[15,19,25,26] Acquisition of monosomy 7 and del(7q) can be considered somatic rescue events because they result in a non-random loss of the mutant allele, conferring an increased competitive fitness of HSPC. Yet, concomitant loss of tumor suppressors located on chromosome 7 renders monosomy 7 and del(7q) a maladaptive somatic mechanism with potential for leukemic transformation. Other somatic rescue events frequently detected in bone marrow (BM) cells of affected patients include somatic loss of function (LOF) mutations of *SAMD9/9L* in *cis* and uniparental isodisomy 7q (UPD7q) with loss of the mutated allele.[19,21,25,27] Due to the strong selection pressure, multiple hematopoietic clones with clone-defining somatic mutations can simultaneously exist within the marrow. Moreover, in line with the distinct plasticity of hematopoiesis in young children, the polyclonal composition of BM cells may change over time.[19] Consequently, monosomy 7 may spontaneously disappear in patients with SAMD9/9L germline disorders, followed by hematologic recovery.[15,16,25,27] This phenomenon, primarily observed in infants, represents a form of "natural gene therapy" that might spare patients from therapy like HSCT. However, little is known about the frequency, natural history of loss of monosomy 7, and factors influencing outcome of affected patients.

Methods

Seven patients less than 5 years of age diagnosed with a SAMD9L germline disorder with monosomy 7 and normal blast percentage in BM were followed closely to allow for spontaneous recovery. BM examinations every 3 to 4 months included histopathology, cytogenetics, and *SAMD9L* sequencing. Six of the seven patients were enrolled in the prospective study EWOG-MDS 2006 (*clinicaltrials gov. Identifier: NCT00662090*); for patient 5 (P5), parental consent was obtained for the respective data analyses. University of Freiburg Institutional Ethics Committee approved the research (ethics vote no. 247/05). Patient 2 (P2, D1300) has already been described by Sahoo *et al*.[19] The diagnosis of RCC and MDS-EB was established according to the International Consensus Classification (ICC) of hematologic neoplasms.[28] Cytogenetics included classical karyotyping and interphase fluorescence *in situ* hybridization (FISH). Targeted next-generation sequencing (NGS) of *SAMD9L* allowed determination of the variant allele frequency (VAF) and detection of newly acquired somatic *SAMD9L* mutations in *cis*. In order to screen for somatic oncogenic mutations and corrective UPD7q, a custom-made NGS panel including genes frequently mutated in myeloid neoplasia (in the following called "myeloid NGS panel", see the *Online Supplementary Appendix S1*) and single nucleotide polymorphism (SNP) array were performed; data from the BM sample prior to HSCT or at last follow-up is reported. The American College of Medical Genetics and Association for Molecular Pathology (ACMG-AMP) 2015 guidelines were employed for the interpretation of variants identified in the myeloid NGS panel.[29]

Results

Clinical presentation with pancytopenia, immunodeficiency, and multiple non-hematological phenotypes

We report on seven patients with SAMD9L germline disorder who presented with cytopenia and monosomy 7 at a median age of 0.6 years (range, 0.4-2.9). At diagnosis, all patients had moderate to severe neutropenia and three children (P1, P2, P3) required platelet transfusions. Six patients had normocytic (n=5) or macrocytic (n=1) anemia, one patient had a normal hemoglobin concentration with macrocytosis of red cells (P5). Histopathology was compatible with RCC in all seven patients. Immunodeficiency with a variable clinical presentation was present in six patients. The most consistent findings of immunological impairment were hypogammaglobulinemia found in five patients (P1, P2, P5, P6, P7) and B- and natural killer (NK)-cell deficiency present in four (P2, P5, P6, P7). Patient characteristics are summarized in Table 1 and in the *Online Supplementary Appendix*; complete genetic data are listed in the *Online Supplementary Table S1*.

Six of the seven patients had a non-hematological phenotype compatible with SAMD9L germline disorder (Table 1). Three patients were born small for gestational age (P1, P2, P7). Patient 1 (P1) was also diagnosed with cerebellar atrophy and global developmental delay. Patient 2 (P2) was a hypotrophic preterm neonate born at 36 gestational weeks with bilateral cleft lip and palate. Patient 3 (P3) presented with macrocephaly. Patient 5 (P5) was a triplet born preterm at 30 gestational weeks who developed hydrocephalus requiring a ventriculoperitoneal shunt in the first year of life. Patient 6 (P6) presented with mild macrocephaly and short thumbs. Patient 7 (P7) had enlarged eye bulbs and failure to thrive.

