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

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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*).

Supplemental data

Supplemental information 1. List of genes included in the myeloid NGS panel.
ANKRD26, ASXL1, ASXL2, BCOR, BCORL1, BRAF, CBL, CDKN2A, CEBPA, CKIT, CUX1, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA1, GATA2, GNAS, IDH1, IDH2, IKZF1, JAK2, JAK3, KRAS, NF1, NPM1, NRAS, PHF6, PIGA, PRPF8, PTEN, PTPN11, RAD21, RUNX1, SAMD9, SAMD9L, SETBP1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, WT1, ZRSR2.

Supplemental information 2. Clinical course of patients with SAMD9L germline disorder and monosomy 7

Patient 1 (D1297) was diagnosed with refractory cytopenia of childhood (RCC) at the age of six months. The boy was small for gestational age (SGA) at birth and presented with global developmental delay. A brain MRI showed cerebellar atrophy. Cytogenetics revealed a monosomy 7 and isochromosome 7 in 14 and 3 of 20 metaphases, respectively. A germline *SAMD9L* variant with a VAF of 30% (*SAMD9L* p.M89R) was detected, confirming the diagnosis of Ataxia-Pancytopenia (ATXPC) syndrome. Repeated complete blood counts (CBCs) showed mild leukopenia with severe to moderate neutropenia, mild macrocytic anemia, and varying thrombocytopenia (white blood cells (WBC) 3.92 – 6.40 x 10^9/L, absolute neutrophil count (ANC) 0.20 – 0.70 x 10^9/L, platelets (PLT) 90 – 139 x 10^9/L, hemoglobin (Hb) 9.5 – 13.0 g/dL, mean corpuscular volume (MCV) 95 fL) without transfusion dependency. The patient also had hypogammaglobulinemia at diagnosis (IgG 54 mg/dL, IgM 17 mg/dL, IgA 12 mg/dL), but no susceptibility to infections. Seventeen months after diagnosis, *SAMD9L* p.M892R VAF in BM cells had slowly decreased to 14%, while the monosomy 7 clone increased, and the isochromosome 7 clone had disappeared. Thereafter, the *SAMD9L* p.M892R VAF stayed between 24% and 35%, while monosomy 7 was detected with a clone size ranging between 40% and 75% of interphases. At the age of 3.3 years, the patient developed severe necrotizing granulomatous lymphadenitis (ANC at the time 0.57 x 10^9/L) with the need for surgical intervention, prompting the indication for HSCT. Successful allogeneic HSCT from an HLA-identified matched unrelated donor (MUD) after conditioning with treosulfan, thiotepa, and fludarabine and serotherapy with anti-thymocyte globulin (ATG) was performed at the age of 3.8 years. The patient remained well and alive 1.8 years after HSCT.

Patient 2 (D1300) was diagnosed with RCC at the age of five months. Monosomy 7 was noted one month after diagnosis, and a germline *SAMD9L* variant (*SAMD9L* p.P1349L) with a VAF of 38% was detected. The girl was born SGA and had a cleft lip and palate. At diagnosis of RCC, she presented with pancytopenia (WBC 3.90 x 10^9/L, ANC 0.39 x 10^9/L, PLT 3 x 10^9/L, Hb 6.7 g/dL, MCV 75 fL (after transfusion)) and transfusion dependency for red blood cells and platelets. Immunological work-up revealed NK cell and B cell deficiency (CD19+ B-cells 5%, abs. 0.18 x 10^9/L; CD16+ CD56+ CD3- cells 2 %, abs. 0.07 x 10^9/L) and hypogammaglobulinemia (IgG 138 mg/dl, IgM 9 mg/dl, IgA 32 mg/dl, IgG <15 U/ml). At the age of 9 months, the CBC improved spontaneously (WBC 5.3 x 10^9/L, ANC 1.43 x 10^9/L, PLT 53 x 10^9/L, Hb 11.8 g/dL). At the age of 15 months, the ANC decreased and the patient received a 12-day treatment course with G-CSF for isolated neutropenia. Subsequent BM analyses showed an increase in cellularity, marked dysplasia, and an excess of blasts consistent with MDS-EB. The patient received an allogeneic HSCT from an HLA-identical matched unrelated donor after conditioning with fludarabine, thiotepa, melphalan, and a serotherapy with anti-thymocyte globulin and rituximab. She developed acute respiratory distress syndrome, veno-occlusive disease with liver failure and died from complications in remission of MDS-EB at the age of 21 months.

