Genetic testing guides therapy in children with refractory cytopenias

Immune cytopenias of childhood encompass a heterogeneous group of disorders characterized by immune-mediated destruction of red blood cells (autoimmune hemolytic anemia [AIHA]), platelets (immune thrombocytopenia [IPT]), neutrophils (autoimmune neutropenia [AIN]) or multiple lineages (Evans syndrome). Most primary or "idiopathic" cases present acutely but respond to first- or second-line therapy (steroids, intravenous immunoglobulin replacement therapy, ± rituximab) without long-term sequelae.[1] In contrast, cytopenias that fail to respond to repeated courses of multi-agent immunosuppressive therapy constitute a severe and often debilitating condition with substantial long-term morbidity.[2] Such non-responsiveness should prompt evaluation for an underlying comorbid disorder, malignancy, infection, lymphoproliferation, rheumatoid disease, or an inborn error of immunity (IEI). Therapy-refractory cytopenias in children frequently conceal unrecognized IEI or other hematopoietic defects that are amenable to targeted treatment. This study was approved by Stanford Institutional Review Board in accordance with the Declaration of Helsinki, and written informed consent was obtained.

We analyzed 24 pediatric and young adult patients with presumed immune cytopenias referred to our multidisciplinary clinic after failing multiple lines of immunosuppressive therapy (Figure 1). Comprehensive immune evaluation and genetic testing were performed in all cases. A contributory diagnosis was identified in 19 of 24 patients, directly guiding therapeutic decisions. Four patients initially thought to have autoimmune cytopenias were subsequently diagnosed with bone marrow failure syndromes: two carried pathogenic variants in *DNAJC21* or *SBDS* consistent with Shwachman-Diamond–like syndrome,[4] and one harbored a *FANCA* mutation consistent with Fanconi anemia. All four underwent hematopoietic stem cell transplantation (HSCT) and were excluded from subsequent analyses.

Among the remaining 20 patients, 14 had multilineage cytopenias, two had isolated AIN (both with monoallelic pathogenic *NFKB1* variants), one had isolated AIHA (*CTLA4* haploinsufficiency), and three had isolated ITP (1 with common variable immunodeficiency [CVID], 1 with systemic lupus erythematosus [SLE], and 1 without an identifiable cause). Clinical and genetic features of these 20 patients are summarized in Table 1.

An underlying genetic variant was identified in 75% (15/20) of patients, conferring a likely predisposition to autoimmunity or autoinflammation in 73% (11/15). Isolated cytopenias were observed in 25% (5/20) of genetically predisposed patients. Among the six patients without any identifiable genetic abnormality, two presented with isolated thrombocytopenia and four with combined anemia and thrombocytopenia (Tables 1 and 2). Genetic diagnoses clustered into four mechanistic categories: (i) disorders driven by excessive type I interferon signaling, (ii) inflammasome activation syndromes, (iii) diseases characterized by imbalance between effector and regulatory T-cell (Treg) activity, and (iv) other rare monogenic disorders. This framework provided a biologic rationale for targeted therapeutic approaches (Figure 1).

(i) Interferonopathy: three patients carried pathogenic variants in *ACP5*, confirming the diagnosis of spondyloenchondrodysplasia with immune dysregulation (SPENCDI), a type I interferonopathy. Ruxolitinib and baricitinib, which inhibit JAK1 and JAK2 downstream of the type I interferon receptor, were used successfully in two patients. The third patient experienced an acute SLE flare with pericarditis and responded to treatment with anifrolumab-fnia, a type I interferon receptor inhibitor approved for SLE.[5]

(ii) Inflammasomopathy: an infant presented with life-threatening AIHA, severe jaundice, recurrent fevers, urticarial-like rash, severe pain, and markedly elevated IL-18 levels. Genetic testing identified a C-terminal *CDC42* variant associated with aberrant inflammasome activation. Treatment with the interleukin-1 receptor antagonist anakinra led to complete and durable resolution of symptoms.[6] Notably, the cytopenia in this patient was secondary to hypersplenism rather than immune-mediated destruction.

