Letter to the Editor

Progression to polythythemia vera from familial thrombocytosis with germline *JAK2* R867Q mutation

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Dear Editor,

Familial thrombocytosis (FT) is a rare, inherited form of myeloproliferative neoplasms (MPN). Germline mutations have been identified mostly in *THPO* [1] and *MPL* [2] genes, while only 6 *JAK2* germline mutations in 5 families have been reported [3-6]. In a previous report, all the members of a family affected with the *JAK2* R867Q mutation showed thrombocytosis alone with normal hemoglobin levels [6]. Here we

report a Japanese FT pedigree with the germline *JAK2* R867Q mutation, in whom progression to polycythemia vera (PV) was observed.

A 31-year-old woman (patient 5) with a 25-year history of thrombocytosis was referred to our hospital (Fig. 1a). Her hemoglobin level was normal. Her father (patient 3) also showed mild thrombocytosis, but had high hemoglobin levels with normal to low erythropoietin levels. His platelets had been persistently high and his hemoglobin levels fluctuated around 16.5 g/dl until he was 56. However, since the age of 59, his hemoglobin levels have been apparently high (> 18 g/dl) while platelet counts have been gradually decreasing (Fig. 1b). His hematocrit levels were also high (53.2%), and mean corpuscular volume was within normal range (95 fl). He had mild splenomegaly. The differential count of his white blood cells was within normal range (Band neutrophils: 2.5%; Segmented neutrophils: 54.5%; Lymphocytes: 25.5%; Monocytes: 4%; Eosinophils: 3%; Basophils: 1%). His erythropoietin level was 3.0-18.4 mIU/ml (normal range, 9.1-32.8). Bone marrow biopsy of patient 3 performed at the age of 62 showed hypercellularity with panmyelosis and loose network of reticulin in perivascular areas. (Fig. 1c-d). The cytogenetics of bone marrow was normal

(46, XY[20]). These results suggest that patient 3 showed ET-like phenotype at first, but now meets the criteria for PV. Some family members of patients 3 and 5, including a 0-year-old infant, also showed marked thrombocytosis (Fig. 1a), which raised the possibility of familial MPN. Using targeted DNA sequencing in neutrophils, we explored 67 genes that are implicated in myeloid malignancies for patients 3 and 5 [7] and found heterozygous *JAK2* R867Q mutations in both cases. We also found a stop-gain mutation of *TET2* S271X with an allele frequency of 5% in patient 3, and no relevant somatic mutations in patient 5. Next, we performed Sanger sequencing using neutrophils (from patients 1 to 7) and buccal swabs (from patients 1 to 8) in the present family members. All affected members (patients 3, 5, 6, and 8) had the heterozygous *JAK2* R867Q mutations in their neutrophils and buccal swabs. In contrast, unaffected members lacked the *JAK2* R867Q mutation.

Our data were mostly consistent with the first report of the pedigree harboring the *JAK2* R867Q mutation. In the report, all 3 affected members were adults at diagnosis, and showed only thrombocytosis [6]. Observations of our pedigree further demonstrated that thrombocytosis could be seen soon after birth and that transformation

to PV could occur. According to the previous report, R867Q is a gain-of-function mutation that activates thrombopoietin signaling depending on the presence of the thrombopoietin receptor, but does not affect erythropoietin signaling [6]. Thus, we hypothesized that transformation to PV in patient 3 might be caused by additional somatic mutations; however, we did not find any relevant additional somatic mutations. Considering the low allele frequency, the *TET2* mutation found in patient 3 may not be related to transformation to PV, but might be consistent with age-related clonal hematopoiesis. Future genome-wide studies may unveil the mechanism of the phenotypic switch from thrombocytosis to PV in germline *JAK2* R867Q-related FT.

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Conflict of interest

The authors declare no conflict of interest.

Informed consent

This study was approved by ethics committee in University of Tsukuba Hospital, and informed consent was obtained from the patient and her family members before the analysis.

Author contributions

KM and YY wrote the manuscript. KM performed the experiments using patient samples. YN and SO performed panel sequencing for 67 genes. YY and MN performed histopathological analysis. YY, TK, MSY, and SC supervised this research. All authors approved the final manuscript.

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Figure legends

Fig. 1 a Pedigree with familial thrombocytosis. Filled black symbols represent members with thrombocytosis. Informed consent was obtained from 8 out of 10 living family members (patient 1-8). Wt, wild type. Het, heterozygous. **b** Clinical course of patient 3. **c** Hematoxylin-eosin staining of bone marrow in patient 3. x200 magnification. **d** Silver staining of bone marrow in patient 3. x200 magnification.