Germline *JAK2* L611S mutation in a child with thrombocytosis

Chronic thrombocytosis is rare in children and is most often secondary to inflammation, iron deficiency or absence of spleen. However, when the cause is unknown, myeloproliferative neoplasms (MPN), such as essential thrombocythemia (ET) as well as hereditary thrombocytosis (HT) must be looked for. Over the last decade, the diagnosis of ET has been facilitated by the discovery of somatic mutations in 3 genes, including *JAK2* (mainly the V617F mutation), *CALR* and *MPL* (the gene that encodes the thrombopoietin receptor, with W515L/K/A/R mutations) and observed in 60%, 25% and 4 % of ET cases, respectively.[1] On the other hand, germline mutations have been reported in HT and involve not only the same genes observed in sporadic cases of MPN in impacting other residues in the proteins, but also the *THPO* gene (which encodes thrombopoietin) and the GSN gene, which encodes Gelsolin protein.[2]

We report here the case of a 3-month-old child with a high platelet count associated with a *de novo* germline JAK2 exon 14 mutation NM_004972.3:c.[1832T>C];[=] p.[(Leu611Ser)];[=] .

A 1,696 G/L thrombocytosis was noted in a 3-month-old child after a routine complete blood count. Moderate leukocytosis (18.7 G/L; N 5-17.5), eosinophilia (1.5 G/L) and monocytosis (1.49 G/L) were also revealed. Hemoglobin levels and red blood count were normal. There was no inflammation, no iron deficiency and no other biological abnormality. The physical examination was normal, and there was no splenomegaly. Due to the persistence of a high platelet count (between 1,175 and 1,480 G/L) during the following months without any obvious etiology, the *JAK2* V617F, *CALR* exon 9, *MPL* exon 10 and *THPO* exons 2-6 mutations were tested and were negative. However, a L611S mutation was noted during the sequencing of the *JAK2* exon 14. A bone marrow aspiration was performed as well as cytogenetic and hematopoietic progenitor growth cultures and a bone marrow biopsy: an isolated megakaryocytic hyperplasia without myelofibrosis was revealed (Figure). The cytogenetic test was normal, and only one endogenous megakaryocytic colony was observed. The *JAK2* L611S mutation was also found in DNA samples from hair follicles and skin biopsy which confirmed the germline feature of the mutation. On the other hand, the *JAK2* L611S mutation was not observed in the tests performed on the relatives including the parents, the paternal grand-parents and aunt, leading to the diagnosis of a *de novo* germline mutation (Figure). No family history of thrombocytosis, erythrocytosis, other blood cancers, or solid tumors was reported. Finally, a NGS analysis using the Qiagen myeloid panel, which includes 140 genes, confirmed the isolated *JAK2* L611S mutation with a variant allele frequency (VAF) of 49% and found no additional somatic variant above 5% of VAF.

So far, to the best of our knowledge, this is the first report of a germline *JAK2* L611S mutation in a patient with HT seeing as the mutation has only been reported previously in 2 different patients. The first was a PV patient where the *JAK2* L611S mutation was alone or in cis with the *JAK2* V617F mutation,[3] and the second was a 3-year-old girl with precursor-B-ALL.[4] In the second case, the mutation was absent in remission marrow and was thus likely an acquired mutation. Moreover, it has been reported that the *JAK2* L611S mutation also caused the constitutive activation of *JAK2* and increased the expression of antiapoptotic proteins including X chromosome-linked inhibitor of apoptosis protein in Ba/F3 murine hematopoietic cells.[5] Finally, Ba/F3 cells expressing a *JAK2* L611S mutation gained the ability to induce tumorigenesis in nude mice, underscoring the potential oncogenic role of this variant.[5] Previously, we reported 3 cases of patients harboring a double L611V/V617F mutation of *JAK2* associated with a phenotype of erythrocytosis: in these cases, in comparison with both wild-type *JAK2* and *JAK2* V617F, a greater constitutive and Epo-stimulated phosphorylation of *JAK2*, AKT and ERK1/2 was noted but with a low activation of STAT5.[6]

Interestingly, Marty *et al.* reported a germline *JAK2* R867Q[7] which had previously been reported in a B-ALL[8], in a family with isolated HT, highlighting a potential link between atypical *JAK2* mutations in HT and in B-ALL. In our case, the presence of a germline *JAK2* mutation in