Patient 3 (GR012) presented with an infection and pancytopenia (WBC 3.14 x 10^9/L, ANC 0.35 x 10^9/L, PLT 12 x 10^9/L, Hb 8 g/dL, MCV 80 fL) at the age of four months. He was subsequently diagnosed with RCC. Further genetic work-up revealed monosomy 7 in 21 of 30 BM cell metaphases (FISH analysis: 37% of interphases) and a germline *SAMD9L* variant with a VAF of 34% (*SAMD9L* p.T1474P). He had normal immunoglobulin levels (IgG 812 mg/dL, IgM 250 mg/dL, IgA 89 mg/dL) and no prior susceptibility to infections. Nine months from diagnosis, the patient's platelet count and hemoglobin concentration had improved spontaneously (WBC 7.70 x 10^9/L, ANC 0.38 x 10^9/L, PLT 179 x 10^9/L, Hb 11.7 g/dL) and the germline *SAMD9L* variant had decreased to a VAF of 13%. Fourteen months from diagnosis, the patient was well without severe infections, the ANC had slightly increased to 0.50 G/L, and monosomy 7 was only present in 9 of 25 BM cell metaphases (FISH analysis: 34% of interphases). Subsequently, the patient withdrew from scheduled BM surveillance. At the age of 4.0 years (3 years and 7 months after diagnosis), the boy was alive and well with a normal CBC (WBC 6.01 x 10^9/L, ANC 2.15 x 10^9/L, PLT 207 x 10^9/L, Hb 12.3 g/dL, MCV 84 fL).

Patient 4 (B063) was diagnosed with RCC at the age of 7 months. His CBC at diagnosis showed moderate neutropenia, thrombocytopenia, and normocytic anemia (WBC 7.10 x 10^9/L, ANC 0.71 x 10^9/L, PLT 107 x 10^9/L, Hb 8.0 g/dL, MCV 78 fL). Due to a positive family history with a germline *SAMD9L* mutation in the older brother (RCC with monosomy 7) and father (healthy, normal CBC), genetic testing was performed and confirmed the familiar germline *SAMD9L* p.R986H variant with a VAF of 50%. The patient had normal immunoglobulin levels (IgG 661 mg/dL, IgM 810 mg/dL, IgA 650 mg/dL) and no susceptibility to infections. Although the first karyotype at diagnosis was normal, monosomy 7 was detected in 7% of interphases by FISH analysis three months later. Six months after diagnosis, two additional missense variants *SAMD9L* p.Y900C and *SAMD9L* p.C228Y were noted with a VAF of 4% and 27%, respectively. Cytogenetics showed a normal karyotype at this time point. Concomitantly, the hemoglobin concentration and WBC normalized, while the thrombocytopenia without transfusion dependency persisted (WBC 12.4 x 10^9/L, ANC 3.97 x 10^9/L, PLT 101 x 10^9/L, Hb 12.1 g/dL, MCV 85 fL). The BM morphology showed normal cellularity with low-grade dysplasia of myelopoiesis and erythropoiesis and reduced megakaryopoiesis. Platelet counts finally normalized 14 months after diagnosis. At last follow-up 4 years and 5 months after diagnosis, the patient was alive and had a normal CBC.

