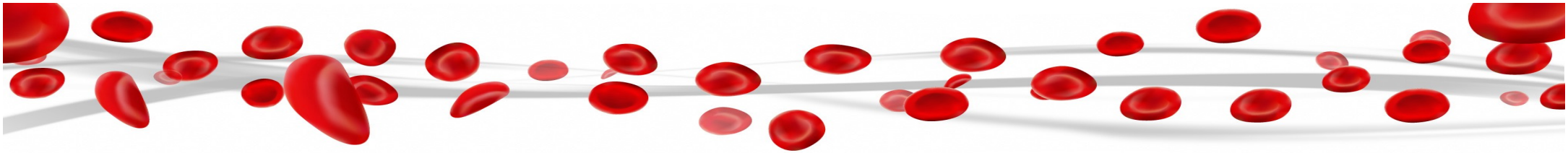


Webinars

Constitutional thrombocytopenia

EuroBloodNet

Benefits and limitations of high-throughput sequencing for the diagnosis of constitutional thrombocytopenia

Kathleen Freson

KULeuven

ERN-EuroBloodNet subnetwork Rare bleeding-coagulation disorders and related diseases

Leuven– Belgium

July 3rd 2024

Co-funded by the Health Programme of the European Union

CRPP

MHEMO

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

Unrestricted research grant from Swedish Orphan Biovitrum (SOBI)

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

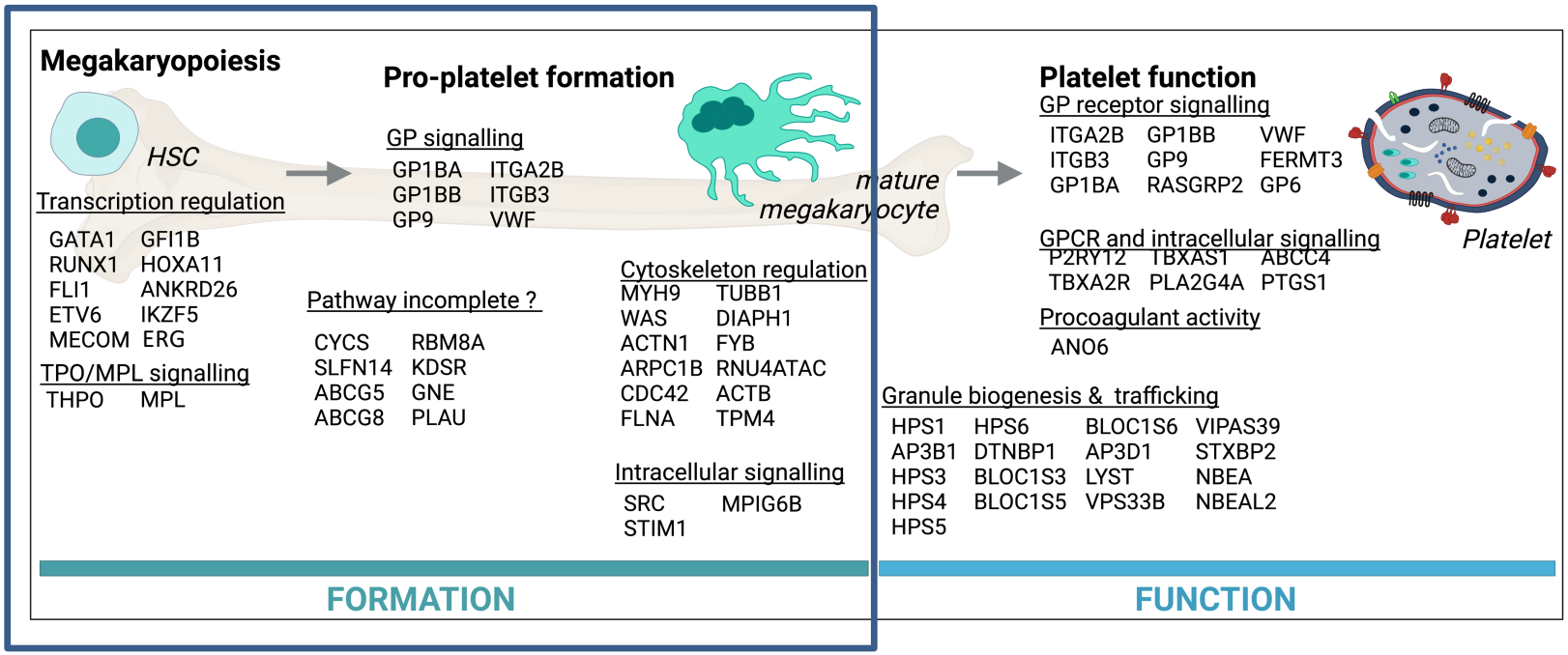
CRPP
MHEMO

Webinars
EuroBloodNet

Learning objectives of the webinar

1. Design of an NGS panel test to diagnose inherited thrombocytopenia
2. Diagnostic rate using NGS panel test for inherited thrombocytopenia
3. Pro and Cons of using NGS panel test for inherited thrombocytopenia: using examples from the clinic

Inherited thrombocytopenia : 41 genes



Variants in these genes cause inherited thrombocytopenia

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Ver Donck F et al. RPTH 2021

Gene curation to deliver diagnostic-grade genes (TIER1)

RECOMMENDATIONS AND GUIDELINES

J Thromb Haemost. 2019;17:1253–1260.

jth

Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH

Karyn Megy[1,2,3] | Kate Downes[1,2,3] | Ilenia Simeoni[1,2,3] | Loredana Bury[4] | Joannella Morales[5] | Rutendo Mapeta[1,2,3] | Daniel B. Bellissimo[6] | Paul F. Bray[7] | Anne C. Goodeve[8] | Paolo Gresele[4] | Michele Lambert[9,10] | Pieter Reitsma[11] | Willem H. Ouwehand[1,2,3] | Kathleen Freson[12] | on behalf of the Subcommittee on Genomics in Thrombosis and Hemostasis

SSC Scientific and Standardization Committee

- www.isth.org/page/GinTh_GeneLists
- Yearly updates during the SSC session

ORIGINAL ARTICLE

J Thromb Haemost. 2024;22:645–665

jth

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

Justyne E. Ross[1] | Shruthi Mohan[1] | Jing Zhang[2] | Mia J. Sullivan[3] | Loredana Bury[4] | Kristy Lee[1] | Isabella Futchi[1] | Annabelle Frantz[1] | Dara McDougal[1] | Juliana Perez Botero[3,5] | Marco Cattaneo[6] | Nichola Cooper[7] | Kate Downes[8] | Paolo Gresele[4] | Catriona Keenan[9] | Alfred I. Lee[10] | Karyn Megy[9] | Pierre-Emmanuel Morange[11,12] | Neil V. Morgan[13] | Harald Schulze[14] | Karen Zimowski[15] | Kathleen Freson[16] | Michele P. Lambert[17,18]

ClinGen Clinical Genome Resource

ClinGen

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Clinical Domain Working Groups

Hemostasis/Thrombosis Gene Curation Expert Panel

Affiliated to Hemostasis/Thrombosis CDWG

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(syndromic) Inherited (macro/micro)thrombocytopenia

	Large	Normal	Small
Syndromic thrombocytopenia	ABCG5 (AR) ABCG8 (AR) ACTB (AD) CDC42 (AD) DIAPH1 (AD) FLNA (X-linked) GATA1 (X-linked) GNE (AR) MPIG6B (AR) MYH9 (AD) SRC (AD)	ANKRD26 (AD) ETV6 (AD) FLI1 as part of large deletion (AD) HOXA11 (AD) KDSR (AR) MECOM (AD) RAP1B (AD) RBM8A (AR) RUNX1 (AD) STIM1 (AD) ERG (AD)	ARPC1B (AR) WAS (X-linked)
Non-syndromic thrombocytopenia	ACTN1 (AD) GFI1B (AD&AR) GP1BA (AD&AR) GP1BB (AD&AR) GP9 (AD&AR) ITGA2B (AD) ITGB3 (AD) NBEAL2 (AR) SLFN14 (AD) TPM4 (AD) TUBB1 (AD&AR)	CYCS (AD) FLI1 (AD&AR) IKZF5 (AD) MPL (AR) THPO (AD&AR)	FYB1 (AR)

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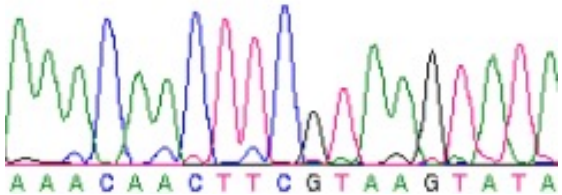
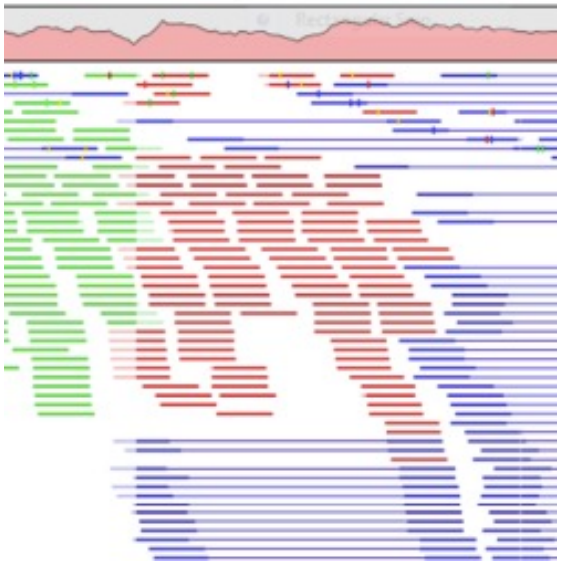
Freson K. *Diagnostic value of multigene sequencing for inherited thrombocytopenia. Br J Haematol. 2022*

2016: From Single gene analysis to Multi-gene panels

Targeted, Whole Exome Sequencing (WES) or
Whole Genome Sequencing (WGS)



