Hereditary iron metabolism disorders,
Where we are?

Mayka Sanchez
The importance of Iron balance

Too much… …too little

IRON

DISEASE

Overload
Hereditary Hemochromatosis

Deficiency
Rare Iron-related Anaemias
Hyperferritinemia project

HIGHFERRITIN Web Server

Algorithms and recommendations for diagnosis and management of hyperferritinemia

HIGHFERRITIN

The HIGHFERRITIN Web Server is a tool for helping the general practitioners (GP) or medical specialists in the diagnosis and management of patients with high levels of serum ferritin or hyperferritinemia. HIGHFERRITIN Web Server provides suggestions and recommendations about the appropriate medical tests and procedures to be done and the possible treatments to follow.

These recommendations have been agreed by a group of experts and they follow the recommendations of international guidelines in Hereditary Hemochromatosis and other diseases together with the personal experience of these experts.

To use this tool, please go to the diagnostic section or just click here.

http://highferritin.imppc.org
Causes of Iron Deficiency Anaemia (IDA)

• Blood loss (intestinal gastric bleeding)
• Limited supply diet (iron, folate, vitamins)
• Increased requirements

• Iron Malabsorption

Adquired (Common form):
• Refractory (no explanation): Helicobacter pylori, Celiac Disease, Autoimmune Atrophic Gastritis

Hereditary (Rare form): Microcytic & hypochromic Anaemia
• Non-sideroblastic
• Sideroblastic
Gene Symbol (Protein) | Chr. | Protein Function | Inheritance | Disease Caused by Mutations
--- | --- | --- | --- | ---
TMPRSS6 (Matriptase -2) | 22 | Regulates hepcidin expression | AR | Iron-refractory Iron-deficiency Anemia (IRIDA)
SLC11A2 (DMT1) | 12 | Transmembrane iron transporter | AR | Autosomal recessive hypochromic, microcytic anaemia with hepatic iron overload
TF (Transferrin) | 3 | Plasma iron binding protein; ligand for TFR1 & TFR2 | AR | Atransferrinaemia: Iron deficiency anaemia with tissue iron overload
CP (Ceruloplasmin) | 3 | Plasma ferroxidase | AR | Aceruloplasmininaemia: Mild iron deficiency anaemia associated with iron accumulation in the liver and brain
Aceruloplasminemia: Deficiency of Ceruloplasmin

- Ceruloplasmin (CP), a copper-containing ferroxidase, cooperates to export iron with ferroportin $^{1}$
- Laboratory and clinical expression of aceruloplasminemia includes low or absence serum ceruloplasmin, low serum copper levels, mild-moderate microcytic anemia with low serum iron and high serum ferritin, diabetes mellitus (iron in pancreas), and late-onset neurological symptoms (iron in brain), including retinal degeneration, ataxia, involuntary movements and dementia$^{1,2}$
- Differential diagnosis$^{1}$
  - Anaemia of chronic diseases (ACD)
  - Wilson’s disease (Cu accumulation, ATP7B)
  - Menkes’s disease (Cu and Cp deficiency, ATP7A)
  - Hypotransferrinaemia or atransferrinaemia
- Treatment: chelation therapy; oral zinc sulfate$^{3}$; no benefit from phlebotomy$^{1}$

Hypotransferrinaemia or Atransferrinaemia


• Hereditary atransferrinaemia has been reported in 12 families world-wide.

