Le iperferritinemie

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Ai sensi dell’art. 3.3 del Regolamento applicativo dell’Accordo Stato-Regioni 05.11.2009,

dichiaro che negli ultimi due anni non ho avuto rapporti, anche di finanziamento, con soggetti portatori di interessi commerciali in campo sanitario.

Hyperferritinemia

- It is a **common finding** in daily practice
- It has **several causes**
- In the **majority** of cases it **does not represent true iron overload**

Hyperferritinemia

HEIRS study:

- population based screening study
- incidence of hereditary hemochromatosis in a large **multi-ethnic, multi-racial primary care setting** within North America
- ≈100000 subjects screened for iron overload and HFE mutations

- 5,9% of Caucasians and 19% of Asians have hyperferritinemia
- Only 0,44% of Caucasians and 0,00004% of Asians were C282Y homozygous

- **Hyperferritinemia is very common**
- In the **majority** of indivisuals it is due to **conditions other than classic adult hereditary hemochormatosis**

Adams PC et al. NEJM 2005

Reference Range for Serum Ferritin

POPULATION studies

- Reference concentrations vary across laboratories due to **differences in analytical techniques and reference populations**.

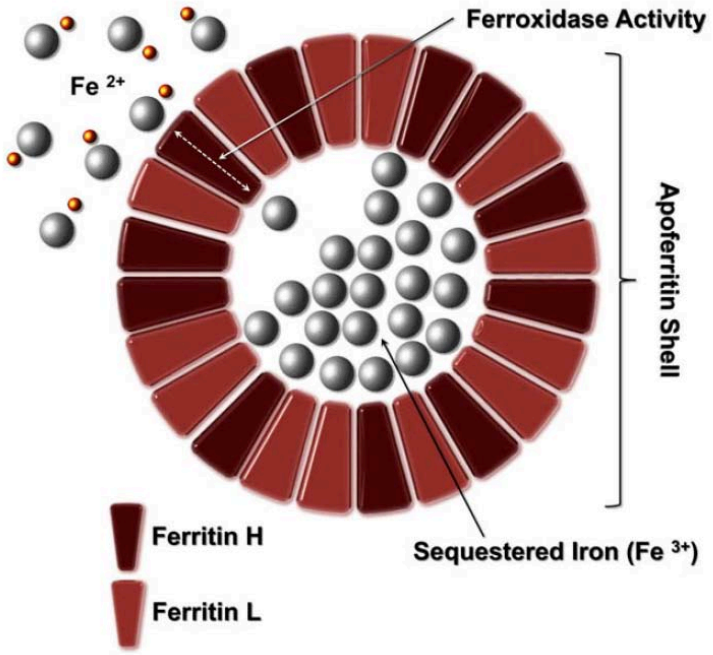
- Age, gender, menopausal status, weight and lifestyle factors (e.g. alcohol intake and smoking) can influence serum ferritin.

- Conventionally, the **reference range** is considered to be:
  - 30–300 µg/L for men and postmenopausal women
  - 15–200 µg/L for premenopausal women.

Ferritin

- **The major intracellular iron storage protein** >> up about 4500 iron atoms.
- **2 subunits types** assembling in different proportion in a 24 subunits-polymer:

- **H-subunit** (*Heavy, cr.11*)
  - mainly in cell cytoplasm
  - ferroxidase activity >> sequestering and detoxification of iron
  - organ of low iron content (hearth, pancreas, kidney)
- **L-subunit** (*Light, cr.19*)
  - also in low amount in serum
  - assist the functionality of H-subunit >> nucleation of the iron core and long-term storage
  - iron storage organs (liver and spleen)



M.A. Knovich et al. / Blood Reviews 23 (2009) 95–104

Ferritin functions

INTRACELLULAR

- **Maintenace of cellular iron homeostasis** by sequestering intracellular iron in a nontoxic readily and available form *(anti-oxidant activity and storage)*

EXTRACELLULAR

- Role as **iron delivery system** *(iron source and pro-oxidant activity).*
- **Different immunological activities** (e.g. inhibiting lymphocyte functions and immunity, decreasing phagocytosis of granulocytes).
- Pro-inflammatory **signaling molecule**

Hyperferritinemia *per se*
may play a role in the development and progression of certain pathologic conditions (e.g. immunological diseases, NAFL/NASH, neurodegeneration…)

Ferritin regulation

The synthesis is regulated:

- by **intracellular iron** (IRP/IRE on FT mRNA)
- by **cytokines** (TNFα, IL1α, IL1β, IL6)
- by **oxidative stress**
- by **hypoxia-ischemia, and hyperoxia** (NO)
- by **hormones** (thyroid hormone, insulin)
- by **growth factors** (IGF-1)

Serum ferritin

✓almost exclusively L-ferritin

✓50-80% in a glycosilated form (during secretion)

✓**surrogate marker of body iron stores**

BUT

✓**Ferritin is an acute phase reactant**

✓**Tissue ferritins can leak from damaged cells**.

LOW

- Evidence of reduced reticuloendothelial iron stores
- **When is very low, is the most useful test in diagnosing iron deficiency** (in otherwise healthy person).

HIGH

- Useful in the:
  - identification or iron overload
  - assessment of risk for organ damage related to iron,
  - treatment monitoring
- **Elevated ferritin levels are far less specific for systemic iron overload.**

The common mechanisms of hyperferritinemia

- **Increased ferritin synthesis and/or secretion**
  - from:
    - ***acquired*** disorders
    - ***genetic*** disorders
  - and:
    - ***with*** iron overload
    - ***without*** iron overload

- **Increased ferritin release** from damaged cells

The common mechanisms of hyperferritinemia

- Increased ferritin synthesis:
  - *HFE* and other types of hemochromatosis.
  - Anemias (heritable and acquired) associated with ineffective erythropoiesis.
  - Aceruloplasminemia.
  - Iron overload secondary to blood transfusion or parenteral iron administration.

- Increased ferritin release from injured cells:
  - Hepatic steatosis and steatohepatitis (alcoholic and nonalcoholic).
  - Chronic viral hepatitis.
  - Massive liver necrosis (ie. due to sepsis, acute hepatitis or toxic injury).
  - Autoimmune and rheumatologic disorders.
  - Acute and chronic infections.
  - Splenic infarction.

