Congenital Dyserythropoietic anemias: where we are

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Disclosure

Nothing to disclose
This talk is applicable for:

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<th>Disease Type</th>
<th>Definite</th>
<th>Probable</th>
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Congenital dyserythropoietic anemia with karyorrhexis and multinuclearity of erythroblasts.
Heimpel H, Wendt F.

[A new variant of the congenital dyserythropoietic anemia].
Heimpel H, Wendt F, Klemm D, Schubothe H, Heilmeyer L.

[Congenital dyserythropoietic anemia in a pair of dizygotic twins].
Wendt F, Heimpel H.
Congenital Dyserythropoietic Anemias (CDAs)

- **CDAs** are mendelian diseases affecting the normal differentiation-proliferation pathway of the erythroid lineage.
- They belong to a subtype of **bone marrow failure syndromes** characterized by monolineage involvement and morphological abnormalities in erythroid precursor cells.

**Erythroid hyperplasia with specific morphological alterations involving late erythroblasts**

- Mild hemolytic anemia (9-10 g/dL)
- Reduced reticulocyte count
- Jaundice
- Splenomegaly

- Hemosiderosis
- Gallstones
- Transfusion dependence (≈ 20%)

*Images and diagrams illustrate the morphological changes and cellular progression associated with CDAs.*

*Williams Hematology, Ninth Edition, Chapter 39 by A. Iolascon - McGraw-Hill _ In press*
Age at diagnosis of CDAs

Age at diagnosis

- CDA I (n=23)
- CDA II (n=106)

Onset age

- CDA II (n=89)
Clinical findings of CDAs

- Anemia
- Jaundice
- Splenomegaly
- Gallstones
- Iron overload
Differential diagnosis

HS

- Splenectomy is the standard treatment
- Autosomal dominant (75%)
- Normal or slightly increased sTFR

CDA II

- Splenectomy slightly increases Hb level
- Autosomal recessive
- Hemosiderosis
- sTFR

- Unc. Bilirubin
- ↑ LDH
- ↓ Haptoglobin
- Hepatosplenomegaly
- RDW

- Reticulocyte count
Preliminary study design for DD: tNGS approach

Selection of **15 patients**: 6 with known genotype; 6 with unknown genotype; 1 family

Panel of **10 causative genes** of HS and CDAs (2012-2013)

Coding regions, UTRs, regulatory regions, **100 bp flanking splice junctions**

Inheritance pattern and validation by Sanger sequencing
Variants in clinical report of targeted-NGS-based diagnosis for HHA patients

Total variants 62–122
- Off-target gene variants 0–2
- Target gene variants 55–105
- Intronic and regulatory gene variants 48–92
- Coding gene variants 5–13

Variants related to clinical phenotype

Variants modifying clinical phenotype

SPTA1 α-LELY

Complete pedigree
(12-father; 13-mother; 14-proband; 15-unaf. sister)
Polygenic contribute in monogenic disease

Hereditary Spherocytosis
- SPTA1 mutations
- αLELY variant

Dyserythropoietic phenotype
- SEC23B mutation
- GATA1 modifier variant

SPTA1 LOCUS
- WT
- c.5029G>A, p.Gly1677Arg
- Alpha Lely
- c.2319C>A, p.Cys773Ter

SEC23B LOCUS
- WT
- c.1254 T>G, p.Ile418Met

GATA1 LOCUS
- WT
- g.4909G>A

GATA1

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Indirect Bilirubin levels and Incidence of gallstone formation in CDAN2 patients divided by their UGT1A genotype

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Iron Overload in CDAs: relevance of this complication

CDA II - Ferritin > 300 ng/ml and Ferritin > 1000 ng/ml

Cumulative Incidence vs Age (years)

- Ferritin >300 ng/ml
- Ferritin >1000 ng/ml
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Average: 21.38, 9.54, 3.22, 28.24, 87.04, 52.31, 181.37, 210.16, 71.48, 375.19, 3.60, 4.57, 836.46

SD: 13.15, 2.04, 0.73, 5.84, 9.76, 33.29, 64.75, 49.51, 28.03, 585.71, 1.68, 7.49, 965.55
Pathogenesis of Iron Overload in CDAII

- **Hepcidin**: CDAII vs. CTRs, P < 0.0001
- **GDF15**: CDAII vs. CTRs, P < 0.016
- **s-TFR**: CDAII vs. CTRs, P < 0.005
- **s-HJV**: CDAII vs. CTRs, P < 0.002
Polychromatic erythroblasts are the main source of ERFE in human and mice

The onset of multinucelarity in in vitro model of CDA II involves polychromatic and orthochromatic precursors.

