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Myeloproliferative disorders

SOMATIC TESTING FOR MYELOPROLIFERATIVE NEOPLASMS AND RE-ANALYSIS OF SEQUENCE DATA IN FIRST-DEGREE RELATIVES ALLOW THE DIAGNOSIS OF MPL-RELATED AUTOSOMAL DOMINANT THROMBOCYTHEMIA A BENIGN CONDITION OR A PRECANCEROUS DISORDER?

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Introduction: Myeloproliferative neoplasms are conditions with abnormal proliferation of mature myeloid cell lines, caused by driver somatic genetic variants. Diagnostic approaches include testing for recurring variants or sequence analysis of genes involved with myeloid neoplasms. We describe a family in which somatic NGS analysis identified a possible autosomal dominant MPL-related thrombocythemia in a father and daughter independently ascertained for suspected MPN. The father developed overt primary myelofibrosis, a myeloproliferative neoplasm.

Methods: A 19-year-old girl was ascertained for increased platelet count (990.000/mm3, multiple measurements. n.v. <400.000). After hematological evaluation, qPCR for recurrent JAK2, CALR and MPL variants was requested (peripheral blood). Two years later, somatic NGS analysis for a panel of myeloid neoplasm genes was performed (peripheral blood). The referring physician reported that her father had been independently ascertained for primary myelofibrosis, with a previous history of thrombocytosis. Data from two NGS analyses previously performed on the father (peripheral blood) were re-analysed.

Results: The father had an initial diagnosis of triple-negative primary myelofibrosis. The second NGS analysis on his peripheral blood identified the pathogenic gain-of-function c.1514G>A, p.(Ser505Asn) and c.1543T>C, p.(Trp515Arg) variants in MPL (NM_005373.3), in the exon 10 hotspot, with 31.33% and 2.26% variant allele frequency (VAF), interpreted as somatic driver variants causing the myeloproliferative disorder, leading to the diagnosis of MPL-positive primary myelofibrosis. Molecular analyses in the daughter did not identify pathogenic somatic variants. The c.1502T>C, p.(Val501Ala) variant in in the MPL gene was identified with 50% VAF, suggesting a germline heterozygous genotype. It was interpreted as Variant of Uncertain Significance in relation to myeloproliferative neoplasms. NGS data re-analysis from the father disclosed the same variant with comparable VAF. The variant had been interpreted as likely benign at first, in accordance with scientific literature at the time. Germline heterozygous activating MPL variants are associated with hereditary Thrombocythemia, usually regarded as a benign condition. The germline c.1502T>C, p.(Val501Ala) variant has recently been proposed as a possible cause for asymptomatic thrombocythemia in isolated cases. It lies in the critical exon 10, which harbors the known gain-of-function pathogenic somatic and germline variants. We first report the variant in a family with two individuals with a history of constitutional thrombocytosis, one of them later developing and overt myeloproliferative neoplasm.

Conclusions: This study strengthens the association between the c.1502T>C MPL variant and hereditary thrombocythemia, but also highlights its potential evolution towards malignancy.