Past → Today



Sanger sequencing, MLPA, CNV

MULTI-GENE PANEL TEST
(Virtual)

European Reference Network
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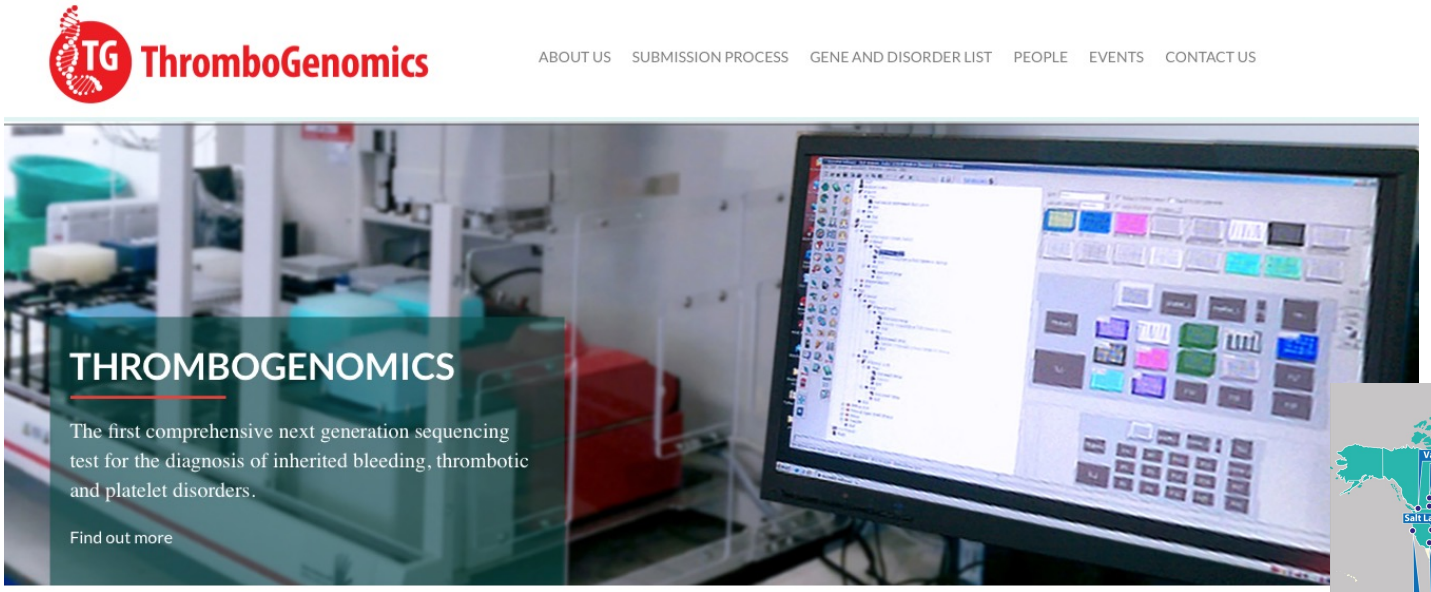
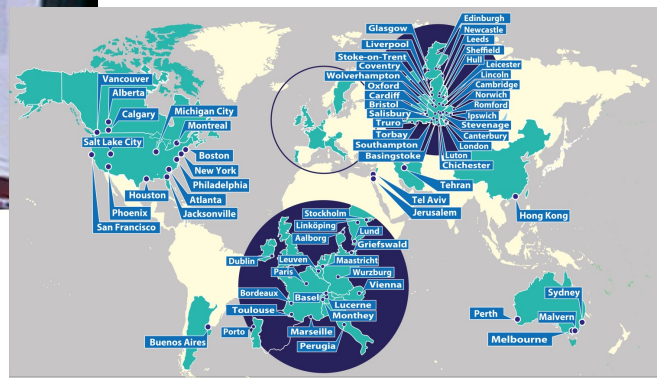
Network Hematological Diseases (ERN EuroBloodNet)

Implementation of multi-gene panel test : ThromboGenomics study





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for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Simeoni I, et al. Blood. 2016

ThromboGenomics Version 1

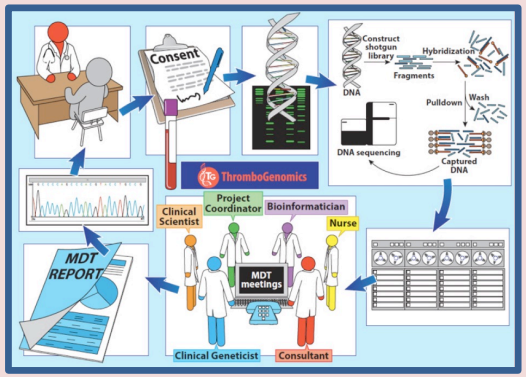
blood

Regular Article

THROMBOSIS AND HEMOSTASIS

Ilenia Simeoni , Blood 2016

A comprehensive high-throughput sequencing test for the diagnosis of inherited bleeding, thrombotic, and platelet disorders



- **Bleeding, Thrombotic and Platelet Disorder genes**
- **Targetted approach with coverage: 99 – 98 %**
- **Detection indels (no inversions)**
- **<u>Mean of 5.34 variants/case after filtering</u>**
- **Multiplexing 24 (later 48) samples**

ThromboGenomics Version 2

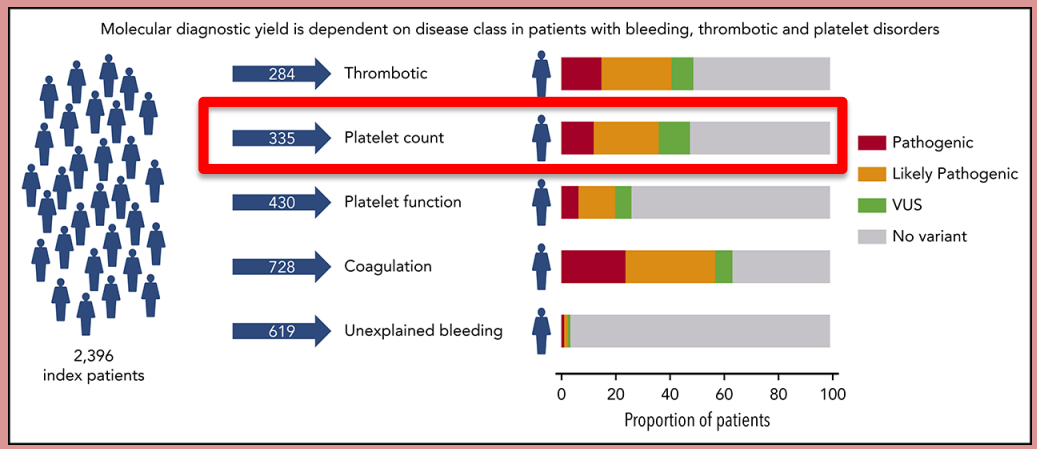
blood

Regular Article

THROMBOSIS AND HEMOSTASIS

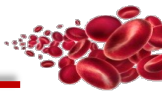
Kate Downes, Blood 2019

Diagnostic high-throughput sequencing of 2396 patients with bleeding, thrombotic, and platelet disorders