- Increased apoferritin (or L ferritin) synthesis or secretion:
  - Chronic ethanol ingestion.
  - Malignancy (malignant histiocytosis, carcinomas of lung, breast, ovary, kidney; lymphoma, liposarcoma).
  - Gaucher disease.
  - Reactive histiocytosis.
  - Hereditary hyperferritinemia-cataract syndrome (HHCS).

from Beaton and Adams, Annals of Hepatology 2011

Hereditary causes of hyperferritinemia

- **with iron overload**
  - *Hereditary Hemochromatosis*
  - *Hereditary Iron-loading anemias* (*Beta-Thalassemia syndromes, congenital sideroblastic anemia or dyserythropoietic anemias*)
  - Ferroportin diseases
  - Aceruloplasminemia
  - A/hypotransferrinemia
  - DMT1 deficiency
  - H-ferrtin related iron overload

- **without iron overload**
  - Hereditary Hyperferritinemia Cataract Syndrome
  - Benign-hyperferritinemia
  - Gaucher disease

OMIM classification

(Online Mendelian Inheritance in Man database)

Genetic Disorders	Inheritance	Gene
Type 1 hemochromatosis	AR	*HFE*
Type 2a hemochromatosis	AR	*HJV*
Type 2b hemochromatosis	AR	*HAMP*
Type 3 hemochromatosis	AR	*TFR2*
Type 4a hemochromatosis	AD	*SLC40A1*
Type 4b hemochromatosis	AD	*SLC40A1*

Non-HFE Hemochromatosis

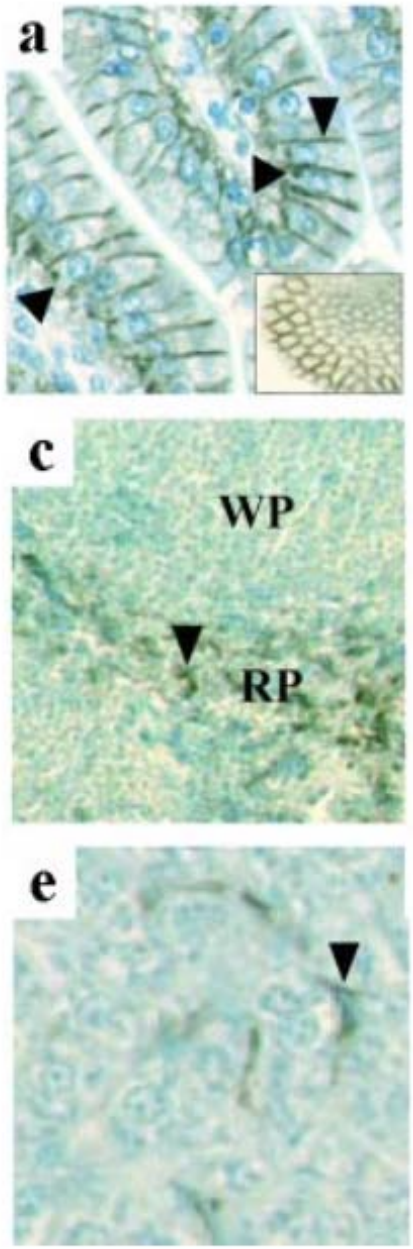
- Once the HFE gene was identified in 1996, it appeared clear that **not all patients with a inherited hemochromatosis-like phenotype carried pathogenic mutations in the HFE gene.**
- **This was particularly evident in southern European countries.**
  - C282Y HZ >90% in the UK and Brittany,
  - C282Y HZ 64% in Italy and 30% and Greece.

- New iron genes and related diseases have been recognized.

- **The most common form of inherited disorder of iron metabolism and the second cause of hereditary hyperferritinemia beyond HFE-hemochromatosis is likely the Ferroportin Disease** (due to pathogenic mutations in the SLC40A1 gene)

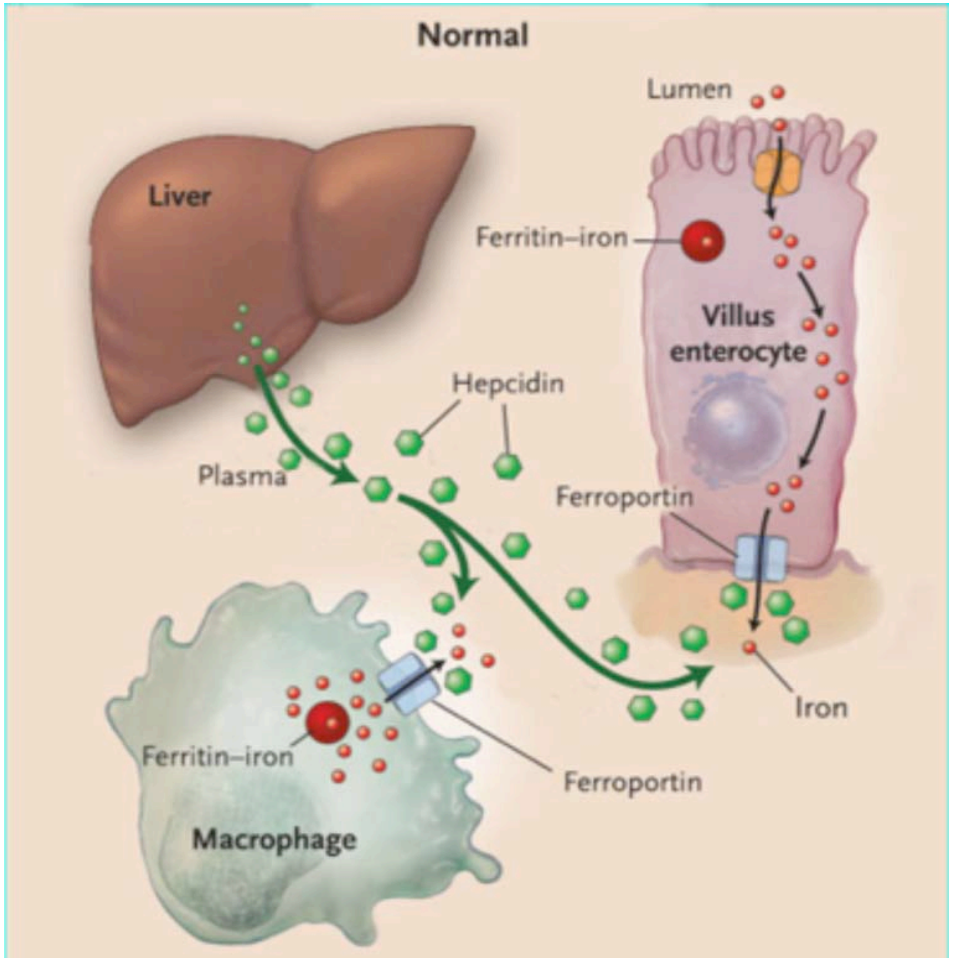
Ferroportin disease

- In 2000, three groups have isolated and characterized the product of the SLC40A1 gene called **Ferroportin** *(Donovan Nature 2000; McKie Mol Cell 2000, Abboud JBC 2000).*
- The only **iron-exporter** identified in mammals.
- It is expressed in several **cell types that play critical roles in mammalian iron metabolism** (placental syncytiotrophoblasts, duodenal enterocytes, hepatocytes, and reticuloendothelial macrophages).
- **Ferroportin is mainly controlled post-translationally by hepcidin**



Canonne-Hergaux et al.
Am J Physiol Gastroi Liver Physiol 2006.

