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Evaluating the clinical validity of genes related to hemostasis and thrombosis using the Clinical Genome Resource gene curation framework

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Abstract

Background: Inherited bleeding, thrombotic, and platelet disorders (BTPDs) are a heterogeneous set of diseases, many of which are very rare globally. Over the past 5 decades, the genetic basis of some of these disorders has been identified, and recently,

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high-throughput sequencing has become the primary means of identifying disease-causing genetic variants.

Objectives: Knowledge of the clinical validity of a gene-disease relationship is essential to provide an accurate diagnosis based on results of diagnostic gene panel tests and inform the construction of such panels. The Scientific and Standardization Committee for Genetics in Thrombosis and Hemostasis undertook a curation process for selecting 96 TIER1 genes for BTPDs. The purpose of the process was to evaluate the evidence supporting each gene-disease relationship and provide an expert-reviewed classification for the clinical validity of genes associated with BTPDs.

Methods: The Clinical Genome Resource (ClinGen) Hemostasis/Thrombosis Gene Curation Expert Panel assessed the strength of evidence for TIER1 genes using the semiquantitative ClinGen gene-disease clinical validity framework. ClinGen Lumping and Splitting guidelines were used to determine the appropriate disease entity or entities for each gene, and 101 gene-disease relationships were identified for curation.

Results: The final outcome included 68 Definitive (67%), 26 Moderate (26%), and 7 Limited (7%) classifications. The summary of each curation is available on the ClinGen website.

Conclusion: Expert-reviewed assignment of gene-disease relationships by the ClinGen Hemostasis/Thrombosis Gene Curation Expert Panel facilitates accurate molecular diagnoses of BTPDs by clinicians and diagnostic laboratories. These curation efforts can allow genetic testing to focus on genes with a validated role in disease.

KEYWORDS

data curation, genetic disorders, genetic variation, hemostasis, reliability and validity, thrombosis

1 | INTRODUCTION

Inherited disorders of hemostasis and thrombosis are a heterogeneous group of conditions that include rare and more common disorders with Mendelian inheritance, a wide spectrum of penetrance, and lower penetrance risk alleles. The clinical phenotype of increased bleeding or venous thromboembolism is common to most of these disorders, and hence, the laboratory phenotype, including blood counts, platelet function assays, and specific clotting factor activities, plays an important role in defining the unique and specific manifestations of each disease state. Genetic conditions that lead to laboratory abnormalities alone and have no clinical repercussions, such as some specific coagulation factor deficiencies, are also frequently encountered in this area [1]. With broader access to genetic sequencing technologies, including more robust bioinformatics platforms, a large number of genes have been reported to be related to disorders of hemostasis and thrombosis [2]. However, the quantity and quality of data available to support each gene-disease relationship vary greatly, making the process of evaluating the available evidence challenging and difficult to accomplish outside of a multidisciplinary, academic, collaborative context [3]. In response to the need to thoroughly and systematically approach the available data, an international group of clinical, scientific, and gene curation specialists was formed to evaluate the evidence supporting each gene-disease

relationship within a standardized framework and provide an expert-reviewed classification for the clinical validity of genes associated with inherited bleeding, thrombotic, and platelet disorders (BTPDs).

2 | METHODS

2.1 | The Clinical Genome Resource Hemostasis/Thrombosis Gene Curation Expert Panel

In 2018, the Clinical Genome Resource (ClinGen) Hemostasis/Thrombosis Clinical Domain Working Group assembled a committee of clinicians and researchers with expertise in BTPDs who prioritized the curation of genes and variants within several relevant domains. The Hemostasis/Thrombosis Gene Curation Expert Panel (HT GCEP) was formed to curate and adjudicate genes associated with BTPDs using the ClinGen gene-disease validity classification framework [4]. The HT GCEP comprises 6 biocurators, a coordinator and assistant coordinator, and 13 experts with significant clinical, molecular diagnostic, and/or research experience in hemostasis and thrombosis (<https://clinicalgenome.org/affiliation/40028/>). This international panel includes members from the United States, the United Kingdom, Belgium, China, France, Germany, Ireland, and Italy, representing 16 institutions.

2.2 | Hemostasis/thrombosis genes and diseases selected for analysis

The Scientific and Standardization Committee for Genetics in Thrombosis and Hemostasis (SSC-GinTH) selected 96 TIER1 core genes for BTPDs [5]. Additionally, they considered genes related to hereditary hemorrhagic telangiectasia, Ehlers-Danlos syndrome, Gaucher syndrome, and Noonan syndrome as part of an “extended TIER1 list,” which are disorders associated with primary phenotypes such as arteriovenous malformations, joint hypermobility, skin hyperextensibility, tissue fragility, and complex syndromic features that result in an increased bleeding tendency. In order to meet the urgent need in diagnostic genetic laboratories, the SSC-GinTH previously applied a scoring system to specify the gene-disease pairs relevant for BTPDs based on the following 3 layers of evidence: genotype-phenotype cosegregation data, supportive molecular assays or laboratory phenotypes, and mouse models. A gene was considered TIER1 if the literature review identified at least 3 genetically independent families with robust gene-phenotype association data or if fewer independent families were paired based on either robust functional studies or a mouse model.

The HT GCEP considered 96 TIER1 core genes and 3 genes associated with hereditary hemorrhagic telangiectasia for curation. Of these 99 genes, 10 were previously curated (*DIAPH1*, *FLNA*, *MYH9*, *NBEA*, *RUNX1*, *STIM1*, *STXBP2*, and *WAS*) by another ClinGen GCEP or were in plans for curation (*RNU4ATAC*) by a GCEP with a more appropriate scope of work. One further gene-disease relationship, *PIGA*-related paroxysmal nocturnal hemoglobinuria, was considered outside the scope of work because it is not primarily a thrombosis disorder and is the only gene related to a somatic rather than germline condition. Thus, 89 genes were finally identified for curation by the HT GCEP.

For genes with assertions relating to multiple diseases in the Online Mendelian Inheritance in Man database or the literature, the HT GCEP evaluated the mode of inheritance, the mechanism of disease, and the phenotypic features of each condition to determine whether to lump the diseases into one curation record or to split them into individual records as per the guidelines from the ClinGen Lumping and Splitting group [6]. This resulted in the identification of 101 gene-disease relationships for curation by the HT GCEP, with 12 genes requiring 2 curations for separate disease entities. Genes with 2 curations are referred to throughout by their difference in inheritance pattern, “-AR” or “-AD” (autosomal recessive and autosomal dominant), or mechanisms of disease, “-LoF” or “-GoF” (loss of function and gain of function). All disease entities were curated using a unique identifier in the Mondo disease ontology (<https://mondo.monarchinitiative.org/>).

2.3 | Implementation of the ClinGen gene clinical validity curation process

The HT GCEP determined the clinical validity for gene-disease relationships using the ClinGen Gene Curation Standard Operating

Procedure, version 6 or 7 (available at https://clinicalgenome.org/site/assets/files/3975/gene-disease_validity_standard_operating_procedures_version_7-1.pdf), based on the framework described in Strande and Riggs et al. [4]. This semiquantitative scoring system uses an evidence-based approach to classify gene-disease relationships based on the strength of supportive evidence as follows: Definitive (12-18 points, with replication over time), Strong (12-18 points), Moderate (7-11 points), and Limited (0.1-6 points). To differentiate a Definitive classification from Strong classification, the role of the gene in the disease would need to be repeatedly demonstrated in research and clinical diagnostic settings and upheld over time (a minimum of 3 years). Additionally, the category of No Known Disease Relationship can be applied when no reports have directly implicated the gene in human disease cases, and 2 classifications, Disputed and Refuted, are available for gene-disease relationships with conflicting evidence.