• Functional deficiency of Transferrin (TF gene Chr 3q21).
Hypotransferrinaemia or Atransferrinaemia

- Onset in early infancy
- Clinically defective expression associated with mutations in the TF gene and results in:
  - reduction in delivery of iron to erythroid cells in the bone marrow
  - reduced haemoglobin synthesis

=> Severe iron deficiency hypochromic–microcytic anaemia resistant iron therapy.
  - Massive but futile iron absorption

=> Severe iron overload in parenchymal organs (liver and heart hemosiderosis)

=> Recurrent infections

- Treatments:
  - fresh plasma infusions
  - purified human apotransferrin

  Participation in clinical Trial: NCT01797055 (Apotransferrin in Atransferrinemia)
  SANQUIN BLOOD (The Netherlands). Measurements of hepcidin and NTBI
A transferrinaemia cases (4 families, 6 affected cases)

Transferrin normal values: 204-360 mg/dl

PUBLICATION:
Iron Refractory Iron Deficiency Anemia (IRIDA)

- Myelocytic hypochromic Anemia without response to oral iron treatment, partial response to iv iron
- AR Disease (OMIM #206200). Mutations in TMPRSS6 (MT-2). Negative regulator of hepcidin
- Hepcidin levels inappropriately high for the level of Anemia (ELISA at UDGAEMH)

IRIDA (Iron-Refractory, Iron-Deficiency Anaemia)

**Treatment**

- Oral iron administration is ineffective
- Response to parenteral iron administration is partial
- Anaemia becomes less severe in adulthood as a consequence of the greater availability of the limited amount of available iron to erythropoiesis
Mutations in the gene SLC11A2 (DMT1)

- Severe microcytic **anaemia** with **high transferrin saturation**
- Severe hypochromia with **liver iron overload** and normal ferritin levels
- 5 cases described world-wide

**France**


**Czech**


**Italy**


**Spain**

Main Biologic and Clinical Differences in Genetic and non-sideroblastic forms of Iron Deficiency Anaemia

Hypochromic microcytic ANAEMIA: LOW MCV, LOW MCHC, LOW Hemoglobin

<table>
<thead>
<tr>
<th>Gene (protein) defect</th>
<th>DMT1-deficiency</th>
<th>IRIDA</th>
<th>Atransferrinaemia</th>
<th>Aceruloplasminaemia</th>
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<tbody>
<tr>
<td></td>
<td>SLC11A2 (DMT1)</td>
<td>TMPRSS6 (MT2)</td>
<td>TF</td>
<td>CP</td>
</tr>
<tr>
<td>Inheritance</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>At birth</td>
<td>18–24 mo</td>
<td>Late onset provided some transferrin is present</td>
<td>Late onset with moderate anaemia</td>
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<tr>
<td>Liver iron overload</td>
<td>Yes</td>
<td>No (or yes due to transfusion treatment)</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Brain damage</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum iron</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ringed sideroblasts</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hepcidin levels</td>
<td>Low</td>
<td>High for low iron values</td>
<td>Low</td>
<td>Not yet measured</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Low or normal</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cases (families)</td>
<td>5 (5)</td>
<td>41(24)</td>
<td>12 (14)</td>
<td>32 (6, Japan)</td>
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<tr>
<td>Inheritance</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td>Very low levels TF</td>
<td>Very low levels CP</td>
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</tbody>
</table>
Congenital Sideroblastic Anemia (CSA)

Classification

- Hereditary forms (RARES)
  - Syndromic or Non-syndromic
  - According to MCV
    - Microcytic (MCV < 80)
    - Normocytic (80 < MCV < 100)
    - Macrocytic (MCV > 100)
  - Inheritance:
    - X-linked
    - Autosomic Recessive
    - Autosomic Dominant
    - Mitochondrial DNA

- Acquired forms (Common)
  - Idiopathic: RARS Refractory anemia with ringed sideroblasts (acquired stem cell disorders), RARS-T
  - Secondary: tumors, alcoholism, antibiotics (linezolid), Pb or Zn intoxication
**Microcytic Congenital Sideoblastic Anemias (CSA)**

**Pathophysiology**
- Disturbances of mitochondrial proteins regulating haem synthesis or Fe/S cluster synthesis

- Ringed sideroblasts form when iron accumulated inside the mitochondria that circle the normoerythroblast nucleus