Spontaneous hematopoietic recovery and clinical course

With a median follow-up of 43 months (range, 40-55), three of the seven patients (P3, P4, P6) experienced spontaneous regression of monosomy 7 (Figure 1; *Online Supplementary Figure S1*). In patient 4 (P4) and patient 6 (P6), monosomy 7 was no longer detectable 6 and 16 months from diagnosis, respectively. P4 presented at 7 months of age with pancytopenia, requirement for platelet transfusions, and a normal karyotype. Three months after the initial presentation, a small monosomy 7 clone of 7% was noted, which was no longer detectable 3 months later. Concurrently, the absolute neutrophil count (ANC) slowly increased to $1.23x10^9$/L at 3 months and $3.97x10^9$/L at 6 months from diagnosis, and hemoglobin concentration and platelet count reached normal values at six and 14 months, respectively. Concomitantly, BM cellularity increased to an age-adjusted normal value. P6 presented with neutropenia, macrocytosis, and moderate thrombocytopenia at the age of 2.8 years. BM analysis was compatible with hypocellular RCC with a monosomy 7 clone in 63% of BM interphases. The ANC had slowly increased 7 months after diagnosis and reached close to normal values (ANC $1.47x10^9$/L) 21 months from diagnosis. By that time, the monosomy 7 clone was no longer detectable and hemoglobin and platelet count were normalized at 16 and 32 months from diagnosis, respectively. P3 presented with pancytopenia at the age of 4 months. BM histopathology was compatible with hypocellular RCC with monosomy 7 in 37% of BM interphases. Nine months later, hemoglobin concentration and platelet count had normalized, but isolated neutropenia (ANC $0.38x10^9$/L) persisted. Thirteen months after diagnosis, trephine biopsy showed a normocellular BM according to age and the complete blood count (CBC) gradually improved. Further invasive procedures were denied, the child was alive with a normalized CBC 4.3 years after diagnosis (age 4.5 years). All four patients that did not experience spontaneous remission (P1, P2, P5, P7) received an allogeneic HSCT with a median interval from diagnosis to HSCT of 26 months (range, 14-40) (*Online Supplementary Figure S1*). Indications for HSCT were severe neutropenia and/or bacterial infection (P1, P7), persistence of monosomy 7 (P5), and disease progression to MDS-EB (P2). Three of the four transplanted patients (P1, P5, P7) were alive with stable engraftment and complete donor chimerism at last follow-up. P2 who succumbed to transplant-related causes had disease progression prior to HSCT. At the age of 15 months (i.e., 10 months after diagnosis), the patient developed severe neutropenia prompting a 12-day treatment course with granulocyte colony-stimulating factor (G-CSF). Subsequently, the BM blast percentage and cellularity increased consistent with progression to MDS-EB and persisted after G-CSF withdrawal. At the time, two *RUNX1* variants (see below) were detected in the BM. After a myeloablative conditioning regimen and an allogeneic HSCT from a matched unrelated donor, the patient developed acute respiratory distress syndrome and veno-occlusive disease and died in hematologic remission.

Somatic events influencing disease outcome

The three patients with spontaneous remission (P3, P4, P6) had somatic *SAMD9L* LOF mutations in *cis* known to disrupt the germline allele. Figure 1 depicts the courses of the VAF of *SAMD9L*, monosomy 7, and ANC. P3 acquired a somatic *SAMD9L* variant (*SAMD9L* c.1765C>T, p.R589*) 13 months from diagnosis (VAF 12%), molecular analyses at later time points could not be obtained. P4 acquired two somatic *SAMD9L* variants with a VAF of 27% (*SAMD9L* c.683G>A, p.C228Y) and 4% (*SAMD9L* c.2699>G, p.Y900C) 6 months from diagnosis concomitantly with loss of the previously diagnosed monosomy 7. Both *SAMD9L* clones remained stable over time, a third somatic *SAMD9L* variant (*SAMD9L* c.3562C>T, p.R1188*, VAF 4%) was detected 41 months after diagnosis. P6 harbored a somatic *SAMD9L* variant (*SAMD9L* c.4224dupA, p.Q1409Tfs*49) with a VAF of 6% at diagnosis. The somatic *SAMD9L* variant slowly in-

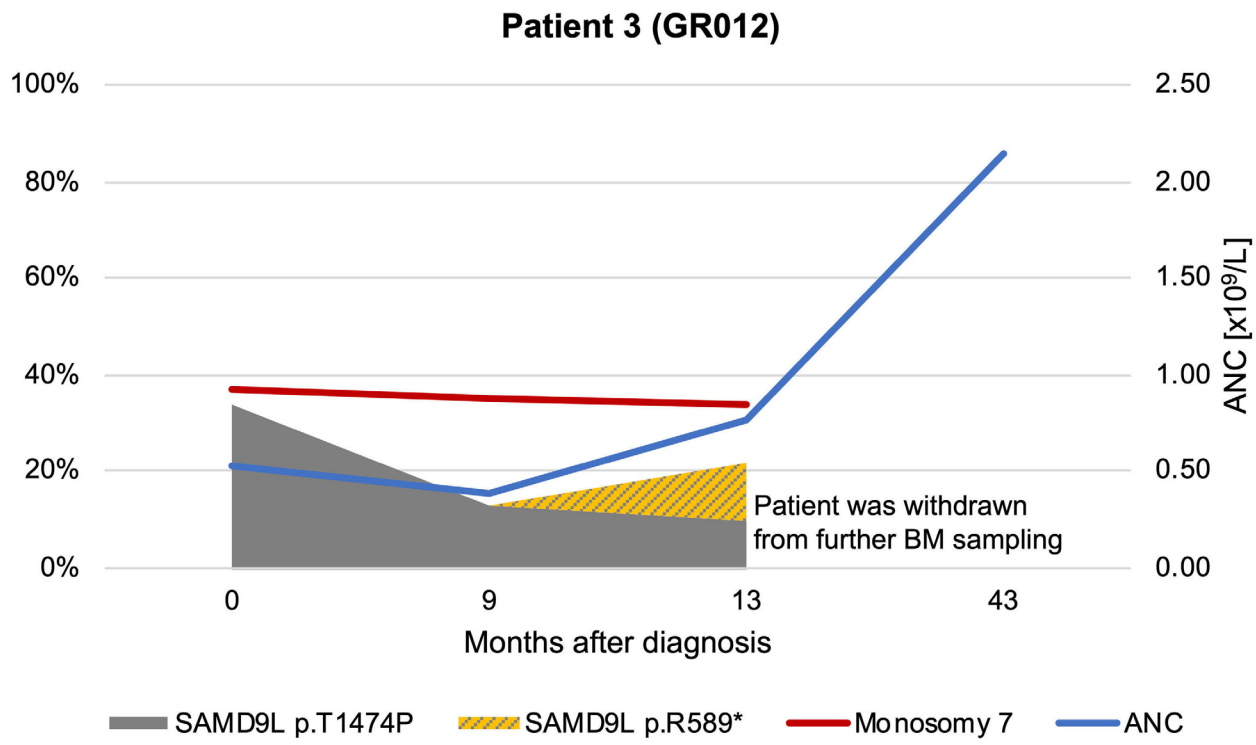
creased to 35%, while the monosomy 7 clone decreased in size over time and subsequently disappeared at 16 months from diagnosis.

