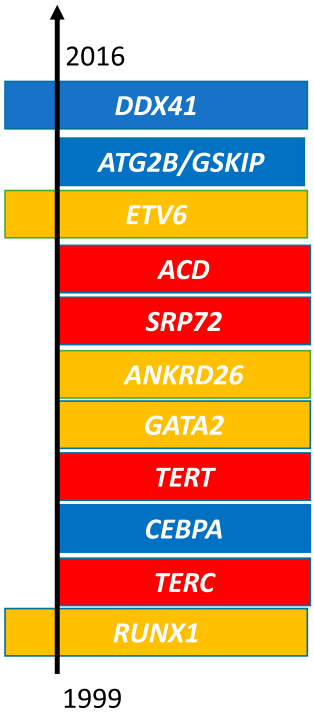
Comment on Lewinsohn et al, page 1017

Inherited *DDX41* mutations: 11 genes and counting

Kiran Tawana and Jude Fitzgibbon QUEEN MARY UNIVERSITY OF LONDON

In this issue of *Blood*, Lewinsohn and colleagues report on the inherited predisposition to hematologic malignancies (HMs) in 9 pedigrees with germ line mutations in the DEAD/H-box RNA helicase gene, *DDX41*.[1]

The current study expands on the first report of these mutations by Polprasert and colleagues,[2] by recognizing further clinical and molecular heterogeneity in this genetic subgroup, with a newly identified predisposition to lymphoproliferative neoplasms and the discovery of germ line missense mutations in over 40% of families.



The genetic landscape of inherited HM. The order of the 11 established germ line mutations is depicted based on their date of discovery. Mutations are broadly assigned to 3 groups according to phenotype: HMs alone (blue), associated bone marrow failure syndromes (red), or characteristic cytopenias and/or platelet dysfunction (yellow). The incidence of these mutations varies considerably with >10 pedigrees reported for mutations in *RUNX1*, *TERC*, *CEBPA*, *TERT*, *ANKRD26*, *GATA2*, and now *DDX41* with, in certain families/genes, apparent clustering of myeloid and lymphoid malignancies.

Next-generation sequencing (NGS) approaches are helping to elucidate the genomic landscape of inherited HMs at a remarkable pace. The recognition of inherited forms of disease can be challenging as patients themselves may be unaware of their predisposition coupled with a wide variation in the age of onset and disease phenotype. To date, research has broadly assembled leukemia predisposition syndromes into 3 groups characterized by HMs alone (*CEBPA*,[3] *ATG2B/GSKIP*,[4] and, most recently, *DDX41*[2]), associated bone marrow failure syndromes (*TERC*,[5] *TERT*,[6] *SRP72*,[5] *ACD*[7]), and HMs with preceding cytopenias and/or platelet dysfunction (*RUNX1*,[8] *GATA2*,[5] *ANKRD26*,[5] *ETV6*[9,10]) (see figure).

Lewinsohn and colleagues[1] report on the inherited predisposition to HMs with germ line mutations in *DDX41*. This collaborative study identified 300 families with evidence of inherited HM, offering an unrivaled opportunity to identify new susceptibility loci and to capture the phenotypic and genetic diversity within a given genetic subgroup. In light of the cumulative report of 16 pedigrees with germ line mutations,[1,2] *DDX41* now represents a significant new addition to the genetic landscape of inherited HM.

In the current series, the authors report 3 additional families with the recently reported p.D140GfsX2 frameshift mutation, all associated with late-onset acute myeloid leukemia (AML). Other pedigrees appear distinctive, and include patients with myelodysplastic syndrome/AML (particularly erythroleukemia), chronic myeloid leukemia, non-Hodgkin lymphoma (principally, follicular lymphoma [FL]), and multiple myeloma, accompanied by immune-mediated and granulomatous disorders. The p.R164W variant is notable by its predisposition to lymphoproliferative neoplasms in 5 family members, suggesting that the disease profile may, in part, be governed by the underlying germ line lesion and the timing and nature of secondary mutations. Such interfamilial and intrafamilial variation underlines the need for heightened clinical awareness to first suspect and then detect the underlying genetic predisposition. This task is made increasingly difficult by the latency of disease onset in these pedigrees with a median age of presentation across all *DDX41* pedigrees of 62 years (33-74 years), contrasting with other leukemia predisposition syndromes where the majority of affected individuals present at an earlier age (<45 years). Indeed, Lewinsohn and colleagues suggest that missense *DDX41* mutations may identify a particular cohort of patients with a relatively younger age of disease onset, as noted by the occurrence of FL in 3 patients all <55 years at diagnosis.

Collectively, these findings highlight the need to integrate this gene into current diagnostic algorithms. In broader terms, perhaps 1 of the key lessons arising from these studies is the importance of collaboration to maximize research efforts within this rare patient population and to promote increased vigilance on behalf of the wider hematology community. Critically, with the advent of NGS technologies, multicenter studies have led to a rapid increase in our understanding of the genetic complexity of inherited HM, with the number of susceptibility loci more than doubling in the last 3 years. These emerging data are essential to enable comprehensive investigation and tailored long-term management of patients and their families, while continuing to offer novel insights into the molecular pathogenesis of HM.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Lewinsohn M, Brown AL, Weinel LM, et al. Novel germ line *DDX41* mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. *Blood.* 2016;127(8):1017-1023.

2. Polprasert C, Schulze I, Sekeres MA, et al. Inherited and somatic defects in DDX41 in myeloid neoplasms. *Cancer Cell.* 2015;27(5):658-670.