For each gene-disease relationship, a structured evaluation of genetic and experimental evidence available in the published literature was recorded in ClinGen’s gene curation interface, providing a summary published directly to the ClinGen website (<https://search.clinicalgenome.org/kb/affiliate/10028>) upon expert approval. Genetic evidence includes variants in the gene of interest identified in patients with the disease entity of interest, including case reports, family studies, and case-control studies. Experimental evidence supports the role of the gene in the disease of interest or phenotypic features associated with the disease entity, incorporating biochemical function, protein interactions, expression, functional alterations in cells, and animal models that recapitulate the disease. A maximum of 12 points can be assigned for genetic evidence and a maximum of 6 points for experimental evidence for a combined maximum total of 18 points. The ClinGen gene curation framework is used as a guide, and each expert panel must adjust scoring or final classifications based on the particulars of the relevant disease area and their professional judgment, particularly when the curation score is near a classification boundary. For scores between the category thresholds, the semiquantitative framework allows for expert adjudication to either the lower or the higher classification. In exceptional cases, the classification may be increased or decreased by no more than 1 level from the calculated classification.

Once the relevant gene-disease relationships were identified, a preliminary evaluation was performed to determine the strategy for curation and review. The preliminary evaluation incorporated expert input and a cursory review of the Online Mendelian Inheritance in Man database and the literature to determine the quantity of evidence available for each gene-disease relationship. When there was expert agreement and abundant literature available, spanning at least a 3-year period, gene-disease relationships were considered likely to reach a Definitive classification and permitted to undergo an expedited curation process. Those not meeting these criteria underwent the standard curation process. For expedited curation, each gene-disease relationship was assigned to 1 curator and 2 experts; standard curations were assigned to 1 curator and 1 expert. For each curation, the biocurator performed a literature review, assessed the genetic and experimental evidence, and made a provisional

classification based on the total points. The biocurator then provided a summary of the curation to the assigned expert(s) for review and revision. Once the biocurator and expert(s) agreed that the curation was complete and accurate, the process diverged between expedited and standard curation strategies. Using the expedited strategy, the classification was finalized if the preliminary classification was Definitive, and both experts agreed. If the preliminary classification was non-Definitive, or consensus was not reached between the curator and 2 experts, the curation was moved to the standard strategy. For the standard curation strategy, the biocurator presented an overview of the curation to the HT GCEP, represented by a quorum of at least 3 experts from at least 2 institutions, on a monthly web conference call and the expert-led group approved a final clinical validity classification by a majority vote.

Curation of the 89 BTPD-related genes took place from 2019 to 2022. Once all gene-disease relationships were classified, a literature search was performed for all non-Definitive gene-disease relationships in order to identify additional evidence published during the working period. When relevant, new evidence was added to the curations, and the classifications were re-evaluated.

3 | RESULTS

Eighty-nine genes were curated in relation to a multitude of disorders, spanning across the spectrum of BTPDs. Each gene was evaluated to determine the most appropriate gene-disease relationship for curation (Table) [7–14]. Of the 89 genes, 77 were evaluated in association with a single disease entity, while 12 underwent 2 curations for separate disease entities. Overall, the ClinGen HT GCEP curated 101 gene-disease relationships, resulting in 68 Definitive (67%), 26 Moderate (26%), and 7 Limited (7%) classifications (Figure 1A). The genes classified as Definitive scored 12 to 18 points and included well-known disease genes such as *ITGA2B*, *ITGB3*, *GP1BA*, *GP1BB*, and *GP9* (Figure 2). Genetic evidence reflecting numerous reports from the literature on causative variants was available for all Definitive curations, reaching a maximum of 12 points in 87% of the Definitive classifications (11.5 ± 1.2 points), and additional experimental evidence (4.4 ± 1.3 points) was available for all Definitive classifications (Figure 1B). No gene-disease relationships were classified as Strong due to the absence of curated genes with a total of ≥ 12 points without replication over time, which is the only criterion distinguishing the Strong classification from the Definitive classification.

The non-Definitive classifications scored 1 to 12 points and lacked evidence in the genetic and/or experimental categories (Figure 3). Twenty-six gene-disease pairs received a Moderate classification; a Moderate classification typically means that there is emerging but insufficient evidence for the validity of the gene-disease relationship at the time to classify as Strong, although it is likely to reach Strong/Definitive with time [15]. In the Moderate classification, all genes had both genetic (4.7 ± 1.7 points) and experimental (3.7 ± 1.4 points) evidence. Seven gene-disease pairs reached only the Limited

classification with genetic evidence of 2.8 ± 1.8 points and experimental evidence of 2.8 ± 2.2 points (Figure 1B).

4 | DISCUSSION

The mission of ClinGen is to curate the clinical genome in order to improve patient care. The HT GCEP has furthered this mission by aggregating structured evidence regarding genetic conditions of BTPDs and the genes that cause them. In total, 101 gene-disease relationships were curated and assigned a clinical validity classification. The majority of the genes investigated are well established and, as expected, resulted in a Definitive classification within our validation. In addition to the 67% Definitive, another 26% Moderate classifications were identified, which are expected to increase to Definitive classifications with time and additional evidence; these curations will be re-evaluated every 2 years to maintain current gene-disease validity classifications. The latest information is regularly updated on the ClinGen website (www.clinicalgenome.org).

The majority (85%) of gene-disease relationships scored clearly within an appropriate validity classification and were approved as such by the HT GCEP. However, scores at the boundary of a classification and/or lacking significant evidence in either genetic or experimental categories were further scrutinized for potential classification modifications. Two gene-disease relationships had curation scores at the lower boundary of the Strong/Definitive classification (12 points). One curation, for *FYB1*-related thrombocytopenia, received 6 points in both experimental and genetic evidence. Robust evidence was included across the experimental evidence categories; the gene-disease relationship was supported by its restricted expression in hematopoietic cells [16], its function as an adaptor protein involved in integrin activation [17], the resulting defect in platelet spreading when this function is disrupted [18,19], and both conventional and conditional knockout mice models that recapitulate disease [18,20]. For genetic evidence, 2 probands have been reported [19,21], and because each proband was homozygous for a null variant, 2 points were awarded for each, and additional 2 points were scored for segregation of the variants in affected family members. Thus, the curation score reached the lower boundary of the Strong classification; however, expert opinion was that with only 2 families reported, both consanguineous, a Moderate classification is appropriate until a third proband is identified for this gene-disease relationship. Meanwhile, *BLOC1S6*-related Hermansky-Pudlak syndrome (HPS) also scored 12 points at the lower boundary of the Strong/Definitive classification but maintained a Definitive classification due to more robust genetic evidence from 5 probands. A modest 3 points were awarded for experimental evidence based on protein interactions with other known HPS-related genes [22] and a mouse model that recapitulates HPS [23]. The *BLOC1S6* curation originally received a Moderate classification in 2020, with 7 points of genetic evidence from 4 probands [24–27], adding to the 3 points of experimental evidence and leading to 10 points in total. However, an additional proband was reported in 2021 [28], adding 2 points to bring the total to 12 points,

TABLE Clinical validity classifications and scores for gene-disease relationships in hemostasis and thrombosis.