(ii) Imbalance between effector and Treg activation: seven patients had IEI associated with dysregulated effector and Treg balance. Three carried a 22q11.2 deletion, a defect in thymic development and function known to predispose to autoimmunity.[7] All were treated with rapamycin, which enhances Treg expansion and promotes immune tolerance.[8-10] Three sisters with variable immune cytopenias were found to have autosomal dominant *NFKB1* loss-of-function variants, a common monogenic cause of CVID.[11] Two of the three responded to rapamycin, achieving normalization of neutrophil and platelet counts. The seventh patient harbored a *FOXP3* variant consistent with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome and presented with aplastic anemia and nephrotic syndrome. After initial therapy with steroids and tacrolimus, he was successfully transitioned to rapamycin following molecular diagnosis; both HSCT and *FOXP3* gene therapy were subsequently offered.

(iv) Conditions with specific or directly targeted therapy: a 28-year-old man with short stature, severe neutropenia,

Table 1. Mechanism-based classification of genetic immune dysregulation underlying therapy-refractory cytopenias.

Patient number/age, yo/sex	Clinical presentation and laboratory findings	Genetic variants	Diagnosis	Targeted treatment and response to therapy
Interferonopathies				
Pat#1/16/M	Severe thrombocytopenia and anemia; fatigue, short stature	Biallelic pathogenic variants in *ACP5* (compound heterozygous; WES trio)	AR SPENCDI - Evans syndrome (warm AIHA, ITP)	Remission on ruxolitinib
Pat#2/4/F	Severe thrombocytopenia and anemia; fatigue, speech delay; SLE flare with pericarditis	Biallelic pathogenic variants in *ACP5* (compound heterozygous; PID panel)	AR SPENCDI - Evans syndrome (warm AIHA, ITP)	Remission on anifrolumab (Saphnelo)
Pat#3/10/F	Severe thrombocytopenia and anemia; fatigue, short stature, speech delay	Biallelic homozygous pathogenic variant in *ACP5* (PID panel)	AR SPENCDI - Evans syndrome (warm AIHA, ITP)	No treatment rendered (posthumous diagnosis)
Inflammasomopathies				
Pat#4/2/F	Bruising, failure to thrive, hepatosplenomegaly, short stature	*De novo* likely pathogenic variant in *CDC42* (WES trio)	AD LOF in *CDC42* - consumptive cytopenia due to hypersplenism	Long-term remission on anakinra
Cytopenias with monogenic disease benefiting from rapamycin				
Pat#5/2/F	Severe neutropenia and thrombocytopenia; frequent infections	Monoallelic pathogenic variant in *NFKB1* (WES trio)	AD LOF in *NFKB1* - Evans syndrome (AIN, ITP)	Remission on rapamycin + monthly IVIG
Pat#6/7/F	Severe neutropenia	Monoallelic pathogenic variant in *NFKB1* (WES trio)	AD LOF in *NFKB1* - severe neutropenia	Partial remission on rapamycin (improved ANC)
Pat#7/11/F	Intermittent mild neutropenia	Monoallelic pathogenic variant in *NFKB1* (WES trio)	AD LOF in *NFKB1* - moderate neutropenia	No treatment rendered
Partial DiGeorge				
Pat#8/0.2/M	Severe thrombocytopenia and anemia; cardiac defect	22q11.2 deletion (*TBX1* hemizygosity; FISH)	Partial DiGeorge - Evans syndrome (warm AIHA, ITP)	Remission on rapamycin
Pat#9/16/M	Severe thrombocytopenia and anemia; speech delay, cardiac defect	22q11.2 deletion (*TBX1* haploinsufficiency; FISH)	Partial DiGeorge - Evans syndrome (warm AIHA, ITP)	Remission on rapamycin
Pat#10/8/M	Severe thrombocytopenia and anemia; developmental delay	22q11.2 deletion (*TBX1* haploinsufficiency; FISH)	Partial DiGeorge - chronic ITP	Durable response on eltrombopag
Regulatory T-cell disorders				
Pat#11/12 /M	Severe thrombocytopenia and anemia; nephrotic syndrome (FSGS)	Monoallelic VUS in *FOXP3* (WES trio)	IPEX syndrome with aplastic anemia	Stable CBC on rapamycin; HSCT and LV-*FOXP3* gene therapy offered
Monogenic diseases predisposing to cytopenia with targeted therapy				
Pat#12/21 /M	Severe neutropenia and thrombocytopenia; recurrent infections	Biallelic pathogenic variants in *G6PC3* (WES trio)	AR *G6PC3* LOF - congenital neutropenia	Stable CBC on SGLT2 inhibitor (empagliflozin)
Pat#13/1/M	Severe thrombocytopenia and anemia; hemorrhagic eye discharge	Monoallelic pathogenic variant in *MAGT1* (PID panel)	X-linked *MAGT1* deficiency - Evans syndrome	Remission on magnesium and eltrombopag
Pat#14/12 /F	Severe anemia; autoimmune enteropathy and Hashimoto thyroiditis	Monoallelic pathogenic variant in *CTLA4* (PID panel)	*CTLA4* haploinsufficiency - warm AIHA	Remission on CTLA-4-Ig (abatacept)

