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Inherited Thrombocytopenia: Update on Genes and Genetic Variants Which may be Associated With Bleeding

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Inherited thrombocytopenia (IT) is comprised of a group of hereditary disorders characterized by a reduced platelet count as the main feature, and often with abnormal platelet function, which can subsequently lead to impaired haemostasis. Inherited thrombocytopenia results from genetic mutations in genes implicated in megakaryocyte differentiation and/or platelet formation and clearance. The identification of the underlying causative gene of IT is challenging given the high degree of heterogeneity, but important due to the presence of various clinical presentations and prognosis, where some defects can lead to hematological malignancies. Traditional platelet function tests, clinical manifestations, and hematological parameters allow for an initial diagnosis. However, employing Next-Generation Sequencing (NGS), such as Whole Genome and Whole Exome Sequencing (WES) can be an efficient method for discovering causal genetic variants in both known and novel genes not previously implicated in IT. To date, 40 genes and their mutations have been implicated to cause many different forms of inherited thrombocytopenia. Nevertheless, despite this advancement in the diagnosis of IT, the molecular mechanism underlying IT in some patients remains unexplained. In this review, we will discuss the genetics of thrombocytopenia summarizing the recent advancement in investigation and diagnosis of IT using phenotypic approaches, high-throughput sequencing, targeted gene panels, and bioinformatics tools.

Keywords: inherited thrombocytopenia, platelets, megakaryocytes, genes, mutations, bleeding

INTRODUCTION

Platelets are small anucleate cells produced by megakaryocytes in the bone marrow (BM) where they circulate in the blood to protect the integrity of blood vessels. They play an important role in normal haemostasis to prevent excessive bleeding at the site of blood vessel injury (1, 2). Inherited Thrombocytopenias (ITs) are a heterogeneous group of disorders characterized by low platelet counts, often manifesting as bleeding diathesis which subsequently result in impaired haemostasis (3). In 1948, the disease inheritance pattern of one IT was initially discovered in a disorder called Bernard-Soulier syndrome (BSS) (4). Since then, the advancement in clinical and scientific research has led to an increased understanding of the molecular defects in patients with ITs. These defects are variable in severity, ranging from severe bleeding, which can be recognized within a few weeks after birth, to mild bleeding that may remain undiagnosed until incidental recognition during
routine blood testing in adulthood (5). They manifest with different symptoms including epistaxis, easy bruising, petechiae, prolonged bleeding from cuts, gum bleeding, excessive bleeding after surgery, hematuria, and menorrhagia in women (6, 7). As bleeding is considered the main clinical complication for patients with IT, some patients with common ITs have the propensity to develop other disorders such as hematological malignancies and kidney failure (4, 8). Although there are other causes of thrombocytopenia, such as infections and immune disorders, IT is primarily caused by mutations in genes involved in megakaryocyte differentiation, maturation and platelet release (9). Since the last decade, next generation sequencing technologies, namely Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) coupled with conventional Sanger sequencing and in-silico bioinformatic tools have been used in parallel to uncover novel genes with a pivotal role in megakaryocyte biology and platelet biogenesis (10, 11). To date, 40 genes have been reported to cause different forms of IT, which reflects the immense difficulty in identifying a single causative gene, particularly when accompanied by other hematological disorders [Table 1; Figure 1; (27, 28, 54)]. These genetic forms have various clinical manifestations, phenotypic presentations and sometimes associated with secondary qualitative defects in platelet function (7). Diverse platelet phenotypes mean there are several approaches in which they can be characterized. One such way is to classify genes based on their influence on megakaryocyte differentiation, platelet production, and removal (54), and will be discussed below. However, despite these advancements, nearly 50% of patients with IT of unknown genetic etiology still remain undiagnosed (6, 10).