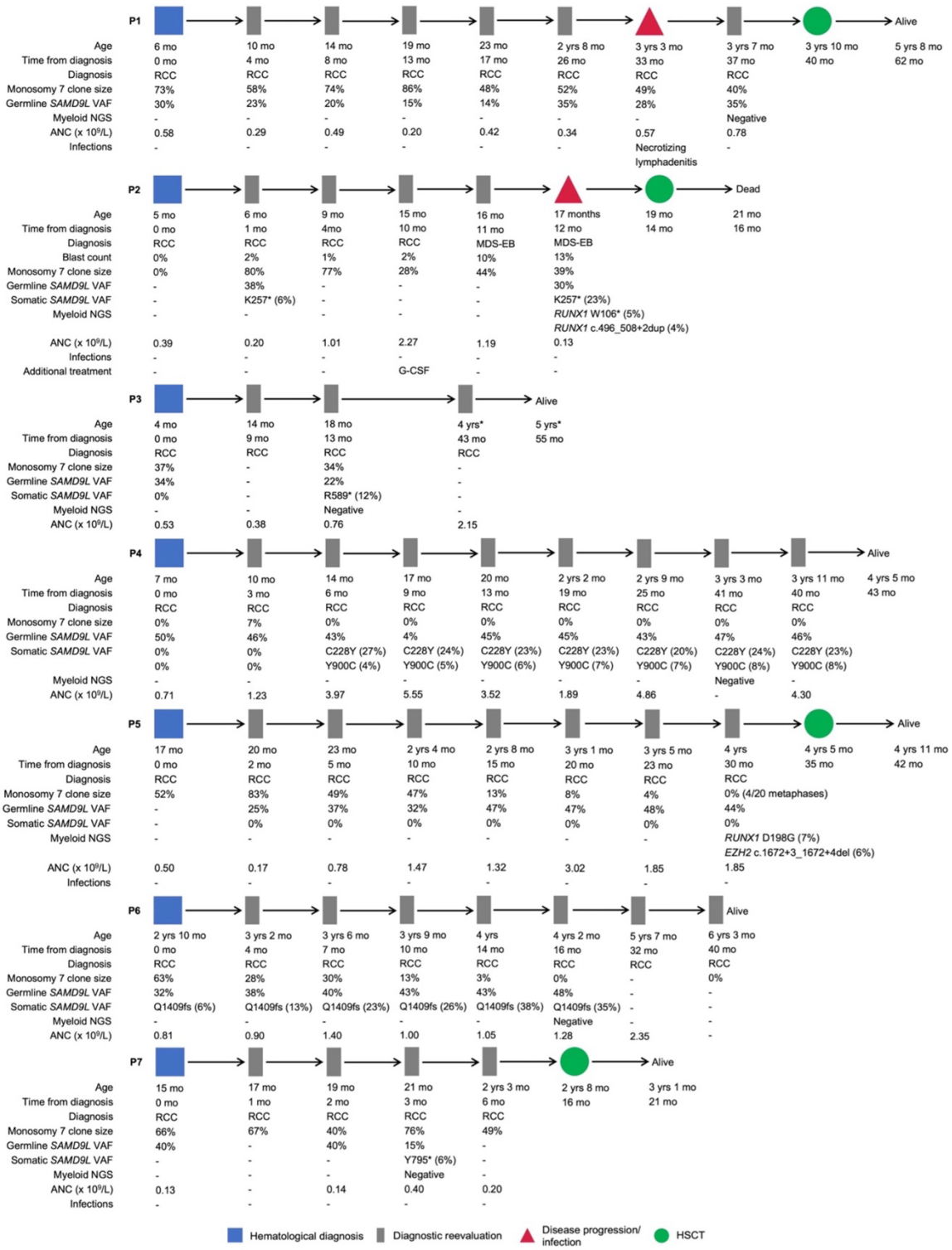
Patient 5 (KM) was born at 30 weeks of gestation after a triplet pregnancy. She was found to have nephrocalcinosis due to prematurity and multiple infantile hemangiomas on her back. Due to hydrocephalus, she received a ventriculoperitoneal shunt at the age of 6 months. Her CBC showed variable severe neutropenia, macrocytosis, and normal platelets (WBC 3.3 - 4.5 x 10^9/L, ANC 0.165 – 0.50 x 10^9/L, PLT 170 x 10^9/L, Hb 12.3 g/dL, MCV 92 fL). The immunological work-up indicated B cell and natural killer (NK) cell deficiency (CD19+ cells 0.6%, abs. 0.03 x 10^9/L; CD16+ CD56+ CD3- cells 0.5 %, abs. 0.02 x 10^9/L) and hypogammaglobulinemia (IgG 310 mg/dL, IgM 13 mg/dL, IgA 16 mg/dL). She received regular immunoglobulin substitution, which was tolerated poorly. For persistent neutropenia, she received her first BM examination at the age of 17 months. Histopathology was compatible with RCC. Cytogenetics showed monosomy 7 in all 15 metaphases (FISH analysis: 52% of interphases) and further genetic work-up revealed a germline *SAMD9L* p.A1195V variant with a VAF of 25%. Although the size of the monosomy 7 clone decreased over time and the *SAMD9L* VAF increased to 44% at the age of 4 years, the myeloid NGS panel revealed a new likely pathogenic *RUNX1* p.D198G variant (VAF 7%) and a variant of unknown significance in *EZH2* (c.1672+3_1672+4del, VAF 6%) indicating clonal evolution. HSCT from an HLA-identical matched unrelated donor was employed following a conditioning regimen with treosulfan, thiotepa, and fludarabine and a serotherapy with ATG at the age of 4.4 years and close to 3 years after diagnosis. At last follow-up 3.5 years after diagnosis and 6 months after HSCT, the patient was alive and well.

