# Evaluation of Anemia in Pediatric Population in the Era of Molecular Diagnosis

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# Learning Objectives

Formulate a differential diagnosis and recognize age-specific clinical and laboratory clues that guide the initial evaluation of anemia in pediatric populations using a few example cases

Identify uncommon causes of anemia, including hereditary hemolytic anemias and bone marrow failure syndromes

Select appropriate clinically available screening and confirmatory tests, including their indication and common pitfalls

Understand the clinical utility of molecular testing and correctly interpret molecular results in the clinical context

# Case Study #1

- 3-year-old, Caucasian girl, lacking regular well-child visits
  - » anemia with reticulocytosis and splenomegaly
- Peripheral blood smear
  - » many spherocytes
- Past history
  - » hyperbilirubinemia in the newborn
- Anemia and splenomegaly worsened
  - » parents declined immunizations and transfusions
- Extensive testing—negative
- Genetic testing was permitted
  - » after dilated cardiomyopathy developed

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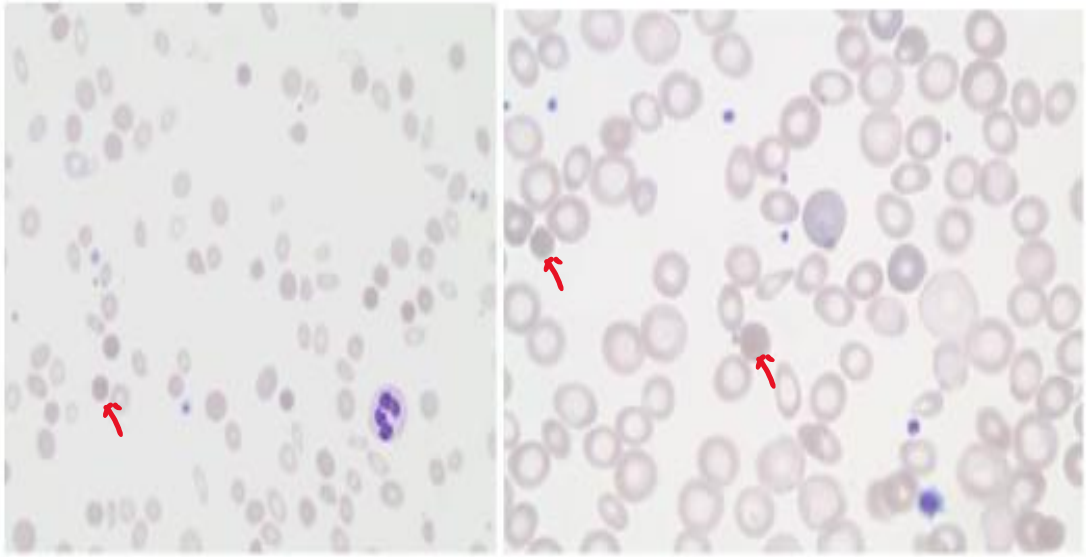
Check for updates

Research Article Volume 8 Issue 5

**Novel mutation in SPTA 1 gene associated with severe hemolytic anemia**

James Polega,[1] Jennifer Stumph,[2] Archana Agarwal,[3] Chi L Braunreiter[4]



# Case Study #2

- 11-year-old male with lifelong hemolytic anemia, failure to thrive, no family history
- DAT negative
- Negative osmotic fragility and EMA band 3 testing
- Negative G6PD testing
- Unremarkable peripheral smear findings
- Genetic testing performed

# Anemia in Pediatric Population

WHO — 40% of pediatric population <5 yrs of age

Anemia is defined by hemoglobin (Hb), hematocrit, or red blood cell (RBC) count—lower than the normal age and sex-adjusted ranges

Use of appropriate ranges when defining anemia is important

Genome-wide association studies — individual genetic variation (PMID: 31097152)

Etiology of pediatric anemia is multifactorial

# Classification of Anemia

## I. Morphologic (MCV-based)

- Microcytic: Iron deficiency, thalassemia, sideroblastic anemia, Anemia of chronic disorder (ACD)
- Normocytic: Acute blood loss, hemolysis, anemia of chronic disorder, marrow failure
- Macrocytic: B12/folate deficiency, congenital dyserythropoetic anemia (CDA), liver disease, alcohol, drugs

## II. Pathophysiologic

- Decreased production
- Increased destruction (hemolysis): hemolytic anemia
  - Acquired
  - Inherited
- Blood loss

## III. Reticulocyte-based

- Low retic:
  - Vitamin B12 and folate def
  - Bone marrow failure
    - Aplastic anemia
    - Diamond-Blackfan anemia
    - Shwachman-Diamond syn
    - Dyskeratosis congenita
    - MDS
    - Drug induced
  - CDA
  - Hypothyroidism
  - Copper def
- High retic: hemolysis or blood loss

# STEP 3: MCV-BASED DIFFERENTIAL DIAGNOSIS | Pediatric Anemia Workup

## MICROCYTIC

*MCV < 80 fL*

### DIFFERENTIAL DIAGNOSIS

- Iron Deficiency Anemia
- Thalassemia
- Anemia of Chronic disease
- Sideroblastic Anemia

### ADDITIONAL TESTS

- Serum ferritin, iron, TIBC
- Hemoglobin electrophoresis
- Molecular tests

**Thalassemia**

- The RBC count in thalassemia is usually more than 5.0 x 106/µL
- MCV usually less than 70 in
- The RDW is usually in the normal range

**Iron deficiency anemia**

- Low RBC count
- MCV usually more than 70
- RDW is usually more than 17

## NORMOCYTIC

*MCV 80–100 fL*

### DIFFERENTIAL DIAGNOSIS

- Hemolytic Anemia
- Acute Blood Loss
- Aplastic Anemia
- Transient Eryth. Aplasia
- Mixed deficiency
- Early iron deficiency

### ADDITIONAL TESTS

- Coombs test (DAT/IAT)
- LDH, haptoglobin, bilirubin
- G6PD/pyruvate kinase assay
- Osmotic fragility, band 3
- Hb electrophoresis
- Bone marrow biopsy*
- (*if aplasia suspected)
- Molecular tests

## MACROCYTIC

*MCV > 100 fL*

### DIFFERENTIAL DIAGNOSIS

- Folate and Vitamin B12 Deficiency
- Diamond-Blackfan Anemia
- Hypothyroidism
- Liver Disease
- Medications (MTX, AZT)

### ADDITIONAL TESTS

- Serum folate, B12 levels
- Methylmalonic acid, Homocysteine
- Thyroid function (TSH)
- Liver enzymes (AST/ALT)
- Reticulocyte count
- Bone marrow biopsy*
- Molecular tests

*Note: Always correlate with clinical findings. Consider bone marrow biopsy if diagnosis unclear after initial workup*

# Causes of Hemolytic Anemia in Pediatric Age Group

## Intrinsic (Corpuscular)

### Membrane Defects

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Hereditary pyropoikilocytosis
- Hereditary stomatocytosis