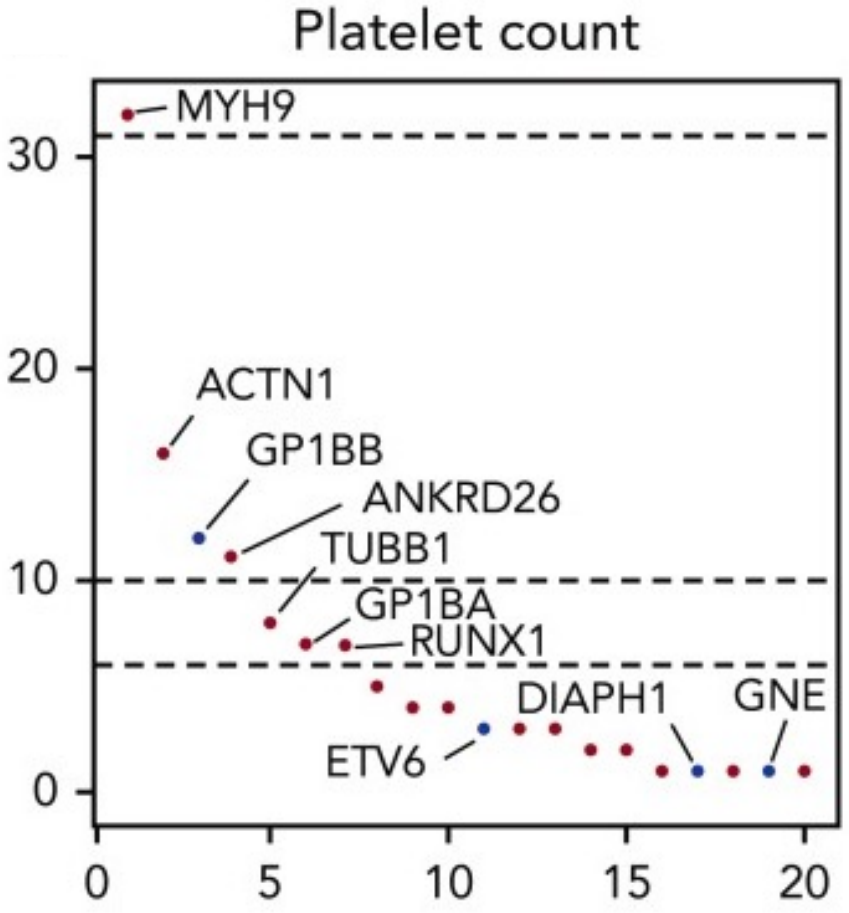


Diagnostic rate for thrombocytopenia is nearly 50%

Genes involved in patients with IT



Number of IT patients



Downes K, et al. Blood. 2019

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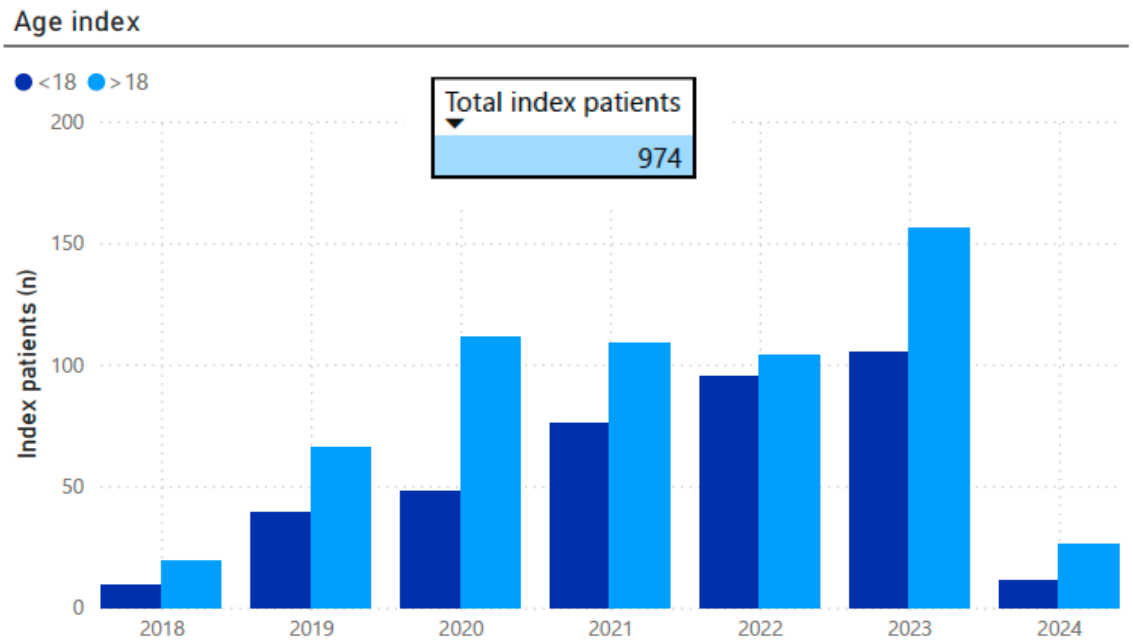
NGS panel for bleeding and thrombosis in the clinic



Christine Van Laer

Interim analysis

https://doi.org/10.1016/j.jtha.2022.12.007

J Thromb Haemost. 2023;21:887–895

jth

BRIEF REPORT

Clinical application of multigene panel testing for bleeding, thrombotic, and platelet disorders: a 3-year Belgian experience

Christine Van Laer[1,2] | Marc Jacquemin[1,2] | Sarissa Baert[3] | Veerle Labarque | Chantal Thys[1] | Thomas Vanassche[1,5] | Chris Van Geet[1,4] | Peter Verhamme | Karen Willekens[3] | Anniek Corveleyn[3] | Kathelijne Peerlinck[1,5] | Kathleen Freson[1]

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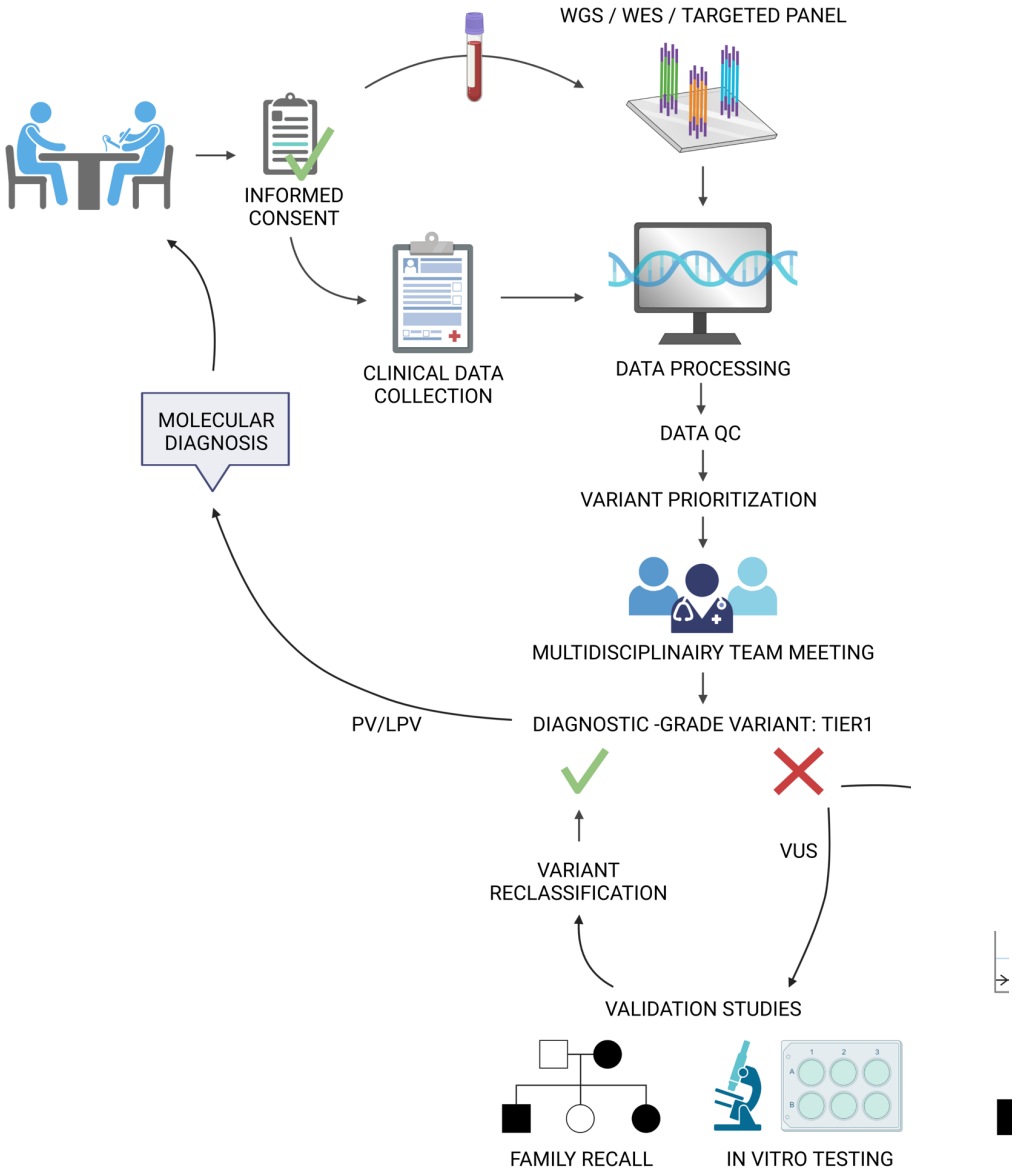
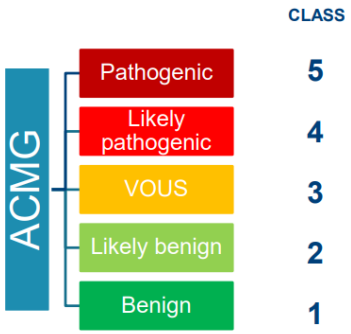
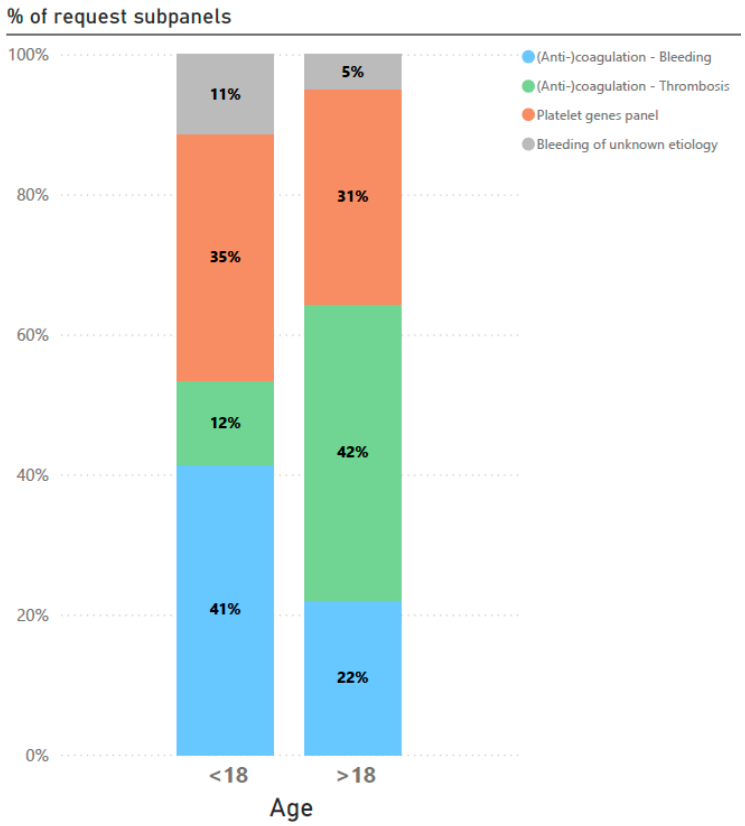
Workflow using multi-gene panel

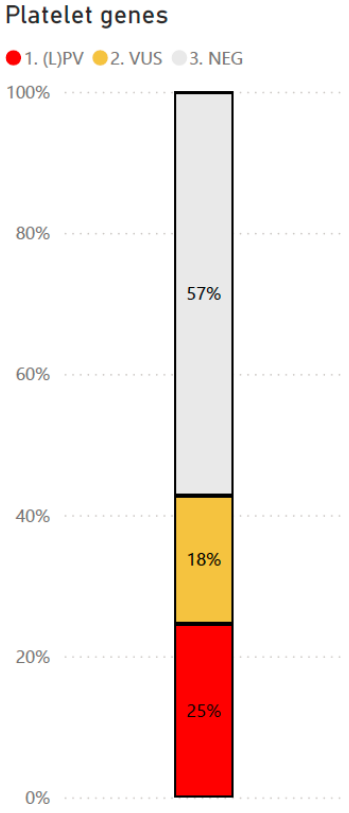




Ver Donck F et al. RPTH 2021

Results genetic testing (2019 –2022)