- Perceived by body as increased need for iron
  - Increased iron absorption results in iron overload
### Genetics of Congenital Sideroblastic Anaemias CSA (Microcytic)

<table>
<thead>
<tr>
<th>Gene Symbol (Protein)</th>
<th>Chr.</th>
<th>Protein Function</th>
<th>Inheritance</th>
<th>Disease Caused by Mutations</th>
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</thead>
<tbody>
<tr>
<td>ALAS2</td>
<td>X</td>
<td>Heme biosynthetic pathway mitochondrial enzyme</td>
<td>X-linked</td>
<td>CSA linked to chromosome X (XLSA)</td>
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<tr>
<td>SLC25A38</td>
<td>3</td>
<td>Erytroid-specific transporter (Glycine?/ALA?)</td>
<td>AR</td>
<td>Autosomal recessive nonsyndromic CSA</td>
</tr>
<tr>
<td>ABCB7</td>
<td>X</td>
<td>Fe/S cluster transporter</td>
<td>X-linked</td>
<td>CSA associated with spinocerebral ataxia (XLA/A)</td>
</tr>
<tr>
<td>GLRX5</td>
<td>14</td>
<td>Fe/S cluster assembly pathway</td>
<td>AR</td>
<td>Sideroblastic anemia with hepatic iron overload</td>
</tr>
<tr>
<td>STEAP3</td>
<td>2</td>
<td>Ferrireductase, acquisition of iron by erythroblasts</td>
<td>AR</td>
<td>Congenital hypochromic anaemia associated with STEAP3 mutations</td>
</tr>
</tbody>
</table>
Microcytic CSA: dysfunctional mitochondrial iron metabolism
AR non-syndromic CSA: gen SLC25A38

• Non-syndromic severe type of autosomic recessive sideroblastic anemia
  • Microcytic & hypochromic sideroblastic anemia (low MCV, low MCHC)
  • Refractory to treatment with pyridoxine and folic acid
  • Increase transferrin saturation and ferritin levels before significant amount of blood received by transfusion
• Early onset
• Iron overload problems
• Patients are transfusion dependent specially first few years of life
• Few patients underwent bone marrow transplantation
  • Genetic diagnostic allows SLC25A38 genotyping of potential bone marrow donors

• Second type more frequent of CONGENITAL SIDEROBLASTIC ANEMIA after XLSA (ALAS2 gene)

NEW MISSENSE MUTATION
NM_017875.2:c.[152T>C];[=];
NP_060345.2:p.(Leu 51Pro);(=)

NEW NONSENSE MUTATION
NM_017875.2:c.[559C>T];[=];
NP_060345.2:p.(R187*);(=)

- Girl 4 years old from Peru
- Severe Anaemia, onset: 1 month
- Transfusion dependent
- Hb:3.5g/dl (1 month)

- 50% BM ring sideroblasts
  (22/05/2013)

ANEMIA WITH RING SIDEROBLASTS

UTILITY OF GENETIC DIAGNOSTIC: It is not going to respond to pyridoxine!
A novel syndrome of congenital sideroblastic anemia, B cell immunodeficiency, periodic fevers and developmental delay (SIFD)
Sideroblastic Anemia, Immunodeficiency, Fevers and Developmental Delay (SIFD)

• **Anemia**
  
  • **Severe** (Hb 7.1g/dL; range 4.8-8.3). Markedly **microcytic** (MCV 62 fl; range 53.6-73.2)
  
  • Hypochromasia, Microcytosis, Schistocytosis, Basophilic stippling, Frequent nucleated erythrocytes
  
  • No hemoglobinopathies, iron deficiency, RBC mb defects, ezymopathies or porphyrias
  
  • BM examination reveals **ringed sideroblasts >45-50%** (1 not performed)
  
  • Erythroid **hyperplasia** and dyserythropoiesis, with deficient cytoplasmic hemoglobinization
  
  • Most children **hyperferritinemia** (due inflammation and secondary iron overload)
  
• **Recurrent high fever syndrome** requiring multiple hospitalizations (11), elevated inflammatory markers, Vomiting, Diarrhea.

