Increased bleeding and thrombosis in myeloproliferative neoplasms mediated through altered expression of inherited platelet disorder genes

Short Title:

Platelet expression elucidates genes of hemorrhagic and thrombotic risk in MPNs

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Abstract

An altered thrombo-hemorrhagic profile has long been observed in patients with myeloproliferative neoplasms (MPNs). We hypothesized that this observed clinical phenotype may result from altered expression of genes known to harbor genetic variants in bleeding, thrombotic, or platelet disorders. Here, we identify 32 genes from a clinically validated gene panel that were also significantly differentially expressed in platelets from MPN patients as opposed to healthy donors.

This work begins to unravel previously unclear mechanisms underlying an important clinical reality in MPNs. Knowledge of altered platelet gene expression in MPN thrombosis/bleeding diathesis opens opportunities to advance clinical care by: (1) enabling risk stratification, in particular, for patients undergoing invasive procedures, and (2) facilitating tailoring of treatment strategies for those at highest risk, for example, in the form of antifibrinolytics, desmopressin or platelet transfusions (not current routine practice). Marker genes identified in this work may also enable prioritization of candidates in future MPN mechanistic as well as outcome studies.

Introduction

Myeloproliferative neoplasms (MPNs) are associated with increased bleeding and thrombotic events[1-6], that are also a significant cause of morbidity and mortality[7-9] in these patients. Alongside molecular tests, bone marrow biopsy is a cornerstone of MPN diagnosis[10,11], with subtype determination informed by characteristic cell morphology and fibrosis assessment. Yet this procedure is not without complication for some patients; and apparent risk factors for hemorrhage post bone marrow aspiration include myeloproliferative disorders.

However, the mechanisms underlying MPN association with thrombo-hemorrhagic events remain unclear[6,12,13]. It has previously been suggested that in MF, hemorrhagic events result from a combination of progressive thrombocytopenia, secondary to bone marrow failure, and abnormalities in platelet function[14,15].

We therefore hypothesized that platelets in MF would demonstrate altered expression of a specific set of genes that are known to be associated with inherited bleeding, thrombosis, and platelet disorders, as characterized (and continuously under review) by an expert panel[14,16], and already validated for clinical use[17-19]. Here, we interrogate this specific gene set for differential platelet expression in a comprehensive cohort of platelet transcriptomes[20] from patients with chronic progressive MPNs.

Methods

Study approval was provided by the Stanford University Institutional Review Board (#18329). We collected blood from MPN patients enrolled in the Stanford University and Stanford Cancer Institute Hematology Tissue Bank after written informed consent from patients or their legally authorized representative. Eligibility criteria included age ≥18 years and Stanford MPN clinic diagnosis of essential thrombocythemia, polycythemia vera or myelofibrosis (defined using the consensus criteria at the time of this study). We use the term 'myelofibrosis' to encompass both primary myelofibrosis and myelofibrosis evolved from essential thrombocythemia or polycythemia vera. For healthy controls, blood was collected from adult donors selected at random from the Stanford Blood Center. All donors were asked for consent for genetic research. Altogether, our platelet transcriptome dataset[20] comprised 118 human peripheral blood samples as follows: healthy controls (n=21) and

World Health Organization-defined MPN patients (24 ET, 33 PV and 40 MF) including seven untreated, and 92 either on cytoreductives/biologics (*e.g.* ruxolitinib, hydroxyurea, interferon-alpha), anti-thrombotic agents (e.g. aspirin, warfarin), or a combination of these reflecting the diversity among MPN patients.

Platelet isolation, library preparation, and RNA sequencing.

All blood samples were collected into acid citrate-dextrose (ACD, 3.2%) sterile tubes (Becton, Dickinson and Co.) and platelets were isolated with an established protocol[21-24] within 4 h of collection. For RNA-sequencing (RNA-seq), $1x10^9$ isolated platelets lysed in Trizol were processed to extract RNA (all integrity numbers >7.0) and library preparation. Twelve pooled samples with individual indices were run on an Illumina HiSeq 4000 (Patterned flow cell with Hiseq4000 SBS v3 chemistry) as 2 X 75bp paired end sequencing with a coverage target of 40M reads/sample.

