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Beyond triple-negative: germline MPL and SH2B3/LNK mutations reshape the genetic landscape of hereditary thrombocytosis

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Beyond triple-negative: germline MPL and SH2B3/LNK mutations reshape the genetic landscape of hereditary thrombocytosis

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Over the past two decades, major advances have defined the molecular basis of thrombocytosis through the discovery of recurrent somatic driver mutations in JAK2, CALR, and MPL. The label "triple-negative" has become a diagnostic catch-all, encompassing both clonal myeloid neoplasms and inherited forms of thrombocytosis. In this issue, Cassinat and colleagues[1] shed new light on this diagnostic blind spot, uncovering a previously unappreciated spectrum of germline and somatic alterations that challenge current distinctions between hereditary thrombocytosis and triple-negative essential thrombocythemia (Figure 1).

Essential thrombocythemia (ET) is a BCR-ABL1-negative myeloproliferative neoplasm characterized by sustained thrombocytosis and abnormal megakaryocyte proliferation. In most patients, ET is driven by acquired somatic mutations that activate thrombopoietin receptor signaling, including mutations in JAK2, CALR, or MPL**,** which together account for approximately 90% of cases[2]. These driver mutations promote aberrant JAK–STAT signaling, expanding the megakaryocytic lineage and increasing platelet production.

The remaining 10 to 15% of patients lack mutations in all three canonical driver genes and are labelled "triple-negative" ET (TN-ET)[3]. This designation lumps together biologically distinct conditions; what separates them most usefully is whether the thrombocytosis is clonal. Godfrey and colleagues have proposed abandoning the binary label for a scheme built first on clonality[4]. Two are clonal: clonal thrombocytosis of undetermined significance and triple-negative ET with clonal markers. Two are non-clonal: idiopathic thrombocytosis of undetermined significance and idiopathic thrombocytosis with atypical megakaryocytes, with bone marrow histology sorting within each pair[4]. The distinction is not academic. A clonal process points toward a myeloid neoplasm, whereas its absence leaves room for a reactive or inherited cause. Yet when the same group evaluated 320 triple-negative thrombocytosis patients, final diagnosis tracked with histology rather than myeloid gene panel results, suggesting that current clonality assays cannot resolve these cases alone[5]. Hereditary thrombocytosis (HT) complicates the picture, since it can mimic ET clinically but arises from constitutional germline changes in thrombopoietin signaling, such as variants in MPL, THPO, and JAK2[6].

In this issue, Cassinat and colleagues report germline MPL compound mutations and truncating SH2B3 mutations in patients with triple negative thrombocytosis. Using a next-generation sequencing (NGS) panel of 36 commonly mutated variations in MPN pathogenesis, they screened 154 patients diagnosed with thrombocytosis, an approach that has increasingly uncovered less common variants[3,7,8]. Thirty-seven patients carried rare but recognized activating MPL mutations such as p.(Ser204Pro), p.(Ser505Asn), and p.(Ser204Phe), supporting a diagnosis of ET. Among the remaining 117 patients, in whom HT was suspected, 73 were negative across the panel; the other 44 harbored variants falling into four distinct molecular patterns (Figure 1).

Fourteen of the 44 carried non-driver mutations in epigenetic regulators such as DNMT3A, TET2, and ASXL1 at variant allele frequencies below 10%, consistent with clonal hematopoiesis of indeterminate potential (CHIP). This echoes an earlier report of CHIP mutations, at allele frequencies as high as 43%, in bone marrow from TN-ET patients[9]. The relationship between CHIP and thrombocytosis here remains unclear: thrombocytosis may promote clonal selection, clonal hematopoiesis may drive a reactive thrombocytosis, or these patients may harbor an unidentified driver, with CHIP mutations simply marking a broader predisposition to clonal disorders. Disentangling these possibilities will require prospective, longitudinal study.

A further 21 patients carried JAK2 or MPL variants previously reported as germline. Three harbored the heterozygous JAK2 R1063H variant, reported to have minimal effect on

JAK2/STAT5 activation[10]; however, recent knock-in mouse studies suggest it markedly increases the risk of thrombosis and disease progression[11]. Its pathogenicity may therefore be context dependent.