### Enzyme Deficiencies

- G6PD deficiency
- Pyruvate kinase deficiency
- Hexokinase deficiency

### Hemoglobinopathies

- Sickle cell disease (HbSS)
- HbSC disease
- β-thalassemia major
- Unstable hemoglobins

## Extrinsic (Extracorpuscular)

### Immune-Mediated

- Autoimmune hemolytic anemia (warm)
- Cold agglutinin disease
- Hemolytic disease of newborn
- Drug-induced hemolysis
- Transfusion reaction

### Microangiopathic (MAHA)

- Hemolytic uremic syndrome (HUS)
- Thrombotic thrombocytopenic purpura
- DIC
- Kasabach-Merritt syndrome

### Infectious

- Malaria, Babesiosis, Clostridial sepsis

## Mixed / Special Contexts

### Oxidative Stress

- G6PD deficiency (infection/drugs/fava beans)
- Favism

### Mechanical / Physical

- March hemoglobinuria
- Prosthetic heart valves
- Burns/thermal injury

### Toxic / Chemical

- Lead poisoning, copper toxicity, snake venom

### Neonatal / Special

- Physiologic jaundice of newborn, ABO incompatibility

# Approach to the Anemic Child

- History, family history, and physical examination
- Symptoms and signs vary based on the duration and severity of anemia
  - » Acute: hypoxia, hypovolemic shock, congestive heart failure
  - » Chronic: pallor, dyspnea, fatigue, exercise intolerance, dizziness, anorexia, and syncope, jaundice, dark urine, poor growth, failure to thrive
  - » Asymptomatic

# Laboratory Investigation: Overview

**01**

### Complete Blood Count (CBC)

Assess anemia severity; identify concurrent leukocyte and platelet abnormalities suggesting systemic illness

**02**

### Erythrocyte Indices

MCV, MCH, reveal microcytosis (hemoglobinopathy/iron deficiency) or elevated MCHC (membrane disorder)

**03**

### Peripheral Blood Smear

Morphological clues: spherocytes, elliptocytes, schistocytes, target cells, inclusions

**04**

### Reticulocyte Count & DAT

Distinguish hemolytic vs. aplastic cause; DAT identifies immune-mediated hemolysis

**05**

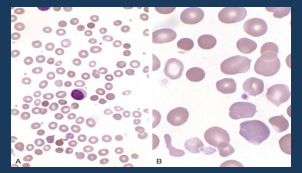
### Molecular Genetic Analysis

Gene panels, whole-exome sequencing for inherited anemias—increasing diagnostic precision

# Common Peripheral Smear Findings

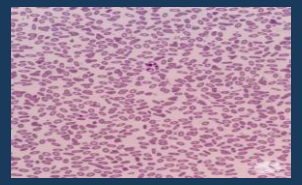
## Spherocytes

Hereditary spherocytosis
Autoimmune hemolytic anemia



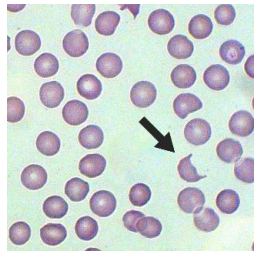
## Elliptocytes

Hereditary elliptocytosis, hereditary pyropoikilocytosis



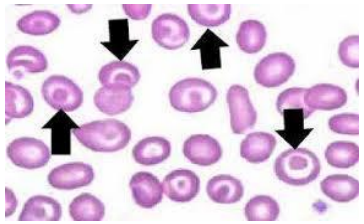
## Schistocytes and Helmet Cells

Microangiopathic hemolytic anemia
(HUS, TTP, DIC)



## Target Cells

**Hemoglobinopathies**
**Liver disease · Post-splenectomy**



## Inclusions

Malaria , Babesiosis

# Reticulocyte Count and DAT

## Reticulocyte Count

### ↑ Elevated

Increased erythropoietic response
→ Hemolysis or blood loss
(Bone marrow is compensating)

### ↓ Low/Inappropriately Low

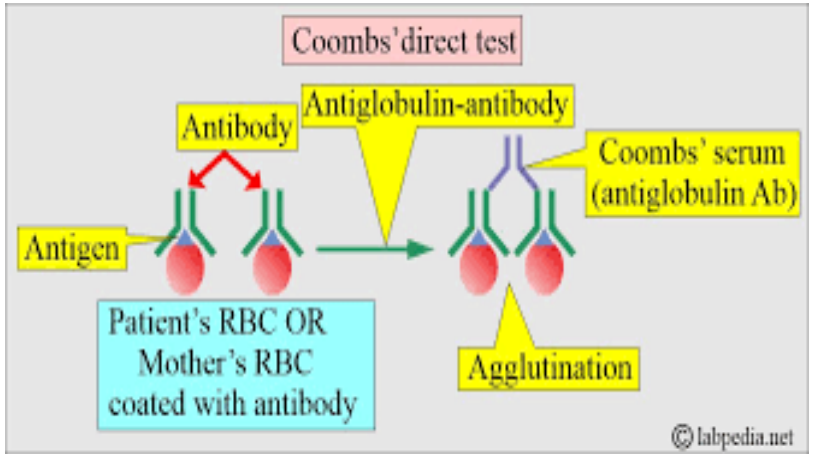
Inadequate erythropoietic response
→ Bone marrow failure or aplasia
(Especially alarming relative to anemia degree)
→ likely would need bone marrow biopsy

## Direct Antiglobulin Test (DAT)/Coombs Test

**Positive DAT**
→ Immune-mediated hemolysis

**Negative DAT + hemolysis + hyperbilirubinemia**
→ Intrinsic erythrocyte defect (membrane, enzyme, hemoglobin)

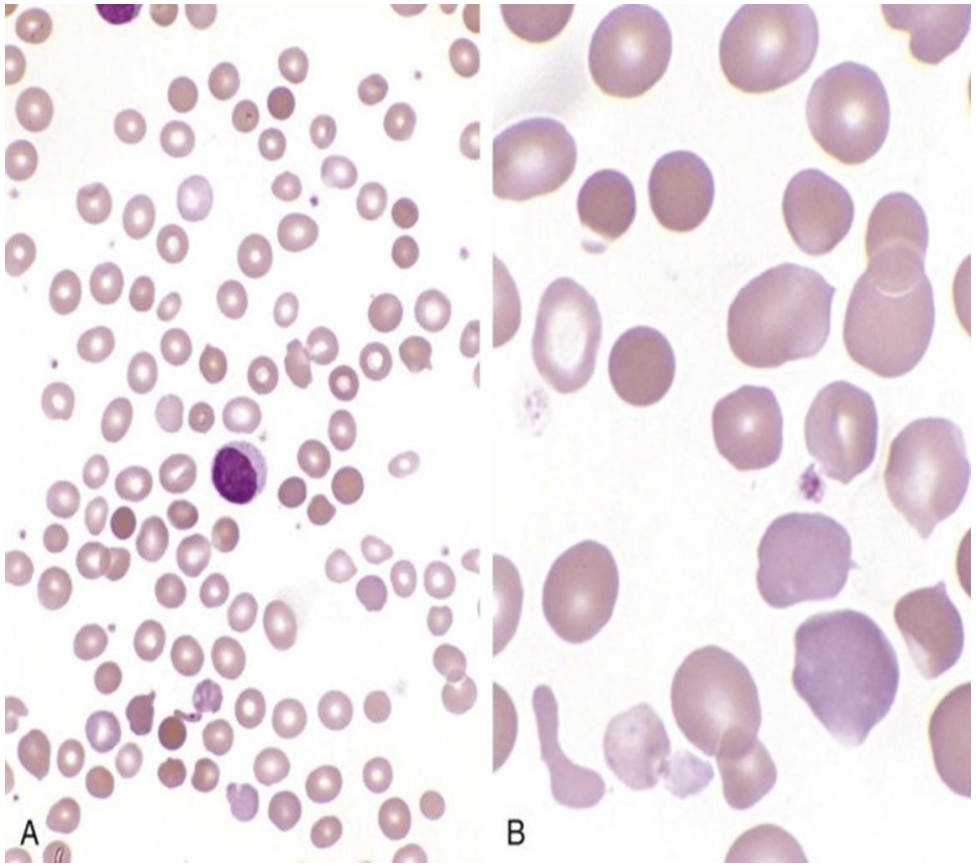
**Negative DAT + normocytic + no hemolysis**
→ Acute or chronic blood loss—further workup indicated