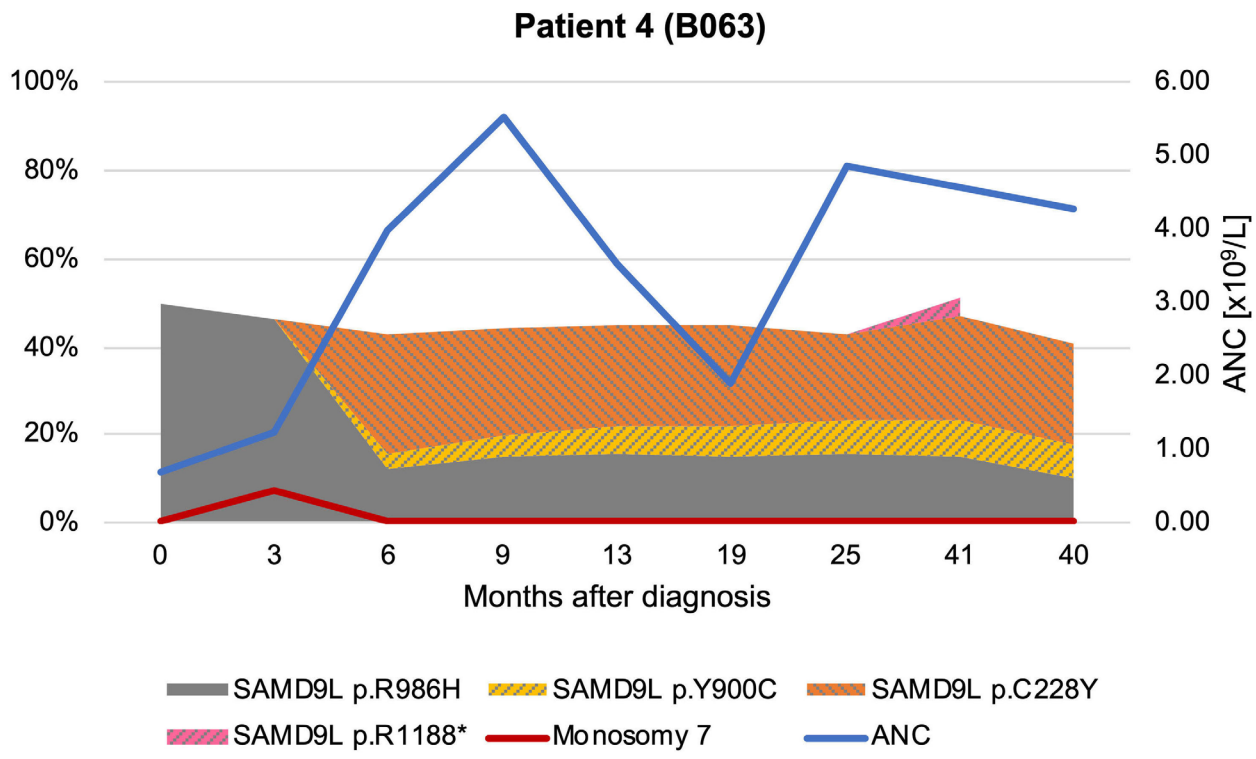
Importantly, we also detected somatic *SAMD9L* mutations in *cis* in two patients (P2, P7) who did not experience hematological recovery and/or a decrease in monosomy 7 clone size (*Online Supplementary Table S1; Online Supplementary Figure S1*). P2 acquired a somatic *SAMD9L* variant 1 month after diagnosis (*SAMD9L* c.768dup, p.K257*, VAF 6%). Within 12 months, the VAF of this variant increased to 23%, however, the disease progressed to MDS-EB. P7 had a large monosomy 7 clone at diagnosis and acquired a somatic *SAMD9L* variant (*SAMD9L* c.2385C>A, p.Y795*) with a VAF of 6% 6 months later. The patient received an allograft for persistent severe neutropenia 10 months later. The myeloid NGS panel analysis demonstrated that two patients (P2, P5) had acquired oncogenic mutations during the course of their disease (*Online Supplementary Table S1; Online Supplementary Figure S1*). P2 acquired two pathogenic *RUNX1* mutations 12 months from diagnosis

Table 1. Phenotype and clinical course of seven patients with *SAMD9L* germline mutations and monosomy 7.