3. Smith ML, Cavenagh JD, Lister TA, Fitzgibbon J. Mutation of CEBPA in familial acute myeloid leukemia. *N Engl J Med.* 2004;351(23):2403-2407.

4. Saliba J, Saint-Martin C, Di Stefano A, et al. Germline duplication of ATG2B and GSKIP predisposes to familial myeloid malignancies. *Nat Genet.* 2015;47(10):1131-1140.

5. Nickels EM, Soodalter J, Churpek JE, Godley LA. Recognizing familial myeloid leukemia in adults. *Ther Adv Hematol.* 2013;4(4):254-269.

6. Yamaguchi H, Calado RT, Ly H, et al. Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *N Engl J Med.* 2005;352(14):1413-1424.

7. Guo Y, Kartawinata M, Li J, et al. Inherited bone marrow failure associated with germline mutation of ACD, the gene encoding telomere protein TPP1. *Blood.* 2014; 124(18):2767-2774.

8. Song WJ, Sullivan MG, Legare RD, et al. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. *Nat Genet.* 1999;23(2):166-175.

9. Zhang MY, Churpek JE, Keel SB, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. *Nat Genet.* 2015;47(2):180-185.

10. Noetzli L, Lo RW, Lee-Sherick AB, et al. Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia. *Nat Genet.* 2015;47(5):535-538.

DOI 10.1182/blood-2016-01-690909

● ● ● THROMBOSIS AND HEMOSTASIS

Comment on Bito et al, page 1036

Knee replacement and HIT without heparin

Theodore E. Warkentin MCMASTER UNIVERSITY

In this issue of *Blood*, Bito et al report that dynamic mechanical thromboprophylaxis (DMT) is a risk factor for forming anti–platelet factor 4 (PF4)/heparin antibodies in patients undergoing knee or hip arthroplasty, which provides insight into a fascinating clinical problem: how can a patient develop heparin-induced thrombocytopenia (HIT) without heparin?[1]

HIT is an unusual drug reaction because its triggers extend beyond mere application of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). For example, the risk of HIT is greater if heparin is given to surgical (vs medical) patients[2] and among surgery or trauma patients if the trauma is major (vs minor).[3] Although the basis for this higher risk of immunization in major surgery or trauma patients is unknown, a plausible explanation lies in the fact that HIT is not provoked by heparin alone but rather by formation of immunogenic PF4/heparin complexes, and it is likely that surgery and major trauma favor formation of such complexes (because PF4 is released from platelet α-granules during surgery- and/or trauma-associated platelet activation).

HIT occurs only in a small minority of those who form anti-PF4/heparin antibodies, particularly the subset who form high levels of immunoglobulin G class antibodies that evince strong platelet-activating properties.[3] The high frequency of anti-PF4/heparin immunization means that serosurveillance studies can provide opportunities for exploring factors that are linked to risk of HIT beyond those that could be identified by studying only the (relatively) small number of patients who develop clinical HIT. By using serosurveillance, other nonpharmacologic risk factors for anti-PF4/heparin immunization have been identified, including type of surgery (knee > hip); body mass index (BMI; higher BMI > lower BMI for fixed-dose thromboprophylaxis), and timing of first heparin injection in relation to surgery (postoperative > preoperative in the setting of elective surgery, but preoperative > postoperative in the setting of trauma surgery).[4] Most (if not all) of these observations can be explained by a stoichiometric model of immunization in which factors that (theoretically) increase concentrations of stoichiometrically optimal PF4/heparin complexes are associated with greater frequency of immunization.[4]

But there remain other HIT mysteries. Spontaneous HIT syndrome is a prothrombotic thrombocytopenic disorder with serologic features of HIT (detectability of anti-PF4/heparin antibodies with strong platelet-activating properties) but which occurs despite lack of preceding exposure to heparin.[5] Interestingly, a large proportion of cases of spontaneous HIT syndrome have been reported in patients after orthopedic surgery, especially total knee arthroplasty (TKA).[6] Another mystery relates to how HIT might occur in patients who receive anticoagulation with fondaparinux,[7] the pentasaccharide anticoagulant modeled after the antithrombin-binding region of heparin, but which shows negligible cross-reactivity (enhancement of platelet-activating properties) with HIT antibodies.[8] Interestingly, so-called fondaparinux-associated HIT has also been seen almost exclusively in TKA patients.[9]

It is therefore of considerable interest that Bito and coworkers (collaborating with the transfusionist and HIT researcher Dr Shigeki Miyata) have reported their prospective serosurveillance study of more than 2000 patients undergoing TKA or total hip arthroplasty (THA).[1] Although many patients received UFH or LMWH thromboprophylaxis, more than half the study patients received either no anticoagulation or were given fondaparinux anticoagulation, with most also receiving DMT (via intermittent plantar or pneumatic compression device). The table shows the anti-PF4/heparin seroconversion rates among these various patient subgroups.

Table: Frequency of anti-PF4/heparin antibody formation in TKA and THA patients

	TKA patients				THA patients			
	No anticoagulation		Fondaparinux		No anticoagulation		Fondaparinux	
	No./Total	%	No./Total	%	No./Total	%	No./Total	%
With DMT	57/370	15.4	63/296	21.3	21/232	9.1	31/214	14.5
Without DMT	13/201	6.5	2/35	5.7	6/130	4.6	0/24	0
	$P = .002$		$P = .025$		$P = .147$		$P = .051$	