Bryce Canyon

# Hereditary Spherocytosis (HS)

- Common inherited hemolytic anemia (1/1000-1/3000)
- All ethnic groups; common in Northern Europeans
- AD (75%) and AR (25%)
- Diagnosed only in one-third of affected infants during the first year of life
  - » Can cause severe hemolysis



# HS: Clinical Presentation

| | |
|---|---|
| 60%—intermediate-severity phenotype | • Moderate hemolysis (Hb 8-11 g/dL)<br>• Reticulocyte count > 8%<br>• Normal hemoglobin at birth that may sharply and transiently decline in the first 3 weeks of life |
| 20%—mildly affected/asymptomatic | • May not be identified until there is a hemolytic crisis in childhood<br>• Often triggered by viral infection<br>• May be diagnosed due to aplastic crisis with parvovirus B19 |
| 20%—have severe disease | • Usually, AR inheritance due to abnormality of α-spectrin |

# Hereditary Elliptocytosis (HE)

Autosomal dominant disorder of horizontal membrane protein interactions causing permanent elliptical RBC shape. Incidence ~1:2,000–4,000. Spectrum ranges from asymptomatic carrier to severe hemolytic anemia.

## Genetic Defects

**α-Spectrin (SPTA1) 65%**

Point mutations in αI spectrin domain → impaired dimer–dimer self-association at head contact site

**β-Spectrin (SPTB) 30%**

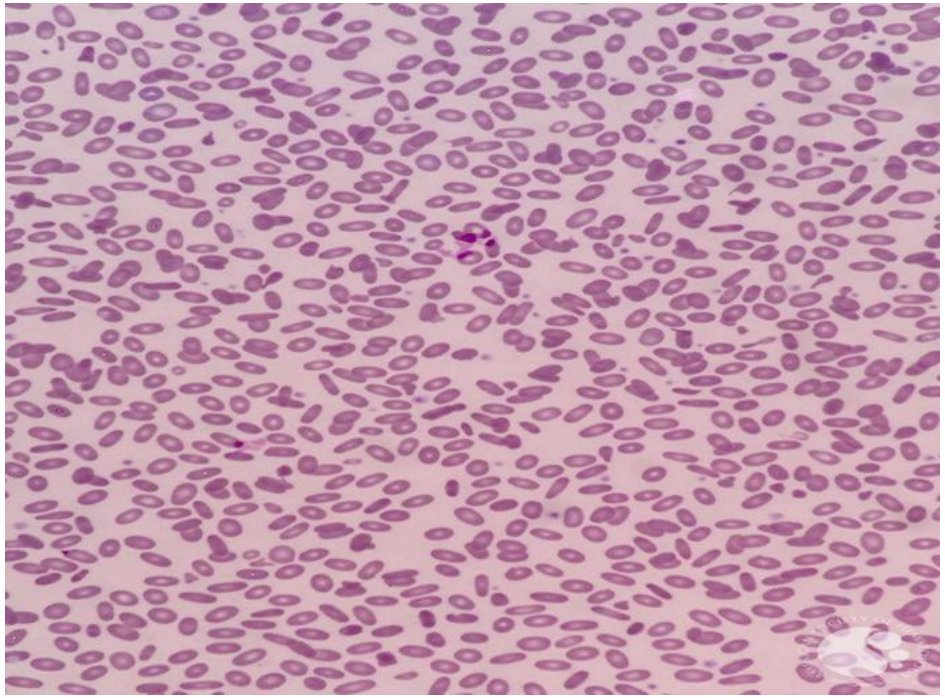
Mutations near N-terminus disrupt heterodimer nucleation site

**Protein 4.1R (EPB41) ~5%**

Deletions in spectrin-actin binding domain destabilize junctional complex

## Pathophysiology

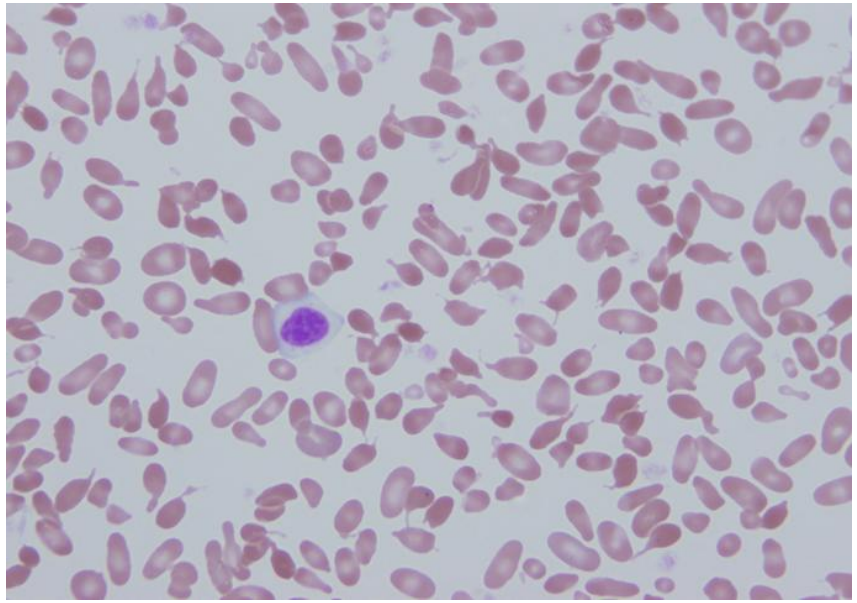
1 **Spectrin dimer self-association defect**
Mutant spectrin dimers fail to assemble into tetramers → weakened horizontal lattice skeleton



*Key smear finding: ≥25% elliptocytes/ovalocytes | Osmotic fragility: normal or slightly increased | Inheritance: Autosomal Dominant*

# Hereditary Pyropoikilocytosis (HPP)

Severe autosomal recessive variant of HE. Compound heterozygous state: one mutant α-spectrin allele + low-expression α-spectrin allele (αLELY). Results in extreme spectrin deficiency, marked thermal instability, and severe hemolysis in infancy.