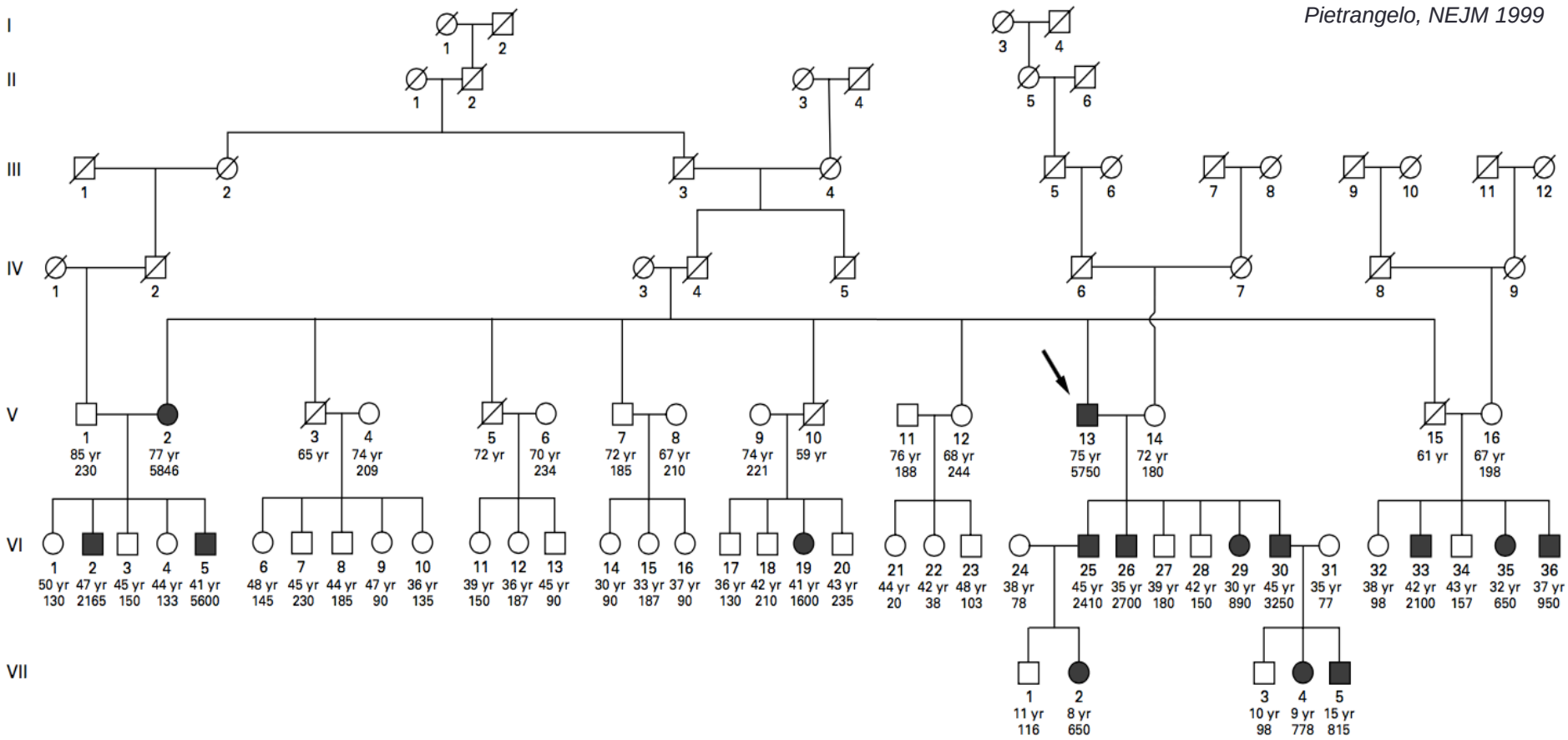
Ferroportin is the receptor for hepcidin, the master regulator of sistemic iron homeostasis



A. Pietrangelo. 2010. Gastroenterology. Review

The hepcidin bound to ferroportin causes its internalization and degradation, inhibiting cellular iron export from enterocytes, macrophages, and hepatocytes

First description of non-HFE related hemochromatosis in adults *(later identified as Ferroportin Disease)*



- In 1999, when only one (*HFE*) gene was known, **an autosomal dominant form of hereditary iron overload** similar to hemochromatosis was described.

- Iron overload was not due to mutations of the HFE gene.

