Response

JAK mutations in Down syndrome–associated transient myeloproliferative disorder and acute megakaryocytic leukemia

We welcome this interesting case report. It is the first description of a *JAK2* mutation in Down syndrome–acute megakaryocytic leukemia (DS-AMKL). It also confirms that some cases of DS-AMKL will harbor a *JAK3* mutation.

However, it is still the case that, taking all the published literature to date, the frequency of *JAK2* and *JAK3* mutations in DS transient myeloproliferative disorder (TMD) and AMKL is low and that these events are not obligate mutations for leukaemogenesis in all cases of DS malignancies, in contrast to the almost invariant finding of a *GATA1* mutation. Given this, we are still of the opinion that there may be several different (epi)genetic events that could be permissive for the progression of TMD to DS-AMKL and that these could individually occur at low frequency.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Response

Mutations of *JAK2, JAK3* and *GATA1* in acute megakaryoblastic leukemia of Down syndrome

For acute myeloid leukemia (AML), the major form that occurs in children with Down syndrome (DS) is acute megakaryoblastic leukemia (AMKL). In 14% of these children, there is a history of transient myeloproliferative disorder (TMD) at birth.[1] Somatic mutations of *GATA1* gene are found in both children with DS-AMKL and TMD.[2] Because acquired mutations of *JAK2* in patients with non–DS-AMKL[3] and mutations of *JAK3* in patients with AMKL with or without DS[4-6] have been described, Norton et al investigated the frequency of *JAK2* and *JAK3* mutations in 19 and 16 children with TMD or DS-AMKL, respectively.[7] However, they failed to detect any mutations for either of the genes in any of the patients. Therefore, they concluded that there is a low incidence of *JAK3* mutation and that there is no evidence yet that *JAK2* mutations contribute to DS malignancies. Here, we report the first case of a DS patient who had mutations of *JAK2*, *JAK3* and *GATA1* in her AMKL cells.

At age 29 months, a female child with DS presented with right exophthalmos. A Head CT scan showed a tumor in her right orbit. An immunohistochemical examination of the tumor revealed that the blast cells were positive for LCA, MT-1 and CD68, and negative for UCHL-1, MB-1, L-26 and Ki-1. Five months later she developed overt leukemia. Bone marrow aspiration revealed a predominance of blast cells with basophilic cytoplasm and cytoplasmic blebs, which were negative for myeloperoxidase and nonspecific esterase stain. Immunophenotypically, the blast cells were positive for CD7, CD13, CD33, CD42b, and CD117. Chromosomal analysis revealed 47, XX, del(7)(p15), +8, del(13)(q12q32), −14, der(14;21)(q10;q10)c, del(17)(p11), +21c, +mar. She was diagnosed as AMKL and received intensive chemotherapy, although she did not respond. She died from the progressive disease 10 months after the initial presentation. We analyzed the *GATA1*, *JAK2* and *JAK3* mutations in her peripheral blood samples. Written informed consent for banking and molecular analysis of leukemic cells in accordance with the Declaration of Helsinki was obtained from the parents of the patient. High-molecular weight DNA was extracted from the samples using standard methods. We amplified the genomic DNA corresponding to exon2 of *GATA1*,[2] exon12 of *JAK2*,[8] and all 23 exons of the *JAK3*[4] gene, respectively and the amplified products were sequenced directly.

Mutations of *JAK2* V617F, *JAK3* Q501H, and *GATA1* (2-3TG > AT, no start codon), were found in the patient (Figure 1). Until now, 4 active mutations (A572V,[4] A573V,[5,6] A593T,[5] and V722I[4]) of the *JAK3* gene have been found in samples obtained from patients with DS-AMKL. All of these were uniformly located in the JH2 pseudokinase domain. A novel mutation (Q501H) that was found in this patient occurred in the JH3 SH2 domain. The

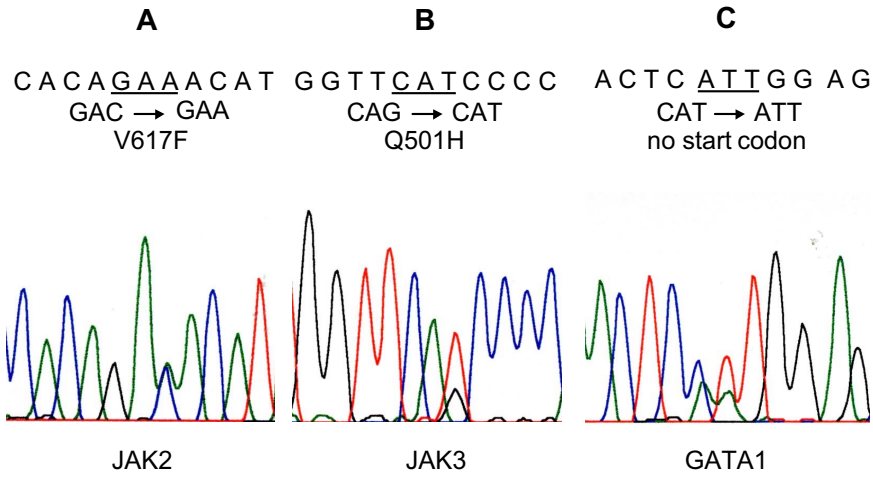

Figure 1. Mutations of *JAK2, JAK3,* and *GATA1* in a child with DS-AMKL. Mutations of *JAK2* V617F (A), *JAK3* Q501H (B), and *GATA1* (2-3TG > AT, no start codon; C) were found in a child with DS-AMKL.

function of this domain is not completely understood and the binding partners also have not yet been identified. Park et al reported that there were no mutations of the *JAK2* gene found in any of the 23 samples from the patients with TMD or DS-AMKL.[9] *JAK2* and *JAK3* mutation may have contributed to the resistance to the intensive chemotherapy in our patient.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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