## Pathophysiology

**1 — Severely deficient spectrin tetramers**

Compound het → only ~40% normal spectrin; tetramers barely form

**2 — Thermal instability of spectrin**

Spectrin denatures at 45–46°C; RBCs fragment on heating (pyropoikilocytosis = pyrexia-like fragmentation)

**3 — Extreme mechanical fragility**

Skeleton collapses under physiologic shear → budding, fragmentation into microspherocytes, elliptocytes, triangulated cells

**4 — Severe hemolytic anemia in infancy**

MCV 50–60 fL; marked poikilocytosis; may require transfusions. Improves with age as HbF→HbA transition strengthens membrane

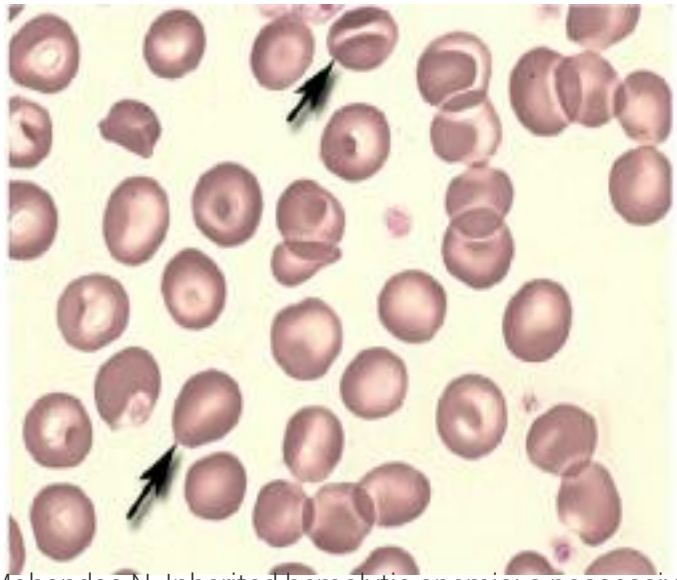
**5 — Transition to typical HE in adulthood**

As red cell volume matures, smear appearance evolves toward elliptocytosis; severity decreases

*Smear: microspherocytes, budding fragments, triangulated cells, elliptocytes | MCV 50–60 fL | RBC fragmentation at 45–46°C | AR inheritance*

# Dehydrated Hereditary Stomatocytosis (DHST)

- Also known as hereditary xerocytosis—most common inherited red cell cation permeability disorders
- Gain-of-function mutations in ***PIEZO1*** → prolonged channel opening → excess $K^+$ efflux > $Na^+$ influx
- High MCHC, and **resistant** osmotic fragility are characteristics
- Hemoglobin and hematocrit values are often normal (compensated hemolysis) and patient blood smears are surprisingly normal, featuring mostly a few target
- Unexplained iron overload



Mohandas N. Inherited hemolytic anemia: a possessive beginner's guide. Hematology Am Soc Hematol Educ Program. PMID: 30504335;

Albuisson J, et al. Dehydrated hereditary stomatocytosis linked to gain-of-function mutations in mechanically activated PIEZO1 ion channels. Nat Commun. 2013;4:1884.

# Enzyme Deficiency

# Enzymopathies

**Table 1.** Clinical phenotypes and associated genes in inherited hemolytic anemia.

| Clinical phenotypes | Genes | Location | Inheritance |
|---|---|---|---|
| RBC enzymopathies | | | |
| G6PD deficiency | *G6PD* | Xq28 | XR |
| Pyruvate kinase deficiency | *PKLR* | 1q22 | AR |
| Enolase deficiency | *ENO1* | 1p36.23 | AD |
| Adenylate kinase deficiency | *AK1* | 9q34.11 | AR |
| Glucose phosphate isomerase deficiency | *GPI* | 19q13.11 | AR |
| Pyrimidine 5′ nucleotidase (UMPH1) deficiency | *NT5C3A* | 7p14.3 | AR |
| Gamma-glutamylcysteine synthetase deficiency | *GCLC* | 6p12.1 | AR |
| Glutathione peroxidase deficiency | *GPX1* | 3p21.31 | AR |
| Glutathione reductase deficiency | *GSR* | 8p12 | AR |
| Glutathione synthetase deficiency | *GSS* | 20q11.22 | AR |
| Hexokinase deficiency | *HK1* | 10q22.1 | AR |
| Bisphophoglycerate mutase deficiency | *BPGM* | 7q33 | AR |
| Phosphoglycerate kinase 1 deficiency | *PGK1* | Xq21.1 | XR |
| Triosephosphate isomerase deficiency | *TPI1* | 12p13.31 | AR |

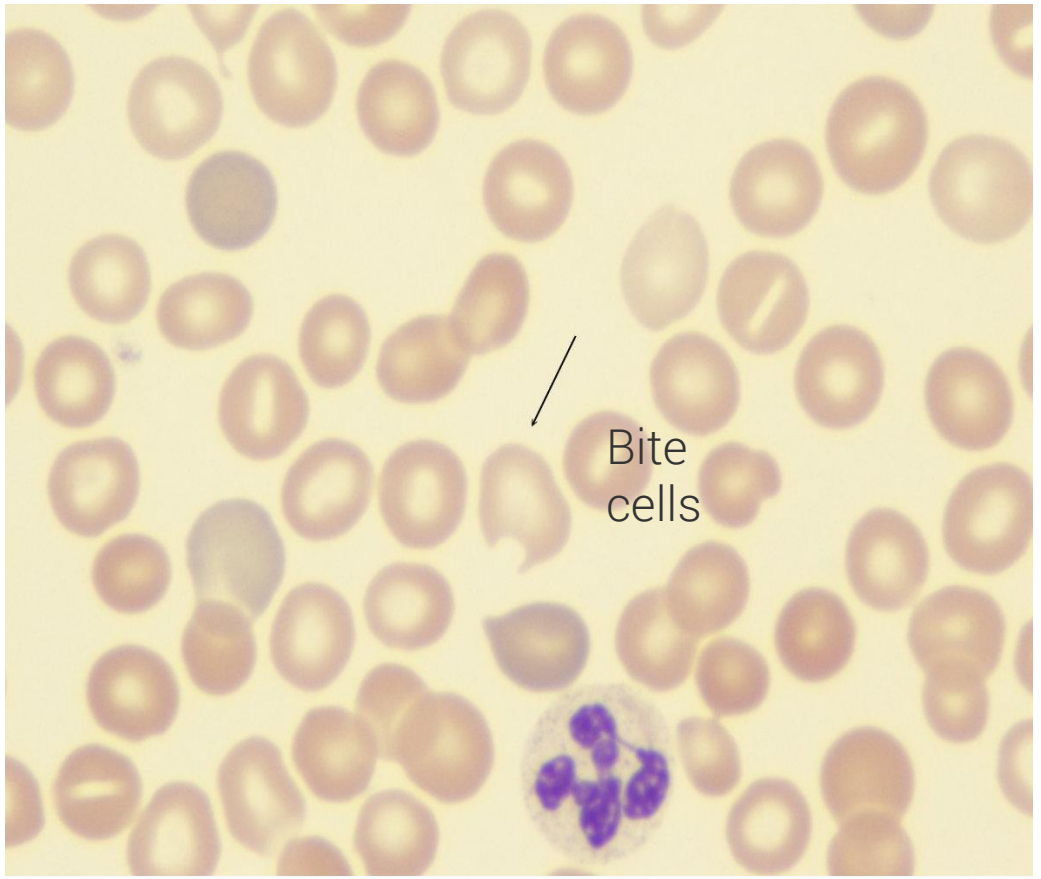
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.