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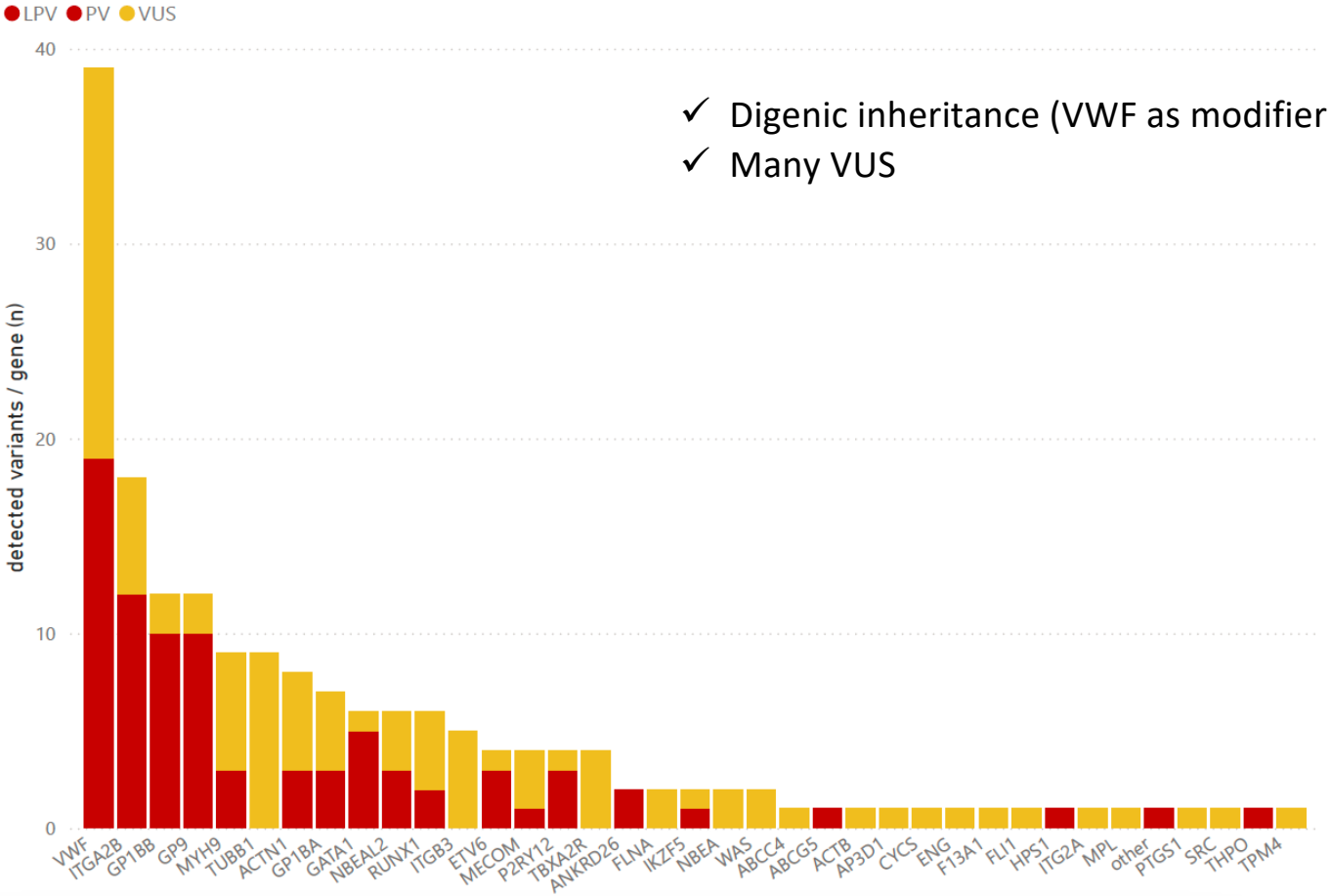
Network Hematological Diseases (ERN EuroBloodNet)

Genes involved in patients with IPD



- ✓ Digenic inheritance (VWF as modifier for bleeding)
- ✓ Many VUS

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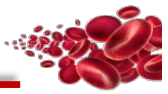
Strengths and Limitations of NGS panel test



Strengths	Cost and time efficient Improved diagnostic rate Improved gene curation for BPD Improved variant curation using ACMG classification rules Allows detection of the unexpected (e.g. oligogenic inheritance, exceptional phenotype-genotype relations)
Limitations	Low diagnostic rate for indistinct phenotypes Many variants are novel (classified as VUS) and require further studies Need for improved DNA variant databases Ethical concerns related to leukemia genes and carrier detection Lack of structural variant detection (including F8 intron 22 inversion)

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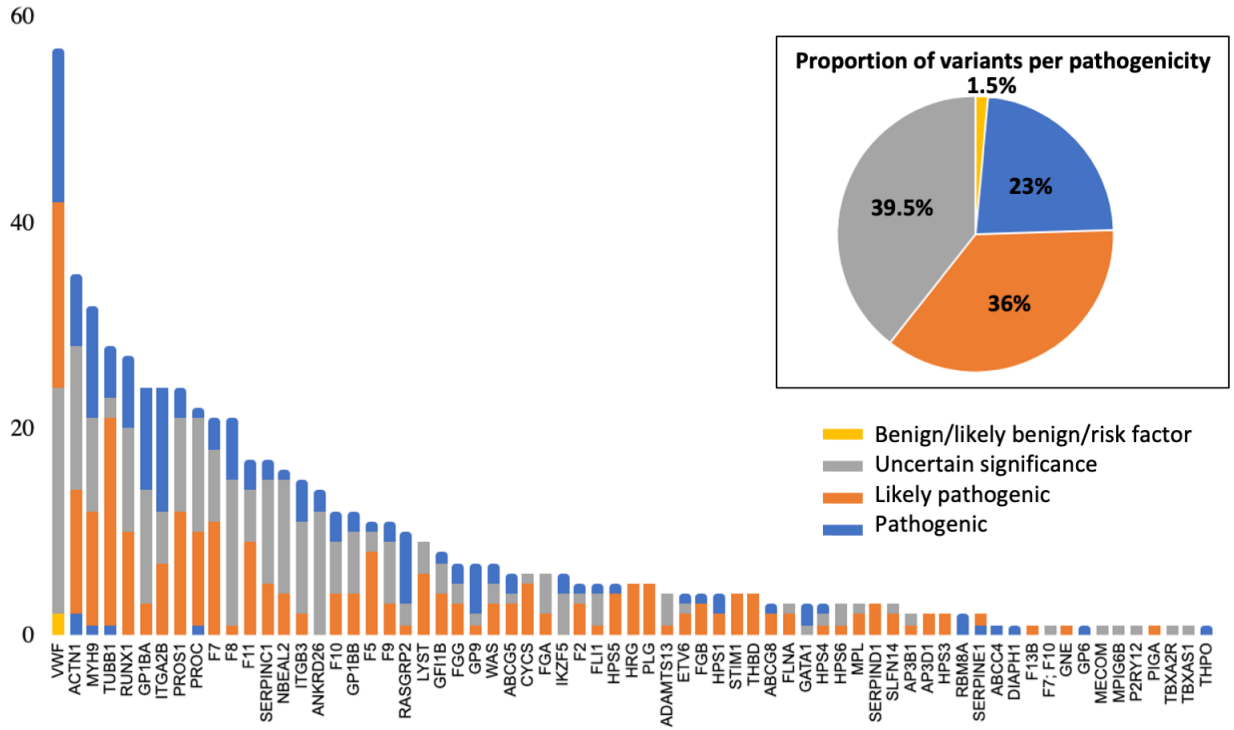
Ver Donck et al, JTH 2020

Variant Capture Tool to improve classification

814 Variants have been submitted from 30 diagnostic labs from 14 countries



GoldVariants

SSC Scientific and Standardization Committee

ISTH SSC-GinTH

ClinVar

Clinically relevant variation

Variant reclassification by ClinGen working groups for thrombosis & hemostasis

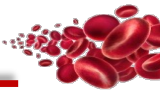
Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

https://www.isth.org/page/GinTh_GeneLists

Megy et al, JTH 2021

What do I tell the patient about NGS testing?



jth journal of thrombosis and haemostasis™

SSC Scientific and Standardization Committee

RECOMMENDATIONS AND GUIDELINES | Open Access

Clinical management, ethics and informed consent related to multi-gene panel-based high throughput sequencing testing for platelet disorders: Communication from the SSC of the ISTH

Kate Downes, Pascal Borry, Katrin Ericson, Keith Gomez, Andreas Greinacher, Michele Lambert, Eva Leinoe, Patrizia Noris, Chris Van Geet, Kathleen Freson ✉, Subcommittee on Genomics in Thrombosis, Hemostasis ... See fewer authors

First published: 08 July 2020 | https://doi.org/10.1111/jth.14993

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Network Hematological Diseases (ERN EuroBloodNet)

Downes K, et al. J Thromb Haemost 2020;18:2751–8.