Patient N (UPN)	Sex	Age at dx in mths	CBC at dx (WBC, ANC, PLT, Hb, MCV)	Non-hematological phenotype / Immunological phenotype	Somatic *SAMD9L* mutation at last FU (N)	Monosomy 7 clone size at dx / Loss of monosomy 7	Somatic cancer gene mutation at last FU (N)	Age at HSCT in mths / HSCT indication	Status at last FU
P1 (D1297)	M	6	6.40x10⁹/L, 0.70x10⁹/L, 100x10⁹/L #, 9.5 g/dL, 79 fL	SGA, cerebellar atrophy, global developmental delay / Hypogammaglobulinemia	No	73% / No	No	46 / Necrotizing granulomatous lymphadenitis	Alive
P2 (D1300)	F	5	3.90x10⁹/L, 0.39x10⁹/L, 3x10⁹/L, 6.7 g/dL, 75 fL	Preterm infant (36 GW), SGA, cleft lip and palate / Hypogammaglobulinemia, B/NK cell deficiency	Yes (1)	80% / No	*RUNX1* (2)	19 / MDS-EB	Dead
P3 (GR012)	M	4	3.14x10⁹/L, 0.35x10⁹/L, 12x10⁹/L, 8 g/dL, 80 fL	Macrocephaly / None	Yes (1)	No / NA	No	NA	Alive
P4 (B063)	M	7	7.10x10⁹/L, 0.71x10⁹/L, 107x10⁹/L #, 8 g/dL, 78 fL	None / None	*Yes* (3)	7% / Yes	No	NA	Alive
P5 (KM)	F	17	4.50x10⁹/L, 0.50x10⁹/L, 170x10⁹/L, 12.3 g/dL, 92 fL	Preterm triplet (30 GW), hydrocephalus / Hypogammaglobulinemia, B/NK cell deficiency	No	52% / No	*RUNX1* (1), *EZH2* (2)	53 / Persistent -7	Alive
P6 (CZ132)	F	34	4.10x10⁹/L, 0.81x10⁹/L, 46x10⁹/L, 11 g/dL, 94 fL	Mild macrocephaly, short thumbs / Hypogammaglobulinemia, B cell deficiency	Yes (1)	63% / Yes	No	NA	Alive
P7 (A146)	F	15	2.54x10⁹/L, 0.25x10⁹/L, 79x10⁹/L, 7.7 g/dL, 89 fL	SGA, failure to thrive, big eye bulbs / Hypogammaglobulinemia, B/NK cell deficiency	Yes (1)	66 % / No	No	32 / Severe neutropenia	Alive

#Post-transfusion. SAMD9L: sterile α-motif domain-containing protein 9-like; N: number; UPN: unique patient number; dx: diagnosis; mths: months; CBC: complete blood count; WBC: white blood cells; ANC: absolute neutrophil count; PLT: platelets; Hb: hemoglobin; MCV: mean corpuscular volume; FU: follow-up; HSCT: hematopoietic stem cell transplantation; SGA: small for gestational age; NA: not applicable; GW: weeks of gestation; MDS-EB: myelodysplastic syndrome with excess blasts.