Statistical Analysis and Variant-Expression Mapping

Platelet transcriptomic data were library-size-corrected, variance-stabilized, and log2-transformed using the R package DESeq2[25]. The same algorithm was used to determine differential gene expression, while adjusting for patient age, gender and treatment as confounding variables and controlling for multiple comparisons using the Benjamini-Hochberg defined false discovery rate (FDR). Significant variance in expressed transcripts were pre-specified as transcripts with an FDR <0.05 and a log2 fold change ≥ 0.5 in MPN, as compared to healthy controls (the entire differential transcriptome was applied toward downstream Gene Set Enrichment Analysis).

Using Mann-Kendall trend test (multiple comparisons adjusted with the Benjamini-Hochberg method) on normalized gene counts, we assessed progressive and monotonic upward or downward trends in gene expression and identified statistically significant progressive genes across the three MPN subtypes, ET, PV, and MF at a false discovery rate FDR <0.05.

Results and Discussion

The bleeding, thrombotic, and platelet disorder panel[17,26] constituted a total of 145 unique genes. Of these, 32 were found to be progressively differentially expressed (FDR <0.05) across MPNs. **Table 1** details these genes with results from both pairwise differential comparisons (each MPN subtype versus healthy donors) as well as progressive expression trend analysis across all three MPN subtypes.

The top 12 progressively differentially expressed genes are also visualized in **Figure 1**. 22 genes showed reduced expression in MPNs relative to healthy donors. These included genes previously linked with granule release and development such as *AP3B1*, *LYST*, and *BLOCS6*, and disorders of platelet function such as *P2RY12* and *AN06.* One noteworthy example is the discordant expression of known anticoagulant genes (*e.g. DSE* downregulation) versus those of platelet dense granule function (*e.g. HPS1* upregulation) across MPNs, likely a factor in the uncertain risk of both thrombosis and bleeding in MPNs. 10 genes were overexpressed compared to healthy donors. Some of the increased expression levels may reflect the underlying neoplastic process in MPNs, such as that observed for *ENG and RUNX1*. Others, such as *PLAT*, *GATA1* and *HDAC6* have been linked to impaired platelet development or activation and may contribute to the bleeding profile observed in MPNs.

Together, these genes offer opportunities for evaluation, not only as biomarkers in assessment of risk, prognosis and monitoring for thrombosis/bleeding in MPN patients but also as candidates for mechanistic interrogations in MPN model systems and future outcome studies.

Figure Legends

Figure 1: Progressive expression of markers of thrombohemorrhagic risk in MPNs

Top 12 genes (out of 32 detailed in Table 1) demonstrating monotonic progressive gene expression (log2 fold change in expression *y*-axis, FDR < 0.01, *Mann-Kendall* test with Bonferroni correction) across *x-axis* MPN subtypes (ET/PV/MF) versus healthy donors (CTRL).

Table Legends

Table 1: Inherited bleeding and platelet disorder genes whose altered expression may explain the increased thrombo-haemorrhagic risk in myeloproliferative neoplasms. Column 1 identifies the candidate gene of interest, Column 2 provides a summary of gene function, and evidence of relationship with either platelet or bleeding disorders and Column 3 highlights the observed differential either as a pairwise comparison between any given MPN subtype versus healthy donors or as a progressive change across all three subtypes.

Author Contributions

A. Krishnan, M. Frontini and S. Sivapalaratnam conceived of the overall study. A.M. and A.K. wrote and edited the manuscript. M.F., A.K. and S.S. critically reviewed and edited the manuscript. All authors approved the final manuscript.

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Conflict of Interest Disclosures: Authors declare no conflict of interest.

Table 1: Inherited bleeding and platelet disorder genes whose altered expression may explain the increased thrombo-haemorrhagic risk in myeloproliferative neoplasms (MPN).