Risk for unsolicited findings using a panel test for IT

Unsolicited findings: refer to variants in disease-causing genes that are unrelated to the original rationale for testing and that are identified inadvertently

Examples:

RUNX1, ETV6 and ANKRD26 variants that are risk factors for leukaemia when testing for platelet disorders

Carriership of variants in recessive genes

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Downes K, et al. J Thromb Haemost 2020

Risk of unsolicitated findings: an example

Index case, 35 y

Mucocutanous bleeding symptoms

Platelet count 145- 161 K, normal size

Platelet delta storage pool disease

RUNX1 p.Glu5ValfsTer5

BRIEF REPORT | DECEMBER 12, 2013

Enrichment of *FLI1* and *RUNX1* mutations in families with excessive bleeding and platelet dense granule secretion defects

Brief Report

Jacqueline Stockley, Neil V. Morgan, Danai Bem, Gillian C. Lowe, Marie Lordkipanidzé, Ban Dawood, Michael A. Simpson, Kirsty Macfarlane, Kevin Horner, Vincenzo C. Leo, Katherine Talks, Jayashree Motwani, Jonathan T. Wilde, Peter W. Collins, Michael Makris, Steve P. Watson,
Martina E. Daly on behalf of the UK Genotyping and Phenotyping of Platelets Study Group

Check for updates

Blood (2013) 122 (25): 4090–4093.

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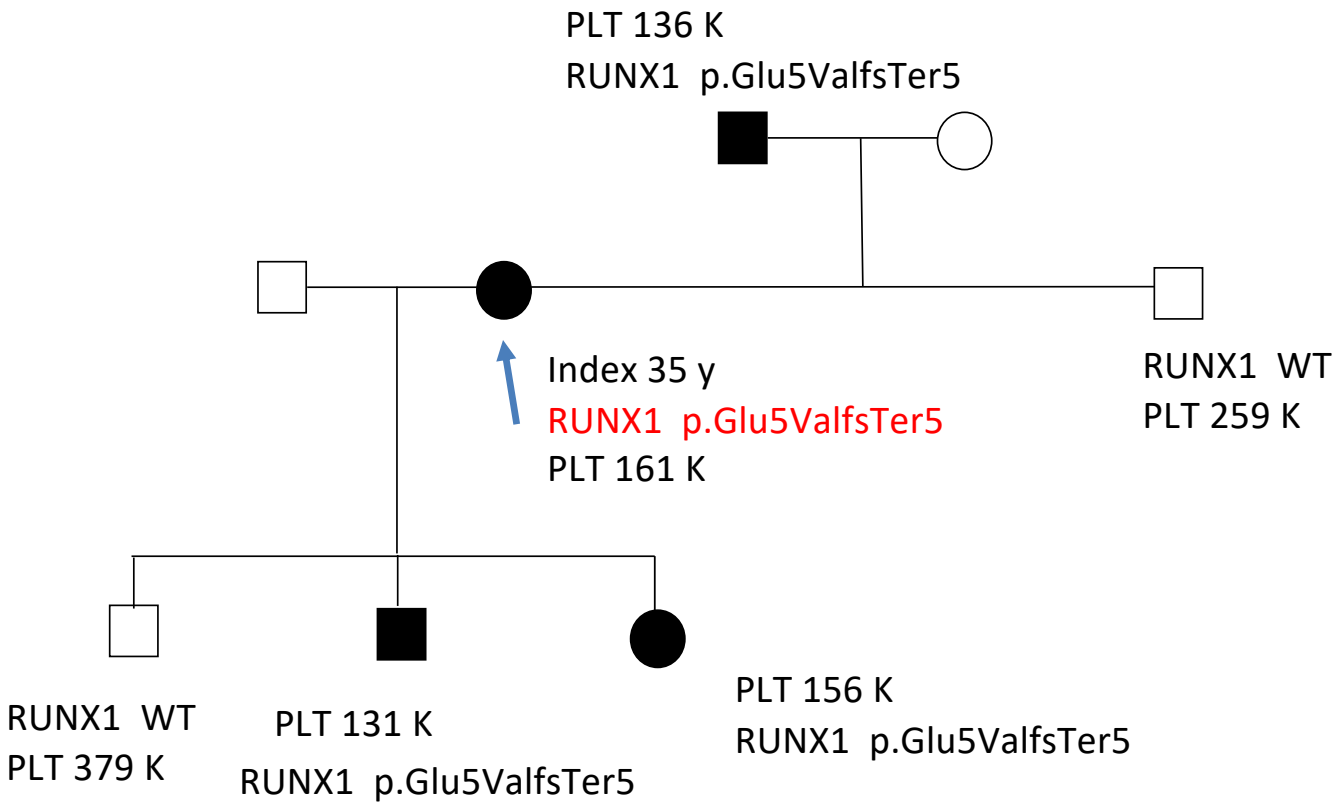

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Poll taken @EAHAD meeting 2019

Question 1

I have requested a genetic panel (or exome) test to diagnose patients with thrombocytopenia and did inform my patient that this test contains genes that are known risk factors for leukaemia?

1. YES
2. NO

Outcome : +/- 50 / 50 %

Question 2

Patients should sign an informed consent before participating in a genetic panel (or exome) with the possibility of an opt_in/opt-out choice to know about variants in leukemic risk genes?

1. YES
2. NO

Outcome : +/- 60 / 40 %

Dectection of a missed diagnosis

- Index case, 22 y
- Bleeding after trauma, menorrhagia (same for her mother)
- Macrothrombocytopenia (PLT 125K, MPV >13fL)
- Normal aggregations and ATP secretion
- FACS normal CD61, CD41 and 50% for CD42
- Prolonged PFA (171 s – COL/EPI and 136s – COL/ADP)

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GP1BB p.Leu16Pro
TUBB1 p.Gly109Glu

GP1BB p.Leu16Pro

BRIEF REPORT | JANUARY 26, 2017

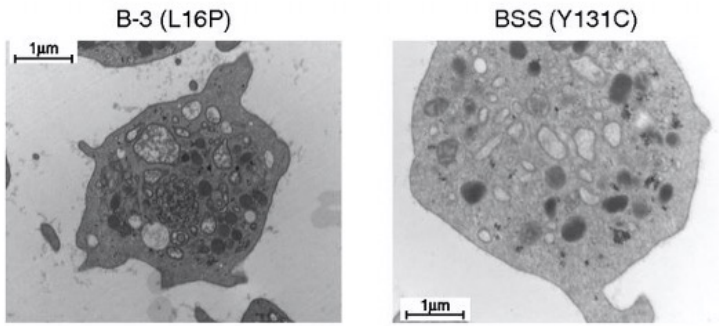
Rare variants in *GP1BB* are responsible for autosomal dominant macrothrombocytopenia

Brief Report

Suthesh Sivapalaratnam, Sarah K. Westbury, Jonathan C. Stephens, Daniel Greene, Kate Downes, Anne M. Kelly, Claire Lentaigne, William J. Astle, Eric G. Huizinga, Paquita Nurden, Sofia Papadia, Kathelijne Peerlinck, Christopher J. Penkett, David J. Perry, Catherine Roughley, Ilenia Simeoni, Kathleen Stirrups, Daniel P. Hart, R. Campbell Tait, Andrew D. Mumford, NIHR BioResource, Michael A. Laffan, Kathleen Freson, Willem H. Ouwehand, Shinji Kunishima, Ernest Turro

Check for updates

Blood (2017) 129 (4): 520–524.



TUBB1 p.Gly109Glu

PLATELETS AND THROMBOPOIESIS | DECEMBER 16, 2021

Expanding the genetic spectrum of *TUBB1*-related thrombocytopenia

Verónica Palma-Barqueros, Loredana Bury, Shinji Kunishima, María Luisa Lozano, Augustín Rodríguez-Alen, Nuria Revilla, Natalia Bohdan, José Padilla, María P. Fernández-Pérez, María Eugenia de la Morena-Barrio, Ana Marín-Quiles, Rocío Benito, María F. López-Fernández, Shally Marcellini, Ana Zamora-Cánovas, Vicente Vicente, Constantino Martínez, Paolo Gresele, José M. Bastida, José Rivera on behalf of the Inherited Platelet Disorders Project, Grupo Español de Alteraciones Plaquetarias Congénitas (GEAPC), Spanish Society of Thrombosis and Haemostasis (SETH)

Check for updates

Blood Adv (2021) 5 (24): 5453–5467.

for rare or low prevalence complex diseases

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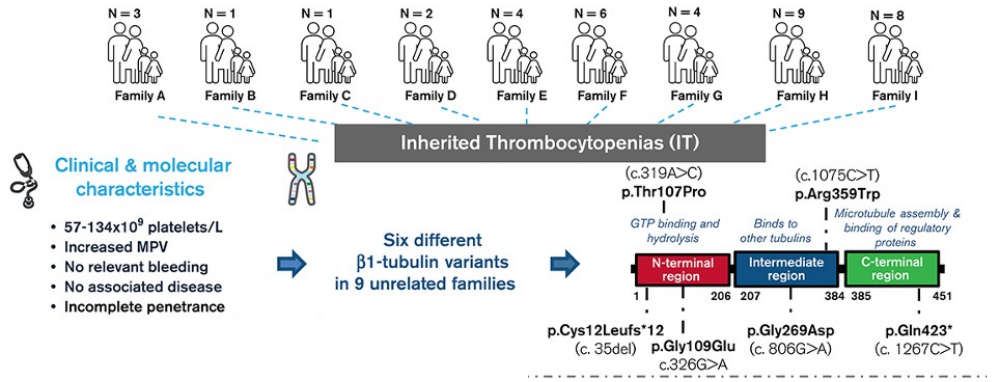

Detection of a missed diagnosis

- ✓ Healthy parents
- ✓ Child (boy) with platelet count of 8K, died after intracranial bleed
- ✓ 2nd child (girl) with platelet count of 12K, easy bruising
- ✓ CAMT screening negative !
- ✓ next WES

Received: 13 August 2022 | Accepted: 15 September 2022

DOI: 10.1111/bjh.18481

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

LETTER TO THE EDITOR

Maternal gonosomal mosaicism in rare autosomal dominant *SLFN14*-related thrombocytopenia