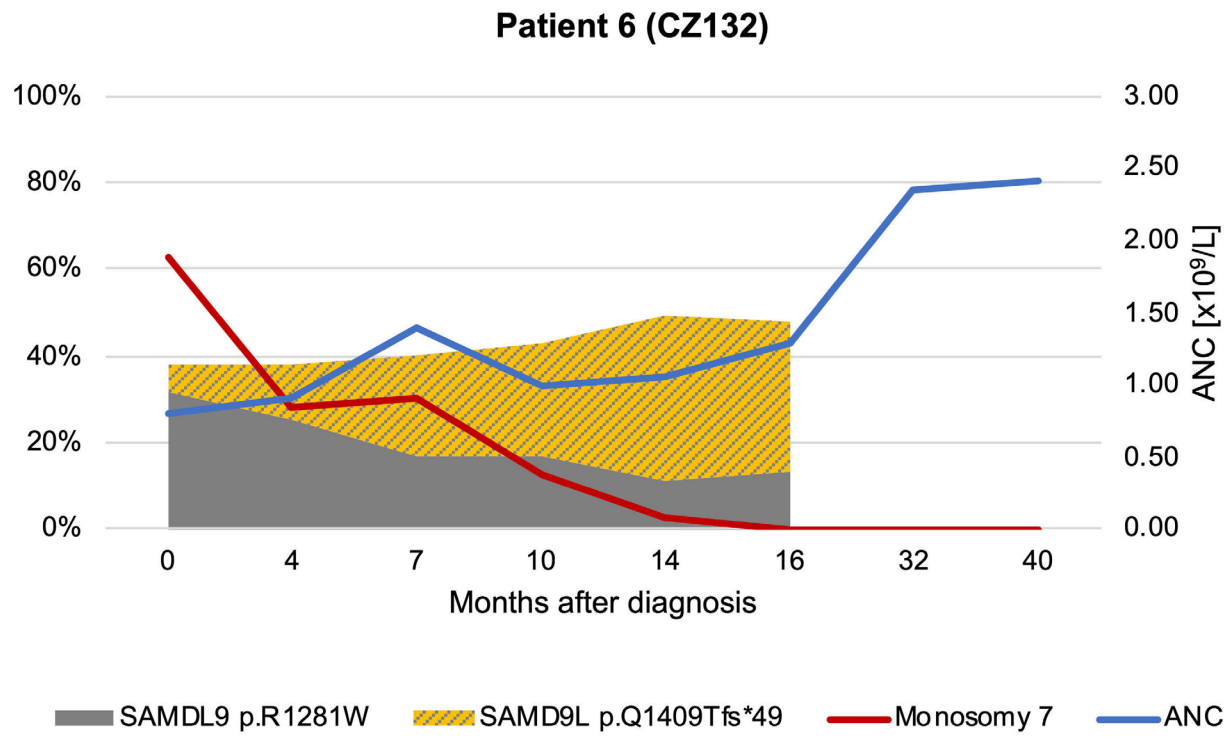


Figure1. Course of *SAMD9L* variant allele frequency, monosomy 7 (analyzed by fluorescence *in situ* hybridization), and absolute neutrophil count of patient 3, 4, and 6. ANC: absolute neutrophil count; BM: bone marrow; SAMD9L: sterile α-motif domain-containing protein 9-like.

(*RUNX1* c.317G>A, p.W106*; *RUNX1* c.496_508+2dup), which was accompanied by disease progression to MDS-EB. In P5, a pathogenic variant in *RUNX1* (*RUNX1* c.593A>G, p.Asp198Gly) and a variant of unknown significance in *EZH2* (*EZH2* c.1672+3_1672+4del) were detected 30 months after diagnosis. At this time point, the monosomy 7 clone size had increased again to 12% following an initial decrease from 52% to 4% and the patient had already been scheduled for HSCT for persistent monosomy 7.

Discussion

Somatic genetic rescue (SGR) events that (at least in part) abrogate an underlying deleterious germline defect and thereby confer a selective advantage have been described in several inherited bone marrow failure and leukemia predisposition syndromes.[30-36] Prime examples are SAMD9/9L germline disorders with multiple SGR events typically resulting in a polyclonal BM (Figure 2).[19]

This case series describes the natural history of transient monosomy 7 in seven children with *SAMD9L* germline disorders below the age of 5 years at diagnosis. Spontaneous hematologic recovery was observed in three children; complete loss of monosomy 7 was demonstrated in two children and can be assumed in the third patient who was withdrawn from follow-up BM studies but normalized his CBC. In all three patients, improvement of blood counts was accompanied by the emergence and/or expansion of clones harboring somatic *SAMD9L* mutations in *cis* as well as a gradual decrease in monosomy 7 clone size. However, somatic *SAMD9L* mutations in *cis* were also detected in two patients who did not experience hematologic recovery. This finding underlines that the acquisition of adaptive SGR clones such as somatic *SAMD9L* mutations in *cis* does not reliably predict loss of monosomy 7 or favorable clinical outcome.[19] Interestingly, we did not detect somatic genetic reversion by UPD7q with non-random loss of the *SAMD9L* germline variant in either of the two patients with spontaneous remission and BM material available for SNP array. Whether somatic *SAMD9L* mutations in *cis* and UPD7q are functionally equivalent with respect to long-term sustainability of normal hematopoietic function is currently unknown.

It is well established that the somatic mutational landscape in children with MDS differs from that observed in adults.[19,21,37-39] The nature of somatic variants noted in pediatric MDS is largely dependent on the underlying genetic predisposition,[19,34,36,40,41] the morphological subtype (MDS-EB *vs*. RCC), and the karyotype (monosomy 7 *vs*. other karyotypes).[15,21] Our recently published data demonstrated that *SAMD9/9L*-mutated patients most frequently harbored mutations in *SETBP1, ASXL1, RUNX1, EZH2*, and the *RAS* pathway genes, thereby resembling the somatic mutational pattern of *GATA2* deficiency and MDS with monosomy 7 without underlying *GATA2* or *SAMD9/9L* germline mutations.[19] In two of the patients described here, we observed the emergence of somatic mutations in *RUNX1* and *EZH2* during BM surveillance. Somatic variants in *RUNX1* play a critical role in leukemic transformation in a number of predisposition syndromes, specifically in severe congenital neutropenia SCN and Fanconi anemia: Skokowa *et al.* detected somatic *RUNX1* mutations in 64% of pediatric patients with MDS/acute myeloid leukemia following SCN,[40] while Sebert *et al.* described *RUNX1* alterations in 34% of Fanconi anemia patients with clonal hematopoiesis.[36]