**IT GENES ASSOCIATED WITH MEGAKARYOCYTE DIFFERENTIATION AND MATURATION**

The process of megakaryopoiesis and thrombopoiesis involves a complicated biological series of events. Megakaryocytes, like all blood cells, are derived from the hematopoietic stem cells (HSC) in the bone marrow during the lineage commitment stages. The hematopoietic stem cell differentiation process involves committed precursors that include the common myeloid progenitor (CMP) and the megakaryocyte-erythroid progenitor (MEP). The erythrocyte cells and megakaryocyte cells result from the MEP. Megakaryocyte precursors encompass a maturation process that results in mature polyploid megakaryocytes, and then leads to the formation of pro-platelets (54, 55). The process of megakaryopoiesis and thrombopoiesis involves multiple genes and transcriptions factors (detailed below) which play important roles in megakaryocyte differentiation, platelet formation, and release. IT can result from defects in these genes which present with variable phenotypic display and clinical presentation. As a result of the numerous clinical demonstrations of ITs, they can be characterized based on genes and their role during megakaryocyte differentiation, platelet production, and release (9, 56).

Some ITs result from defective changes from haemopoietic progenitor cells to MKs, leading to reduction or absence in the number of bone marrow MKs. Thrombopoietin (TPO), an acidic glycoprotein, is the main regulator of the megakaryopoiesis and thrombopoiesis mechanism in humans, acting through its receptor c-Mpl. It is required for megakaryocytes to fulfill their developmental proliferation and for the subsequent maturation of platelets (57). Affected individuals from a large Micronesian family displayed idiopathic anemia and mild thrombocytopenia as a result of mutations in TPO and MPL genes (21, 58). The main defective mechanism in several forms of IT is a change in MK maturation which therefore leads to the production of immature and dysfunctional MKs. However, the differentiation and maturation of MKs is regulated by several transcription factors such as GATA1. GATA1 is highly expressed in the erythroid and megakaryocytic lineage, and plays a vital role in the maturation and development of erythroid cells and megakaryocytes (59). X-linked thrombocytopenia with thalassemia and X-linked thrombocytopenia with dyserythropoietic anemia are both caused by mutations in GATA1, resulting in impaired MK and erythroid cell maturation. As a consequence, GATA1-mutated patients are characterized with large platelets and reduced α-granule contents. They also display a variable degree of anemia and abnormal morphology of red blood cells (60). Additional transcription factors known to be involved in the maturation of megakaryocytes are RUNX1, ETV6, ANKRD26, FLI-1, and the transcriptional repressor GFI1B acting by binding to promoter regions in MK expressed genes. Thus, multiple mechanisms in MK and platelet maturation are affected as result of alterations in these genes (61, 62). A previous study identified a point mutation in the third helix of HOXA11 homeodomain causing an inherited syndrome of congenital amegakaryocytic thrombocytopenia and radio-ulnar synostosis (19). Thrombocytopenia absent radii (TAR) syndrome results from a combination of a microdeletion on Chromosome 1 including the RBBM8A gene alongside a low frequency non-coding single nucleotide polymorphism (SNP) within the regulatory region of RBBM8A (23). As a consequence, hematopoietic progenitors from patients with TAR syndrome fail to differentiate into MKs in vitro (63). Gray Platelet syndrome is characterized by a deficiency in α granule content which also results in a platelet function defect. It is associated with enlarged platelets and mild thrombocytopenia with moderate to severe bleeding as a result of biallelic mutations in NBEAL2, the gene encoding the neurobeachin-like-2 protein (22). Variants in the 5’UTR of ANKRD26 cause familial thrombocytopenia type-2 (THC2) with propensity to leukemia, which result in loss of RUNX1 and FLI1 binding and prevents gene silencing (12). Moreover, heterozygous variants specifically located in the promoter region between c.-134G and c.-113 region highly affect gene expression. Patients with THC2 are characterized by small MKs with hypolobulated nuclei as a result of dysmegakaryopoiesis (64). A mutation in the FYB1 gene has recently been identified to cause IT and although the exact mechanism of the mutation is still ambiguous, it has been suggested that thrombocytopenia arises from a reduction of mature MKs in the bone marrow and synthesis of small platelets (16).
TABLE 1 | The direct genetic causes of inherited thrombocytopenia and their associated syndromes.