They also identified germline MPL variants, including the well-characterized K39N variant, which typically causes HT in the homozygous state. K39N appeared in both homozygous and heterozygous states and, notably, in novel compound heterozygous combinations with Y252H or P106L. One instructive pediatric case carried both P106L and Y252H, each inherited from an unaffected heterozygous parent. Together these findings reveal a diverse mutational architecture in HT and the pathogenic potential of compound heterozygous MPL variants individually insufficient to cause disease.

The most clinically impactful findings concern loss-of-function mutations in SH2B3/LNK, which encodes a negative regulator of JAK/STAT signaling downstream of the TPO/MPL axis[12]. Nine patients carried SH2B3 mutations spanning missense and frameshift variants; six shared an identical frameshift, c.685_691dup p.(Asp231Glyfs*39), germline in five and somatic in one. Five of the six experienced severe arterial or venous thrombosis, and the same variant was found in a mother and daughter from an external cohort, arguing for a causative role in both phenotypes. Thrombocytosis without a JAK2 mutation is generally regarded as low risk, and antiplatelet therapy is often withheld under 60. The thrombotic risk associated with germline SH2B3 variants challenges that assumption and suggests that management should follow the specific mutation rather than the triple-negative label.

To probe the functional role of SH2B3, the authors analyzed total protein extracts from platelets of patients with frameshift mutations. No truncated LNK protein was detected by western blotting or by flow cytometry of HEK cells transduced with wild-type or mutant cDNA. Yet total LNK protein was significantly reduced in platelets from patients with p.(Asp231Glyfs*39), suggesting that the truncated product is unstable or its transcript rapidly degraded. The authors then transduced the UT7 megakaryoblastic cell line with wild-type or frameshift mutant constructs. The frameshift increased STAT5 signaling with and without TPO stimulation, linking LNK disruption to JAK/STAT hyperactivation. Heterozygous SH2B3/LNK knock-out mice likewise showed increased platelet counts and elevated colony-forming unit-megakaryocyte counts. Together, these data establish that heterozygous SH2B3/LNK mutations can cause HT with increased thrombotic risk.

Cassinat and colleagues meaningfully expand the mutational landscape of hereditary thrombocytosis. Their work, alongside the classification proposed by Godfrey and colleagues, argues that patients should no longer be grouped simply as non-clonal or triple-negative but resolved to the specific variant driving their thrombocytosis. Because particular germline alterations, such as SH2B3 frameshift mutations, carry a distinct thrombotic risk, this is more than an academic exercise. It raises the prospect of variant-specific management guidelines and reinforces the case for comprehensive NGS, paired with careful histology, in the workup of unexplained thrombocytosis, both to identify causative mutations and to guide risk stratification and therapy.

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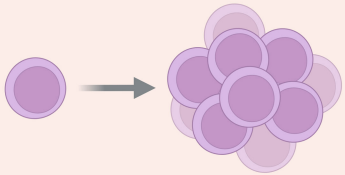
Figure Legend:

Figure 1. Unique molecular heterogeneity and patterns observed in patients diagnosed with triple negative essential thrombocythemia.

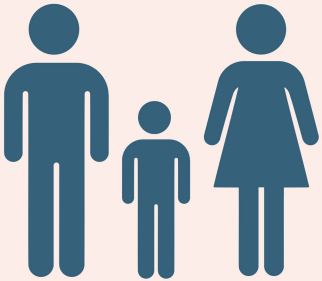
Mutational Landscape of Triple Negative Essential Thrombocythemia

Clonal hematopoiesis of indeterminate potential



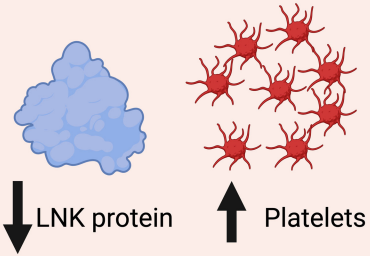
Mutations in DNMT3a, TET2, and ASXL1 with low variant allele frequency

Germline *JAK2* and *MPL* variants



Heterozygous germline JAK2 R1063H variants or compound heterozygous MPL variants

Truncating *SH2B3/LNK* variants



Loss of function mutations in SH2B3/LNK