Hypothesis: The accumulation of highly expressing FAM132B polychromatic erythroblasts in CDA II marrow could account for the pathological overexpression of ERFE.
Classification and distinguishing features of CDAs

CDA TYPE I

Clinical features: anemia with neonatal appearance; jaundice, splenomegaly; rare syndactyly;

Common complication: hemochromatosis

Bone marrow morphology
- MO: megaloblastoid erythroid hyperplasia; nuclear bridges
- ME: spongy-appearing nuclei and invagination of the cytoplasm in the nucleus.

Inheritance: Autosomal recessive
Locus: 15q15.1-15.3 (Codanin-1)
Mutations in \textit{CDAN1} gene
Homzygous mutations in a predicted endonuclease are a novel cause of congenital dyserythropoietic anemia type I


A  

2 helix-turn-helix domains (4-129 aa)  
Nuclease domain (161-259 aa)

B  

structure-specific activity. A recent report suggests C15ORF41 interacts with Asf1b. This is significant as Codanin-1 has been proposed to play a role in the transport of histones through interaction with Asf1b and supports the hypothesis that the primary defect in CDA-I is in DNA replication and chromatin assembly.
CDA type III

Västerbotten family

American family
CDA III genetics

By linkage analysis CDA III locus was mapped to an 11 cM interval on chromosome 15 (15q21-q25)

Lind et al, Hum Mol Genet 1995

KIF23 localizes in the midbody

KIF23 (MLKP1) localization (green) relative to DNA (blue) in Hela cells
Congenital dyserythropoietic anemia 2009: CDA-II, all European Countries
CDA II History

1967 - CDA II description (H. Heimpel and F. Wendt)

1982 - Band 3 hypoglycosilation

1990 - Identification of enzymatic deficiency

1996 - Identification of double membranes on GR surface

1997 - Localization of CDAN2 locus in 20q11.2 by genomewide search

1998 - Activity reduction of band 3

2001 - Description of natural history of CDA II

2009 - Identification of the causative gene
SEC23B is a component of COPII complex.
In no case homozygosity or compound heterozygosity for two nonsense mutations was found, a situation likely to be lethal.

However, few cases with two hypomorphic mutations have been described so far.

Iolascon A et al, Curr Opin Hematol 2011
Molecular geocode of SEC23B alleles in Europe

Dotted red line highlights the geographical areas where a founder effect has been demonstrated or suggested.

Dissemination of the E109K mutation in the Mediterranean area

SEC23B is required for the maintenance of murine professional secretory tissues

A. Diagram showing the molecular process involving RT1s, F3, R2, RT1as, and other elements.

B. Gel electrophoresis showing bands at 400bp, 300bp, 200bp, V13+R2, and F3+R2.

C. Graph showing fold decrease of Sec23b mRNA in liver, pancreas, and salivary gland compared to WT.

D. Western blot showing SEC23B/βGEO fusion protein and β-actin bands.

E. Images showing Sec23b−/− and WT mice.

F. Graph showing glucose levels in Sec23b−/−, Sec23b+/−, and WT groups, with a P < 0.001.

G. Scatter plots showing RBC, HGB, and HCT levels for Sec23b−/− and WT groups, with P > 0.4, P > 0.2, and P > 0.2, respectively.

Tao J. et al. PNAS 2012
General Pathogenesis of CDAs

Figure 1
XVIII Congresso Nazionale SIGU

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Antonella Gambale
Immacolata Andolfo
Luigia De Falco

Medical Genetics Unit

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