Genes showing decreased MPN expression relative to healthy donors.		
Candidate Gene	**Gene function and relationship with thrombosis, bleeding, or platelet disorders**	**Platelet expression in MPNs and how this may relate to thrombosis/bleeding**
P2RY12	*P2RY12* belongs to the family of G-protein coupled receptors. The receptor is involved in platelet aggregation at sites of vascular injury, in both physiological hemostasis and pathological thrombosis. Indeed, deficiency of *P2RY12* is associated with both excessive bleeding and prolonged bleeding times[27]. Furthermore, inherited defects with *P2RY12* are associated with abnormal platelet function, and mild or moderate bleeding diathesis[28].	*P2RY12* expression was downregulated in all MPN subgroups, in keeping with the bleeding phenotype.
TRPM7	The protein encoded by *TRPM7* is both an ion channel and a serine/threonine protein kinase. This dual nature is critical for the ion channel function, as it regulates intracellular calcium and magnesium ion homeostasis[29]. Impaired TRPM7 channel function within megakaryocytes in mice, results in macrothrombocytopenia[30]. These mutant mice had impaired proplatelet formation, which was associated with abnormal cytoskeletal structure.	*TRPM7* was downregulated, in keeping with the observed bleeding pattern. This could result in impaired proplatelets with subsequent impaired platelet function.
COL4A2	*COL4A2* encodes a major component of the basement membrane of blood vessels. Pathogenic variants within this gene result in cerebral vascular defects, ocular dysgenesis, and renal abnormalities, with an increased susceptibility to intracerebral haemorrhage[31].	*COL4A2* expression was reduced within each of the ET, PV, and MF subgroups relative to the healthy donors.
FLI1	Platelet disorders including bleeding disorder, platelet-type, 21, and isolated delta storage pool disease have been linked with defects in the protein coding gene *FLI1* [32,33]. These disorders are caused by variants in the gene, resulting in decreased protein formation.	*FLI1* expression was downregulated, within each subgroup, but most notably within the MF cohort. This would be in keeping with previous studies noting that reduced *FLI1* expression can result in bleeding disorders.

SMAD1* and *SMAD4	*SMAD1* and *SMAD4* encode proteins which act as a signal transducer to multiple signaling pathways, including those implicated in cell growth, apoptosis, and immune response. Pathological variants in *SMAD1* have been linked with Buschke-Ollendorff Syndrome and Osteopoikilosis[34]. Pathological variants in SMAD4 have been linked to hereditary hemorrhagic telangiectasia syndrome[35].	*SMAD1* was found to be downregulated compared to healthy donors, in each of the MPN subgroups. This dysregulation in cell growth and apoptosis may be critical to the development of MPN. *SMAD4* expression was reduced within MF.
DSE	*DSE* variants have previously been associated with the musculocontractural subtype of Ehlers-Danlos syndrome. The gene product is key to dermatan sulfate biosynthesis[36]. Dermatan sulfate is a glycosaminoglycan which acts as an anticoagulant to prevent inappropriate coagulation, through binding to heparin cofactor II [37].	*DSE* showed decreased expression in all subgroups, maximally reduced within MF. The reduction in dermatan sulfate product would result in a decoupling of normal coagulation and may contribute to the increased thrombotic profile recognized within MPNs.
F8	*F8* encodes coagulation factor VIII which acts in the intrinsic pathway of the clotting cascade. Factor VIII is a cofactor for factor IXa which converts factor X to the activated form. Truncating variants within the *F8* gene can result in the bleeding disorder haemophilia A [38].	*F8* was downregulated within the MF subgroup alone.
F13A1	*F13A1* encodes the A subunit of coagulation factor XIII, a component of the coagulation cascade. Variants within the *F13A1* gene causing a deficiency of factor XIII result in a clear bleeding tendency [39,40].	*F13A1* was downregulated within the MF subgroup alone.
TREX1	This gene encodes a nuclear protein with 3' exonuclease activity. It may be involved in DNA repair and serve as a proofreading function for DNA polymerase. Deficiency of the protein has been linked with the development of autoimmune conditions [41].	*TREX1* was downregulated within the MF subgroup alone.
GFI1B	This gene encodes a transcriptional regulator which complexes with other regulatory proteins, to control expression of genes involved in the development and maturation of erythrocytes and megakaryocytes. Variants within the gene can result in platelet-type bleeding disorder[42].	*GFI1B* expression was reduced in MF, relative to healthy donors. Potentially explaining the bleeding phenotype by impaired platelet development.