PMID: 28698843

# Glucose-6-Phosphate Dehydrogenase Deficiency

- Most common human enzyme defect! >400-600 million people
- X-linked
  - » prevalent in populations with endemic malaria
- Enzyme deficiency leading to NADPH-glutathione (GSH) depletion
  - » Oxidative stress, hemolysis
- *Diagnosis*
  - » G6PD (false negative with reticulocytes)
  - » Heinz bodies (denatured Hb) and bite cells in PB smear

# Heinz (denatured Hb) and bite cells



# Pyruvate Kinase Deficiency

- Common cause of congenital nonspherocytic chronic hemolytic anemia
- Autosomal recessive disorder
- Found in north Europeans; high frequency in Pennsylvania Amish population
- Diagnosis
  - Direct measurement of enzyme activity in RBCs-↓ PK activity
- Severe disease may require frequent red cell transfusion throughout infancy and into adulthood.
- Splenectomy ameliorates the severity of hemolysis

- Management: Supportive
- Small molecule allosteric PK activator, Mitapivat AG-348
- FDA approved in 2022; Adults with PK deficiency
- Mitapivat is not yet FDA-approved for children with pyruvate kinase deficiency, but Phase 3 trials (ACTIVATE-Kids and ACTIVATE-KidsT) have shown positive results, demonstrating improved hemoglobin levels and reduced hemolysis in patients aged 1 to <18 years.
- Will likely be approved

# Unstable Hemoglobins

- Due to structural abnormalities of the α- or β-globin chain
  - » Hemoglobin F-Poole (gamma globin)
- Underappreciated and underdiagnosed cause of dominantly inherited
- Leads to precipitates of heme and globin chain fragments forming Heinz bodies
- Diagnosis:
  - » Isopropanol precipitation testing
    - hemolysate is incubated at 37 degrees C for 20 minutes and examined for turbidity. There is no turbidity with normal hemoglobins
    - Hb F can interfere with testing
  - » Not all unstable Hbs are associated with abnormally migrating bands on Hb electrophoresis
  - » Molecular testing can verify the diagnosis.
- Treatment is supportive.

# Anemia Due to Hereditary Bone Marrow Failure

## 1.Unilineage defect

Erythroids: Diamond-Blackfan anemia,
Congenital dyserythropoietic anemia

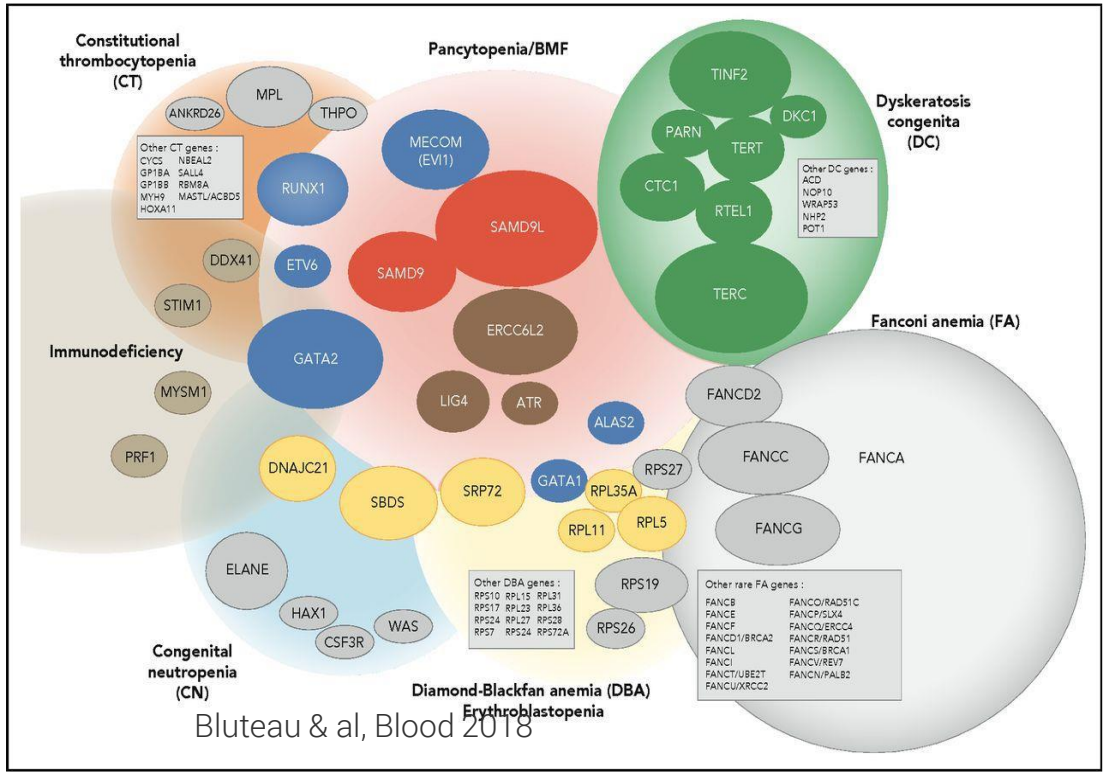
## 2. Trilineage defect

Fanconi anemia (FA)

Shwachman-Diamond syndrome (SDS)

Dyskeratosis congenita (DC)

- Bone marrow failure due to germline variants
- Often have extra-hematological features unique to the syndromes




Bluteau & al, Blood 2018

# Congenital Dyserythropoietic Anemia

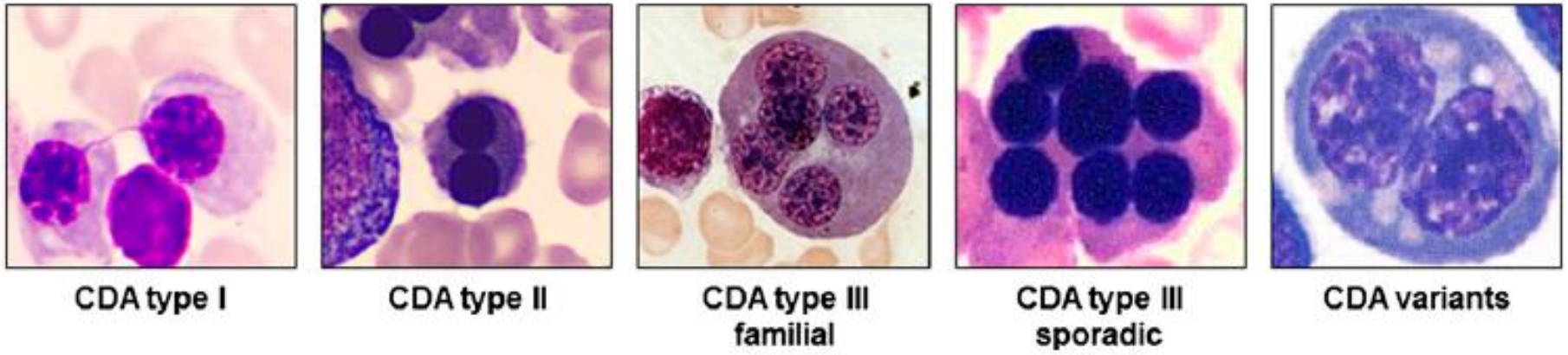



**Figure 1. Pathognomonic marrow erythroblasts.** The BM erythroblasts morphology (light microscopy) of different types of CDA is shown. See Table 1 for the description.