Patient 6 (CZ132) was diagnosed with RCC at the age of 2.8 years. Her CBC showed moderate neutropenia, moderate thrombocytopenia, and macrocytic anemia (WBC 4.1 x 10^9/L, ANC 0.81 x 10^9/L, PLT 46 x 10^9/L, Hb 11 g/dL, MCV 94 fL). There was mild B cell deficiency (CD19 12%, abs. 0.35 x 10^9/L; CD3 78%, abs. 2.25 x 10^9/L; CD3+HLADR+ 0,8%, abs. 0.02 x 10^9/L; CD3neg16,56+ 8,6%, abs. 0.25 x 10^9/L; CD4 43%, abs. 1.24 x 10^9/L; CD8 32%, abs. 0.92 x 10^9/L) and mild hypogammaglobulinemia (IgG 603 mg/dl, IgM 64 mg/l, IgA 29 g/l). Monosomy 7 was detected in 20 of 23 BM cell metaphases (FISH analysis: 63% of interphases) at diagnosis. A germline *SAMD9L* p.R1281W mutation with a VAF of 32% and a somatic *SAMD9L* p.Q1409Tfs*49 variant with a VAF of 6% were identified shortly after. BM examination 4 and 7 months after diagnosis showed persistent monosomy 7, but 10 months after diagnosis, cytogenetics revealed monosomy 7 in only 7 of 20 metaphases, while the germline and somatic *SAMD9L* VAF had increased to 43% and 26%, respectively. Subsequently, cytogenetic studies repeatedly indicated a normal karyotype, and the CBC normalized over time. At last follow-up 40 months after diagnosis, the patient was alive with a normal CBC and normal karyotype.

Patient 7 (A146) is a girl diagnosed with RCC and monosomy 7 (in 17 of 20 BM cell metaphases) at the age of 15 months. CBC at diagnosis showed leukopenia, severe neutropenia, moderate thrombocytopenia, and normocytic anemia (WBC 2.54 x 10^9/L, ANC 0.25 x 10^9/L, PLT 79 x 10^9/L, Hb 7.7 g/dL, MCV 89 fL). Lymphocyte phenotyping showed B cell and NK cell deficiency. The further work-up also revealed moderate hypogammaglobulinemia (IgG 273 mg/dL IgA 23 g/l, IgM 28 mg/dL). The girl displayed a failure to thrive and big eye bulbs. Genetic testing identified a germline *SAMD9L* p.D1034Y variant with a VAF of 40%. Six months after diagnosis, a somatic *SAMD9L* p.Y795* resulting in a stop codon was detected with a VAF of 7%. In the further course, the monosomy 7 clone was ranging between 40% and 76% in interphase nuclei. However, almost 12 months after diagnosis, the CBC still showed persistent leukopenia (WBC 3.75 x 10^9/L) and severe neutropenia (ANC 0.14 – 0.40 x 10^9/L). Therefore, allogeneic HSCT from an HLA-identical MUD after conditioning with treosulfan, thiotepa, and fludarabine and a serotherapy ATG was successfully performed 21 months after RCC diagnosis at the age of 2.7 years.

Patient characteristics		Genetic characteristics		
No. (UPN)	**Sex**	**Germline genotype (VAF)**	**Somatic *SAMD9L* mutation (VAF)**	**Somatic cancer gene mutation (VAF), ACMG variant interpretation**
P1 (D1297)	M	*SAMD9L* c.2675T>G, p.M892R (30%)	No	No
P2 (D1300)	F	*SAMD9L* c.4046C>T, p.P1349L (38%)	*SAMD9L* c.768dup, p.K257* (23%)	*RUNX1* c.317G>A, p.W106* (5%), P; *RUNX1* c.496_508+2dup (4%), LP
P3 (GR012)	M	*SAMD9L* c.4420A>C, p.T1474P (34%)	*SAMD9L* c.1765C>T, p.R589* (12%)	No
P4 (B063)	M	*SAMD9L* c.2957G>A, p.R986H (50%)	*SAMD9L* c.2699>G, p.Y900C (8%); c.683G>A, p.C228Y (26%); c.3562C>T, p.R1188* (4%)	No
P5 (KM)	F	*SAMD9L* c.3584C>T, p.A1195V (25%)	No	*RUNX1* c.593A>G, p.D198G (7%), LP; *EZH2* c.1672+3_1672+4del (6%), VUS
P6 (CZ132)	F	*SAMD9L* c.3841A>T, p.R1281W (32%)	*SAMD9L* c.4224dupA, p.Q1409Tfs*49 (35%)	No
P7 (A146)	F	*SAMD9L* c.3100G>T, p.D1034Y (40%)	*SAMD9L* c.2385C>A, p.Y795* (6%)	No

Supplemental Table S1. Genetic findings of all patients with SAMD9L germline disorder
Abbreviations: UPN: unique patient number. VAF: variant allele frequency. ACMG: American College of Medical Genetics. P: pathogenic. LP: likely pathogenic. VUS: variant of unknown significance.



Supplemental Figure S1. Clinical course of patients with germline SAMD9L disorders. Abbreviations: VAF: Variant allele frequency. NGS: next-generation sequencing. ANC: absolute neutrophil counts. Yrs: years. Mo: months. RCC: refractory cytopenia of childhood. MDS-EB: myelodysplastic syndrome with excess of blasts. *Patient 3 was withdrawn from further BM sampling.