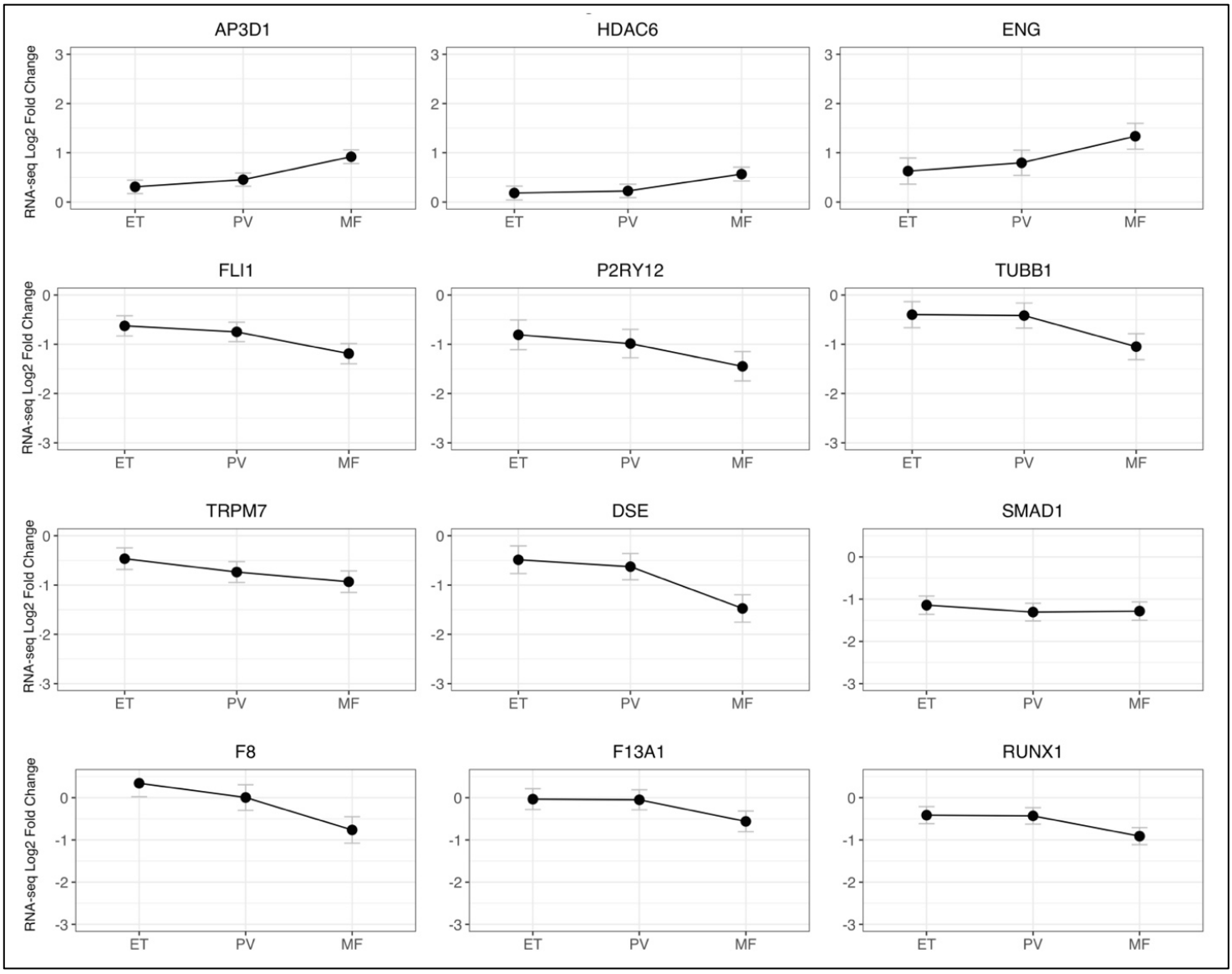
LYST	*LYST* encodes a protein which has been linked with the regulation of intracellular vesicles, and exocytosis [43,44]. Variants within the gene can cause Chediak-Higashi syndrome, one feature of which is a bleeding tendency[45]. This is believed to be due to absent or severely diminished platelet dense granules[46].	Expression of *LYST* was reduced in MF and may contribute to the observed bleeding pattern.
RUNX1	*RUNX1* encodes a subunit of a transcription factor (Core binding factor) which has been linked with normal haematopoiesis [47]. Variants within the gene have been linked with familial platelet disorder with associated myeloid malignancy. This is characterized by a qualitative and quantitative platelet defect, alongside a tendency to develop acute myeloid leukaemia[48].	*RUNX1* expression was downregulated, within MF and PV cohorts suggesting a dysregulation of the normally tightly regulated haemopoietic process.
FOXC1	*FOXC1* encodes a transcription factor which has previously been found to be preferentially expressed in CXCL12 abundant reticular (CAR) cells essential for hematopoietic stem and progenitor cell maintenance[49].	*FOXC1* was found to be reduced in MF and PV cohorts. This may relate to the underlying neoplastic process.
RASGRP2	The protein encoded by this gene is a nucleotide exchange factor. Variants in this gene have been linked with Bleeding Disorder, platelet-type, 18. This is a functional platelet disorder, with defective signaling resulting in impaired platelet aggregation and prolonged bleeding times[50].	*RASGRP2* was found to be reduced in MF, in line with the observed bleeding pattern.
BLOC1S6	This gene encodes a protein which has been linked to intracellular vesicle trafficking[51]. Pathological variants in the gene result in Hermansky-Pudlak Syndrome, which is associated with platelet dysfunction and prolonged bleeding times[52].	*BLOC1S6* was found to be reduced in MF in line with the observed bleeding tendency.
PRRT2	This gene encodes a transmembrane protein, which may be involved in synaptic transmission, and believed to play a role in neurotransmitter release[53].	*PRRT2* was found to be reduced in MF relative to healthy donors.
ITM2B	ITM2B encodes a transmembrane protein. A short form of the encoded protein, generated by alternative splicing has previously been shown to induce apoptosis within hematopoietic cell lines[54].	The expression of *ITM2B* was found to be reduced in MF. This may relate to the neoplastic process.
ANO6	The transmembrane protein encoded by *ANO6*, is a critical component for the calcium dependent	*ANO6* was under expressed in MF, in keeping with the bleeding