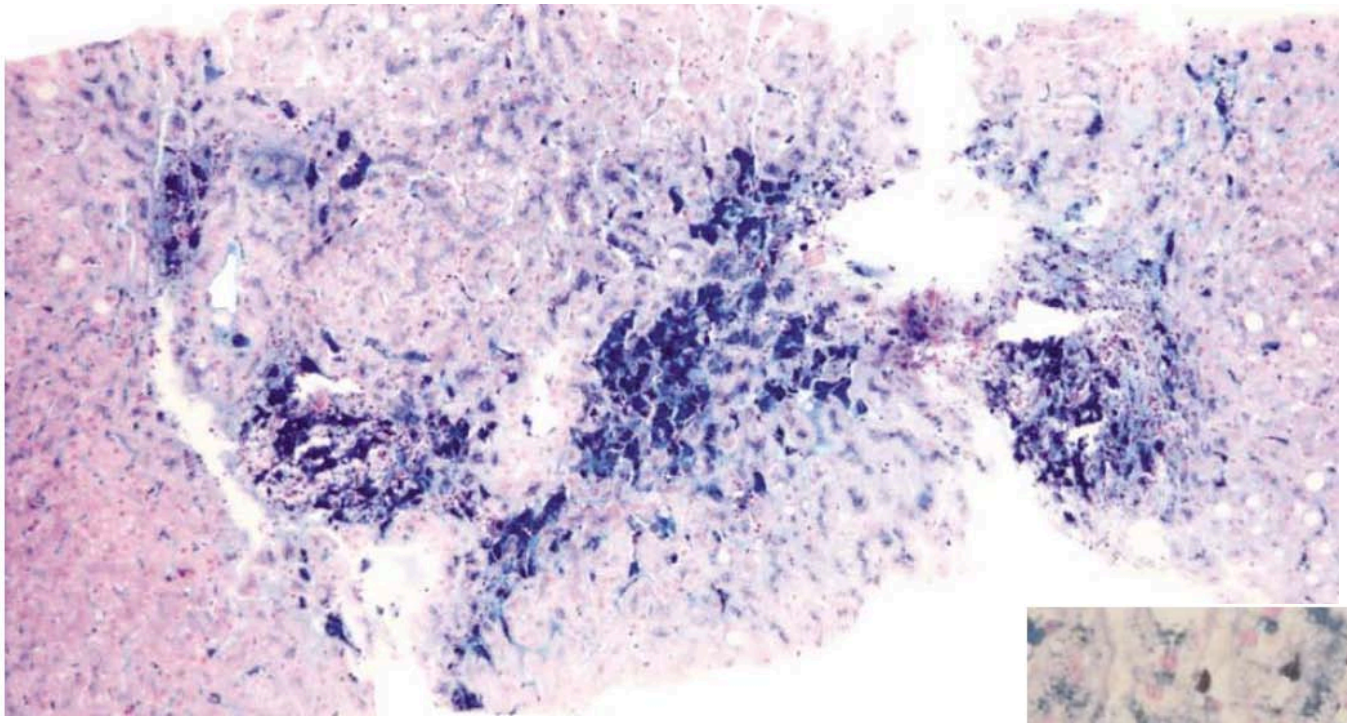
First description of non-HFE related hemochromatosis in adults *(later identified as Ferroportin Disease)*

Subject	Age at Diagnosis	Sex	Hemo-globin†	Transferrin Saturation	Serum Ferritin	Hepatic Iron	Hepatic Iron Index‡	Total Iron Removed§	H63D Mutation	Liver Fibrosis
	yr		g/dl	%	ng/ml	μmol/g of liver (dry weight)		g		
V-2	61	F	14.5	89	5846	310	5.1	12	−/−	Yes
V-13 (proband)	59	M	16.0	75	5750	646	10.9	35	−/−	Yes (minimal)
VI-2	35	M	13.8	78	2165	518	14.8	14	+/−	Yes
VI-5	30	M	14.3	88	5600	815	27.2	16	+/−	Yes
VI-19	35	F	13.7	35	1600	155	4.4	5	−/−	No
VI-25	34	M	15.7	60	2410	810	23.8	31	−/−	No
VI-26	20	M	15.0	40	2700	220	11.0	12	+/−	No
VI-29	21	F	14.2	30	890	110	5.2	6	+/−	No
VI-30	37	M	15.0	65	3250	1050	28.4	20	−/−	No
VI-33	39	M	15.5	78	2100	655	16.8	8	−/−	No
VI-35	29	F	14.1	30	650	110	3.8	4	−/−	No
VI-36	34	M	15.7	80	950	456	13.4	6	−/−	No
VII-2	7	F	12.5	24	650	ND	ND	ND	−/−	ND
VII-4	8	F	13.1	20	778	ND	ND	ND	−/−	ND
VII-5	14	M	13.8	28	815	75	5.4	4	+/−	No

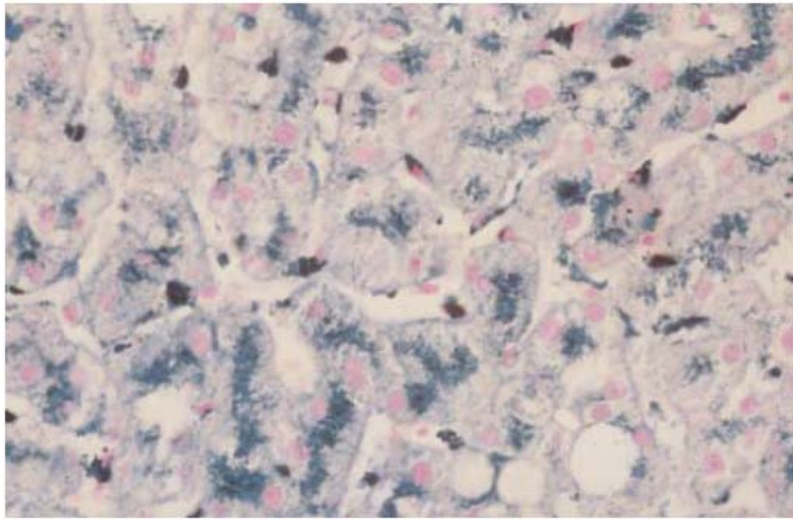
Affected subjects showed **distinctive features** as compared to hemochromatosis:

- **early increase in serum ferritin in the presence of a low-normal transferrin saturation;**
- **several were anemic earlier in life;**
- **early drop of serum iron parameters** and hemoglobin levels as compared to ferritin levels **during phlebotomy;**
- **i**n some cases **low tolerance** to the phlebotomy program.