<table>
<thead>
<tr>
<th>Area of mutational effect</th>
<th>Gene</th>
<th>Syndrome</th>
<th>Other syndromic and features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megakaryopoiesis</td>
<td>ANKRD26</td>
<td>ANKRD26-related thrombocytopenia</td>
<td>Predisposition to leukemia. Reduction of platelet α-granules. Normal in vitro platelet aggregation and mean platelet volume. Some patients have high level of hemoglobin and leukocyte.</td>
<td>(12, 13)</td>
</tr>
<tr>
<td></td>
<td>ETV6</td>
<td>ETV6-related thrombocytopenia</td>
<td>Leukemia predisposition. High erythrocyte mean corpuscular volume (MCV). Some patients have elevated red cell MCV.</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td>FYB</td>
<td>FYB-related thrombocytopenia</td>
<td>Small platelets. Reduction of mature MKs in BM. Significant bleeding tendency. Normal WBCs count. Low mean platelet volume MPV. Mild iron deficiency anemia.</td>
<td>(16)</td>
</tr>
<tr>
<td></td>
<td>GATA1</td>
<td>GATA1-related disease: X-linked thrombocytopenia (XLT) and X-linked thrombocytopenia with thalassemia (XLT'T)</td>
<td>Dyserthropoietic anemia. Macrothrombocytopenia. Beta-thalassemia Congenital erythropoietic porphyria. Erythrocyte abnormalities. Splenomegaly.</td>
<td>(17)</td>
</tr>
<tr>
<td></td>
<td>GR11B</td>
<td>Macrothrombocytopenia and platelet function defects</td>
<td>Macrothrombocytopenia. Red cell anisopoikilocytosis Platelet dysfunction. Reduction of platelet α-granules.</td>
<td>(18)</td>
</tr>
<tr>
<td></td>
<td>HOXA11</td>
<td>Amegakaryocytic thrombocytopenia with radio-ulnar synostosis</td>
<td>Bilateral radial synostosis. Severe bone marrow failure. Cardiac and renal malformations. B-cell deficiency. Hearing loss. Clinodactyly. Some patients show skeletal anomalies. Some patients have developed pancytopenia.</td>
<td>(19)</td>
</tr>
<tr>
<td></td>
<td>MECOM</td>
<td>Congenital amegakaryocytic thrombocytopenia and radio-ulnar synostosis</td>
<td>Bilateral radial aplasia. Elevated hemoglobin level in patients with 5'UTR SNP. Normal WBCs count and some patients have leucocytosis and eosinophilia. Anemia. Skeletal, urogenital, kidney, and heart defects. Reduced MKs in BM.</td>
<td>(20)</td>
</tr>
<tr>
<td></td>
<td>MPL</td>
<td>Congenital amegakaryocytic thrombocytopenia (CAMT)</td>
<td>Absence or reduced of MKs in BM. No physical anomalies. Development to BM aplasia in infancy.</td>
<td>(21)</td>
</tr>
<tr>
<td></td>
<td>NBEAL2</td>
<td>Gray platelet syndrome</td>
<td>Impaired platelet function. Severe reduction of platelet α-granules contents. Large platelets. Development of myelofibrosis and splenomegaly in some patients. Abnormalities in megakaryocyte development.</td>
<td>(22)</td>
</tr>
<tr>
<td></td>
<td>RBM8A</td>
<td>Thrombocytopenia-absent radius syndrome</td>
<td>Bilateral radial aplasia. Elevated hemoglobin level in patients with 5'UTR SNP. Normal WBCs count and some patients have leucocytosis and eosinophilia. Anemia. Skeletal, urogenital, kidney, and heart defects. Reduced MKs in BM.</td>
<td>(23)</td>
</tr>
<tr>
<td></td>
<td>RUNX1</td>
<td>Familial platelet disorder with propensity to acute myelogenous leukemia (FPD/AML)</td>
<td>Platelet defects. Variable platelet counts. Reduction in dense granule secretion observed in secondary qualitative abnormality. Myelodyplasia. Reduced response to several platelet agonists.</td>
<td>(24)</td>
</tr>
<tr>
<td></td>
<td>SLFN14</td>
<td>SLFN14-related thrombocytopenia</td>
<td>Giant platelets. Decreased ATP secretion. Reduced number of dense granules.</td>
<td>(24)</td>
</tr>
<tr>
<td></td>
<td>THPO</td>
<td>Inherited thrombocytopenia from monoallelic THPO mutation</td>
<td>Bone marrow aplasia. Normal or enlarged platelet morphology.</td>
<td>(26)</td>
</tr>
<tr>
<td></td>
<td>PTPRJ</td>
<td>Inherited thrombocytopenia</td>
<td>Syndromic thrombocytopenia characterized by spontaneous bleeding, small-sized platelets. Impaired platelet function.</td>
<td>(27)</td>
</tr>
<tr>
<td></td>
<td>GALE</td>
<td>Inherited thrombocytopenia</td>
<td>Dysplastic megakaryocytes. Some patients have mild anemia and febrile neutropenia. Big and pale platelets. Galactosemia, hypotonia, seizures, jaundice, galactosuria, and hepatomegaly.</td>
<td>(28)</td>
</tr>
<tr>
<td>Platelet production/ clearance</td>
<td>ACTIN1</td>
<td>ACTIN1-related thrombocytopenia</td>
<td>Congenital macrothrombocytopena. Anisocytosis. Absent or mild bleeding diathesis.</td>
<td>(29)</td>
</tr>
<tr>
<td></td>
<td>CYCS</td>
<td>CYCS-related thrombocytopenia</td>
<td>Normal platelet size and volume.</td>
<td>(30)</td>
</tr>
<tr>
<td></td>
<td>GNE</td>
<td>GNE myopathy with congenital thrombocytopenia</td>
<td>Rimmed vacuoles. Hematological complications are rare. Proteinuria and hematuria in some patients. Membranoproliferative glomerulonephritis. Platelets size are normal to large.</td>
<td>(31–33)</td>
</tr>
</tbody>
</table>