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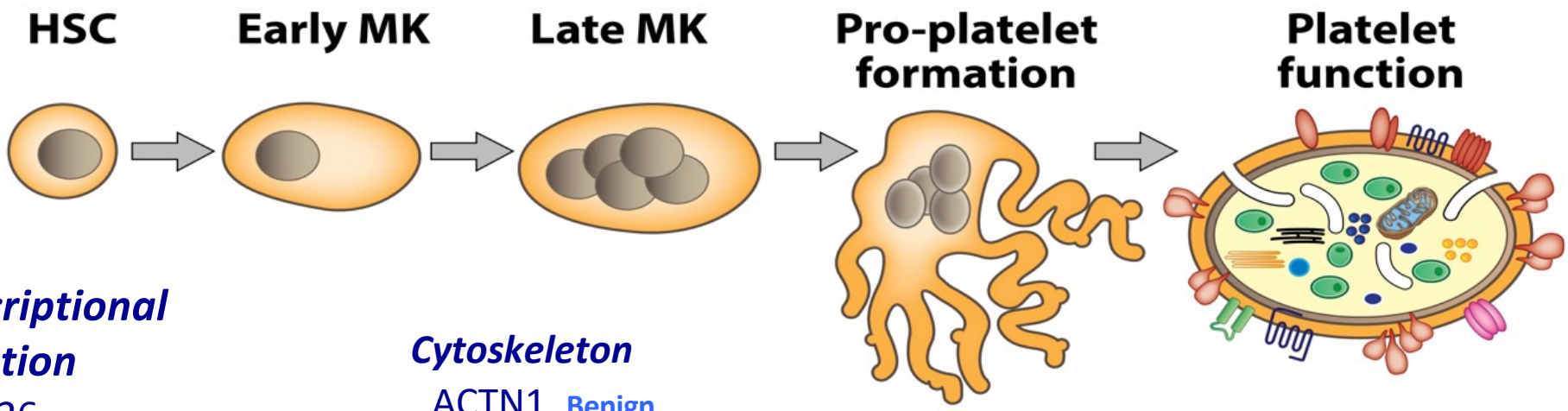
Network Hematological Diseases (ERN EuroBloodNet)

Precision diagnosis of IT can influence management



Transcriptional regulation

ANKRD26
RUNX1 — Leukaemia risk
ETV6
GATA1 — Dyserythropoiesis/ anaemia
GFI1B

Cytoskeleton

ACTN1 — Benign
TUBB1
MYH9 — Genotype/phenotype hearing loss/ kidney failure
DIAPH1 — Hearing loss/ TPO mimetics
WAS — Infections/transplant

TPO signaling

MPL — Pancytopenia /transplant
THPO — Pancytopenia /TPO mimetics

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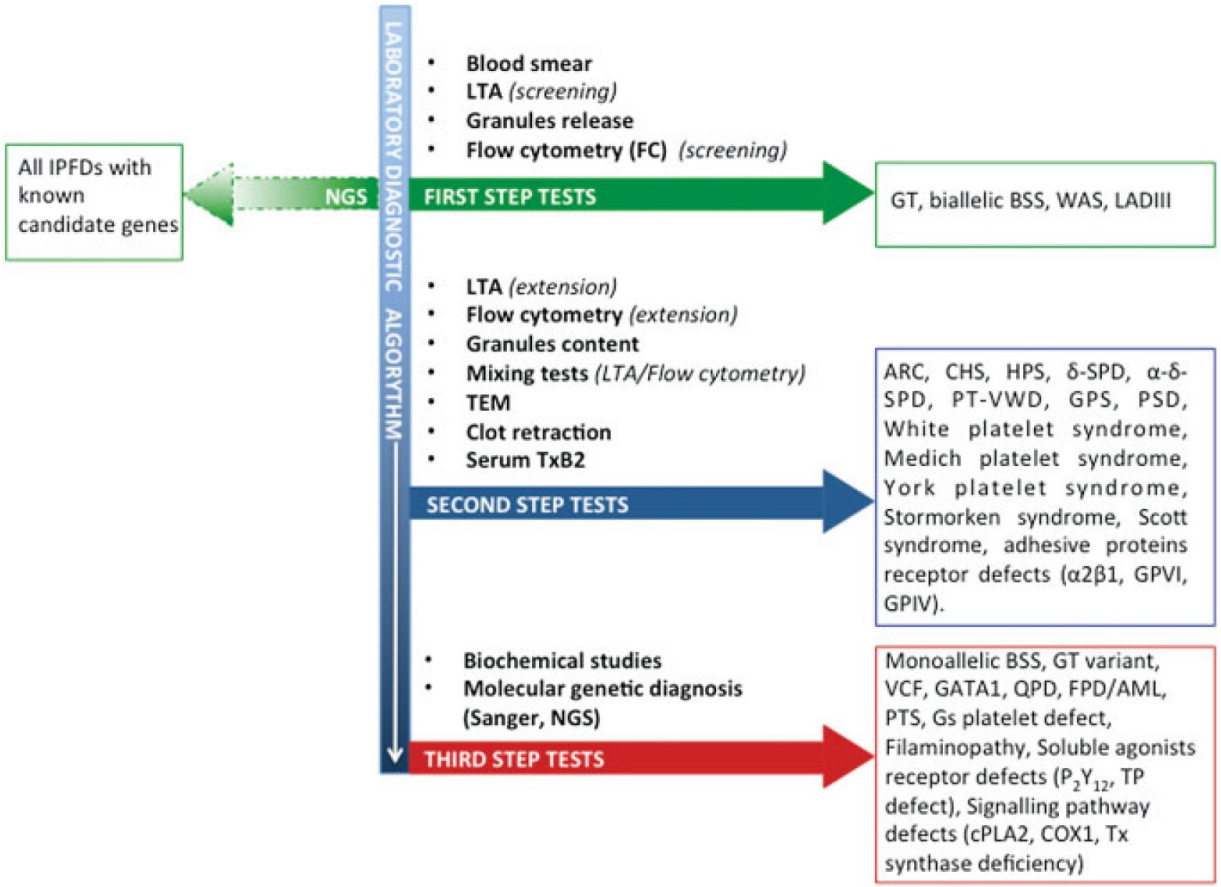
Lentaigne C, et al. Blood 2016;127:2814–23.

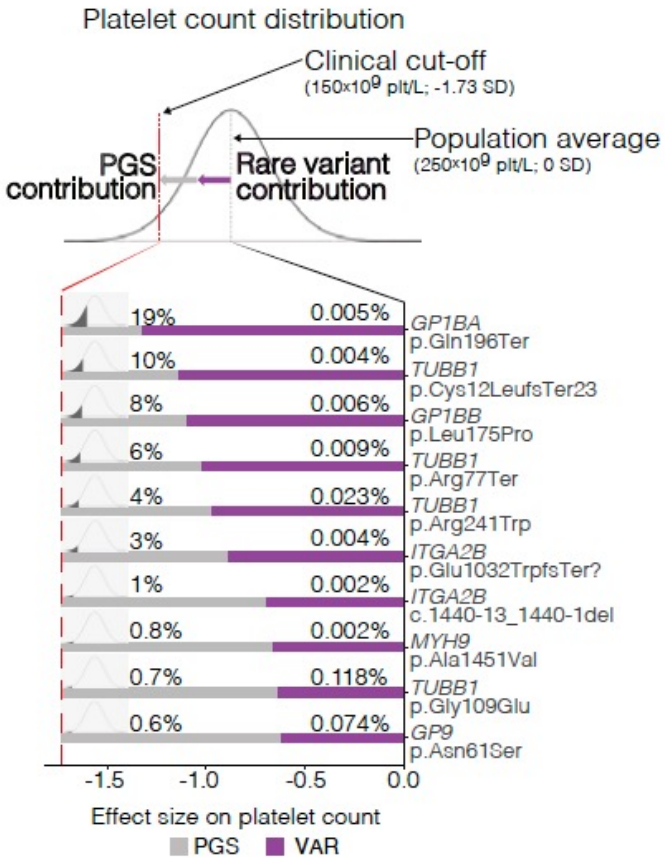
When do we use the multi-gene panel test in the diagnostic algorithm?



Gresele et al. Inherited Platelet Function Disorders: Algorithms for Phenotypic and Genetic Investigation. Seminars in Thrombosis and Hemostasis. 2016

Other genetic studies for IT (outside diagnostic environment)

Clinical relevance of rare variants & polygenic scores for IT?



The effects of pathogenic variants for inherited hemostasis disorders in 140,214 UK Biobank participants

- **Effect of Rare and Common variants**
- **Common variants are polygenic scores (PGS)**