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>ABCC4</i>	Moderate (9.25)	Qualitative platelet defect (AR)	MONDO:0001197	-	-
<i>ABCG5</i>	Definitive (18)	Sitosterolemia (AR)	MONDO:0008863	Sitosterolemia 2 (#618666)	-
<i>ABCG8</i>	Definitive (17)	Sitosterolemia (AR)	MONDO:0008863	Sitosterolemia 1 (#210250)	-
<i>ACTB</i>	Moderate (7.6)	Thrombocytopenia (AD)	MONDO:0002049	-	<i>ACTB</i> was curated for its relationship with syndromic thrombocytopenia and not the relationship with Baraitser-Winter syndrome 1, which is clinically distinct and not classically associated with thrombocytopenia. Specific variants in the region of exons 5 and 6 are associated with syndromic thrombocytopenia.
<i>ACTN1</i>	Definitive (13)	Platelet-type bleeding disorder 15 (AD)	MONDO:0014078	Bleeding disorder, platelet-type, 15 (#615193)	-
<i>ACVRL1</i>	Definitive (17)	Telangiectasia, hereditary hemorrhagic, type 2 (AD)	MONDO:0010880	Telangiectasia, hereditary hemorrhagic, type 2 (#600376)	-
<i>ADAMTS-13</i>	Definitive (17)	Congenital thrombotic thrombocytopenic purpura (AR)	MONDO:0010122	Thrombotic thrombocytopenic purpura, hereditary (#274150)	-
<i>ANKRD26</i>	Definitive (13.5)	Thrombocytopenia 2 (AD)	MONDO:0008555	Thrombocytopenia 2 (#188000)	-
<i>ANO6</i>	Moderate (7.5)	Scott syndrome (AR)	MONDO:0009885	Scott syndrome (#262890)	-
<i>AP3B1</i>	Definitive (17)	Hermansky-Pudlak syndrome 2 (AR)	MONDO:0011997	Hermansky-Pudlak syndrome 2 (#608233)	-
<i>AP3D1</i>	Limited (8)	Hermansky-Pudlak syndrome 10 (AR)	MONDO:0014885	Hermansky-Pudlak syndrome 10 (#617050)	-
<i>ARPC1B</i>	Definitive (14)	Platelet abnormalities with eosinophilia and immune-mediated inflammatory disease (AR)	MONDO:0060583	Immunodeficiency 71 with inflammatory disease and congenital thrombocytopenia (#617718)	-
<i>BLOC1S3</i>	Moderate (10)	Hermansky-Pudlak syndrome 8 (AR)	MONDO:0013560	Hermansky-Pudlak syndrome 8 (#614077)	-
<i>BLOC1S6</i>	Definitive (12)	Hermansky-Pudlak syndrome 9 (AR)	MONDO:0013606	Hermansky-Pudlak syndrome 9 (#614171)	-
<i>CDC42</i>	Definitive (14.5)	Macrothrombocytopenia, lymphedema, developmental delay, facial dysmorphism, camptodactyly syndrome (AD)	MONDO:0014757	Takenouchi-Kosaki syndrome (#616737)	-
<i>CYCS</i>	Limited (6.8)	thrombocytopenia 4 (AD)	MONDO:0012775	Thrombocytopenia 4 (#612004)	-

(Continues)

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>DIAPH1</i> ^a	Definitive (16)	Diaph1-related sensorineural hearing loss-thrombocytopenia syndrome (AD)	MONDO:0044635	Deafness, autosomal dominant 1, with or without thrombocytopenia (#124900)	<i>DIAPH1</i> was curated by the ClinGen Hearing Loss GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_43c017fd-ce70-4fbe-ad30-90f216adaa7d-2018-01-05T170000.000Z). All variants for this gene-disease relationship are loss of function or truncating variants in exon 27. Of note, variants in other exons of this gene have been implicated in autosomal recessive seizures, cortical blindness, and microcephaly syndrome (MIM #616632), which is not covered in the scope of this curation.
<i>DTNBP1</i>	Definitive (12.5)	Hermansky-Pudlak syndrome 7 (AR)	MONDO:0013559	Hermansky-Pudlak syndrome 7 (#614076)	-
<i>ENG</i>	Definitive (18)	Hereditary hemorrhagic telangiectasia (AD)	MONDO:0019180	Telangiectasia, hereditary hemorrhagic, type 1 (#187300)	-
<i>ETV6</i>	Definitive (17.5)	Thrombocytopenia 5 (AD)	MONDO:0014536	Thrombocytopenia 5 (#616216)	-
<i>F10</i>	Definitive (16.5)	Congenital factor X deficiency (AR)	MONDO:0009212	Factor X deficiency (#227600)	-
<i>F11</i>	Definitive (16.5)	Congenital factor XI deficiency (SD)	MONDO:0012897	Factor XI deficiency, autosomal dominant (#612416) Factor XI deficiency, autosomal recessive (#612416)	The factor XI deficiency results from either biallelic loss of function or monoallelic dominant negative variants, which were considered to cause the same clinical disease and curated jointly.
<i>F12</i>	Moderate (10)	Hereditary angioedema type 3 (AD)	MONDO:0012526	Angioedema, hereditary, 3 (#610618)	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (gain of function variants in exon 9 vs loss of function) underlying the 2 disease entities, these were curated separately.
<i>F12</i>	Definitive (16.5)	Congenital factor XII deficiency (AR)	MONDO:0009315	Factor XII deficiency (#234000)	-
<i>F13A1</i>	Definitive (16)	Factor XIII, A subunit, deficiency of (AR)	MONDO:0013187	Factor XIII A deficiency (#613225)	-
<i>F13B</i>	Definitive (12.5)	Factor XIII, B subunit, deficiency of (AR)	MONDO:0013190	Factor XIII B deficiency (#613235)	-

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>F2</i>	Definitive (17)	Congenital prothrombin deficiency (AR)	MONDO:0013361	Dysprothrombinemia (#613679) Hypoprothrombinemia (#613679)	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (loss of function vs gain of function) underlying the 2 disease entities, these were curated separately.
<i>F2</i>	Definitive (13)	Thrombophilia due to thrombin defect (AD)	MONDO:0008559	Thrombophilia due to thrombin defect (#188050)	
<i>F5</i>	Definitive (16.5)	Congenital factor V deficiency (AR)	MONDO:0009210	Factor V deficiency (#227400)	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (loss of function vs gain of function) underlying the 2 disease entities, these were curated separately.
<i>F5</i>	Definitive (14.7)	Thrombophilia due to activated protein C resistance (AD)	MONDO:0008560	Thrombophilia due to activated protein C resistance (#188055)	
<i>F7</i>	Definitive (16.5)	Factor VII deficiency (AR)	MONDO:0002244	Factor VII deficiency (#227500)	-
<i>F8</i>	Definitive (16.5)	Hemophilia A (XL)	MONDO:0010602	Hemophilia A (#306700)	-
<i>F9</i>	Definitive (16.5)	Hemophilia B (XL-LOF)	MONDO:0010604	Hemophilia B (#306900)	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (loss of function vs proposed gain of function) underlying the 2 disease entities, these were curated separately.
<i>F9</i>	Limited (1)	Thrombophilia, X-linked, due to factor IX defect (XL-GOF)	MONDO:0010432	Thrombophilia, X-linked, due to factor IX defect (#300807)	
<i>FERMT3</i>	Definitive (18)	Leukocyte adhesion deficiency 3 (AR)	MONDO:0013016	Leukocyte adhesion deficiency, type III (#612840)	-
<i>FGA</i>	Definitive (18)	Congenital fibrinogen deficiency (SD)	MONDO:0018060	Afibrinogenemia, congenital (#202400) Dysfibrinogenemia, congenital (#616004) Hypodysfibrinogenemia, congenital (#616004)	Congenital afibrinogenemia, congenital dysfibrinogenemia, and congenital hypodysfibrinogenemia represent a spectrum of severity associated with either monoallelic or biallelic loss of function variants and were curated jointly. Of note, <i>FGA</i> is also related to familial visceral amyloidosis (#105200), which has a distinct phenotype and molecular mechanism but does not fall under the purview of the HT GCEP.