• **Immunodeficiency**

  • Recurrent inflammatory episodes, B-cell lymphopenia and hypogammaglobulinemia (11),
  
  • No good response to intravenous replacement with immunoglobulins (Ig)

• **Developmental delay** variable but alarming:

  • **Generalized and truncal hypotonia**, often severe, progressive and associated with gross motor developmental delay
  
  • Comprehension and communication were impaired in many

  • Other symptoms were present in some of the patients: sensorineural hearing impairment (5), Recurrent seizures (5). **Neurological/neuromuscular abnormalities**, Nephrocalcinosis/renal tubular dysfunction (3), Aminoaciduria (6), Cardiomyopathy (2) and cardiac failure (contribution to death in 5 cases). **Pigmentary retinitis** (4), hepatosplenomegaly (4), brittle hair (3), chronic ichthyotic skin changes (1)
# Main Biologic and Clinical Differences in Genetic and Congenital Microcytic Sideroblastic Anaemia

<table>
<thead>
<tr>
<th></th>
<th>XLSA</th>
<th>Non-syndromic SA</th>
<th>XLSA/A</th>
<th>GLRX5-deficiency</th>
<th>SIFD</th>
<th>STEAP3-deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene (protein) defect</td>
<td>ALAS2</td>
<td>SLC25A38</td>
<td>ABCB7</td>
<td>GLRX5</td>
<td>?</td>
<td>STEAP3</td>
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<tr>
<td>Inheritance</td>
<td>X-linked</td>
<td>AR</td>
<td>X-linked</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>Variable</td>
<td>Variable</td>
<td>Neonatal/infancy</td>
<td>Usually midlife</td>
<td>Neonatal/infancy</td>
<td>Infancy/Adolescent</td>
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<tr>
<td>Liver iron overload</td>
<td>Yes</td>
<td>Yes</td>
<td>Variable</td>
<td>Yes</td>
<td>2ndary to blood transfusions</td>
<td>Yes</td>
</tr>
<tr>
<td>Brain damage</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Some cases</td>
<td>No</td>
</tr>
<tr>
<td>Serum iron</td>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>-</td>
<td>High</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Variable</td>
<td>High</td>
<td>Normal</td>
<td>High</td>
<td>Normal (High after few transfusions)</td>
<td>High</td>
</tr>
<tr>
<td>Ringed sideroblasts</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepcidin levels</td>
<td>Not yet measured</td>
<td>Normal/high</td>
<td>Not yet measured</td>
<td>Not yet measured</td>
<td>Not yet measured</td>
<td>Normal/high</td>
</tr>
<tr>
<td>Ferritin</td>
<td>High</td>
<td>Normal/high</td>
<td>Variable</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cases (families)</td>
<td>&gt;70</td>
<td>29 (26)</td>
<td>10 (3)</td>
<td>2 (2)</td>
<td>12 (10)</td>
<td>3(1)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Pyridoxine</td>
<td>BM transplantation?</td>
<td>Chelation!</td>
<td>Transfusion+IV Ig. Iron chelation, BM transplantation (1)</td>
<td>Transfusion + chelation</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Anaemia</td>
<td>Anaemia</td>
<td>Anaemia and ataxia</td>
<td>Anaemia</td>
<td>Severe anaemia, B-lymphopenia or panhypogammaglobulinemia, Fevers, developmental delay</td>
<td>Anaemia, growth retardation, hepatosplenomegaly</td>
</tr>
</tbody>
</table>
Congenital dyserythropoietic anemia (CDA)

- Rare Anaemias with ineffective erythropoiesis (iron overload) and distinct morphological abnormalities of erythroblasts in the Bone Marrow