Stefanucci L et al, Blood 2023

Network
for rare or low prevalence complex diseases

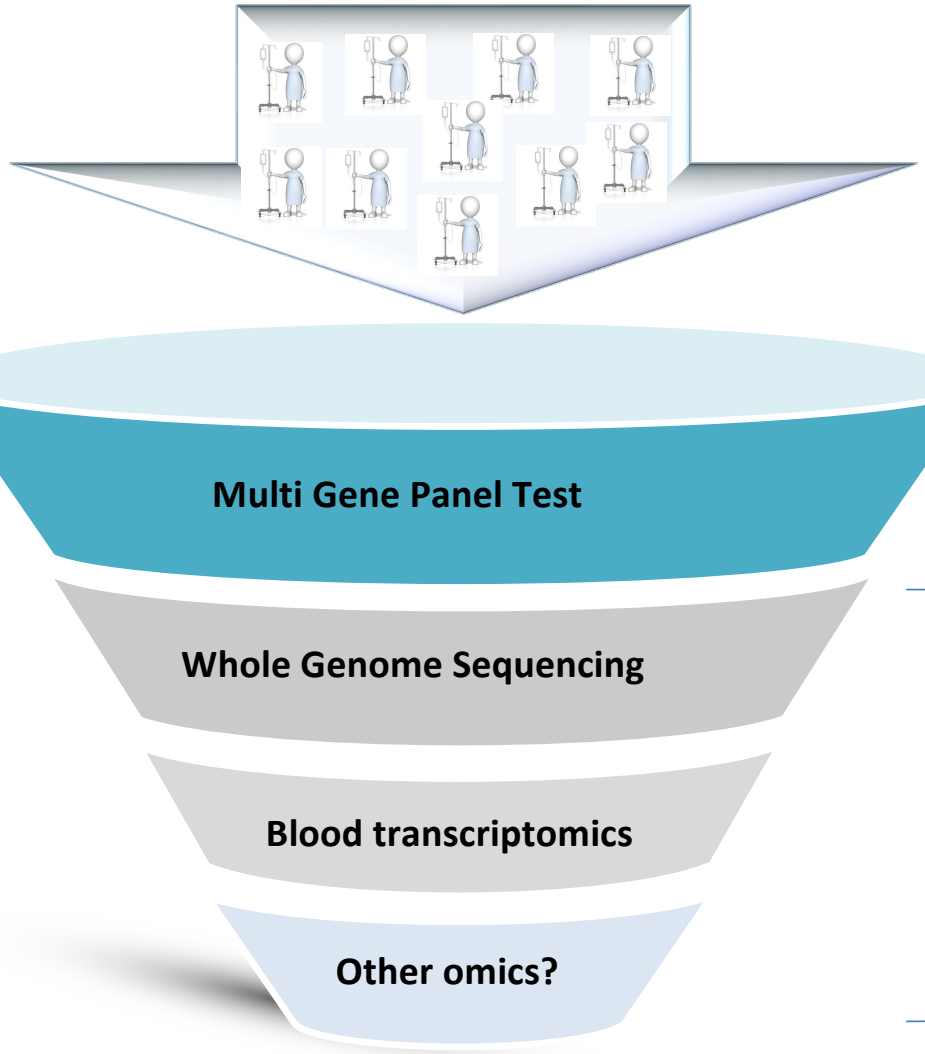
Network Hematological Diseases (ERN EuroBloodNet)

Diagnostic rate

+/- 55%

Plus 10%

?



1. Clinic

2. Research

European Reference Network
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Network Hematological Diseases (ERN EuroBloodNet)

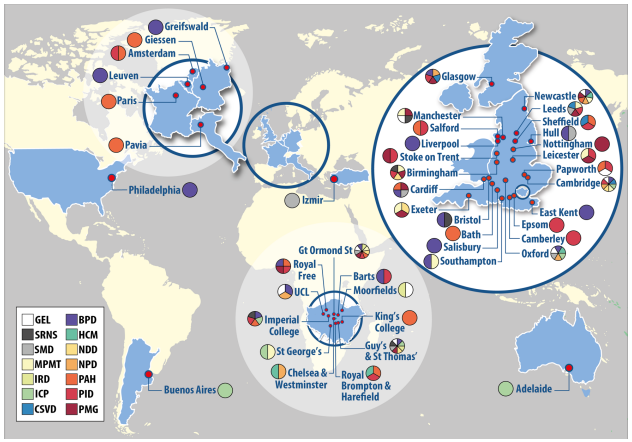
Gene discovery using WGS

NIHR BioResource
Rare Diseases

	Bleeding, thrombotic and Platelet Disorders	BPD		Multiple Primary Malignant Tumours	MPMT
	Cerebral Small Vessel Disease	CSVD		Neurological and Developmental Disorders	NDD
	Ehler-Danlos Syndromes	EDS		Neuropathic Pain Disorders	NPD
Genomics england	Rare Diseases Pilot-II	GEL		Pulmonary Arterial Hypertension	PAH
	Hypertrophic Cardiomyopathy	HCM		Primary Immune Disorders	PID
	Intrahepatic Cholestasis of Pregnancy	ICP		Primary Membranoproliferative Glomerulonephritis	PMG
	Inherited Retinal Disorders	IRD		Stem cell and Myeloid Disorders	SMD
	Leber Hereditary Optic Neuropathy	LHON		Steroid Resistant Nephrotic Syndrome	SRNS
biobank uk Improving the health of future generations				UK Biobank – Extreme Red Cell Traits	UKBio

- **57** NHS Hospitals and **26** non-UK Hospitals

  (Bleeding & Platelet Disorders 1916 patients)
- **13,037 index patients**



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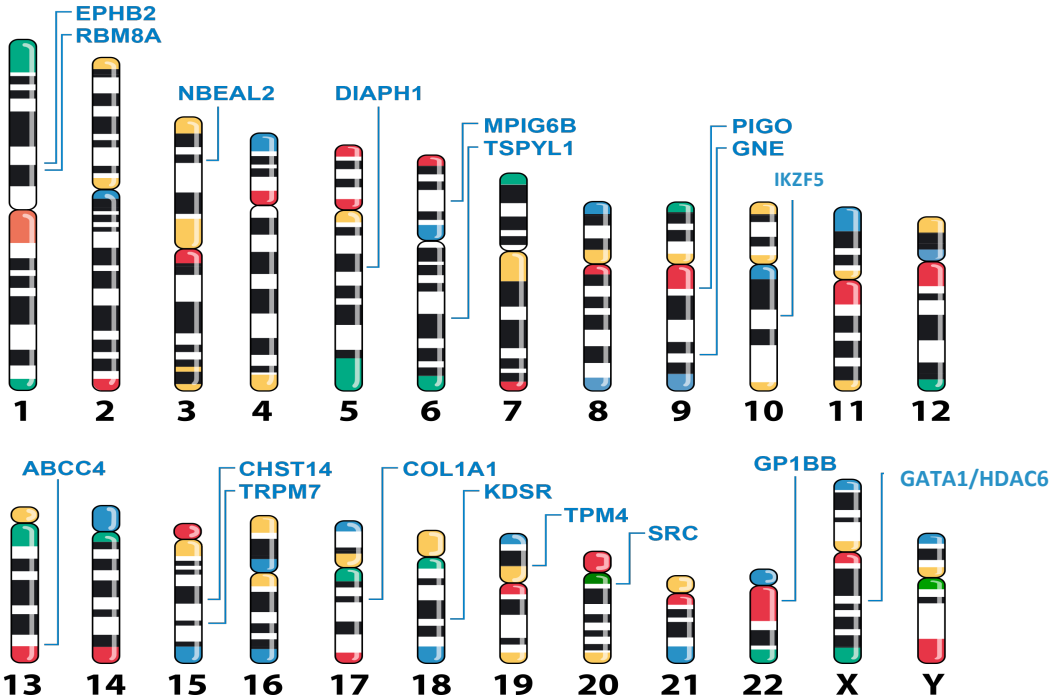
Turro et al, Nature. 2020
WGS by Illumina UK
Coordinator: Willem Ouwehand (Cambridge)

2011-2020: 18 new genes for bleeding & platelet disorders



UZLeuven (543 patients): Only 10% diagnostic rate

Albers *et al*, Nat Genetics 2011; Albers *et al*, Nat Genetics 2012; Cvejic *et al*, Nat Genetics 2013; Chen *et al*, Science 2014; Westbury *et al*, Genome Medicine 2015*;* Green *et al,* AJHG 2016; Stritt *et al*, Nat Comm 2016; Turro *et al,* Science Transl Med 2016; Stritt *et al*, Blood 2016; Simeoni *et al*, Blood 2016; Lentaigne e*t al*, Blood 2016; Poggi *et al,* Haematologica 2016; Bariana *et al*, BJH 2017; Siva-palaratnam *et al,* Blood 2017; Pleines *et al*, JCI 2017; Greene *et al*, AJHG 2017; Westbury *et al,* Blood 2017; Sivapalaratnam *et al,* BJH 2017; Morren *et al,* Orphanet 2017*; Freson et al,* JTH 2017; Sowerby *et al,* JCI 2017; Mayer *et al*, Blood 2018; Revel-Vilk *et al,* Blood 2018; Berrou *et al*, Blood 2018; Hofman *et al*, Blood 2018; Bariana *et al,* Haematologica 2018; Westbury *et al,* Blood Adv 2018; Lentainge et al, Blood 2019; Buyse et al, HMG 2021

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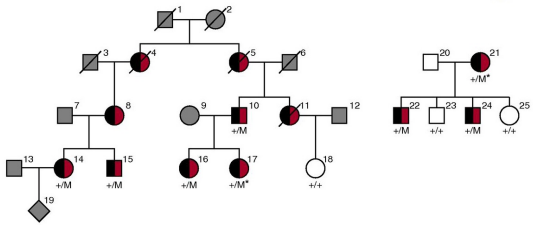
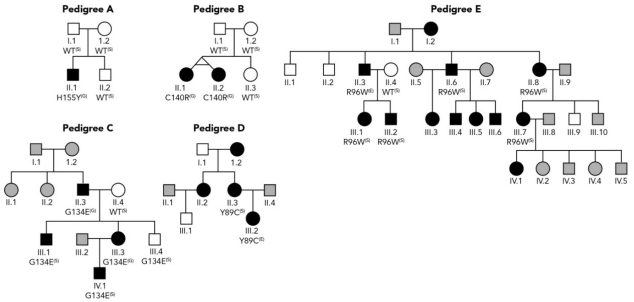
Gene discovery using Whole Genome Sequencing

NIHR | BioResource

DIAPH1-related thrombocytopenia + deafness



IKZF5-related thrombocytopenia



Unrelated patients with same genotype-phenotype

BeviMed (Ernest Turro, Daniel Greene- Mount Sinai NY)

Stritt et al, 2016, Blood
Lentaigne et al, 2019, Blood

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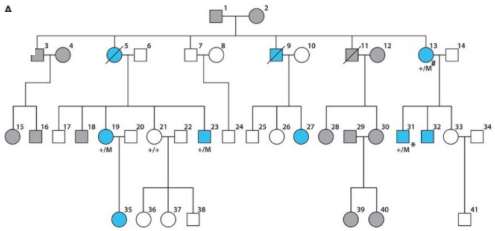
SRC-related syndromic thrombocytopenia