(Continues)

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>FGB</i>	Definitive (15)	Congenital fibrinogen deficiency (SD)	MONDO:0018060	Afibrinogenemia, congenital (#202400) Dysfibrinogenemia, congenital (#616004) Hypofibrinogenemia, congenital (#202400)	Congenital afibrinogenemia, congenital dysfibrinogenemia, and congenital hypodysfibrinogenemia represent a spectrum of severity associated with either monoallelic or biallelic loss of function variants and were curated jointly.
<i>FGG</i>	Definitive (18)	Congenital fibrinogen deficiency (SD)	MONDO:0018060	Afibrinogenemia, congenital (#202400) Dysfibrinogenemia, congenital (#616004) Hypodysfibrinogenemia (#616004) Hypofibrinogenemia, congenital (#202400)	Congenital afibrinogenemia, congenital dysfibrinogenemia, hypodysfibrinogenemia, and congenital hypodysfibrinogenemia represent a spectrum of severity associated with either monoallelic or biallelic loss of function variants and were curated jointly.
<i>FLI1</i>	Moderate (7.5)	Bleeding disorder, platelet-type, 21 (AD)	MONDO:0054577	Bleeding disorder, platelet-type, 21 (#617443)	A single family with biallelic <i>FLI1</i> variants [7] has been noted here for posterity but not considered within this curation of autosomal dominant disease. Should additional evidence arise in the future, additional consideration will be made for lumping or splitting these 2 inheritance patterns.
<i>FLNA</i> ^a	Definitive (13.85)	Periventricular nodular heterotopia (XL)	MONDO:002034	FG syndrome 2 (#300321) Cardiac valvular dysplasia, X-linked (#314400) Congenital short bowel syndrome (#300048) Heterotopia, periventricular, 1 (#300049) Intestinal pseudoobstruction, neuronal (#300048)	<i>FLNA</i> was curated by the Intellectual Disability and Autism GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_80bc6280-7c21-4168-8a98-93c31fead5d7-2020-12-27T231155.213Z). Loss of function variants lead to FG syndrome 2, X-linked cardiac valvular dysplasia, congenital short bowel syndrome, and neuronal intestinal pseudoobstruction, all of which share overlapping phenotypes (including thrombocytopenia) with some patients with periventricular nodular heterotopia. Of note, gain of function variants cause X-linked otopalatodigital spectrum disorders (https://www.ncbi.nlm.nih.gov/books/NBK1393/) and were not within the scope of this curation.
<i>FYB1</i>	Moderate (12)	Thrombocytopenia 3 (AR)	MONDO:0010120	Thrombocytopenia 3 (#273900)	-

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>GATA1</i>	Definitive (14.7)	GATA1-related X-linked cytopenia (XLR)	MONDO:0100089	Anemia, X-linked, with or without neutropenia and/or platelet abnormalities (#300835) Thrombocytopenia with beta-thalassemia, X-linked (#314050) Thrombocytopenia, X-linked, with or without dyserythropoietic anemia (#300367)	GATA1-related cytopenia is the accepted term to encompass the heterogeneity of this single disorder [8].
<i>GFI1B</i>	Definitive (14.4)	Platelet-type bleeding disorder 17 (AD)	MONDO:0008553	Bleeding disorder, platelet-type, 17 (#187900)	The predominant form of inheritance autosomal dominant was considered in this curation, though 3 homozygous cases have been reported [9–12].
<i>GGCX</i>	Definitive (17)	Vitamin K-dependent clotting factors, combined deficiency of type 1 (AR)	MONDO:0010187	Pseudoxanthoma elasticum-like disorder with multiple coagulation factor deficiency (#610842) Vitamin K-dependent clotting factors, combined deficiency of 1 (#277450)	Overlapping phenotypes, autosomal recessive inheritance patterns, and molecular mechanisms (inactivating variants) resulted in these phenotypes being curated jointly.
<i>GNE</i>	Moderate (8.1)	Isolated hereditary giant platelet disorder (AR)	MONDO:0016361	-	Of note, this gene has also been implicated in both Nonaka myopathy (MIM#605820) and sialuria (MIM#269921). However, only this distinct phenotype was curated.
<i>GP1BA</i>	Definitive (17)	Bernard-Soulier syndrome (AR)	MONDO:0009276	Bernard-Soulier syndrome, type A1 (recessive) (#231200) Bernard-Soulier syndrome, type A2 (dominant) (#153670)	Interfamilial phenotypic variability is observed between individuals harboring the same genetic variant between different inheritance patterns, and the difference in the inheritance pattern for the disease entities is representative of a continuum of disease, ie, mild carrier phenotypic features are observed in the recessive disease [13]. Thus, the disease entities were lumped, and the well-established autosomal recessive inheritance pattern has been curated here.
<i>GP1BA</i>	Definitive (14.5)	Platelet-type von Willebrand disease (AD)	MONDO:0008332	von Willebrand disease, platelet-type (#177820)	This was curated as a distinct disease due to differences in molecular mechanism (gain of function vs loss of function), inheritance pattern (autosomal dominant vs predominantly autosomal recessive), and phenotypic variability.

(Continues)

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>GP1BB</i>	Definitive (18)	Bernard-Soulier syndrome (AR)	MONDO:0009276	Bernard-Soulier syndrome, type B (#231200) Giant platelet disorder, isolated (#231200)	Giant platelets are a part of the phenotypic spectrum of Bernard-Soulier syndrome.
<i>GP6</i>	Definitive (13)	Platelet-type bleeding disorder 11 (AR)	MONDO:0013623	Bleeding disorder, platelet-type, 11 (#614201)	-
<i>GP9</i>	Definitive (14.5)	Bernard-Soulier syndrome (AR)	MONDO:0009276	Bernard-Soulier syndrome, type C (#231200)	-
<i>HOXA11</i>	Limited (6)	Radioulnar synostosis with amegakaryocytic thrombocytopenia 1 (AD)	MONDO:0024558	Radioulnar synostosis with amegakaryocytic thrombocytopenia 1 (#605432)	-
<i>HPS1</i>	Definitive (17.5)	Hermansky-Pudlak syndrome 1 (AR)	MONDO:0008748	Hermansky-Pudlak syndrome 1 (#203300)	-
<i>HPS3</i>	Definitive (17)	Hermansky-Pudlak syndrome 3 (AR)	MONDO:0013555	Hermansky-Pudlak syndrome 3 (#614072)	-
<i>HPS4</i>	Definitive (15.5)	Hermansky-Pudlak syndrome 4 (AR)	MONDO:0013556	Hermansky-Pudlak syndrome 4 (#614073)	-
<i>HPS5</i>	Definitive (18)	Hermansky-Pudlak syndrome 5 (AR)	MONDO:0013557	Hermansky-Pudlak syndrome 5 (#614074)	-
<i>HPS6</i>	Definitive (18)	Hermansky-Pudlak syndrome 6 (AR)	MONDO:0013558	Hermansky-Pudlak syndrome 6 (#614075)	-
<i>HRG</i>	Moderate (6.6)	Hereditary thrombophilia due to congenital histidine-rich (poly-L) glycoprotein deficiency (AD)	MONDO:0013143	Thrombophilia due to HRG deficiency (#613116)	-
<i>IKZF5</i>	Moderate (9.2)	Thrombocytopenia 7 (AD)	MONDO:0030867	Thrombocytopenia, autosomal dominant, 7 (#619130)	-
<i>ITGA2B</i>	Definitive (15.5)	Glanzmann thrombasthenia (AR)	MONDO:0100326	Glanzmann thrombasthenia 1 (#273800)	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (loss of function vs gain of function) underlying the 2 disease entities, these were curated separately.
<i>ITGA2B</i>	Moderate (9.5)	Platelet-type bleeding disorder 16 (AD)	MONDO:0008552	Bleeding disorder, platelet-type, 16, autosomal dominant (#187800)	