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Patient number/age, yo/ sex	Clinical presentation and laboratory findings	Genetic variants	Diagnosis	Targeted treatment and response to therapy
Others				
Pat#15/14 /F	Severe thrombocytopenia and anemia; arthralgia, hypothyroidism	Negative PID panel	SLE - Evans syndrome (warm AIHA, ITP)	Remission on rapamycin + hydroxychloroquine
Pat#16/15 /F	Severe thrombocytopenia and anemia; oral ulcers	Monoallelic VUS in *TNFRSF6B* (PID panel)	SLE-like syndrome - chronic ITP	Remission on eltrombopag
Pat#17/5/M	Severe thrombocytopenia; arthralgia, fatigue	Negative WES trio	SLE - Evans syndrome (warm AIHA, ITP)	Remission on rapamycin + hydroxychloroquine
Pat#18/18 /M	Thrombocytopenia; no other symptoms	Negative WES trio	CVID - chronic ITP	Remission on rituximab + IVIG
Pat#19/17 /F	Thrombocytopenia and anemia; post-Fontan status	Negative PID panel	Fontan syndrome - Evans syndrome (warm AIHA, ITP)	Remission on rapamycin
Pat#20/17 /F	Thrombocytopenia; depression	Negative WES trio	Chronic ITP	Remission on rapamycin

Comprehensive overview of the genetic and mechanistic categories uncovered in this study. Variants were grouped by dominant immune pathway disturbance type I interferon (INF) signaling, inflammasome activation, effector regulatory T cell (Treg) imbalance, thymic dysfunction, effector T-cell defect, and bone marrow failure syndromes. Each segment lists key representative genes and the corresponding targeted or repurposed therapy applied in affected patients, highlighting the translational value of pathway-guided treatment. Severe thrombocytopenia: platelet counts commonly in the range of 10-50×10^9/L during acute cytopenic episodes. Severe anemia: hemoglobin levels most often between 5 and 6 g/dL during acute cytopenic episodes. ACP5: acid phosphatase 5, tartrate-resistant; AD: autosomal dominant; AIHA: autoimmune hemolytic anemia; AR: autosomal recessive; CDC42: cell division cycle 42; *CTLA4*: cytotoxic T lymphocyte-associated protein 4; CBC: complete blood count; CVID: common variable immunodeficiency; *G6PC3*: glucose-6-phosphatase catalytic subunit 3; F: female; FISH: fluorescence *in situ* hybridization; FSGC: focal segmental glomerulosclerosis, Hb: hemoglobin; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked; ITP: immune thrombocytopenia; IVIG: intravenous immunoglobulin replacement therapy; HSCT: hematopoietic stem cell transplantation; LV-*FOXP3*: lentiviral *FOXP3*; M: male; *MAGT1*: magnesium transporter 1; MMF: mycophenolate mofetil; *NFKB1*: nuclear factor NF-κB subunit 1; LOF: loss of function; PID panel: primary immunodeficiency genetic panel (Invitae, San Francisco, CA, USA); SPENCDI: spondyloenchondrodysplasia with immune dysregulation; SGLT2: sodium-glucose cotransporter 2; Plt: platelet; SLE: systemic lupus erythematosus; TBX1: T-box transcription factor 1; TNFRSF6B: tumor necrosis factor receptor superfamily member 6B; VUS: variant of uncertain significance; yo: year old; WES: whole-exome sequencing; WES trio: WES from patient and both biological parents.

oral ulcers, and recurrent bacterial infections, previously treated with steroids and granulocyte colony-stimulating factor (G-CSF) for presumed autoimmune neutropenia and thrombocytopenia, was found to harbor a pathogenic variant in *G6PC3*, confirming *G6PC3* deficiency, a congenital neutropenia unresponsive to immunosuppression.[12] *G6PC3* deficiency causes neutrophil dysfunction due to accumulation of 1,5-anhydroglucitol-6-phosphate (1,5-AG6P). Reducing 1,5-AG6P via inhibition of the sodium-glucose co-transporter 2 (SGLT2) restores neutrophil counts and function. Accordingly, treatment with the SGLT2 inhibitor empagliflozin led to complete normalization of neutrophil counts and resolution of symptoms.