First description of non-HFE related hemochromatosis in adults *(later identified as Ferroportin Disease)*



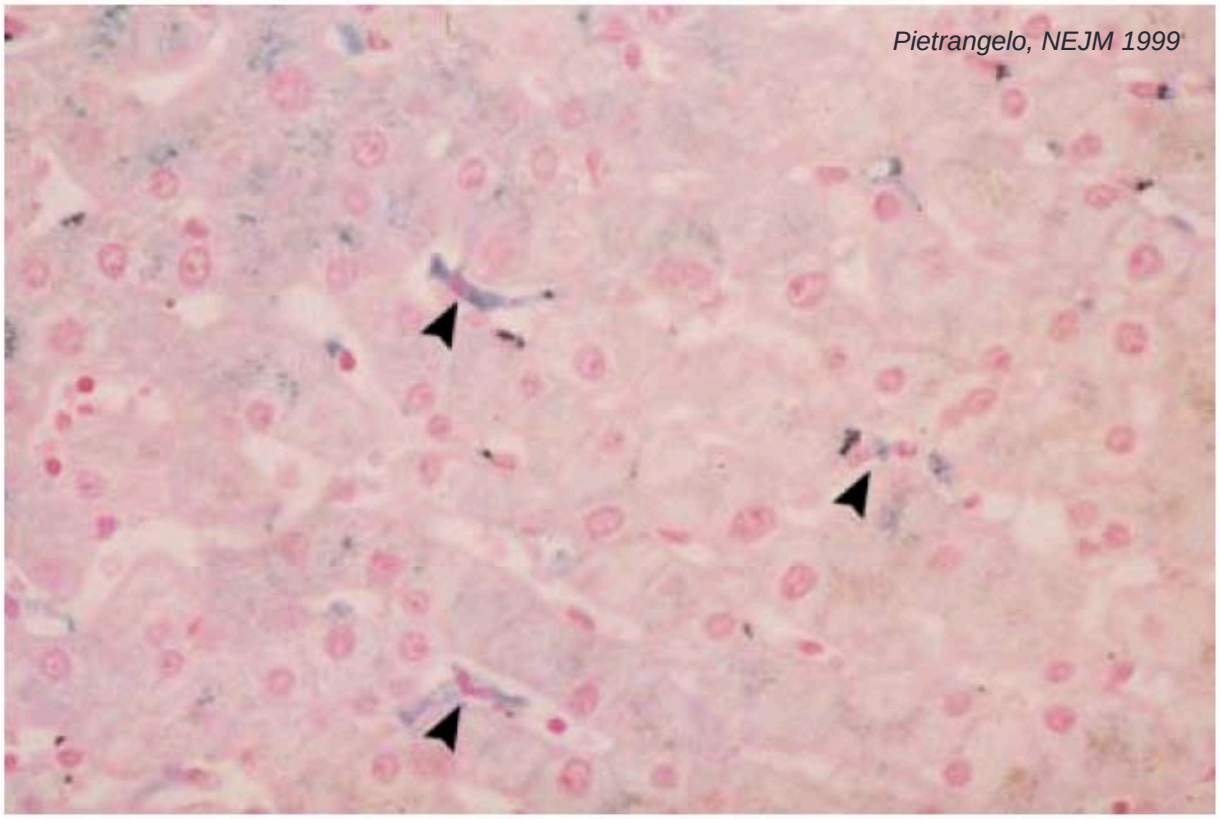
59 y.o., male,
LIC 646 umol/g
dry weight



Mixed pattern of iron accumuation, involving both parenchymal cells and mesenchymal cells, with **large, coalescent iron deposits in Kupffer cells and portal macrophages.**
There was **minimal portal fibrosis.**

Pietrangelo, NEJM 1999 and BCMD 2004

First description of non-HFE related hemochromatosis in adults *(later identified as Ferroportin Disease)*

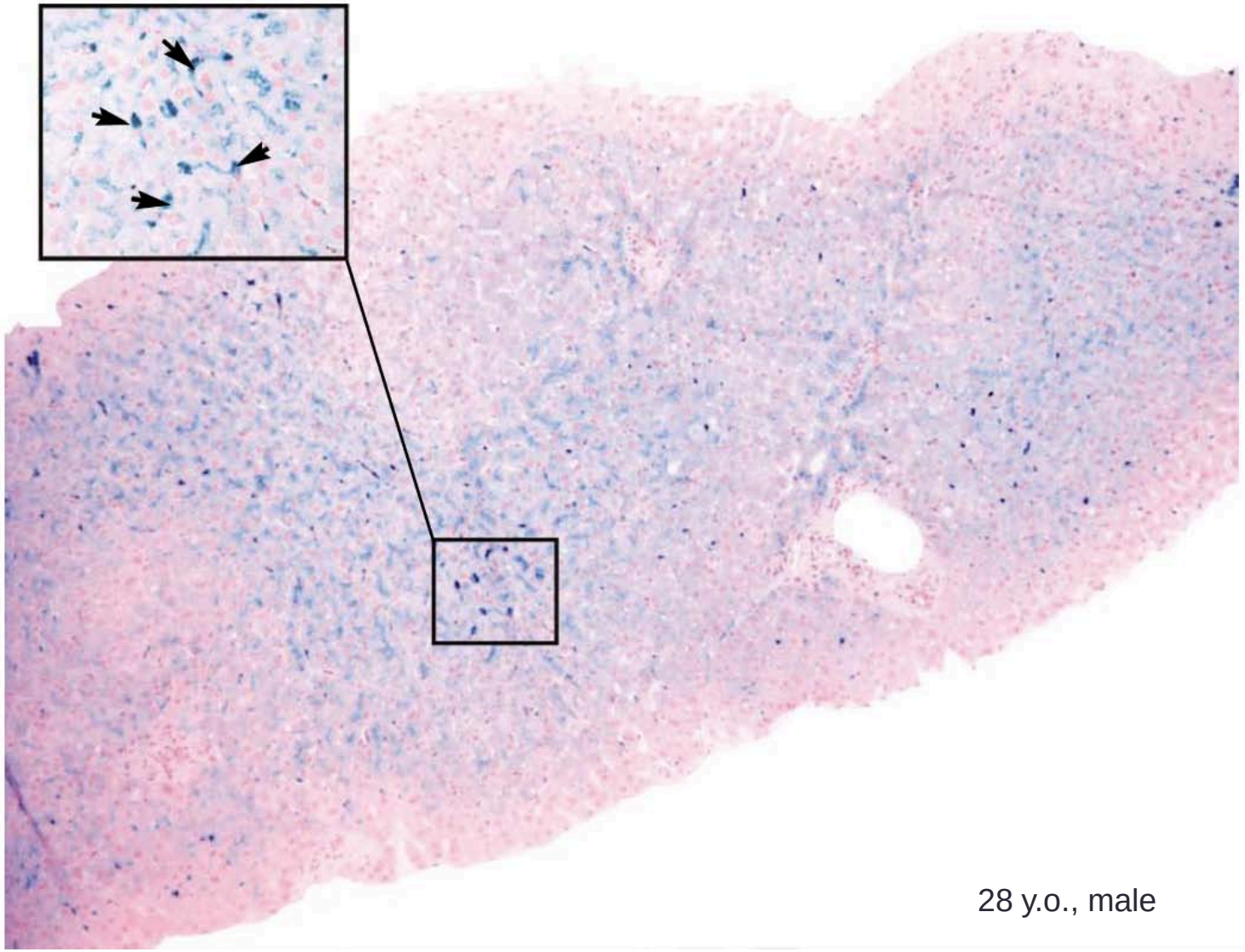


29 y.o., female,
LIC 110 umol/g
dry weight

In early stages, hepatic **iron accumulation is predominant in Kupffer cells** (the liver macrophages).