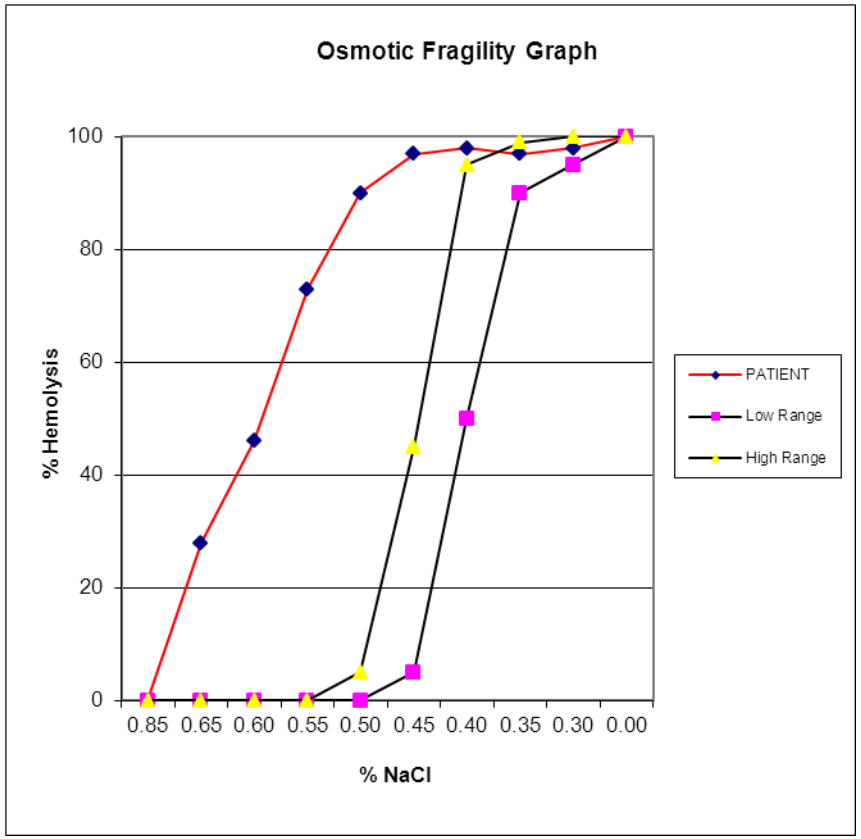
**Table 1. Characteristic features of different types of CDA**

| CDA type | I | II | III Familial | III Sporadic | Variants |
|---|---|---|---|---|---|
| Inheritance | Autosomal recessive | Autosomal recessive | Dominant | Variable | Autosomal dominant or X linked or recessive |
| Cases reported | >300 | >450 | 2 families | <20 | ~70 |
| BM morphology (light microscopy) | Abnormal chromatin structure, chromatin bridges | Binuclearity, multinuclearity of mature erythroblasts | Giant multinucleated erythroblasts | Giant multinucleated erythroblasts | CDA I–like, CDA II–like, others |
| BM EM findings | "Spongy" heterochromatin, invagination of cytoplasm into the nucleus | Peripheral cysternae beneath the plasma membrane | Clefts in heterochromatin, autophagic vacuoles, intranuclear cisternae | Various | Various |
| Mutated gene | *CDAN1*, *C15ORF41* | *SEC23B* | *KIF23* | Unknown | *KLF1*, *GATA-1*, unknown |
| Associated dysmorphology/organ involvement | Skeleton | Variable, rare | Monoclonal gammopathy, myeloma, angioid streaks | Variable | CNS, others |

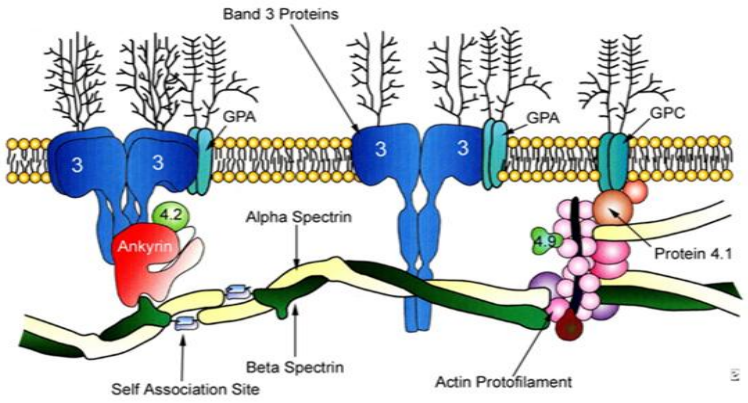
Iolascon et al. Blood, 2013

# Diagnosis of RBC Membrane Disorders

- Peripheral blood smear: elliptocytes, spherocytes, stomatocytes, and fragmented cells (in HPP)
- Osmotic fragility
  - » Sensitive but not  specific
  - » Measures the in vitro lysis of RBCs suspended in solutions of decreasing osmolarity
  - »  Spherocytes are characterized by membrane loss and less redundancy