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>ITGB3</i>	Definitive (17)	Glanzmann thrombasthenia (AR)	MONDO:0100326	Glanzmann thrombasthenia 2 (#619267)	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (loss of function vs gain of function) underlying the 2 disease entities, these were curated separately.
<i>ITGB3</i>	Moderate (9.1)	Platelet-type bleeding disorder 16 (AD)	MONDO:0008552	Bleeding disorder, platelet-type, 24, autosomal dominant (#619271)	
<i>KDSR</i>	Definitive (12.25)	Erythrokeratoderma variabilis et progressiva 4 (AR)	MONDO:0033014	Erythrokeratoderma variabilis et progressiva 4 (#617526)	-
<i>KNG1</i>	Definitive (14)	Congenital high molecular weight kininogen deficiency (AR)	MONDO:0009234	High molecular weight kininogen deficiency (#228960) Kininogen deficiency (#228960)	This curation is considered a gene-deficiency curation due to the lack of evidence supporting the involvement of this gene in any disease or disorder beyond a prolonged partial thromboplastin time. Autosomal dominant angioedema was not considered in this curation.
<i>LMAN1</i>	Definitive (14.5)	Factor V and factor VIII, combined deficiency of type 1 (AR)	MONDO:0009206	Combined factor V and VIII deficiency (#227300)	-
<i>LYST</i>	Definitive (16.5)	Chediak-Higashi syndrome (AR)	MONDO:0008963	Chediak-Higashi syndrome (#214500)	-
<i>MCFD2</i>	Definitive (14.5)	Factor V and factor VIII, combined deficiency of 2 (AR)	MONDO:0013331	Factor V and factor VIII, combined deficiency of (#613625)	-
<i>MECOM</i>	Definitive (15.5)	MECOM-associated syndrome (AD)	MONDO:0100458	Radioulnar synostosis with amegakaryocytic thrombocytopenia 2 (#616738)	-
<i>MPIG6B</i>	Definitive (13.5)	Thrombocytopenia, anemia, and myelofibrosis (AR)	MONDO:0044316	Thrombocytopenia, anemia, and myelofibrosis (#617441)	-
<i>MPL</i>	Definitive (18)	Congenital amegakaryocytic thrombocytopenia (AR)	MONDO:0011469	Thrombocytopenia, congenital amegakaryocytic (#604498)	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (loss of function vs gain of function) underlying the 2 disease entities, these were curated separately.
<i>MPL</i>	Definitive (12.7)	Thrombocythemia 2 (AD)	MONDO:0011173	Thrombocythemia 2 (#601977)	
<i>MYH9^a</i>	Definitive (18)	MYH-9 related disease (AD)	MONDO:0015912	Deafness, autosomal dominant 17 (#603622) Macrothrombocytopenia and granulocyte inclusions with or without nephritis or	<i>MYH9</i> was curated by the ClinGen Hearing Loss GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_d6801442-c490-44a0-9a60-84ab5b20f7ac-2018-07-17T191819.148Z) for MYH9-related disorders, a

(Continues)

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
				sensorineural hearing loss (#155100)	class of autosomal dominant disorders characterized by congenital macrothrombocytopenia and variable leucocyte inclusion bodies, renal abnormalities, cataracts, and progressive sensorineural hearing loss.
<i>NBEA</i> ^a	Definitive (16)	Complex neurodevelopmental disorder (AD)	MONDO:0100038	Neurodevelopmental disorder with or without early-onset generalized epilepsy (#619157)	<i>NBEA</i> was curated by the ClinGen Intellectual Disability and Autism GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_f40357db-6cc2-4240-8771-1206cd27298a-2020-12-02T170000.000Z), including the patient with dense granules in platelets [14].
<i>NBEAL2</i>	Definitive (17.5)	Gray platelet syndrome (AR)	MONDO:0007686	Gray platelet syndrome (#139090)	-
<i>P2RY12</i>	Moderate (7)	Platelet-type bleeding disorder 8 (AD)	MONDO:0012354	-	Due to differences in molecular mechanism, (purportive) dominant negative vs inactivating variants, autosomal dominant and recessive cases were considered separately.
<i>P2RY12</i>	Moderate (7.5)	Platelet-type bleeding disorder 8 (AR)	MONDO:0012354	Bleeding disorder, platelet-type, 8 (#609821)	
<i>PLA2G4A</i>	Moderate (6.5)	Cytosolic phospholipase-A2 alpha deficiency-associated bleeding disorder (AR)	MONDO:0018794	Gastrointestinal ulceration, recurrent, with dysfunctional platelets (#618372)	-
<i>PLAU</i>	Moderate (7)	Quebec platelet disorder (AD)	MONDO:0011136	Quebec platelet disorder (#601709)	-
<i>PLG</i>	Definitive (16.5)	Hypoplasminogenemia (AR)	MONDO:0009009	Dysplasminogenemia (#217090) Plasminogen deficiency, type I (#217090)	Due to differences in phenotype and inheritance pattern, autosomal dominant angioedema was not considered in this curation.
<i>PROC</i>	Definitive (17)	Hereditary thrombophilia due to congenital protein C deficiency (SD)	MONDO:0019145	Thrombophilia due to protein C deficiency, autosomal dominant (#176860) Thrombophilia due to protein C deficiency, autosomal recessive (#612304)	Both monoallelic and biallelic cases with inactivating mutations representative of a continuum of diseases were curated as a single disease entity.
<i>PROS1</i>	Definitive (15.5)	Hereditary thrombophilia due to congenital protein S deficiency (SD)	MONDO:0019144	Thrombophilia due to protein S deficiency, autosomal dominant (#612336) Thrombophilia due to protein S deficiency, autosomal recessive (#614514)	Both monoallelic and biallelic cases with inactivating mutations representative of a continuum of diseases were curated as a single disease entity.

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>PTGS1</i>	Limited (5.9)	Platelet-type bleeding disorder 12 (SD)	MONDO:0011588	-	Given the similarity in phenotype and the fact that the mode of inheritance remains to be fully elucidated, monoallelic and biallelic cases were considered in a single curation.
<i>RAP1B</i>	Limited (3)	Syndromic constitutional thrombocytopenia (AD)	MONDO:0018795	-	-
<i>RASGRP2</i>	Definitive (18)	Platelet-type bleeding disorder 18 (AR)	MONDO:0014386	Bleeding disorder, platelet-type, 18 (#615888)	-
<i>RBM8A</i>	Definitive (15.25)	Thrombocytopenia-absent radius syndrome (AR)	MONDO:0010121	Thrombocytopenia-absent radius syndrome (#274000)	-
<i>RNU4ATAC</i> ^a	-	-	-	-	The ClinGen SCID-CID GCEP will curate <i>RNU4ATAC</i> , including Roifman syndrome (with the thrombocytopenia phenotype).
<i>RUNX1</i> ^a	Definitive (17.5)	Hereditary thrombocytopenia and hematologic cancer predisposition syndrome (AD)	MONDO:0011071	Platelet disorder, familial, with associated myeloid malignancy (#601399)	Curation was completed by the ClinGen Hereditary Cancer GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_06aed341-58db-459b-a750-7142e29b420b-2018-06-04T194655.831Z).
<i>SERPINC1</i>	Definitive (16.5)	Hereditary antithrombin deficiency (SD)	MONDO:0013144	Thrombophilia due to antithrombin III deficiency (#613118)	Both monoallelic and biallelic cases with inactivating mutations representative of a continuum of diseases were curated as a single disease entity.
<i>SERPIND1</i>	Definitive (12.9)	Heparin cofactor 2 deficiency (AD)	MONDO:0012876	Thrombophilia due to heparin cofactor II deficiency (#612356)	-
<i>SERPINE1</i>	Moderate (10.5)	Congenital plasminogen activator inhibitor type 1 deficiency (AR)	MONDO:0013227	Plasminogen activator inhibitor-1 deficiency (#613329)	-
<i>SERPINF2</i>	Definitive (16)	Alpha-2-plasmin inhibitor deficiency (AR)	MONDO:0009883	Alpha-2-plasmin inhibitor deficiency (#262850)	-
<i>SLFN14</i>	Moderate (7.7)	Platelet-type bleeding disorder 20 (AD)	MONDO:0014830	Bleeding disorder, platelet-type, 20 (#616913)	-
<i>SMAD4</i>	Definitive (16)	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (AD)	MONDO:0008278	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (#175050)	Of note, this gene has also been implicated in Myhre syndrome (MIM#139210), which was not considered in this curation due to the

(Continues)