First description of non-HFE related hemochromatosis in adults

(later identified as Ferroportin Disease)



28 y.o., male

First description of non-HFE related hemochromatosis in adults *(later identified as Ferroportin Disease)*

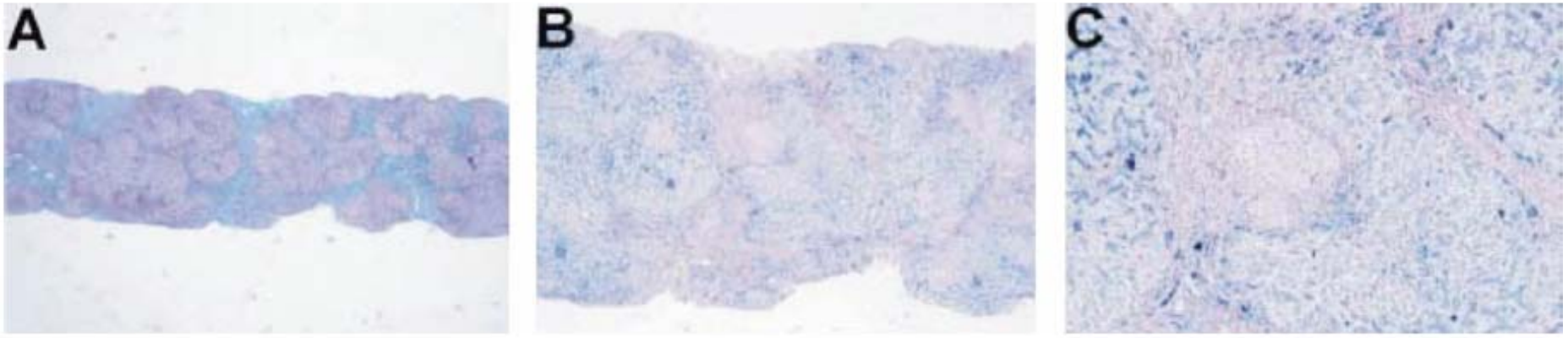
- In 2001, a genome-wide screen in the original pedigree provided evidence of linkage to 2q32.
- A candidate gene was identified in that region: **Ferroportin (SLC40A1).**
- **All affected patients were heterozygous** for a c. 230 C>A substitution resulting in replacement of alanine 77 with aspartate (**A77D**) *(Montosi et al. JCI 2001).*

- Another group reported at the same time that a non-HFE hereditary iron overload was associated with heterozygosity for another ferroportin mutation, c. 430 A>C (**N144H**), in a Dutch pedigree *(Njajou et al. Nat Gen 2001)*.
- *The phenotypic presentation was different, and similar to classic hemochromatosis.*

Ferroportin-related hemochromatosis (type 4b)

After few years, “Non-Classical Ferroportin Disease” with a **phenotypic presentation similar to other adult onset forms of autosomal recessive hereditary haemochromatosis** was reported:

- elevated Tf.sat% and serum ferritin,
- liver fibrosis/cirrhosis,
- diabetes mellitus,
- skin hyperpigmentation,
- arthralgia



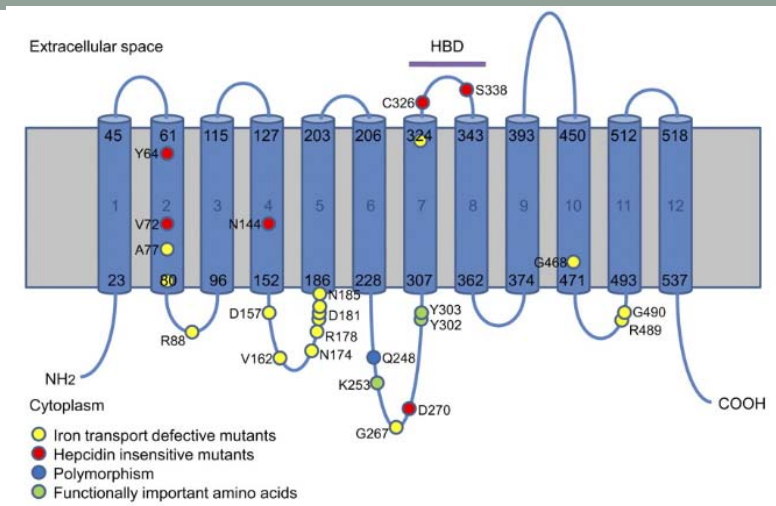
32 y. men with parenchymal iron overload and cirrhosis

Wallace et al., J Hep 2004

Type 4 Hereditary Hemochromatosis epidemiology (Ferroportin Disease and FPN-related Hemochromatosis)

- Following these initial observations, other studies have been published reporting ferroportin mutations in many countries, **regardless of ethnicity:**
  - approx. **50 heterozygous missense mutations**,
  - in **Europe, Africa-America, Australia, Asia, and India.**
- All are **missense heterozygous** mutations (**AD disease)**.
- **Most mutations are very rare**
- **A few common FPN mutations** have been independently reported in different countries (A77D, G80S, Val162del).
- Ferroportin disease is the **second most frequent cause of hereditay hyperferritinemia after the classic HFE-related hemochromatosis.**