(Continued)
DEFECTS IN PROPLATELET FORMATION AND PLATELET RELEASE

After megakaryopoiesis, proplatelets form extensions which lead to “budding” at the tips and platelet release into the circulation. Mature MKs undergo essential processing by extending long branches called proplatelets via the bone marrow sinusoids, and subsequently release platelets into the blood circulation. These processes are underpinned by cytoskeletal changes and cellular signaling where most causative mutations of IT disrupt the pathway reducing the circulating platelet count (34–36). Mature MKs cytoplasm extend long beaded cytoplasmic protrusions, as a result of microtubule sliding. The dimerisation of β1-tubulin with α-tubulin polymerizes into long microtubule bundles inside the MK cortex. A mixed polarity of microtubule bundles runs throughout the extension of proplatelets which are thought to provide fundamental force for microtubule sliding and proplatelet elongation (65). TUBB1 encodes for β1-tubulin and mutations within TUBB1 are associated with an autosomal dominant form of IT known as a congenital macrothrombocytopenia (43). WASp is a multidomain protein belonging to a family of actin nucleation-promoting factors (NPFs) which are specifically expressed in hematopoietic cells. WASp plays an important role in actin polymerization by transmission of surface signals via the actin-related protein (Arp)2/3 complex (44, 67). Mutations have been identified in the WAS gene which cause a rare X-linked disorder called Wiskott-Aldrich syndrome (WAS). Patients are characterized by microthrombocytopenia and immunodeficiency with predisposition to malignancies (68). The transmission of extracellular signals into the cytoskeleton is mediated via membrane bound receptors which have been associated with mutations in IT. One of the main membrane receptors in platelets/MKs is the GP1b-IX-V complex, which binds specifically to Von-Willebrand factor (VWF). This receptor is comprised of four subunits including GP1bα, GP1bβ, GPIX, and GPV. Binding of VWF with GP1bα
leads to activation and signal transmission to form the extending proplatelet. Mutations in the encoding genes GP1BA, GP1BB, and GP9 cause monoallelic and biallelic forms of BSS (69, 70). Other receptors include the receptor for fibrinogen, integrin GPIIb-IIIa, which is encoded by the genes ITGA2B and ITGB3. Affected mutations in ITGA2B and ITGB3 have been identified to cause Glanzmann thrombasthenia (GT) (71), but patients have a normal platelet count.