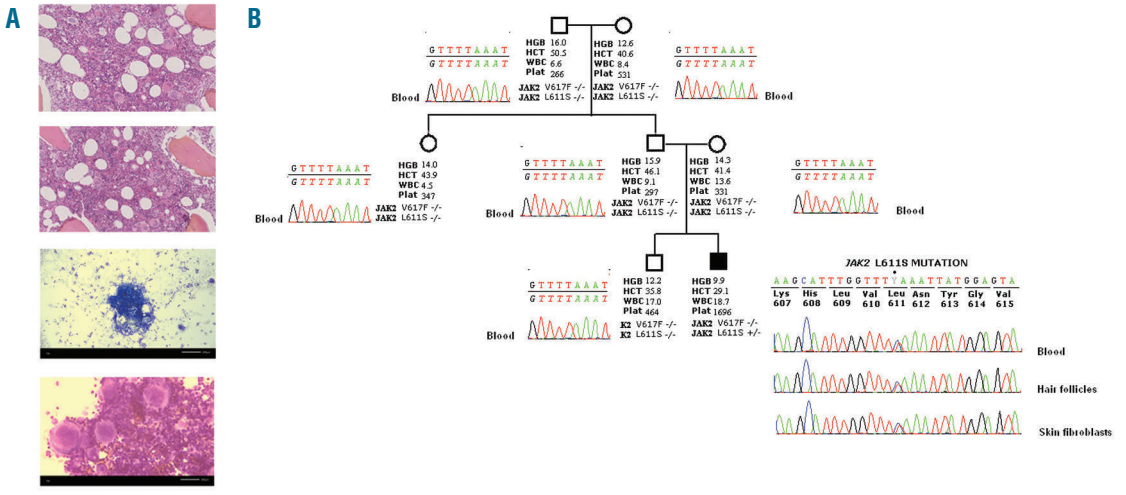

Figure 1. Hereditary thrombocytosis associated with *JAK2* L611S mutation. A. Bone marrow morphology of (a) biopsy (X20) and (b) bone marrow aspirate (X10 and X50). B. Extended pedigree for the proband and family members with full blood count results and Sanger sequencing chromatograms.

hematopoietic progenitors is theoretically associated with a risk (though possibly low) of disease progression, underscoring the need for regular follow up. Consequently, a frequent full blood count has been implemented to evaluate the kinetics of blood parameters. So far, after four years of follow up, the child is in good health and still harbors an isolated and stable thrombocytosis of around 1,000 G/L. He has been receiving regular medical supervision as well as blood tests every 3 months to monitor the blood features. Due to epistaxis when the child was initially treated using low dose of aspirin, he did not go through this treatment. Finally, in this *de novo* case, from a medical genetic point of view and given the nature of the transmission mode of the described genetic variation, one may imagine a possible germinal mosaicism. However, due to the absence of the *JAK2* L611S mutation in the younger brother of the proband, this hypothesis is very unlikely.

Because of the absence of similar mutations and biological abnormalities in the relatives, the present case cannot be considered family MPN or hereditary MPN. To date, other germline *JAK2* mutations associated with thrombocytosis have been reported in the domains of the JAK2 protein: the FERM domain (G335D), the pseudokinase domain (R564Q, G571S, V617I, V625F, H608N and S755R) and the kinase domain (R867Q, R938Q).[9] Some of these reported mutations are considered sporadic cases since the family history was negative for the presence of the MPN phenotype in other family members.[10] It is worth noting, from a functional standpoint, that only some of the *JAK2* mutations associated with thrombocytosis (V617I, G625F, R867Q, S755R/R938Q) were considered as gain-of-function mutations,[7,10,11] whereas the others (G571S, G335D) did not play a role in pathogenesis.[10]

Bernard Aral,[1] Martine Courtois,[2] Sylviane Ragot,[1] Valentin Bourgeois,[2] Elodie Bottolier-Lemallaz,[3] Claire Briandet[3] and François Girodon[2,4]

[1]Laboratoire de génétique chromosomique et moléculaire, Pôle Biologie, CHU de Dijon; [2]Service d'Hématologie Biologique, Pôle Biologie, CHU de Dijon; [3]Service d'Immuno-Hématologie Pédiatrique, CHU de Dijon and [4]Inserm U1231, Université de Bourgogne, Dijon, France

Correspondence: francois.girodon@chu-dijon.fr
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