A 2-year-old boy presenting with ITP and anemia carried a *MAGT1* variant causing a magnesium transporter defect that disrupts intracellular magnesium homeostasis and immune function. Although magnesium supplementation alone was insufficient, his cytopenias stabilized on thrombopoietin mimetics. Another patient with *CTLA4* haploinsufficiency achieved sustained remission of autoimmune hemolytic anemia on CTLA-4-Ig (abatacept).

No pathogenic variants predisposing to immune dysregulation were identified in six of the 20 patients. Two of these fulfilled clinical criteria for SLE and responded well to rapamycin, which suppresses the expansion of proinflammatory double-negative T cells in SLE. A third patient with an SLE-like phenotype harbored a heterozygous variant of uncertain significance (VUS) in *TNFRSF6B*, potentially predisposing to autoimmunity.[13] Another patient with severe ITP met clinical criteria for CVID. The remaining two patients with ITP, one of whom was status post Fontan procedure, achieved sustained remission on rapamycin.

Distinguishing germline from somatic variants in patients (Pat) with (i) a confirmed *de novo* pathogenic mutation (Pat#4) or (ii) a pathogenic variant without available parental testing (Pat#3 and Pat#13) remains challenging without multi-tissue analysis. Age at presentation, clinical severity, and an allele frequency near 50% are insufficient to determine variant origin. Given the variable expressivity and incomplete penetrance often seen in IEI, phenotypic overlap between germline and somatic cases is common.[14] In the patient with a *de novo CDC42* mutation (Pat#3), low-level parental mosaicism cannot be excluded. In the patient carrying a *MAGT1* variant (Pat#13), an allele frequency of 50% in blood is consistent with a hemizygous germline change but does not exclude somatic mosaicism.

Table 2. Clinical, genetic, and therapeutic characteristics of the patient cohort before precision-guided treatment.

Patient number/ age, yo/sex	Clinical features and comorbidities	Other laboratory findings/bone-marrow biopsy	Genetic variants	Diagnosis	Previous therapies
Interferonopathies					
Pat#1/16/M	Fatigue, short stature	No BMB performed	Biallelic pathogenic variants in *ACP5* (WES trio)	AR SPENCDI	Steroids, rituximab ×4, MMF, rapamycin, bortezomib, TPO-RA
Pat#2/4/F	Fatigue, short stature, speech delay; acute SLE flare with pericarditis	Normocellular marrow with trilineage hematopoiesis	Biallelic pathogenic variants in *ACP5* (PID panel)	AR SPENCDI	Steroids + azathioprine for SLE
Pat#3/10//F	Fatigue, short stature, speech delay	Hypercellular marrow with erythroid hyperplasia	Biallelic pathogenic variant in *ACP5* (PID panel)	AR SPENCDI	Steroids
Inflammasomopathies					
Pat#4/2/F	Bruising, failure to thrive, hepatosplenomegaly, developmental delay	Normocellular marrow with maturing trilineage hematopoiesis	*De novo* likely pathogenic variant in *CDC42* (WES trio)	AD LOF in *CDC42*	High-dose steroids
Cytopenias with monogenic disease benefiting from rapamycin					
Pat#5/2/F	Frequent infections, easy bruising, fatigue	Normocellular marrow with trilineage hematopoiesis	Monoallelic pathogenic variant in *NFKB1* (WES trio)	AD LOF in *NFKB1*	-
Pat#6/7/F	No clinical symptoms	No BMB performed	Monoallelic pathogenic variant in *NFKB1* (WES trio)	AD LOF in *NFKB1*	-
Pat#7/11//F	No clinical symptoms	No BMB performed	Monoallelic pathogenic variant in *NFKB1* (WES trio)	AD LOF in *NFKB1*	No treatment rendered
Partial DiGeorge					
Pat#8/0.2/M	Bleeding, fatigue, cardiac defect	Normocellular marrow with myeloid left shift and ↑ hematogones	22q11.2 deletion (*TBX1* hemizygosity; FISH)	Partial DiGeorge	Steroids, IVIG
Pat#9/16//M	Bleeding, fatigue, cardiac defect, speech delay	No BMB performed	22q11.2 deletion (*TBX1* haploinsufficiency; FISH)	Partial DiGeorge	Steroids, IVIG
Pat#10/8//M	Bleeding, developmental delay, learning differences	No BMB performed	22q11.2 deletion (*TBX1* haploinsufficiency; FISH)	Partial DiGeorge	Steroids, IVIG (DLT with rapamycin oral ulcers)
Regulatory T-cell disorders					
Pat#11/12/M	Bruising, fatigue, nephrotic syndrome (FSGS)	Markedly hypocellular marrow	Monoallelic VUS in *FOXP3* (WES trio)	IPEX syndrome	IVIG, steroids, eltrombopag
Monogenic diseases predisposing to cytopenia					
Pat#12/21/M	Recurrent infections, short stature, mouth ulcers	Normocellular marrow with relative myeloid hyperplasia (G-CSF)	Biallelic pathogenic variants in *G6PC3* (WES trio)	AR *G6PC3* LOF	Steroids, G-CSF