**INITIAL DIAGNOSIS OF HEREDITARY THROMBOCYTOPENIA**

Identification of the genetic cause in patients with IT is challenging and many patients may be misdiagnosed with acquired thrombocytopenia such as immune thrombocytopenic purpura (ITP). IT can be recognized in patients when a low platelet count has been identified after birth, the presence of familial medical history with similar clinical presentations, evaluation of peripheral blood films, and physical examination. Moreover, the presence of a severe bleeding tendency (in combination with a low platelet count), a lifelong history of diathesis, and evidence of other clinical complications that are typically associated with thrombocytopenia in syndromic forms, and all help to diagnose IT (4, 72). Platelets are involved in other biological roles beyond hemostasis, such as immunity and inflammation (73–75) therefore, mutations in platelet specific genes may cause functional disruption in hemostasis, other biological pathways or both. Furthermore, some proteins are expressed in megakaryocytes and platelets and can be found in other cell types. GATA1 is a prominent example which involves megakaryopoiesis and erythropoiesis (76). MYH9 also has an important role in the platelet cytoskeleton and has been found expressed in kidney and inner ear cilia (77). Based on this, inherited bleeding disorders can be classified into three categories including disorders that (i) affect only platelets, (ii) disorders that are associated with syndromic or non-syndromic phenotypes, and (iii) disorders with increased risk of hematologic malignancies. This classification can be used for both diagnostic and prognostic purposes (4, 11).

**SYNDROMIC DISORDERS ASSOCIATED WITH IT**

The number of IT forms identified has increased over the last few years since the implementation of NGS. Consequently, it has been shown that the bleeding is not the only clinical phenotype with IT, but patients with some IT forms have propensity to develop more syndromic disorders as result of molecular defects in genes responsible for thrombocytopenia. For instance, hematological malignancies, bone marrow aplasia, skeletal malformation, liver and kidney malfunction, and deafness (Figure 2). The development of these diseases can be more severe for patients than the bleeding itself (4) however, it is still important to recognize if these manifestations are present in the relatives. Some syndromic phenotypes associated with ITs are variable between family members or can arise later in life. For example, development of deafness, kidney malfunction and/or cataract in patients with MYH9-RD occur only in adult individuals and it has been reported that patients of the same MYH9-RD pedigrees have variable clinical manifestations (78).

**THE GENETIC DIAGNOSIS OF IT**

Some patients with a low platelet count may be falsely diagnosed and receive unnecessary treatments such as immunosuppression and splenectomies and therefore it is paramount that strong evidence must prove that the condition is truly genetic. Genetic diagnosis is a vital approach in providing patients with clinical benefits and prevent unnecessary treatments. Patients with genetic mutations in RUNXI have a predisposition to develop hematological malignancies where the genetic information can be used to monitor the patients’ hematological parameters very closely. This emphasizes the importance and need for definitive genetic diagnostic tools to provide quick and cost-effective diagnosis for screening patients with IT (6, 8). The molecular basis of ITs has been elucidated since the adoption of Sanger sequencing and linkage analysis in the 1990s. Recently, Sanger sequencing is considered a low throughput and time-consuming approach which can be used initially as a standard tool to investigate patients based on precise clinical findings and phenotype (4). A targeted thrombocytopenia gene specific panel is a useful approach which can be used as initial screening prior to WES. This targeted panel encompasses all known genes associated with IT and their related genes. The aim of using an IT gene specific panel is to filter out patients based on variants in known IT-causal genes and subsequently allowing for WES for patients with unknown genetic etiology (4, 6). The ThromboGenomics project provided a multi-gene high-throughput sequencing platform (HTS) for the diagnosis of heritable bleeding disorders (79). The HTS platform covers approximately 96 genes associated with inherited bleeding, thrombotic, coagulation, and platelet disorders. The panel showed high sensitivity in detecting causative variants in patients who had not been previously investigated at the molecular level. It has a high sensitivity to detect variants in the exonic region as well as many of exonic-intronic boundaries and untranslated regions (UTRs) (6, 79).