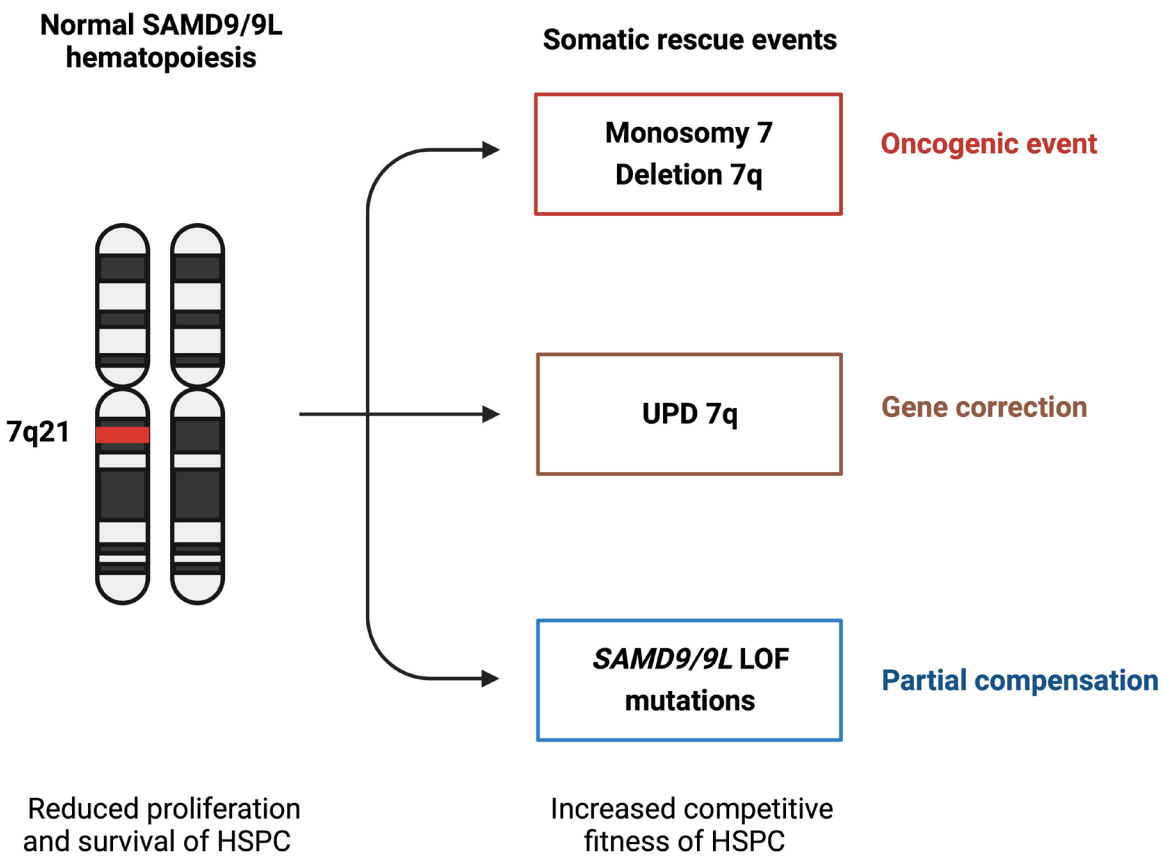


Figure 2. Somatic rescue events in *SAMD9/9L* germline disorders. UPD: uniparental isodisomy; LOF: loss-of-function; HSPC: hematopoietic stem and progenitor cells; SAMD9L: sterile α-motif domain-containing protein 9-like. Created with BioRender.com.

Meticulous description of the sequence of acquisition of individual somatic aberrations during leukemogenesis is a prerequisite for unraveling their impact on outcome of patients with pediatric MDS. Schwartz *et al.* reported that the presence of somatic *SETBP1* mutations is associated with a poor outcome in patients with MDS-EB.[21] *SETBP1* mutations are often noted in the context of monosomy 7.[15] In our previous report, 16 of 59 patients (27%) with SAMD9/9L germline disorders and normal blast count carried somatic oncogenic mutations, and twelve of the 16 patients had monosomy 7. The presence of monosomy 7 had a negative impact on patient outcome; among patients with SAMD9/9L syndrome and normal blast count, 5-year overall survival was 93% in patients with normal karyotype and 73% in the presence of monosomy 7.[19]

To the best of our knowledge, somatic genetic rescue with complete hematological recovery in SAMD9L syndrome and monosomy 7 has only been observed in patients less than 5 years of age.[15,16,19,22,42] This age dependency may indicate that BM plasticity substantially decreases during the first years of life. At the same time, it provides a window of opportunity for BM surveillance that might spare some of these affected children from allogeneic HSCT. Reoccurrence of monosomy 7 has not been described, the longest reported follow-up is 20 years.[15]

Nevertheless, monosomy 7 remains a risk factor for potential disease progression. Although BM sampling is an invasive procedure requiring analgesic sedation or anesthesia in small children, frequent BM examinations (e.g., q3-4 months) are advised to detect emerging oncogenic mutations early during malignant transformation. Of note, two of the seven patients included in the surveillance strategy reported were transplanted for infection and severe neutropenia. When initiating a surveillance strategy, treating physicians need to be aware that these young children with severe to moderate neutropenia, B- and NK-cell deficiency, and/or hypogammaglobulinemia are at increased risk for life-threatening infections.

This case series has two main limitations. First, the small number of patients renders it difficult to draw definitive conclusions about patient management. Furthermore, since our myeloid NGS panel has a detection limit of 5%, small somatic clones might have been missed in some patients. Future studies of larger patient cohorts using more sensitive sequencing methods such as duplex unique molecular identifiers sequencing[43] or single-cell sequencing approaches could address these open questions.

In summary, surveillance instead of upfront HSCT can give some patients less than 5 years of age with SAMD9L syndrome and monosomy 7 a chance to experience spontaneous hematological remission. However, stringent indications for HSCT are recommended to render this expectant approach a safe procedure in this young patient population. Although the mechanism of loss of monosomy 7 is not fully elucidated yet, clinical experience indicates that expansion of clones with somatic rescue mutations in *cis* is sufficient to allow for hematopoietic regeneration in some patients. Such "natural gene therapy" provides a promising template for novel gene therapy approaches. Introducing stop mutations, which are the most frequent somatic rescue events in SAMD9L disease, is technically well feasible rendering SAMD9/9L germline syndromes most amenable to gene therapy.