**General characteristics:**

- Fatigue
- Pallor
- Scleral icterus
- Jaundice
- Splenomegaly
- Abnormal fingernails
- Macrocytic/Normocytic RBC
- Anaemia
- Ineffective erythropoiesis
- Increased iron absorption
- Abnormal expression of membrane antigens
Congenital dyserythropoietic anemia (CDA)

## Classification

<table>
<thead>
<tr>
<th>CDA Type</th>
<th>Protein</th>
<th>Gene</th>
<th>Chromosome Location</th>
</tr>
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<tbody>
<tr>
<td>CDA I</td>
<td>Codanin-1</td>
<td>CDAN1</td>
<td>15q15.1-15.3</td>
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<tr>
<td></td>
<td>Endonuclease</td>
<td>C15orf41</td>
<td>15q14</td>
</tr>
<tr>
<td>CDA II</td>
<td>SEC23B</td>
<td>SEC23B</td>
<td>20p11.23-20p12.1</td>
</tr>
<tr>
<td>CDA III</td>
<td>KIF23</td>
<td>KIF23</td>
<td>15q22</td>
</tr>
<tr>
<td>CDA IV</td>
<td>KLF1</td>
<td>KLF1</td>
<td>19p13.13-p13.12</td>
</tr>
<tr>
<td>CDA with thrombocytopenia</td>
<td>GATA1</td>
<td>GATA1</td>
<td>Xp11.23</td>
</tr>
</tbody>
</table>
CDA: Congenital dyserythropoietic anemias

CDAI = gene CDAN1

CDAII = gene SEC23B

Microscopy:
Chromatin bridges
Electron microscopy:
Heterochromatin “swiss cheese appearance”

Microscopy: bi or multi-nucleated erythroid precursors.
Electron microscopy: double mb inside cytoplasmic membrane
Intravascular hemolysis **low haptoglobin**, high LDH. **High bilirubin**. Inappropriately low **reticulocyte count** for the degree of anemia compared with other hemolytic anemias (normal or slight increased absolute reticulocytes).

Jaundice, erythroid hyperplasia, splenomegaly and or hepatomegaly. Iron overload

| Main Biologic and Clinical Differences in Congenital Dyserythropoietic Anaemias (CDAs) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Gene (protein) defect** | **Inheritance** | **Age at diagnosis** | **Liver iron overload** | **Transferrin saturation** | **Hepcidin levels** |
| CDA I | CDA II (HEMPAS) | CDA III | CDA IV | CDA with thrombocytopenia |
| CDAN1, C15ORF14 | SEC23B | KIF23 | KLF1 | GATA1 |
| AR | AR | AD | AD | X-linked |
| Infancy-Adult | Infancy-Adult | - | - | - |
| Yes | Yes | - | - | - |
| High | High | - | - | - |
| Low | Low | - | - | - |
| Ferritin | High | High | - | - | - |
| Bone marrow (BM) | Hyperplasia of erythroblasts lineage | E/G ratio 3-8 (N:0.2-1) | BM: Bi, Tri-nucleated erythroblasts. Chromatin bridges Electron microscopy (EM) BM: Spongy heterochromatin Swiss cheese appearance. | BM: large number 10-35% binucleated erythroblasts. EM:Double membrane | Gigant multinucleate (up to 12 nuclei) erythroblasts Megakaryocytes display also ultrastructural abnormalities Iron filled mitochondria |
| Peripheral blood (PB) | Macrocytosis (normo in childhood) | Normocytosis | Low reticulocytes | Absence exp CD44 and AQP1 in RBC Nucleated RBC in PB (>210%), severe anisopoikilocytosis |
| Anysocytosis, poikilocytosis, nucleated RBC | SDS-PAGE: narrow and fast migration of Band3 (EA1) | | | |
| Other | 1/3 Congenital malformations (limbs, heart, kidney, hip dysplasia, nail deformities), scoliosis | Positive test Ham (acidified-serum test) | Gammapathies/multiple myeloma and Retinal angioid streaks | High levels of fetal and embryonic hemoglobin Hydrops fetalis, dysmorphic features (1 case) |
| Cholelithiasis. Gallstones | Gallstones | Biliary problems | High serum thymidine kinase | Macrotrombocytopenia. |
| Retinal angioid streaks | | | | Thrombocytopenia with 6p-Thalassemia |
| Cases | 150 | 370 | 43 cases in 2 fam (Sweden 39, American 4). Argentinien (n=? 4 + 1 no publicado (AI)) |
| Exclude | Hemolytic anaemias | Hereditary spherocytosis (HS) | Macrocytic anaemias | KLF1 mut also in HPFH+/-ZnPP |
| Gilbert syndrome | Macrocytic anaemias (B12, folic acid defic) | Hemolytic anaemias | | |
The future is here