Pathophysiology

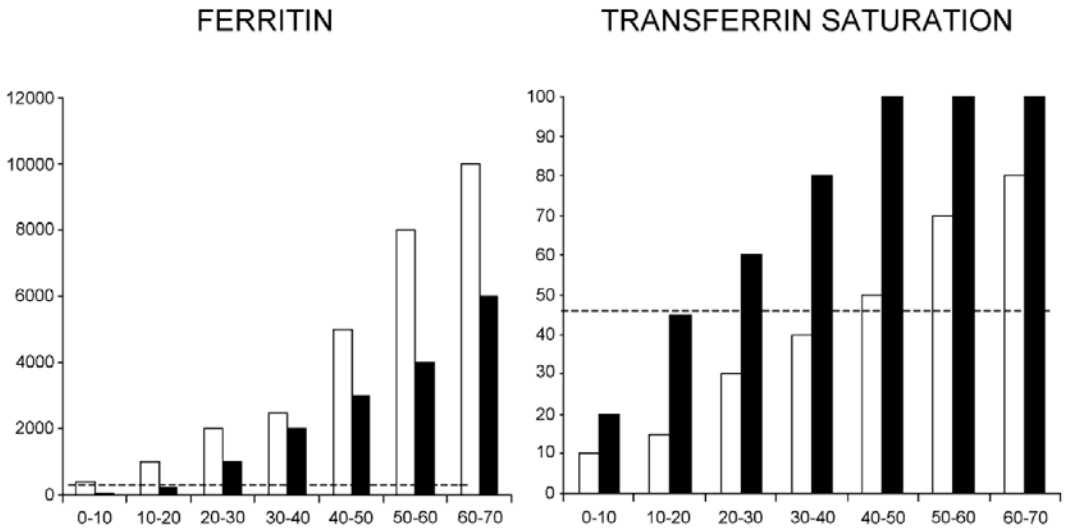


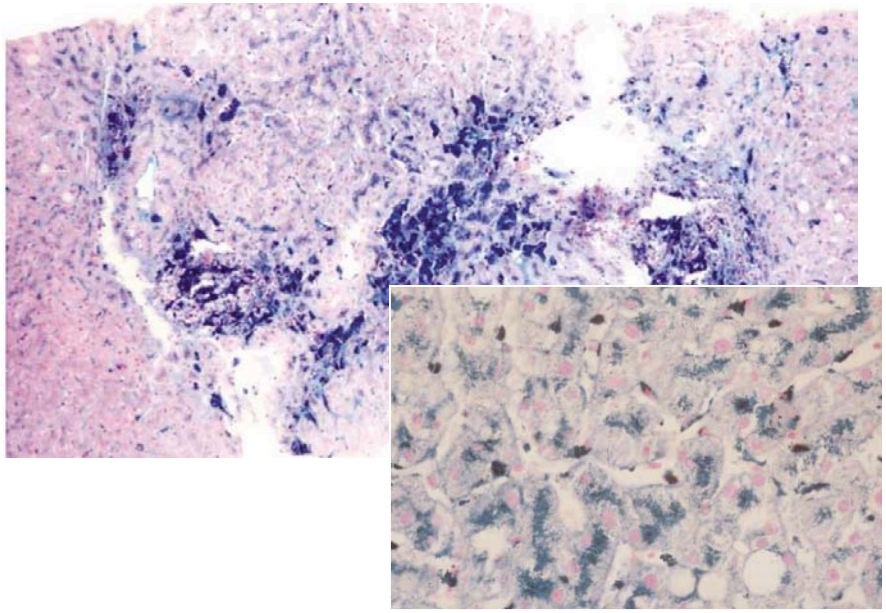
Mutations are usually classified into two groups:

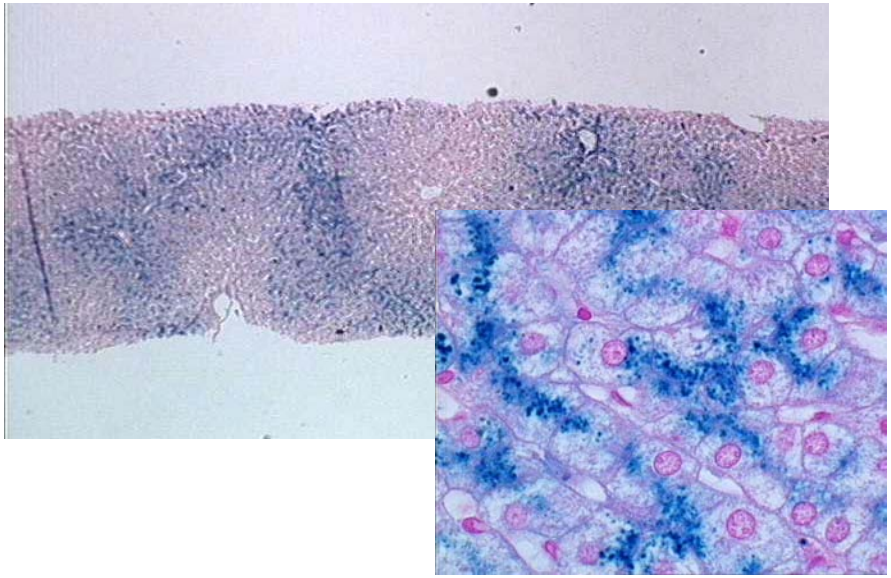
- **“loss of function”:**
  - affect **the localization of FPN to the cell membrane and/or iron export function** leading to iron sequestration within the cell;
  - associated with **hyperferritinemia, normal or low Tfsat%, and iron accumulation principally within the macrophages (type4a).**

- **“gain of function”:**
  - **affect the interaction between hepcidin and FPN**, making FPN resistant to hepcidin which normally leads to internalization and degradation of the FPN protein. **Iron is thus continually exported from the cells to the plasma**;
  - Associated **with high Tfsat%, hyperferritinemia and iron overload, mostly affecting hepatocytes** similarly to classic hereditary hemochromatosis **(type4b).**