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Patient number/ age, yo/sex	Clinical features and comorbidities	Other laboratory findings/bone-marrow biopsy	Genetic variants	Diagnosis	Previous therapies
Pat#13/1//M	Bleeding, hemorrhagic eye discharge	Normocellular marrow with trilineage hematopoiesis	Monoallelic pathogenic variant in *MAGT1* (PID panel)	X-linked *MAGT1* deficiency	-
Pat#14/12/F	Hashimoto thyroiditis, autoimmune enteropathy, short stature	No BMB performed	Monoallelic pathogenic variant in *CTLA4* (PID panel)	*CTLA4* haploinsufficiency	-
Others					
Pat#15/14/F	Arthralgia, hypothyroidism	ANA positive; no BMB	Negative PID panel	SLE	Steroids, IVIG
Pat#16/5/F	Fatigue, oral ulcers	ANA positive; no BMB	Monoallelic VUS in *TNFRSF6B* (PID panel)	SLE-like syndrome	Steroids, IVIG
Pat#17/5//M	Arthralgia, fatigue	ANA positive; no BMB	Negative WES trio	SLE	Steroids, IVIG, rituximab ×4
Pat#18/18/M	No clinical symptoms	No BMB performed	Negative WES trio	CVID	Steroids
Pat#19/17/F	Depression; post-Fontan status	Normocellular marrow with trilineage hematopoiesis	Negative PID panel	Fontan syndrome	Steroids
Pat#20/17/F	Depression	No BMB performed	Negative WES trio	Chronic ITP	Steroids, IVIG, rituximab ×4, MMF, eltrombopag

Comprehensive overview of the diagnostic evaluation of 20 children with therapy-refractory cytopenias. For each case, age, clinical presentation, laboratory findings, bone marrow morphology, and identified genetic variants are shown, together with relevant comorbidities and prior therapies. Variants were identified by primary immunodeficiency genetic panel (Invitae, San Francisco, CA, USA) (PID panel) or whole-exome sequencing (WES) and classified according to American College of Medical Genetics and Genomics (ACMG) guidelines. The table highlights the diagnostic heterogeneity of cytopenias and underscores how genetic testing clarified disease mechanism and therapeutic direction. ACP5: acid phosphatase 5, tartrate resistant; AD: autosomal dominant; AIHA: autoimmune hemolytic anemia; ANA: antinuclear antibody; AR: autosomal recessive; BMB: bone marrow biopsy; CBC: complete blood count; CDC42: cell division cycle 42; *CTLA4*: cytotoxic T lymphocyte-associated protein 4; CVID: common variable immunodeficiency; DAT: direct antiglobulin test; DLT: dose-limiting toxicity; G-CSF: granulocyte colony-stimulating factor; *G6PC3*: glucose-6-phosphatase catalytic subunit 3; F: female; Hb: hemoglobin; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked; ITP: immune thrombocytopenia; IVIG: intravenous immunoglobulin replacement therapy; HSCT: hematopoietic stem cell transplantation; LOF: loss of function; LV-*FOXP3*: lentiviral *FOXP3*; M: male; *MAGT1*: magnesium transporter 1; MDS: myelodysplastic syndrome; MMF: mycophenolate mofetil; *NFKB1*: nuclear factor NF-κB subunit 1; SPENCDI: spondyloenchondrodysplasia with immune dysregulation; SGLT2: sodium-glucose cotransporter 2; Plt: platelet; SLE: systemic lupus erythematosus; *TBX1*: T-box transcription factor 1; TNFRSF6B: tumor necrosis factor receptor superfamily member 6B; TPO-RA: thrombopoietin receptor agonist; VUS: variant of uncertain significance; yo: year old; WES trio: WES from patient and both biological parents.