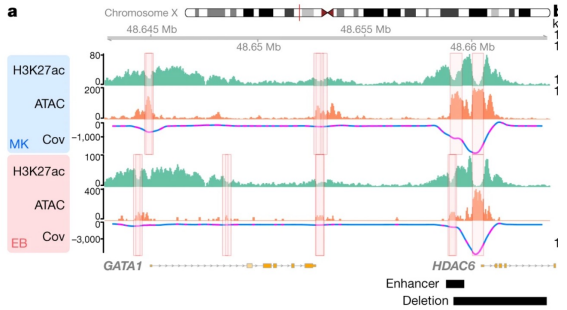
Large pedigrees

Turro et al, 2016, Science Translational Medicine

GATA1/HDAC6-related thrombocytopenia + Autism

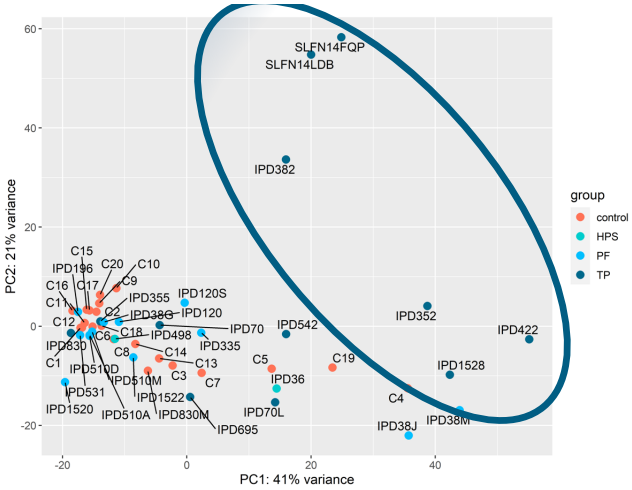
Unique DELETION

Turro et al, 2020, Nature

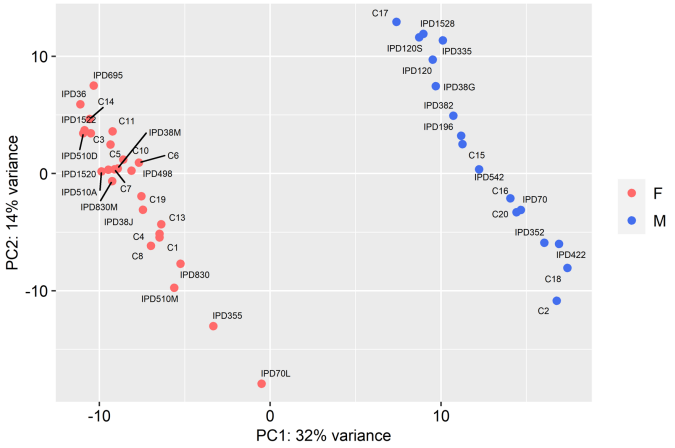


Blood cell RNAsequencing

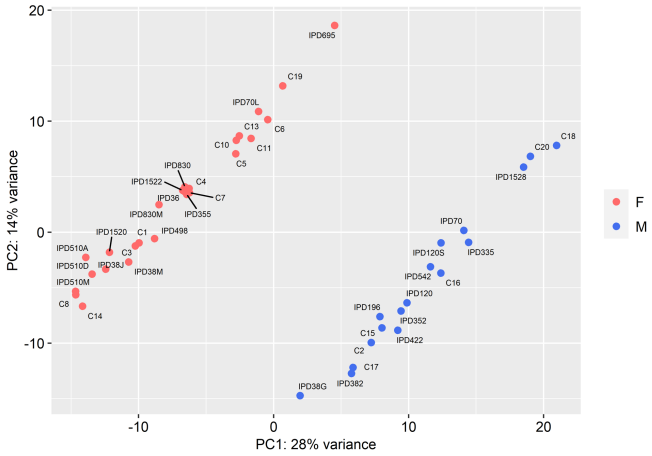
20 controls
9 Thrombocytopenia patients
18 platelet functional disorders



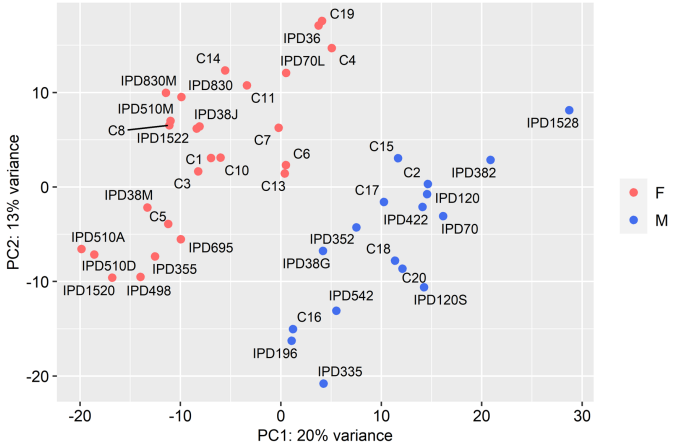
PLATELETS



CD4+ T cells



monocytes



Neutrophils

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Raresevoir (Variant filtering) & Chromoscope (Variant display)

A002707

kathleen.freson@kuleuven.be / IP: 193.60.92.187 (proxy for 134.58.253.56)

sample: A002707, gnomad: absent, cadd_thresh: 10, filter: moderate, splice_ai: null, biallelic: false

Main page DB info Logout

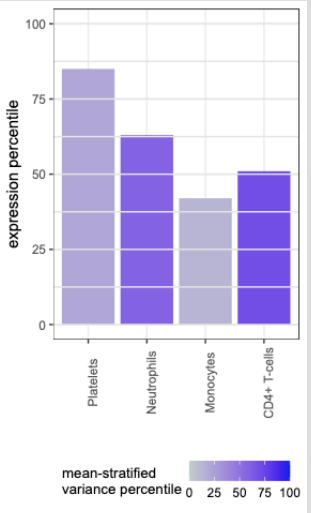
Show sample data

Help Download Highlight domain: None Retain highlighted SpliceAI threshold for intronic: 0

Include variants by consequence: no gene consequence | coding_sequence_variant | exonic_splice_region_variant | five_prime_UTR_variant | frameshift_variant | inframe_deletion | intron_variant | missense_variant | splice_donor_variant

Gene	CHR	POS	REF	ALT	Samples	Consequence	HGVS	CADD	gnomAD freq	SpliceAI	HGMD
OR10J1	1	159410244	C	G	A002707	missense_variant	Ile232Met	22.30	absent	0.01	
KCNJ10	1	160011584	G	A	A002707	missense_variant	Pro247Ser	26.30	absent	0.04	
RXRG	1	165378877	G	T	A002707	missense_variant	Gln322Lys	19.48	absent	0.16	
ZNF281	1	200377438	T	C	A002707	missense_variant	Arg466Gly	16.53	absent	0.00	
ENSG00000268146	1	244228363	C	T	A002707, M006451	missense_variant	Arg150Cys	10.72	absent	0.00	
C2orf80	2	209045956	C	T	A002707	missense_variant	Ala94Thr	25.90	absent	0.11	
ABHD14B ABHD14A-ACY1 ACY1 ABHD14A	3	52009186	T	C	A002707	missense_variant & five_prime_UTR_variant & intron_variant	Leu12Pro,Leu12Pro,Leu12Pro,Leu12Pro,Leu12Pro,Leu12Pro,Leu12Pro,Leu12Pro	22.40	absent	0.00	
APBB2	4	41016334	G	A	A010817, A002707, A002720	missense_variant	Thr34Ile	23.70	absent	0.00	
KDM3B	5	137721856	T	G	A002707	missense_variant	Val309Gly	19.26	absent	0.22	
CDHR2	5	176004545	T	C	A002707	missense_variant	Met447Thr	22.70	absent	0.01	
NSD1	5	176636935	A	G	A002707	missense_variant		21.40	absent	0.00	
DEK	6	18264081	CTC[22]TCG	C	A002707	inframe_deletion	Asp37_Glu45del		absent	0.19	
NR2E1	6	108497902	A	G	A002707	missense_variant	Glu189Gly	23.30	absent	0.00	
PNPLA8	7	108137930	T	C	A002707	missense_variant	Thr484Ala	26.10	absent	0.01	
CPA6	8	68397000	G	A	A002707	missense_variant	Pro221Ser	18.55	absent	0.12	
ADAMTSL2	9	136435570	G	A	G003517, K002589, S013694, T011086, A002707, W000325, W000328, B012575, U007109, C006877,	missense_variant	Glu954Lys	22.70	absent	0.00	

KDM3B Close



Panels

GENE: ENSG00000120733
HGNC: KDM3B
PANEL: Hearing loss
SCORE: 2
DOMINANT: yes
RECESSIVE: no

GENE: ENSG00000120733
HGNC: KDM3B
PANEL: Intellectual disability
SCORE: 3
DOMINANT: yes
RECESSIVE: no

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Key messages for use of an NGS panel test for diagnostics

- ✓ A (virtual) panel test is fast (TAT 4-6 months) and cheap
- ✓ It detects unexpected phenotype-genotype associations (including unsolicitated findings)
- ✓ Panel test is typically ordered by specialist with knowledge of the complexity of such test and its inclusion/exclusion criteria. Patients should be aware of what this test means (opt-out for RUNX1, ETV6, ANKRD26 and consenting).
- ✓ Sufficient phenotype information should be provide to allow variant classification
- ✓ Variants of Unknown clinical Significance (VUS- need further research (improved variant databases) before they can be used in the clinic

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Acknowledgements

UZLeuven & CMVB

Veerle Labarque
Chris Van Geet

Kathelijne Peerlinck
Thomas Vanassche
Peter Verhamme

CMVB

Chantal Thys
Christine Van Laer
Andreas Verstraete

Human Genetics, UZLeuven

Anniek Corverleyn
Sarissa Baert
Karen Willekens

KU LEUVEN

Center for Molecular and Vascular Biology

UZ LEUVEN

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All Belgian Clinical Centers for thrombosis & Hemostasis