Disclosures

No conflicts of interest to disclose.

Contributions

ME and FA designed the research, analyzed, interpreted clinical data and wrote the manuscript. CM, CMN and MWW contributed to the manuscript conception. ME, BS, AY, CMN, MS, JS, BdW, JvdWTB, MD, MGS, SP, RB, CK, MN and MCF were involved in patient care, testing and data presentation. All authors contributed to the manuscript and approved its final version.

Acknowledgments

We thank A-R. Kaya, M. Teller, C. Jaeger, and S. Zolles, for excellent laboratory assistance; P. Noellke for assistance with the statistical analysis; A. Breier, W. Truckenmueller, and A. Gebert for data management (all University of Freiburg). We acknowledge the contribution of the Hilda Biobank at the Department of Pediatrics and Adolescent Medicine, Freiburg, Germany. We are also deeply grateful for continuous effort of the National Reference Pathologists, National Reference Cytogeneticists, physicians, nurses and other staff of pediatric hematology/oncology units and transplant centers in all participating countries within the EWOG-MDS consortium (www.ewog-mds-saa.org).

Funding

This work was generated within the European Reference Network for Pediatric Cancer (PAEDCAN). It was supported by the German Federal Ministry of Education and Research (BMBF) 01GM1911A "MyPred - Network for young individuals with syndromes predisposing to myeloid malignancies" to BS, CMN, GG, ME, AY and MWW.

Data-sharing statement

All data relevant to the study are included in the article or uploaded in the Online Supplementary Appendix.