**NEXT GENERATION SEQUENCING**

Targeted NGS platforms can be efficiently applied to determine the causative genes of IT. As the molecular basis of ITs remain unknown in many patients, WGS or WES may be required which improves the knowledge of ITs at the molecular level. Several national and international consortia have adopted these approaches to identify disease-causing genes associated with IT. The genes SLFN14, FYB, STIM1, GFI1b, and ETV6 are some examples of causative genes detected by these approaches. The results obtained by HTS improves the understanding of the functional role in some causative genes, whose function in platelet production was previously unknown. These techniques will bring substantial benefits to improve our...
understanding of the molecular mechanisms in megakaryocyte and platelet biogenesis (14, 16, 24, 49, 80, 81). However, distinguishing pathogenic variants from non-pathogenic variants often requires complex functional and cell line studies to prove causality (7).

**BIOINFORMATIC TOOLS**

Bioinformatic tools can be conducted to determine candidate variants from WES or WGS data. A wide range of variants, ~25,000–40,000 variants can be identified per single patient in WES. These variants can be filtered for novelty by direct comparison using a database from the 100,000 Genomes Project, Exon Variant Server (EVS), dbSNP versions, Exome Aggregation Consortium (ExAC) (gnomAD), and in-house databases of whole exomes and/or whole genomes. A database of known platelet-related genes and genes involved in platelet formation, function, lifespan, or death can be compared with the patient’s genes in order to narrow the candidate genetic variants down. Variants with MAF (minor allele frequency) ≥0.01 are generally excluded given the rarity of most of...
these genetic defects in IT. Variants not known to change the amino acid or those that do not have a potential effect on protein, such as synonymous variants and intron variants can also be excluded. Splice site variants occurring on protein, such as synonymous variants and intron variants the amino acid or those that do not have a potential effect these genetic defects in IT. Variants not known to change Almazni et al. Genes Defects in Inherited Thrombocytopenia of ITs and disorders involved in hematopoiesis, identifying a disorders rather than bleeding itself. Due to the polygenic nature patients with ITs is the development of additional syndromic disorders. Despite the polygenic nature of ITs and disorders involved in hematopoiesis, identifying a singular causative gene for platelet and megakaryocyte function is particularly difficult. A combination of whole blood counting and platelet functional assays will highlight the platelet phenotype, however only familial studies and genetic sequencing will help to identify any genetic defect. With the introduction of HTS and various genome browser software such as Sapienta, the diagnosis process has been modernized to highlight candidate variants in known platelet affected genes and reveal variants in novel genes in which hemostatic input remains to be explored. Approaches such as these may be implemented within clinical settings in the future, however, bioinformatic pipelines are yet to be standardized across all facilities. Aside from bioinformatic training and the initial financial burden of installation of the software, there are clear reasons that updating current genetic analysis in hematological disorders benefits healthcare in the wider community. This will ensure IT families obtain a clear diagnosis and receive correct treatment based on their genetically influenced megakaryocyte or platelet defect.

**CONCLUSIONS**

The advances in NGS techniques improve our knowledge about the molecular mechanisms of IT. The major risk factor for patients with ITs is the development of additional syndromic disorders rather than bleeding itself. Due to the polygenic nature of ITs and disorders involved in hematopoiesis, identifying a

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**AUTHOR CONTRIBUTIONS**

IA wrote the manuscript. IA, RS, and NM critically reviewed and edited the review.

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61. Tijssen MR, Ghevaert C. Transcription factors in late megakaryopoiesis.

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