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>STIM1</i> ^a	Definitive (17)	Tubular aggregate myopathy (AD)	MONDO:0008051	Polyposis, juvenile intestinal (#174900) Myopathy, tubular aggregate, 1 (#160565) Stormorken syndrome (#185070)	distinct phenotypes and molecular mechanisms (Myhre syndrome is associated with variation at Ile500 and nearby amino acids only). Stormorken syndrome (including the thrombocytopenia phenotype) was found to form a clinical continuum of phenotypic severity with tubular aggregate myopathy, and so, these were curated jointly by the ClinGen Congenital Myopathies GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_9419adda-b3fb-4c2d-8562-6a0318260bbd-2021-04-01T160000.000Z). Of note, <i>STIM1</i> is also implicated in immunodeficiency type 10 (MIM3#612783); however, due to differences in molecular mechanism, inheritance pattern, and phenotypic variability, it was not considered in this curation or within the purview of the HT GCEP.
<i>STXBP</i> ^a	Definitive (15.5)	Familial hemophagocytic lymphohistiocytosis 5	MONDO:0013135	Hemophagocytic lymphohistiocytosis, familial, 5, with or without microvillus inclusion disease (#613101)	Curation was completed by the ClinGen Primary Immune Regulatory Disorders GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_0b5c9256-89e0-4f97-a7ca-dd07bdd237f9-2023-09-19T160000.000Z).
<i>TBXA2R</i>	Moderate (9.5)	Qualitative platelet defect (AD)	MONDO:0001197	-	-
<i>TBXAS1</i>	Moderate (7.5)	Ghosal hematodiaphyseal dysplasia (AR)	MONDO:0009274	Ghosal hematodiaphyseal syndrome (#231095)	-
<i>THBD</i>	Moderate (9)	Thrombomodulin-related bleeding disorder (AD)	MONDO:0013775	-	Differences in inheritance pattern correspond to differences in variant type (truncating dominant variants and missense recessive variants) that result in either increased or decreased plasma thrombomodulin, respectively. As such, these were considered distinct disease entities.

TABLE (Continued)

Gene	Classification (points)	Disease (inheritance mechanism)	MonDO ID	OMIM phenotype(s) included	Comments
<i>THBD</i>	Limited (8)	Thrombomodulin-related bleeding disorder (AR)	MONDO:0013775	-	
<i>THPO</i>	Moderate (7.9)	Congenital amegakaryocytic thrombocytopenia (AR)	MONDO:0011469	-	Given the differences in the phenotype, inheritance pattern, and molecular mechanism (loss of function vs gain of function) underlying the 2 disease entities, these were curated separately.
<i>THPO</i>	Moderate (9.1)	Thrombocythemia 1 (AD)	MONDO:0008554	Thrombocythemia 1 (#187950)	
<i>TPM4</i>	Moderate (7)	Autosomal dominant macrothrombocytopenia (AD)	MONDO:0015372	-	-
<i>TUBB1</i>	Definitive (18)	Macrothrombocytopenia, isolated, 1, autosomal dominant (AD)	MONDO:0800047	Macrothrombocytopenia, autosomal dominant, TUBB1-related (#613112)	-
<i>VIPAS39</i>	Definitive (15.5)	Arthrogryposis, renal dysfunction, and cholestasis 2 (AR)	MONDO:0013255	Arthrogryposis, renal dysfunction, and cholestasis 2 (#613404)	-
<i>VKORC1</i>	Moderate (7)	Vitamin K-dependent clotting factors, combined deficiency of type 2 (AR)	MONDO:0011837	Vitamin K-dependent clotting factors, combined deficiency of 2 (#607473)	-
<i>VPS33B</i>	Definitive (17.5)	Arthrogryposis, renal dysfunction, and cholestasis 1 (AR)	MONDO:0008822	Arthrogryposis, renal dysfunction, and cholestasis 1 (#208085)	-
<i>VWF</i>	Definitive (18)	Hereditary von Willebrand disease (AD/AR-LOF)	MONDO:0019565	von Willebrand disease, type 1 (#193400) von Willebrand disease, type 3 (#277480) von Willebrand disease, types 2A, 2M, and 2N (#613554)	Differences in molecular mechanisms (gain of function in type 2B vs inactivating and loss of function in types 1, 2A, 2M, 2N, and 3) and phenotypic variability (type 2B having the unique phenotypes of thrombocytopenia, increased platelet volume, and enhanced ristocetin-induced platelet aggregation) were considered for separate curations for hereditary von Willebrand disease entities (curated for the predominant autosomal dominant form, though recessive type 2N and type 3 were also included) and von Willebrand disease type 2B.
<i>VWF</i>	Definitive (18)	Von Willebrand disease type 2B (AD-GOF)	MONDO:0015629	von Willebrand disease, type 2B (#613554)	

(Continues)

TABLE (Continued)

AD, autosomal dominant; AR, autosomal recessive; ClinGen, Clinical Genome Resource; GOF, gain of function; HT, GCEP, Hemostasis/Thrombosis Gene Curation Expert Panel; LOF, loss of function; OMIM, Online Mendelian Inheritance in Man database; SCID, Severe Combined Immune Deficiency and Combined Immune Deficiency; SD, semidominant; XL, X-linked.	Gene WAS ^a
Classification (points) Definitive (1R)	
Disease (inheritance mechanism)	Wiskott-Aldrich syndrome
MonDO ID	MONDO:0010518
OMIM phenotype(s) included	OMIM phenotype(s) included
Thrombocytopenia, X-linked (#313900)	Thrombocytopenia, X-linked (#313900)
Thrombocytopenia, X-linked, intermittent (#313900)	Thrombocytopenia, X-linked, intermittent (#313900)
Wiskott-Aldrich syndrome (490400)	Wiskott-Aldrich syndrome (490400)
Deficiency; SD, WAS was curated by the ClinGen Hereditary Cancer GCEP (https://search.clinicalgenome.org/kb/gene-validity/CGGV:assertion_a936b3ba-f1d0-4f14-bd56-14f64ad4de3a-2018-10-12T205425.459Z) for Wiskott-Aldrich syndrome (including the thrombocytopenia phenotype). Of note, WAS is also implicated in neutropenia, severe congenital, X-linked (MIM#300299), but it was not considered within this curation due to differences in phenotype and molecular	

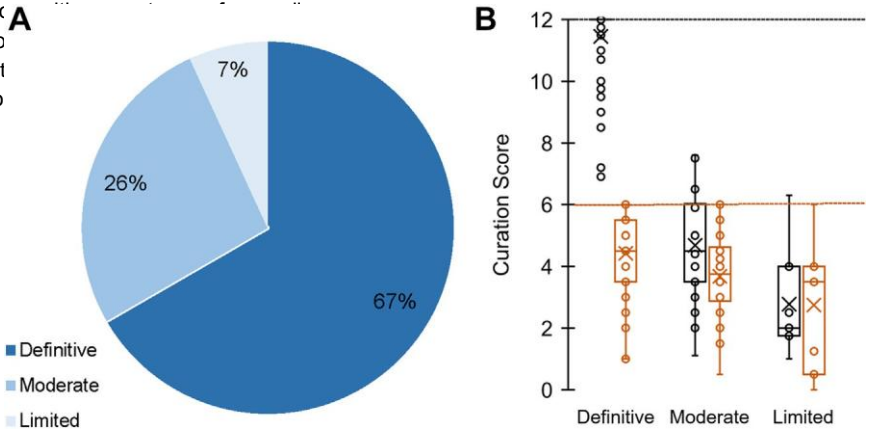
and a classification of Definitive was approved by the HT GCEP in 2022. The importance of re-evaluation and additional case reports is exemplified by the curation of *BLOC1S6*, which was reclassified from Moderate to Definitive with the addition of a newly published case during the GCEP's 3-year working period.