Manual sequencing
1 gene at a time
Sanger Sequencing

Gene PANELS
Many genes at one time
MiSeq NGS
Take home message!

- Recent advances in iron metabolism led to the recognition of new entities of iron deficiency anaemia
- New technology (NGS gene panels, exome, genome) is going to change the Clinical Genetics in the close future
- These genetic forms of iron deficiency anaemia should be recognized by haematologists, as they are refractory to classical oral or intravenous iron administration
Agradecimientos

• Advanced Genetic Diagnostic Unit for Rare Iron Metabolism Disorders
  • Dr. Erica Morán
  • Jessica Aranda
• Grupo Ibérico de Ferropatología (GIF)
• Iron Metabolism Community (EIC, IBIS)

Research Projects and Contracts
Ramón y Cajal Research Contract
Technician Contrat (Carlos III)
Plan Nacional (SAF) – 2013-2015
European Project E-rare –2009-2012
Proyectos de Investigación Fundamental no Orientada - SAF 2012.
European Project e: e-ENERCA –2013-2016
Postdoctoral Fellowship FEBS  2012-2015
<table>
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<tr>
<th>CATEGORIES</th>
<th>GENE</th>
<th>DISEASE</th>
<th>PRICE (euros)</th>
<th>OMIM</th>
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<tbody>
<tr>
<td>IRON OVERLOAD</td>
<td></td>
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<tr>
<td>Classical Hemochromatosis</td>
<td>HFE</td>
<td>HH1</td>
<td>200</td>
<td>235200</td>
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<tr>
<td>Non-HFE Hemochromatosis</td>
<td>HAMP</td>
<td>HH2 (juvenile form)</td>
<td>150</td>
<td>613313</td>
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<td>HH2 (juvenile form)</td>
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<td>SLC40A1</td>
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<td>FTL</td>
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<td>Benign Hyperferretinemia</td>
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<td>FTH</td>
<td>Hyperferretinemia with iron overload</td>
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<td>RARE IRON RELATED ANEMIAS</td>
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<tr>
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<td>Aceruloplasminemia</td>
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<td></td>
<td>TF</td>
<td>Hypotransferrinemia</td>
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<td></td>
<td>SLC11A2</td>
<td>Familiar microcytic hypochromic anemia with hepatic iron overload</td>
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<td>206100</td>
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<td>TMPRSS6</td>
<td>IRIDA, Iron-refractory iron deficient anemia</td>
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<td>Congenital dyserythropoietic anemia</td>
<td>CDAN1</td>
<td>CDA type I</td>
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<td>Non syndromic autosomal recessive CSA</td>
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Unidad de Diagnóstico Genético Avanzado de Enfermedades del Metabolismo del Hierro (UDGAEMH)

Diagnóstico Genético
Enfermedades del Metabolismo del Hierro

Jefe:
• Dra. Mayka Sánchez
Técnicos:
• Dr. Erica Morán
• Jessica Aranda

GIF Medical Doctors network

Servicios
- Hepcidina sérica/plasmática (ELISA)
- Diagnóstico Genético de enfermedades raras del metabolismo del hierro

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