Notably, somatic *MAGT1* variants have not been reported. Genetic causes of immune dysregulation should be systematically considered in children with therapy-refractory cytopenias, as molecular diagnoses carry prognostic significance and directly inform treatment. Patients with identified monogenic disorders experienced substantial benefit from targeted therapies, which were generally well tolerated. Those with primary immune regulatory diseases (PIRD) involving effector-Treg imbalance or thymic dysfunction improved with mTOR inhibition; patients with interferonopathies responded to JAK inhibitors; and those with inflammasomopathies achieved remission with IL-1 blockade. In select ultra-rare conditions, such as *G6PC3* deficiency, repurposed therapies like SGLT2 inhibitors produced transformative outcomes.

Hadjadj *et al*. demonstrated that pediatric Evans syndrome is associated with a high frequency of potentially damaging variants in immune-related genes.[16-20] In a national cohort of 203 children with early-onset Evans syndrome, systematic genetic testing of 80 consecutive cases revealed that 65% carried pathogenic or likely pathogenic variants. These were identified in genes associated with autoimmune lymphoproliferative syndrome (e.g., *FAS*), primary immunodeficiency (*CTLA4*, *LRBA, STAT3*), or genes not previously linked to autoimmunity (e.g., *KRAS*).[18] Consistent with our findings, patients with such variants exhibited more severe disease, required more intensive therapy, and frequently presented with additional immunopathologic