References

1. Hasle H, Arico M, Basso G, et al. Myelodysplastic syndrome, juvenile myelomonocytic leukemia, and acute myeloid leukemia associated with complete or partial monosomy 7. European Working Group on MDS in Childhood (EWOG-MDS). Leukemia. 1999;13(3):376-385.
2. Stieglitz E, Taylor-Weiner AN, Chang TY, et al. The genomic landscape of juvenile myelomonocytic leukemia. Nat Genet. 2015;47(11):1326-1333.
3. Gohring G, Michalova K, Beverloo HB, et al. Complex karyotype newly defined: the strongest prognostic factor in advanced childhood myelodysplastic syndrome. Blood. 2010;116(19):3766-3769.
4. Inaba T, Honda H, Matsui H. The enigma of monosomy 7. Blood. 2018;131(26):2891-2898.
5. An N, Khan S, Imgruet MK, et al. Gene dosage effect of CUX1 in a murine model disrupts HSC homeostasis and controls the severity and mortality of MDS. Blood. 2018;131(24):2682-2697.
6. Chen C, Liu Y, Rappaport AR, et al. MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia. Cancer Cell. 2014;25(5):652-665.
7. Mochizuki-Kashio M, Aoyama K, Sashida G, et al. Ezh2 loss in hematopoietic stem cells predisposes mice to develop heterogeneous malignancies in an Ezh1-dependent manner. Blood. 2015;126(10):1172-1183.
8. Nagamachi A, Matsui H, Asou H, et al. Haploinsufficiency of SAMD9L, an endosome fusion facilitator, causes myeloid malignancies in mice mimicking human diseases with monosomy 7. Cancer Cell. 2013;24(3):305-317.
9. Kardos G, Baumann I, Passmore SJ, et al. Refractory anemia in childhood: a retrospective analysis of 67 patients with particular reference to monosomy 7. Blood. 2003;102(6):1997-2003.
10. Hasle H, Alonzo TA, Auvrignon A, et al. Monosomy 7 and deletion 7q in children and adolescents with acute myeloid leukemia: an international retrospective study. Blood. 2007;109(11):4641-4647.
11. Pastor V, Hirabayashi S, Karow A, et al. Mutational landscape in children with myelodysplastic syndromes is distinct from adults: specific somatic drivers and novel germline variants. Leukemia. 2017;31(3):759-762.
12. Scheurlen W, Borkhardt A, Ritterbach J, Huppertz HI. Spontaneous hematological remission in a boy with myelodysplastic syndrome and monosomy 7. Leukemia. 1994;8(8):1435-1438.
13. Mantadakis E, Shannon KM, Singer DA, et al. Transient monosomy 7: a case series in children and review of the literature. Cancer. 1999;85(12):2655-2661.
14. Parker TM, Klaassen RJ, Johnston DL. Spontaneous remission of myelodysplastic syndrome with monosomy 7 in a young boy. Cancer Genet Cytogenet. 2008;182(2):122-125.
15. Pastor VB, Sahoo SS, Boklan J, et al. Constitutional SAMD9L mutations cause familial myelodysplastic syndrome and transient monosomy 7. Haematologica. 2018;103(3):427-437.
16. Wong JC, Bryant V, Lamprecht T, et al. Germline SAMD9 and SAMD9L mutations are associated with extensive genetic evolution and diverse hematologic outcomes. JCI Insight. 2018;3(14):e121086.
17. Tsang MMC, Ha SY, Chan N, So CC, Cheuk DKL, Chan GCF. Spontaneous resolution of refractory cytopenia of childhood with monosomy 7 in an infant without an identifiable genetic cause. Pediatr Blood Cancer. 2022;69(10):e29654.
18. Kozyra EJ, Gohring G, Hickstein DD, et al. Association of unbalanced translocation der(1;7) with germline GATA2 mutations. Blood. 2021;138(23):2441-2445.
19. Sahoo SS, Pastor VB, Goodings C, et al. Clinical evolution, genetic landscape and trajectories of clonal hematopoiesis in SAMD9/SAMD9L syndromes. Nat Med. 2021;27(10):1806-1817.
20. Dutzmann CM, Spix C, Popp I, et al. Cancer in children with Fanconi anemia and ataxia-telangiectasia - a nationwide register-based cohort study in Germany. J Clin Oncol. 2022;40(1):32-39.
21. Schwartz JR, Ma J, Lamprecht T, et al. The genomic landscape of pediatric myelodysplastic syndromes. Nat Commun. 2017;8(1):1557.
22. Bluteau O, Sebert M, Leblanc T, et al. A landscape of germ line mutations in a cohort of inherited bone marrow failure patients. Blood. 2018;131(7):717-732.
23. Narumi S, Amano N, Ishii T, et al. SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. Nat Genet. 2016;48(7):792-797.
24. Chen DH, Below JE, Shimamura A, et al. Ataxia-pancytopenia syndrome is caused by missense mutations in SAMD9L. Am J Hum Genet. 2016;98(6):1146-1158.
25. Tesi B, Davidsson J, Voss M, et al. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. Blood. 2017;129(16):2266-2279.
26. Thomas ME, 3rd, Abdelhamed S, Hiltenbrand R, et al. Pediatric MDS and bone marrow failure-associated germline mutations in SAMD9 and SAMD9L impair multiple pathways in primary hematopoietic cells. Leukemia. 2021;35(11):3232-3244.
27. Buonocore F, Kuhnen P, Suntharalingham JP, et al. Somatic mutations and progressive monosomy modify SAMD9-related phenotypes in humans. J Clin Invest. 2017;127(5):1700-1713.
28. Rudelius M, Weinberg OK, Niemeyer CM, Shimamura A, Calvo KR. The International Consensus Classification (ICC) of hematologic neoplasms with germline predisposition, pediatric myelodysplastic syndrome, and juvenile myelomonocytic leukemia. Virchows Arch. 2023;482(1):113-130.
29. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424.
30. Ramirez MJ, Pujol R, Trujillo-Quintero JP, et al. Natural gene therapy by reverse mosaicism leads to improved hematology in Fanconi anemia patients. Am J Hematol. 2021;96(8):989-999.
31. Jongmans MC, Verwiel ET, Heijdra Y, et al. Revertant somatic mosaicism by mitotic recombination in dyskeratosis congenita. Am J Hum Genet. 2012;90(3):426-433.
32. Sharma R, Sahoo SS, Honda M, et al. Gain-of-function mutations in RPA1 cause a syndrome with short telomeres and somatic genetic rescue. Blood. 2022;139(7):1039-1051.
33. Perdigones N, Perin JC, Schiano I, et al. Clonal hematopoiesis in patients with dyskeratosis congenita. Am J Hematol. 2016;91(12):1227-1233.
34. Kennedy AL, Myers KC, Bowman J, et al. Distinct genetic pathways define pre-malignant versus compensatory clonal hematopoiesis in Shwachman-Diamond syndrome. Nat Commun. 2021;12(1):1334.
35. Revy P, Kannengiesser C, Fischer A. Somatic genetic rescue in Mendelian haematopoietic diseases. Nat Rev Genet. 2019;20(10):582-598.

36. Sebert M, Gachet S, Leblanc T, et al. Clonal hematopoiesis driven by chromosome 1q/MDM4 trisomy defines a canonical route toward leukemia in Fanconi anemia. Cell Stem Cell. 2023;30(2):153-170.
37. Coutinho DF, Boroni M, Batalha ABW, et al. Somatic genomic variants in refractory cytopenia of childhood. J Pediatr Hematol Oncol. 2021;6(3):123-126.
38. Noy-Lotan S, Krasnov T, Dgany O, et al. Incorporation of somatic panels for the detection of haematopoietic transformation in children and young adults with leukaemia predisposition syndromes and with acquired cytopenias. Br J Haematol. 2021;193(3):570-580.
39. Tan S, Kermasson L, Hilcenko C, et al. Somatic genetic rescue of a germline ribosome assembly defect. Nat Commun. 2021;12(1):5044.
40. Skokowa J, Steinemann D, Katsman-Kuipers JE, et al. Cooperativity of RUNX1 and CSF3R mutations in severe congenital neutropenia: a unique pathway in myeloid leukemogenesis. Blood. 2014;123(14):2229-2237.
41. West RR, Calvo KR, Embree LJ, et al. ASXL1 and STAG2 are common mutations in GATA2 deficiency patients with bone marrow disease and myelodysplastic syndrome. Blood Adv. 2022;6(3):793-807.
42. Csillag B, Ilencikova D, Meissl M, 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(4):e27589.
43. Schmitt MW, Kennedy SR, Salk JJ, Fox EJ, Hiatt JB, Loeb LA. Detection of ultra-rare mutations by next-generation sequencing. Proc Natl Acad Sci U S A. 2012;109(36):14508-14513.