To the editor:

SPRED1 disorder and predisposition to leukemia in children

In 2007, the germline loss-of-function mutations in *SPRED1* were reported to originate a new autosomal dominant human disorder with multiple café-au-lait spots, axillary freckling, macrocephaly, and learning difficulties.[1,2] This disorder belongs to the recently identified and phenotypically overlapping neuro-cardio-facial-cutaneous (NCFC) syndromes which comprise Costello, Noonan, LEOPARD, cardio-facio-cutaneous, and neurofibromatosis 1 syndromes.[2] NCFCs are all caused by germline mutations in genes of the Ras–mitogen-activated protein kinase (MAPK) extracellular signal–regulated kinase pathway and are associated with predisposition to cancer in children, notably juvenile myelomonocytic leukemia and lymphoblastic acute leukemia.[3,4] SPRED1 is a member of the SPROUTY/SPRED family of proteins that act as negative regulators of Ras/Raf interaction and MAPK signaling.[5] Moreover, *SPRED1* is highly expressed in hematopoietic cells and negatively regulates hematopoiesis by suppressing stem cell factor– and interleukin-3–induced ERK activation.[6] Since the original report, very little information concerning leukemia incidence and phenotype of patients with *SPRED1* mutations has been described.[6] Here, we report the observation of an 11-month-old boy with a *SPRED1* germline mutation who developed an acute myeloblastic leukemia.

The child was admitted in our department in May 2006 because of necrotic appendicitis and pseudomonas aeruginosa septicemia. White blood count was 8.6/μL with 85% blast cells, platelet count 202/μL, and hemoglobin level 8.3 g/dL. Analysis of the bone marrow smears revealed a large population of malignant immature monoblasts typical of an M5a acute myeloblastic leukemia. Cerebrospinal fluid was infiltrated by 5 blast cells/mm^3. The cytogenetic analysis of the bone marrow showed a complex karyotype: 47,XY, −7,del(9)(q13-22q32-33), add(12)(p1?3), add (18)(q23), +19, + mar [24]/ 46, XY[4]. Search for *FLT3* and *NPM1* gene mutations was negative. *N-RAS* gene was mutated at codon 12 (G12D, GGT>GAT), although the frequency of the mutated allele was low (estimated at 5%-10%). Ten days after appendectomy, the child was included in ELAM02 protocol and received a first course of aracytine 200 mg/m^2 per day × 7 and mitoxantrone 12 mg/m^2 per day × 5, followed by consolidation course by high-dose aracytine 2 × 3 g/m^2 per day × 3 and amsacrine 100 mg/m^2 per day × 3.

Complete remission was obtained in June 2006. As no HLA-matched sibling donor was available, the child received 2 subsequent consolidation courses of chemotherapy. He is currently in complete remission at 34 months of follow-up. During this period, he developed some speech and learning difficulties and hyperactivity syndrome. Numerous café-au-lait spots (> 10) appeared progressively from the age of 18 months to 24 months, and clinical examination revealed macrocephaly (+2 DS) with normal CNS MRI and ophthalmologic examination. After informed consent, a comprehensive *NF1* gene mutation screening was done and found normal. A *SPRED1* mutation screening analysis was then performed and showed an exon 3 c.46C>T mutation leading to p.Arg16Stop in the child and his father. This mutation may result in a truncated nonfunctional protein. Blasts cells analysis displayed the same abnormality as germline mutation with one mutated allele (no somatic *SPRED1* single-point mutation or loss of heterozygosity was found). The M4/M5 phenotype of AML are most closely associated with Ras pathway mutations and interestingly our patient developed M5 AML. Ras pathway mutations are also associated with monosomy 7.[7]

Our conclusion is that *SPRED1* disorder generates predisposition to leukemia in children. The existence of an N-Ras mutation in this case infers that the SPRED mutation may have been a predisposing event that partially deregulated Ras signaling but acquired complex karyotype structural abnormality are essential to generate fully transformation to AML. Clinical follow-up and screening for *SPRED1* mutation has to be performed in mild NCFC phenotype.

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