	exposure of phosphatidylserine on platelet surfaces, which is necessary to trigger the clotting system[55]. This can manifest clinically as the bleeding disorder Scott syndrome[56].	phenotype.
NBEA	*NBEA* encodes an A-kinase anchor protein, which targets the activity of protein kinase A, playing a role in vesicle trafficking[57]. Variants within the NBEA have previously been linked with a bleeding disorder phenotype[58]. However, the evidence for pathogenicity has subsequently been disputed.	*NBEA* was found to be reduced in both MF and PV cohorts.
AP3B1	The *AP3B1* gene encodes a protein which has been linked with organelle biogenesis including platelet dense granules[59]. Variants within the gene can result in a subtype of Hermansky-Pudlak Syndrome, which is associated with platelet dysfunction and prolonged bleeding times[52].	Expression of *AP3B1* was decreased in MF, in keeping with the bleeding profile.
TUBB1	The *TUBB1* gene encodes a beta tubulin protein, which are one of two core protein families which are key to the assembly of microtubules [60]. This protein is specifically expressed within platelets and megakaryocytes and has been linked with both proplatelet production and release. Variants within the *TUBB1* gene have been linked with autosomal dominant isolated macorthrombocytopenia-1[61]. Megakaryocytes from these patients have abnormal large and irregular bleb protrusions, suggesting impaired megakaryocyte fragmentation and the release of large platelets.	Within our MPN cohort *TUBB1* gene expression was found to be reduced in all subgroups, and maximally in MF. This reduction in *TUBB1* expression, and the critical role it has in platelet stability may explain the observed MPN thrombohemorrhagic profile.
Genes showing increased MPN expression relative to healthy donors.		
ENG	*ENG* is known to encode a transmembrane protein which is a major glycoprotein found within vascular endothelium. Variants in the gene have been linked to hereditary hemorrhagic telangiectasia, which is a vascular dysplasia associated with bleeding episodes[62]. It is also an important regulator of the hematopoietic lineage. Expression of ENG has previously been noted in myelodysplastic syndromes, acute myeloid leukaemia, and chronic lymphocytic leukaemia[63-65]. Previous overexpression studies during embryoid body differentiation resulted in an increase of haemopoietic progenitors	The *ENG* gene displayed a nearly 1.5-2-fold higher expression in each of ET, PV and MF versus healthy donors. This may be reflective of the underlying neoplastic process.