- RBC membrane

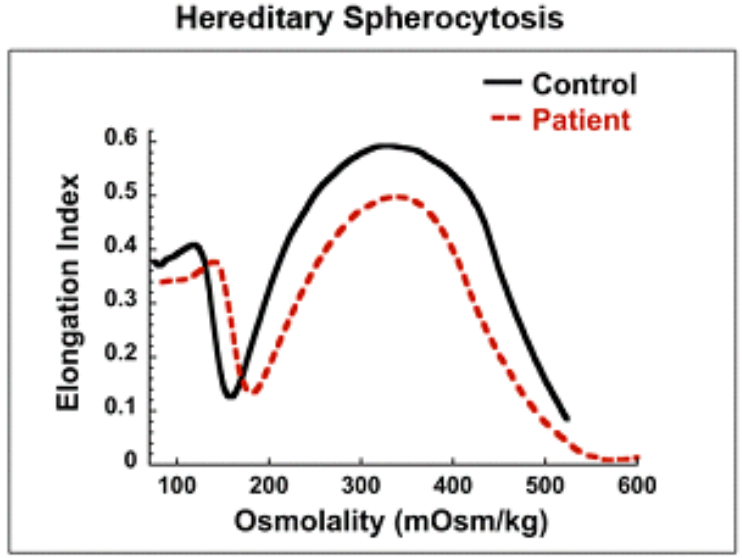


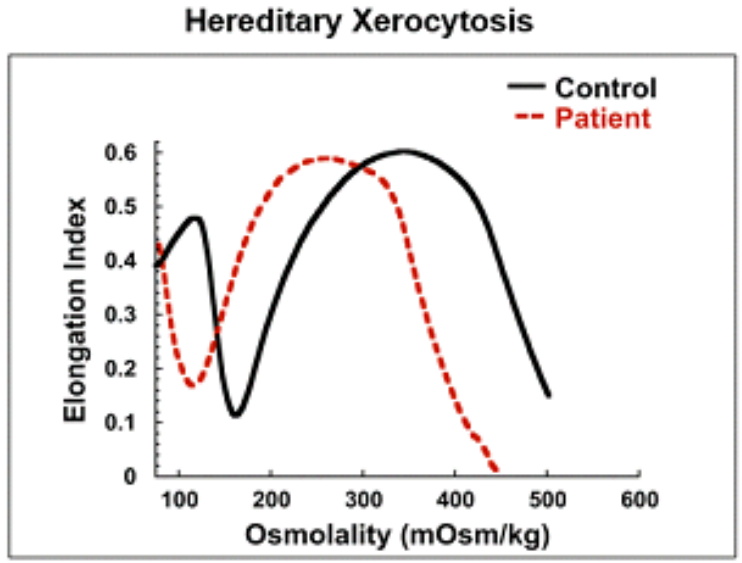

## EMA Band 3

- Flow cytometry
  - » Measures the fluorescent intensity of intact red blood cells labeled with EMA (eosin-5-maleimide)
  - » EMA binds specifically with band 3 protein
  - » EMA binding is affected by all sorts of membrane protein abnormalities
  - » Greater than 90-95% sensitive and specific for HS
  - » Positive in CDA type 2
    - **decrease in fluorescence** because of the **defective configuration of the band 3 protein** reduces its affinity for the EMA dye.

# Ektacytometry

- Briefly, RBCs are subjected to a defined value of shear stress and an osmotic gradient
- Laser diffraction pattern generated by the RBC suspension is recorded



# Diagnostic Algorithm Summary

**CBC**

Severity + multilineage involvement?

**Indices**

Microcytic / normocytic / macrocytic?

**PB Smear**

Morphological clues to etiology

**Retic + DAT**

Hemolytic vs. aplastic vs. blood loss

## Key Decision Points

### Hemolytic Anemia

- Positive DAT → immune-mediated
- Negative DAT + PB smear findings →, consider osmotic fragility and band 3 testing, hemoglobin electrophoresis
- Negative DAT+ no significant findings=Consider enzyme assays, unstable hemoglobins, Hb electrophoresis

### Aplastic/Hypoplastic

- Low reticulocyte count relative to anemia degree
- Bone marrow biopsy indicated
- Consider aplastic anemia, Diamond-Blackfan, TEC

### Genetic Workup

- Inherited anemias: gene panels / WES
- Whole genome sequencing for undiagnosed cases
- Interpret VUS with clinical correlation

# Arches National Park, Utah

# Why Do We Need Molecular Testing?
# Utility of this testing during neonatal period

HS of AR variant without family history → Screening tests not that useful during neonatal period → Spherocytes on the blood smear are not specific for HS and peripheral smear findings are not informative in all cases

Some patients may require transfusion, making the biochemical testing unreliable and uninformative → G6PD/PK deficiency of mild-to-moderate severity can be missed in neonates when reticulocyte counts are high → To diagnose complex interactions (HHA +Bilibrubin metabolism disorders)

# Molecular Genetic Analysis

| Targeted Gene Capture | Gene Panels | Whole Exome Sequencing |
|---|---|---|
| Focused sequencing of known disease genes; fast and cost-effective for suspected single-gene disorders | Multigene analysis for conditions with genetic heterogeneity; high sensitivity across related disorders | Broad approach capturing all protein-coding regions; effective for undiagnosed inherited anemias |

## Benefits

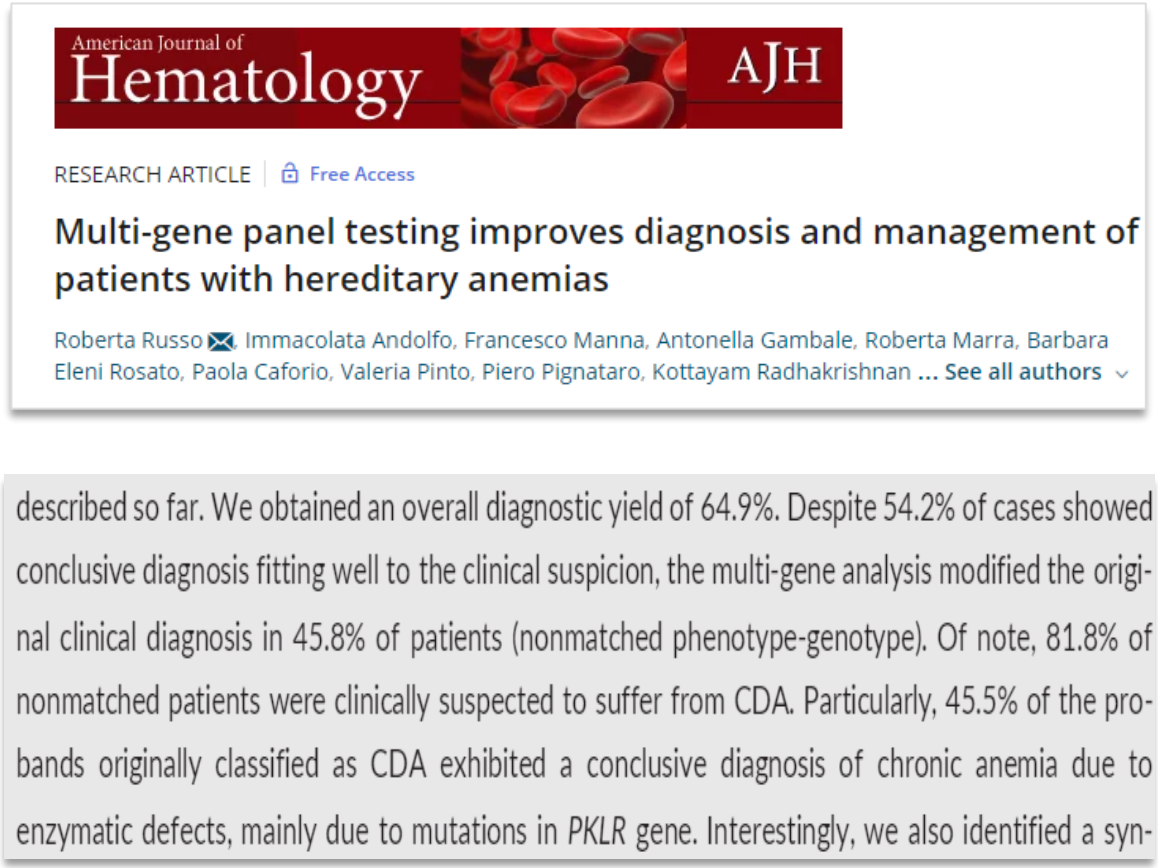
- Improved accuracy of precise genetic diagnosis
- New mechanistic insights into inherited anemias
- Answers in previously undiagnosed cases
- Genetic counseling