Similarly, several genes (*CYCS*, *HRG*, *PLAU*, *PLA2G4A*, *P2RY12-AD*, *TPM4*, and *VKORC1*) scored at the lower boundary of the Moderate classification (6.5-7 points). Each of these genes, except *CYCS*, had at least a modest experimental evidence score (≥ 3), and all genes, except *PLAU*, also had genetic evidence from ≥ 3 unrelated probands; thus, *P2RY12-AD*, *TPM4*, *VKORC1*, *HRG*, and *PLA2G4A* each received a Moderate clinical validity classification, while *CYCS* and *PLAU* were considered for downgrading to Limited. *CYCS* was first reported in relation to autosomal dominant thrombocytopenia in 2008 [29] and received a score between the Limited and Moderate thresholds (6.8 points). At least 15 probands have been reported, all harboring heterozygous missense variants in *CYCS* [29–34]. Most of these variants have not been functionally characterized, resulting in a minimum score of 0.1 points each, totaling 6.3 points. Despite 6.3 points of genetic evidence, expert opinion was that a Limited classification was appropriate due to the lack of experimental evidence (0.5 points) tying the gene to a disease mechanism. While functional alteration of platelet formation was shown in patient cells [35], the normal function of *CYCS* in relation to platelet formation remains unclear. Until additional evidence, such as a model organism, is produced, these types of curations will remain Limited. On the other hand, the *PLAU*-Quebec platelet disorder curation has only 1 scored proband, but it was identified in a large family from the Canadian province of Quebec and has been described in at least 3 dozen members of this single family [36,37]. Alongside substantial experimental evidence (4 points), cosegregation within this large pedigree was sufficient genetic evidence (3 points), without additional probands, to maintain the Moderate classification. Indeed, it only lacks a Definitive classification because all reported cases are within one family, constraining the genetic evidence total.

Two additional curations received modified classifications due to the lack of reported probands. Both *AP3D1* and *THBD-AR* had point totals of 8 (with 4 or 6 points of experimental evidence, respectively), which reached the threshold for a Moderate classification; however, with just 2 probands reported for each gene-disease relationship, expert opinion was that the genetic evidence, of 2 to 4 points, was insufficient for a Moderate classification. As with the *FYB1* curation, the lack of probands for genetic evidence resulted in the classification being downgraded 1 level to a final classification of Limited for *AP3D1* and *THBD-AR*.

The scores for the remaining 4 genes (*HOXA11*, *PTGS1*, *RAP1B*, and *F9-GoF*) with their respective disease relationships were in the Limited classification. Data have shown that most genes in the Limited category, particularly those that remain in the Limited category for more than 5 years, do not accumulate evidence to move to a higher classification in the future [15]. Four of the Limited curations are for recent disease gene discoveries (*AP3D1*, *PTGS1*, *RAP1B*, and *THBD-AR*) between 2016 and 2020, and although more genetic and/or experimental evidence is needed to support a causal role, no

FIGURE 1 (A) Distribution of gene- disease classificatic relationships at each clinical validity classification. A total o (B) Distribution of scores for genetic (black) and experiment classification. Dashed lines indicate the maximum score fo mean scores.



convincing evidence has emerged that contradicts the gene-disease relationship. Another recently identified disease gene, *GNE* [38], was originally curated in 2020, with 4 probands (scoring 4.6 points), and while its role in autosomal recessive isolated macrothrombocytopenia is supported by its function in the sialylation pathway, which is known to affect platelet lifespan [39,40], there was insufficient experimental evidence (0.5 points) to score it above the Limited classification. Subsequent studies [41–45] provided a significant amount of additional genetic evidence, with 5 probands added to the curation in 2022, leading to a total of 7.6 points of genetic evidence and reclassification of this gene-disease relationship as Moderate.

The 2 additional Limited classifications for *HOXA11* and *F9-GoF*, with their respective disease entities, each have just 1 proband publication, greater than 5 years old, from 2000 or 2009, respectively [46,47]. For *HOXA11*, related to radioulnar synostosis with amegakaryocytic thrombocytopenia, 1 frameshift variant has been reported in 2 probands in a single publication, segregating in 4 additional affected family members [46]. This gene-disease relationship is supported by its expression during limb development and a mouse model with skeletal malformations in the limbs [48], as well as its expression and function in early hematopoietic development [49]. *F9* and thrombophilia due to increased factor IX plasma clotting activity, an X-linked disorder, was first reported based on 1 missense variant with a suspected gain of function mechanism identified in 2 siblings [47]. This is the only family and only variant considered in the curation; while a few other polymorphisms, including F9 Malmo, have been reported in association with the risk of deep vein thrombosis [50], these variants have not been included in the curation, which only considered a monogenic disease. Of note, *F9-LoF* has been evaluated in relation to hemophilia B, reaching a Definitive classification. Although more evidence is needed to support a causal role, no convincing evidence has emerged that contradicts these 2 Limited gene-disease relationships. Replication of the gene-disease relationships is necessary to confirm more than a Limited classification. These Limited curations will be re-evaluated every 3 years to maintain current gene-disease validity

classifications. In this regard, the ClinGen HT GCEP recommends clinicians/investigators publish new cases of rare variants, even if the gene-disease relation has already been reported, and journal editors allow these publications in order to reach a Definitive classification. Clinicians/investigators can consult clinicalgenome.org, or access gene curation results through The Gene Curation Coalition (thegenc.org) database [51] to determine if their gene of interest has reached the Definitive threshold.

While most genes were evaluated for a single gene-disease relationship, the ClinGen Lumping and Splitting process identified 12 genes (*F2*, *F5*, *F9*, *F12*, *GP1BA*, *ITGA2B*, *ITGB3*, *MPL*, *P2RY12*, *THBD*, *THPO*, and *VWF*), each related to 2 distinct diseases within the purview of the HT GCEP (Table). The hemostatic system is a balance between pro- and antihemostatic forces, and disruption of this balance can cause either thrombosis or bleeding, depending on how the scale is tipped. For this reason, inactivating versus activating mutations in the same gene (ie, *F2*, *F5*, *F9*, *MPL*, and *THPO*) can cause either a bleeding/coagulation disorder or a thrombotic disorder, respectively, which is generally correlated with differences between recessive and dominant inheritance patterns. Other genes (ie, *GP1BA*, *ITGA2B*, *ITGB3*, *P2RY12*, *THBD*, and *VWF*) involved in platelet function were also split due to differences between inactivating and activating molecular mechanisms with recessive versus dominant inheritance, although diseases of both mechanisms may result in bleeding phenotypes. Seven additional gene-disease relationships (ie, *FGA*, *FGB*, *FGG*, *F11*, *PROC*, *PROS1*, and *SERPINC1*) were associated with both monoallelic and biallelic cases, but in these cases, all were inactivating mutations (except *F11*, which had both biallelic loss of function and dominant negative variants related to congenital factor XI deficiency). Here, the difference in the inheritance patterns was representative of a continuum of disease in a single disease entity and was curated using the inheritance pattern descriptor of semidominant.

Based on the previous work by the SSC-GinTH, all 89 genes are considered TIER1 genes on the ThromboGenomics high-throughput sequencing panel, given their relationship with at least 1 BTPD [31].