	and a correlated upregulation of *SCL*, *GATA1*, and *RUNX1*[66].	
HPS1	*HPS1* encodes a protein which is believed to be involved with organelle biogenesis, including platelet dense granules. Variants in this gene are related to Hermansky-Pudlak Syndrome, which is associated with platelet dysfunction and prolonged bleeding times[52].	Within each subgroup of our MPN cohort, expression of *HPS1* was increased relative to the healthy donors. This may represent dysregulation of underlying physiological function.
GATA1	The *GATA1* gene encodes a transcription factor which plays a critical role in the normal development of haemopoietic cell lines. It's previously been demonstrated that *GATA1* deficient platelets show abnormal cell-structure, and defects in platelet activation with prolonged bleeding times[67]. Precise regulation of *GATA1* has previously shown to be critical for its physiological roles, with fluctuations in expression resulting in disorganized erythropoiesis [68]. Overexpression of *GATA1* has previously been shown to result in a lethal anaemia[69].	The PV and MF cohorts were found to have overexpressed *GATA1.* This may be contributing to disorganized erythropoiesis, and subsequently resulting in the observed altered bleeding profile.
WAS	The *WAS* gene codes for the WASP protein, which is found in all blood cells enabling adhesion between each other and other tissues. Pathogenic variants within the gene can result in Wiskott-Aldrich syndrome which results in immune deficiency and prolonged bleeding [70]. Reduced platelet numbers and size, and prolonged bleeding is characteristic of X-linked thrombocytopaenia. This condition is also associated with variants in the *WAS* gene[71]. Increased *WAS* activity has been associated with marked derangements of cytoskeletal structure and function [72]. This altered function has resulted in myelodysplasia and an altered bleeding profile.	*WAS* was overexpressed in PV and MF cohorts relative to healthy donors. This altered expression may result in the observed bleeding profile, through the previously observed derangements of cytoskeletal structure and function, subsequently causing an altered bleeding profile.
VIPAS39 **and** ***VPS33B***	*VIPAS39* and *VPS33B* encode key components of intracellular trafficking of lysosomal proteins [73]. Variants within these genes can result in arthrogryposis, renal dysfunction, and cholestasis (ARC)[74]. In this condition a grey platelet like syndrome defect and bleeding are accompanied	*VIPAS39* showed almost two-fold increase in expression in both the PV and MF subgroups, and *VPS33B* similarly in MF. This overexpression may result in a dysregulation of intracellular

	with developmental and functional deficiencies within multiple organs.	trafficking, contributing to a bleeding profile.
AP3D1	*AP3D1* encodes a protein comprising a subunit of the AP3 adaptor-like complex. This complex enables the budding of vesicles from the Golgi membrane and has been linked to intracellular biogenesis and possibly the trafficking of platelet dense granules. It has been linked to a new variant of Hermansky-Pudlak Syndrome[75].	AP3D1 was overexpressed in PV and MF, relative to healthy donors.
EIF2AK4	*EIF2AK4* encodes a kinase family which results in the downregulation of protein synthesis through the phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2. Associated diseases include pulmonary veno-occlusive disease[76].	*EIF2AK4* was overexpressed in MF, and result in a downregulation of protein synthesis.
HDAC6	*HDAC6* encodes a protein which results in the repression of gene transcription through histone deacetylase activity[77]. It has previously been shown that this gene product is critical to the tightly regulated process of platelet activation[78].	*HDAC6* expression was increased in MF, and may explain the observed bleeding profile through impaired platelet activation.
PLAT	This gene encodes a tissue-type plasminogen activator which converts the proenzyme plasminogen to plasmin[79]. Increased enzymatic activity causes hyperfibrinolysis, which manifests as excessive bleeding.	*PLAT* is progressively increased in all subgroups, and maximally in MF. This is in keeping with the observed bleeding phenotype.

FIGURE 1



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