## Limitations

- Variants of unknown significance (VUS)
- Cannot detect deep intronic splicing mutations
- Misses mutations in distant regulatory elements
- Intragenic deletions may be undetected

# Targeted NGS Panels: Importance

- Russo et al. 74 patients with HHA with an emphasis on congenital dyserythropoietic anemia (CDA)
- CDA misdiagnosed as enzyme deficiency particularly PK deficiency
  - » Out of 22 patients initially diagnosed as CDA, 10/22 were later diagnosed with enzyme deficiencies



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**Multi-gene panel testing improves diagnosis and management of patients with hereditary anemias**

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described so far. We obtained an overall diagnostic yield of 64.9%. Despite 54.2% of cases showed conclusive diagnosis fitting well to the clinical suspicion, the multi-gene analysis modified the original clinical diagnosis in 45.8% of patients (nonmatched phenotype-genotype). Of note, 81.8% of nonmatched patients were clinically suspected to suffer from CDA. Particularly, 45.5% of the probands originally classified as CDA exhibited a conclusive diagnosis of chronic anemia due to enzymatic defects, mainly due to mutations in *PKLR* gene. Interestingly, we also identified a syn-

# Moving on to the cases

# Case Study #1

- 3-year-old, Caucasian, lacking regular well-child visits
  - » anemia and splenomegaly
- Peripheral blood smear
  - » many spherocytes
- Past history
  - » hyperbilirubinemia in the newborn
- Anemia and splenomegaly worsened
  - » parents declined immunizations and transfusions
- Extensive testing—negative
- Genetic testing was permitted
  - » after dilated cardiomyopathy developed

- Two variants—*SPTA1* gene identified
  - » A novel mutation (c.7134+2T>G, p.?), predicted to cause abnormal splicing of *SPTA*1 gene, was identified in addition to heterozygous low expression variants $\alpha^{LEPRA}$

- $\alpha^{LEPRA}$ in trans to a pathogenic *SPTA1* variant- associated with **autosomal recessive HS**

# Case Study #1: Continued

- Final diagnosis: Autosomal recessive hereditary spherocytosis
- Given the genetic testing results, the parents consented to immunizations and splenectomy
- Four months after splenectomy, the patient's hemoglobin improved to 15.2g/dL and echocardiogram changes were resolving

# Case Study #2

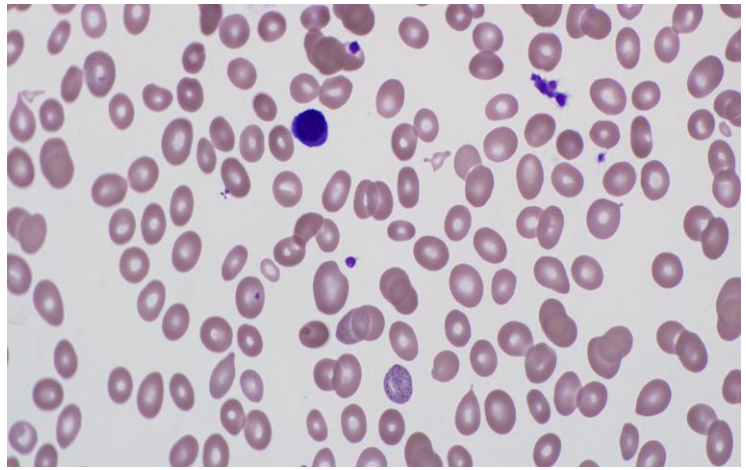
- 11-year-old male with lifelong hemolytic anemia, failure to thrive, no family history
- DAT negative
- Negative osmotic fragility and EMA band 3 testing
- Negative G6PD testing
- Unremarkable peripheral smear findings
- Genetic testing performed

- HHA NGS SEQ
  - » Pathogenic variant
- Gene: *PKLR* (NM_000298.5)
- Nucleic Acid Change: c.1436G>A; homozygous
- Amino Acid Alteration: p.Arg479His
- Low pyruvate kinase

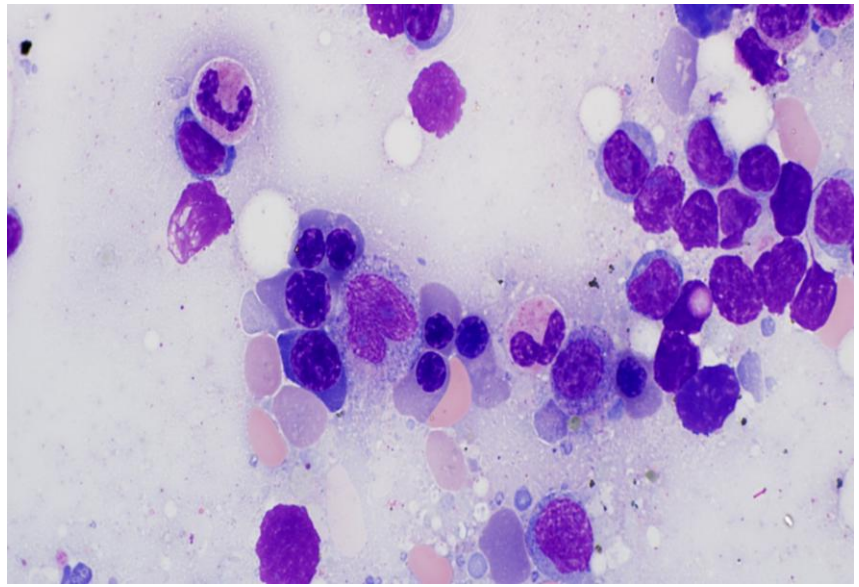
# Overlap between the entities

# Case Study #3

- 3-year-old child with chronic macrocytic anemia
  - » suspected diagnosis of HS because of positive band 3 testing
- s/p vitamin B12 and folate supplementation
- Splenomegaly, hepatomegaly
  - » normal LFTs



- HGB 9.1 g/dL
- HCT 39%
- MCV 108 fL
- MCH 37 pg
- MCHC 35 g/dL



# Case Study #3: Continued

- Diagnosis; congenital dyserythropoietic anemia type 2 based on NGS HHA
- Two pathogenic variants detected in the *SEC23B* gene
- CDA II specifically features a *glycosylation defect* in the band 3 protein
  - » In CDA II, the EMA test often shows a **decrease in fluorescence** because the defective configuration of the band 3 protein reduces its affinity for the EMA dye.

# Summary

- Anemia in pediatric population is common and multifactorial
- Overlap between disorders
- Stepwise approach is helpful in diagnosis
- Molecular diagnosis can be helpful
  - » Diagnosis in certain scenarios
  - » Treatment decisions
  - » Genetic counseling

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# Lake Powell, Utah

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