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Case Report

A novel Germline JAK2 Splice-Site Variant Causing Exon 10 Skipping in a Patient with an ET-Like Thrombocytosis Phenotype and Early-Onset Tophaceous Gout

Keywords: Germline JAK2 splice-site variant; Exon 10 skipping; Essential thrombocythemia; Tophaceous gout.

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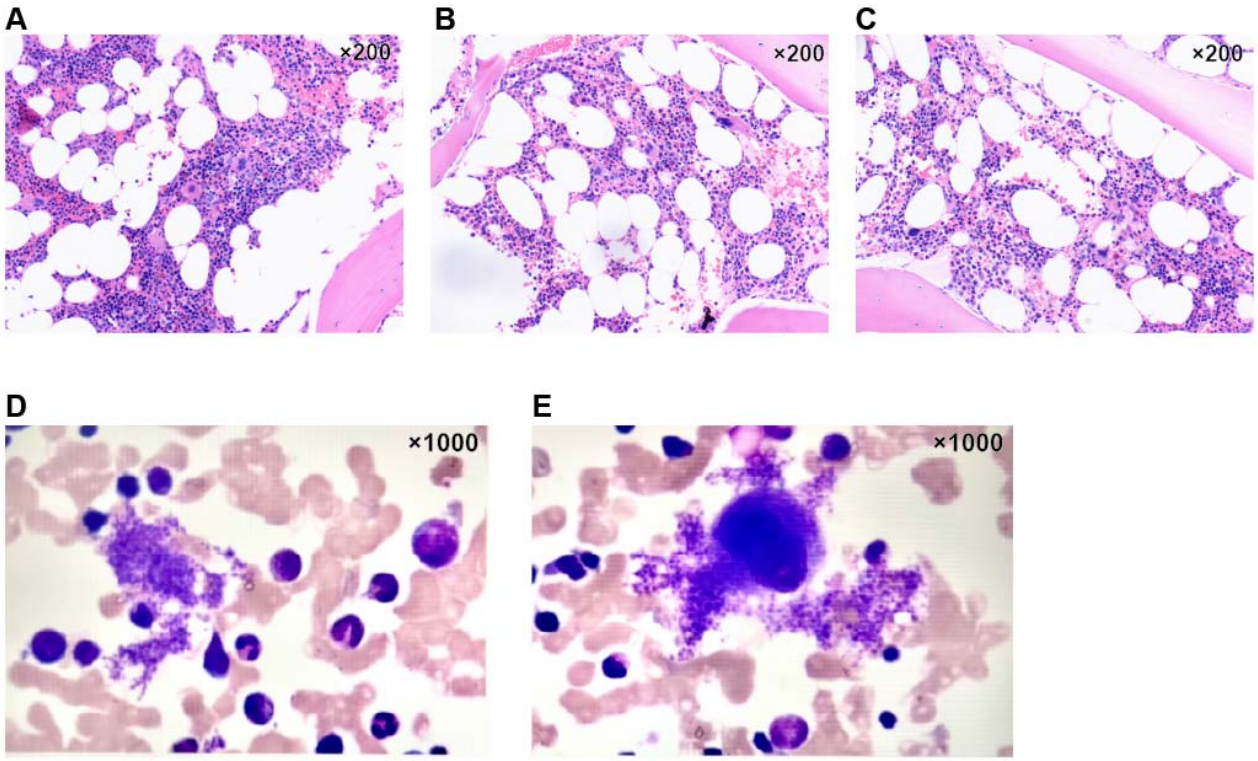
Supplementary Files.

Supplementary Table 1. Annotation and ACMG/AMP-style assessment of the JAK2 c.1326+2T>A and KMT2A c.1474G>C variants

Item	*JAK2*	*KMT2A*
Reference genome	GRCh37	GRCh37
Genomic HGVS	NC_000009.11:g.5066791T>A	NC_000011.9:g.118343348G>C
Transcript	NM_004972.4	NM_001197104.2 (MANE Select)
Coding DNA change	c.1326+2T>A	c.1474G>C
Location / type	Intron 10, +2 splice-donor position	Exon 3, missense
Predicted protein consequence	p.?	NP_001184033.1:p.(Ala492Pro)
Bone marrow NGS	VAF 51.4%, depth 1,219×	VAF 50.3%, depth 2,687×
Buccal epithelial-cell NGS	VAF 48.10%, depth 526×	VAF 47.40%, depth 853×
Inferred origin	Germline	Germline
gnomAD v2.1.1 (exomes, PASS)	Not observed	1/250,936 alleles (AF 3.99 × 10^{-6}); no homozygotes; rs782462364
ClinVar	No entry	No entry
In-silico prediction	SpliceAI donor loss 0.99; Pangolin splice loss 0.87	REVEL 0.361; AlphaMissense 0.2323; PrimateAI-3D 0.70; SIFT 0.00 — discordant
Additional annotation	Canonical +2 donor position of intron 10	Residue located within a predicted disordered region (aa 445–585)
RNA evidence	Complete skipping of the 112-nucleotide exon 10 confirmed by RT-PCR and bidirectional Sanger sequencing (non-quantitative)	Not applicable
Protein / signaling evidence	Not assessed	Not assessed
Family segregation	Offered; declined	Offered; declined
ACMG/AMP criteria applied	PM2_Supporting	PM2_Supporting
Criteria considered but not applied	PVS1 — although c.1326+2T>A disrupts the canonical donor site and RNA analysis demonstrated exon 10 skipping, PVS1 was not applied because loss of *JAK2* function is not an established disease mechanism for *JAK2*-related thrombocytosis; PS3 — no protein-level or signaling evidence available; PP3 — not counted in addition to the direct RNA evidence, to avoid double-weighting the same line of evidence; PP1 — segregation data unavailable.	BP4/PP3 — discordant in-silico predictions; PS3, PP1 — not available
Automated computational output (VarSome v13.18.7)	**Likely pathogenic**	**Likely benign**

Item	*JAK2*	*KMT2A*
Diagnostic-laboratory classification	Variant of uncertain significance	Variant of uncertain significance
Classification adopted in this report	**Variant of uncertain significance**	**Variant of uncertain significance**
Interpretation	Germline splice-donor variant with experimentally demonstrated exon 10 skipping; a contribution to the thrombocytosis is hypothesized but unproven	Extremely rare germline missense variant with no established association with thrombocytosis, myeloid neoplasia or gout; not interpreted as an acquired clonal marker

Notes. VAF, variant allele fraction. SpliceAI and Pangolin scores range from 0 to 1; higher values indicate a greater predicted probability of splice-site disruption. Automated outputs generated by VarSome are shown for transparency only; they are not phenotype-informed and were not adopted as the final classification in this report. Buccal epithelial cells were collected after mouth rinsing, with precautions to minimize leukocyte contamination.



Supplementary Figure 1.