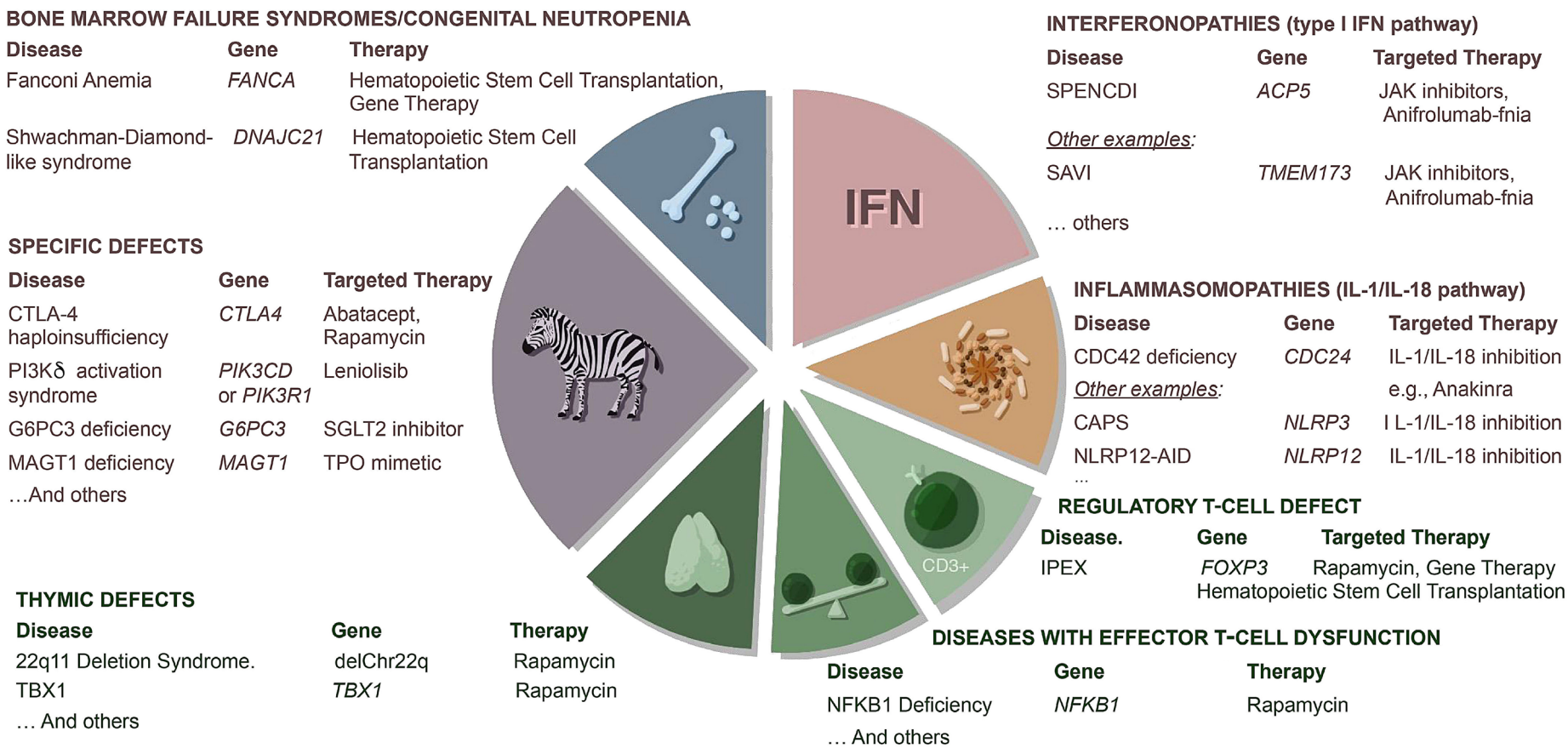

Figure 1. Genetic immune diseases in the hematologist's waiting room. Breakdown of genetic variants identified in our patient cohort according to disease mechanism and corresponding targeted therapies. Comprehensive overview of the diagnostic evaluation of 20 children with therapy-refractory cytopenias. For each case, age, clinical presentation, laboratory findings, bone-marrow morphology, and identified genetic variants are shown, together with relevant comorbidities and prior therapies. Variants were identified by primary immunodeficiency panel (PID) or whole-exome sequencing (WES) and classified according to American College of Medical Genetics and Genomics (ACMG) guidelines. The table highlights the diagnostic heterogeneity of cytopenias and underscores how genetic testing clarified disease mechanism and therapeutic direction. All variants were classified according to ACMG guidelines. ACP5: acid phosphatase 5, tartrate resistant; CAPS: cryopyrin-associated periodic syndrome; CDC42: cell division cycle 42; *CTLA4*: cytotoxic T lymphocyte-associated protein 4; *G6PC3*: glucose-6-phosphatase catalytic subunit 3; F: female; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked; *MAGT1*: magnesium transporter 1; NLRP12-AID: NLRP12 associated autoinflammatory disease; *NFKB1*: nuclear factor NF-κB subunit 1; SAVI: STING-associated vasculopathy with onset in infancy; SPENCDI: spondyloenchondrodysplasia with immune dysregulation; SGLT2: sodium-glucose cotransporter 2; SLE: systemic lupus erythematosus; *TBX1*: T-box transcription factor 1.

features compared to those without identified variants. Long-term immunomodulation is often required to maintain remission, underscoring the need for coordinated multidisciplinary care among immunologists, hematologists, geneticists, and transplant specialists. As genomic testing becomes routine, the number of patients with genetic immune disorders identified in hematology clinics will continue to grow. Broad implementation of these tools will expand the hematologist's therapeutic repertoire. Currently available testing is aimed at identifying germline variants in IEI-defining genes,[15] however, detecting IEI variants on a clonal level could become the next diagnostic frontier, rendering "idiopathic" immune cytopenias a diagnosis of the past.

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No conflicts of interest to disclose.

Contributions

YG and KGW saw and assessed patients, performed research and wrote the manuscript. BS, LR, BG, DS, MC and DBL saw patients. AMC, JDH and RB revised manuscript.

Data-sharing statement

The authors can make their original data and protocols available to other investigators without unreasonable restrictions except for de-identifying patient's information.

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