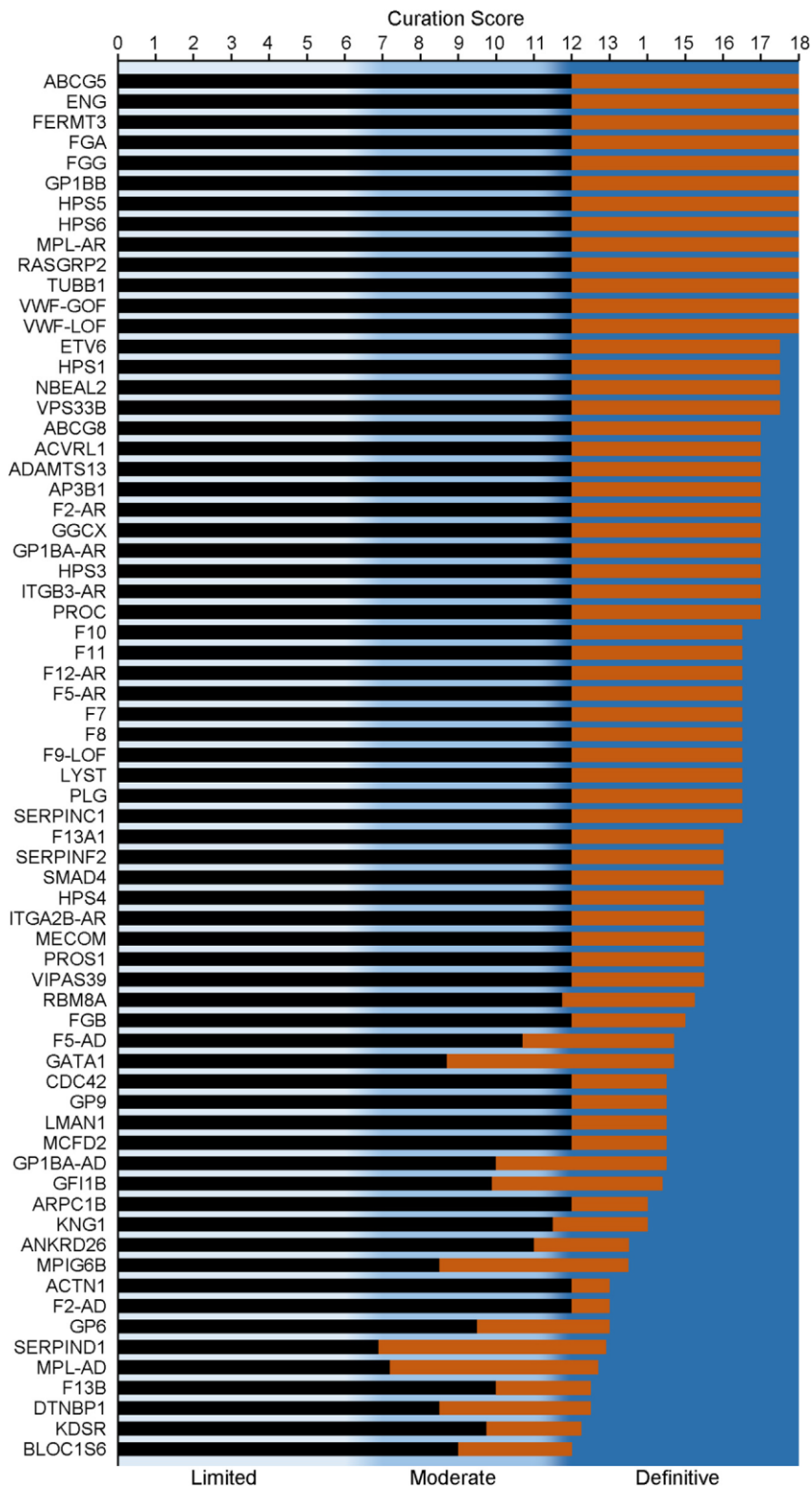
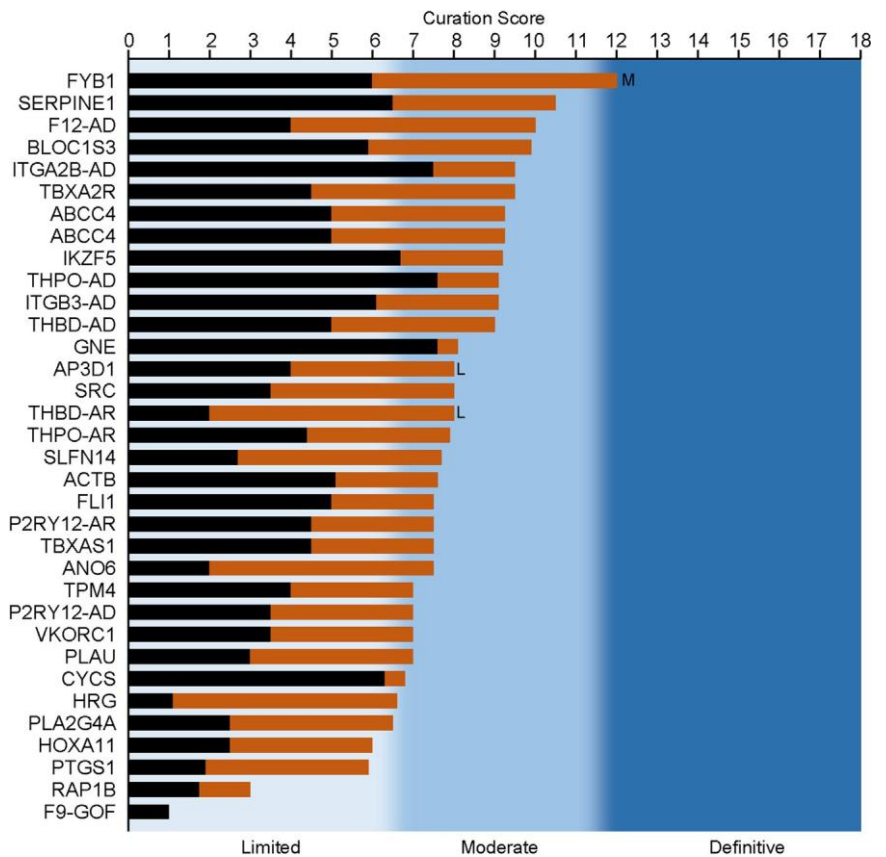


FIGURE 2 Hemostasis and thrombosis Definitive gene-disease classifications with genetic and experimental scores. Genetic and experimental points are depicted by black and orange bars, respectively. Total points for each classification are as follows: Limited (0-6 points; light blue), Moderate (7-11 points; medium blue), and Definitive (12-18 points; dark blue). The Strong classification is not depicted because there were no gene-disease relationships in this category.

FIGURE 3 Hemostasis and thrombosis non-Definitive gene-disease classifications with genetic and experimental scores. Genetic and experimental points are depicted by black and orange bars, respectively. Total points for each classification are as follows: Limited (0.1-6 points; light blue), Moderate (7-11 points; medium blue), and Definitive (12-18 points; dark blue). The Strong classification is not depicted because there were no gene-disease relationships in this category. Classifications modified for either insufficient genetic or experimental evidence are indicated to the right of the bars (M, moderate; L, limited).



Here, these genes were rigorously assessed by the ClinGen clinical validity curation process, resulting in an agreement that all genes were categorized in levels of supportive evidence; however, the TIER1 genes spanned the Definitive, Moderate, and Limited classifications. Moving forward, the HT GCEP will continue to evaluate novel genes put forward by the SSC-GinTH because their gene list is re-assessed at the yearly International Society on Thrombosis and Hemostasis meeting, including those currently considered TIER2 with only a single small pedigree and little-to-no functional studies. The main goal of ClinGen is to generate a public resource that defines the clinical relevance of genes and variants for precision medicine and research. This work will inform gene panel recommendations for clinical testing, highlighting the importance of assessing gene-disease clinical validity in order to facilitate variant interpretation and diagnosis for patients with BTPDs.

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AUTHOR CONTRIBUTIONS

K.L., K.F., and M.L. conceptualized the study. K.L., I.F., A.F., and D.M. provided coordination for the ClinGen HT GCEP. J.E.R., S.M., J.Z., M.J.S., and L.B. curated and evaluated the data. J.P.B., M.C., N.C., K.D., P.G., C.K., A.I.L., K.M., P.M., N.V.M., H.S., K.Z., K.F., and M.L. reviewed and interpreted the data. J.E.R. and J.P.B. wrote the manuscript. All authors revised and approved the final version of the manuscript.

DECLARATION OF COMPETING INTERESTS

The following authors are employee, trainee, or consultant for a commercial laboratory offering genetic testing related to disorders of hemostasis/thrombosis: L.B., K.F., P.G., C.K., J.P.B., M.S., and J.Z. The following authors have made substantial contributions to the literature on gene-disease relationships relevant to this work: L.B., K.D., K.F., P.G., C.K., M.L., K.M., P.M., N.M., J.P.B., N.S., and K.Z. Additionally, K.F. chairs the Scientific and Standardization Committee for Genetics in Thrombosis and Hemostasis of the International Society on Thrombosis and Hemostasis. The other authors declare no conflicts of interest.

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