Clinical features of Type 4a *versus* Type4b/classic hemochromatosis





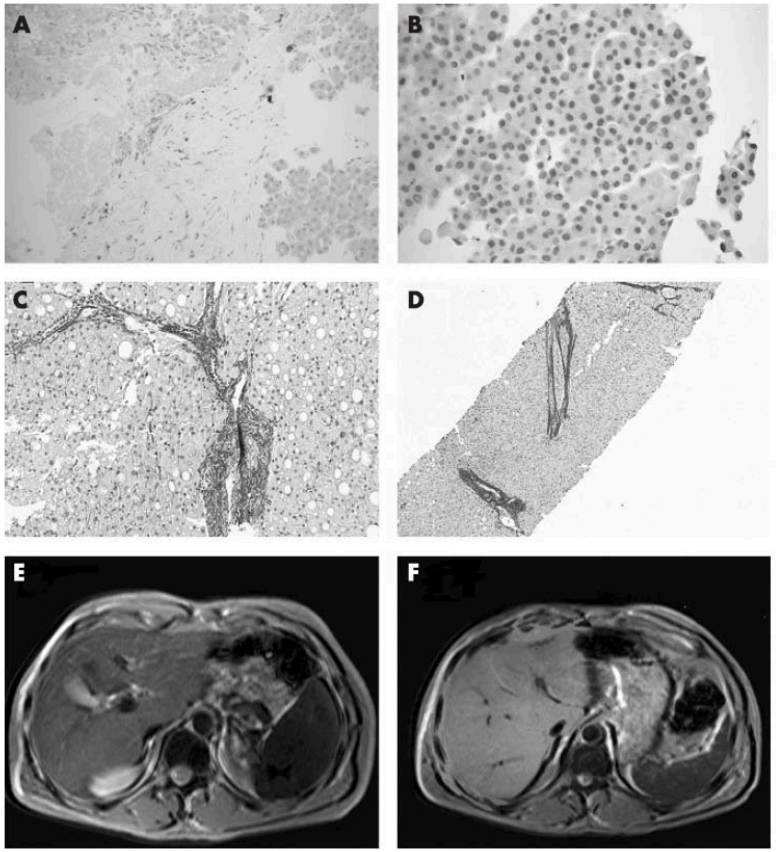


Natural History

- **Case reports** and small series
- **Meta-analysis** of literature and **review** of case series
- **MRI** studies

Natural history

- **Case reports and small series**



Disease progression and liver cancer in the Ferroportin Disease
(Corradini et al. Gut 2007):

- HCC
- Liver fibrosis
- Residual iron accumulation in spleen

Table 1 Biochemical and clinical data of the subjects with ferroportin-related iron overload

No	Subjects	Age at diagnosis (years)*	Years on phlebotomy	Serum ferritin level at present, (µg/l)	Liver iron concentration at present, (µmol/g)	Liver fibrosis at diagnosis	Liver fibrosis at present
1	V_{13}	59	20	690	55	F1	F2
2	VI_{25}	34	15	650	35	F0	F0
3	VI_{26}	20	11	670	35	F0	F0
4	VI_{30}	37	12	410	28	F0	F0
5	VI_{33}	39	11	827	75	F0	F3
6	VI_{36}	34	15	750	65	F0	F2

Patient numbering is the same as that used in the original publication[1].
*All patients were male.

Natural history

- Case reports and small series

- **Meta-analysis of literature and review of case series**:
  - age, hepatic iron content, and comorbidities associated with fibrosis *(Mayr, J.Hep 2010)*;
  - phenotype is milder in women and younger subjects *(Le Lan, Gastro 2011);*
  - trasferrin saturation, which correlates with fibrosis and AST/ALT, may be a marker of disease severity *(Le Lan, Gastro 2011);*
  - Ferroportin Disease is an iron overload disease with limited consequences in the absence fo environmental/acquired cofactors *(Le Lan, Gastro 2011);*
  - Ferroportin Disease has incomplete penetrance *(Mayr J.Hep 2010, Le Lan, Gastro 2011)*
  - phenotypic variability may be related to co-inheritance of other genes involved in iron homeostasis *(Le Lan, Gastro 2011)*
  - not all mutations were unambiguosly correlated with *classic or non classic* phenotype *(Mayr J.Hep 2010, Le Lan, Gastro 2011)*

- MRI studies

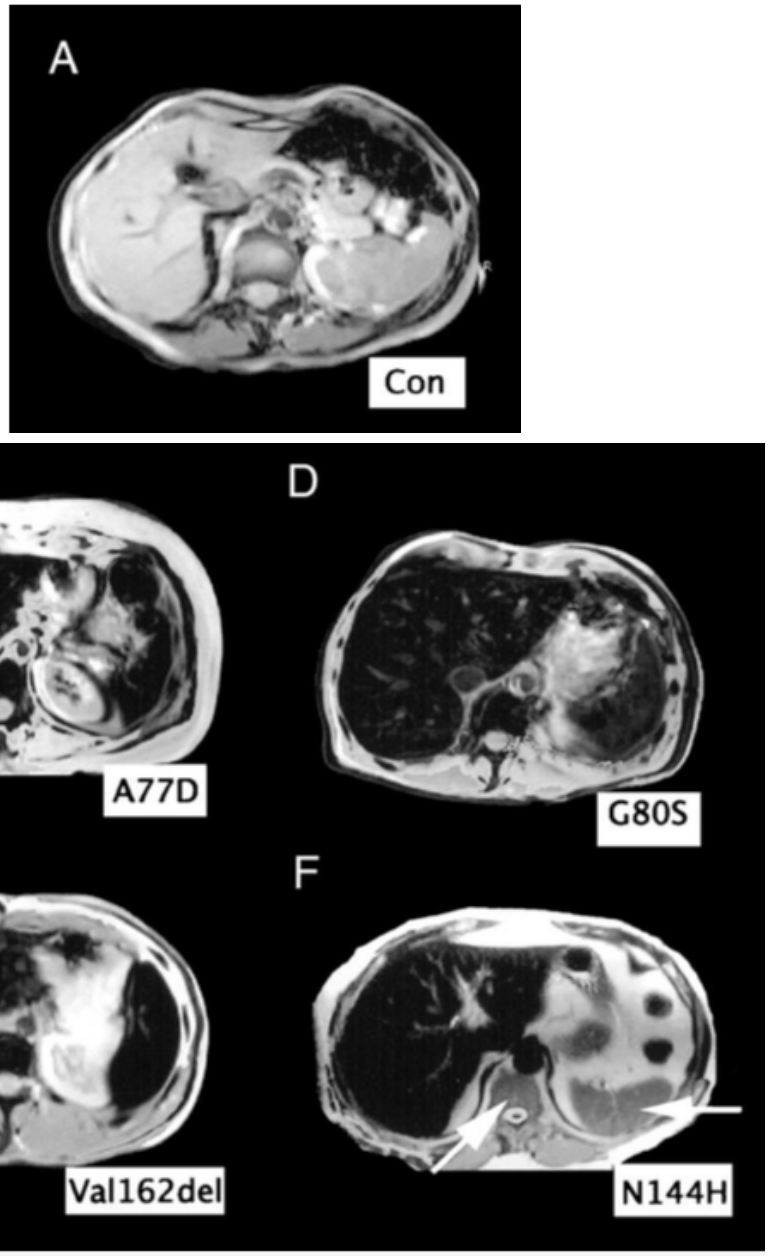
Natural history

- Case reports and small series
- Meta-analysis of literature and review of case series
- **MRI studies**

MRI

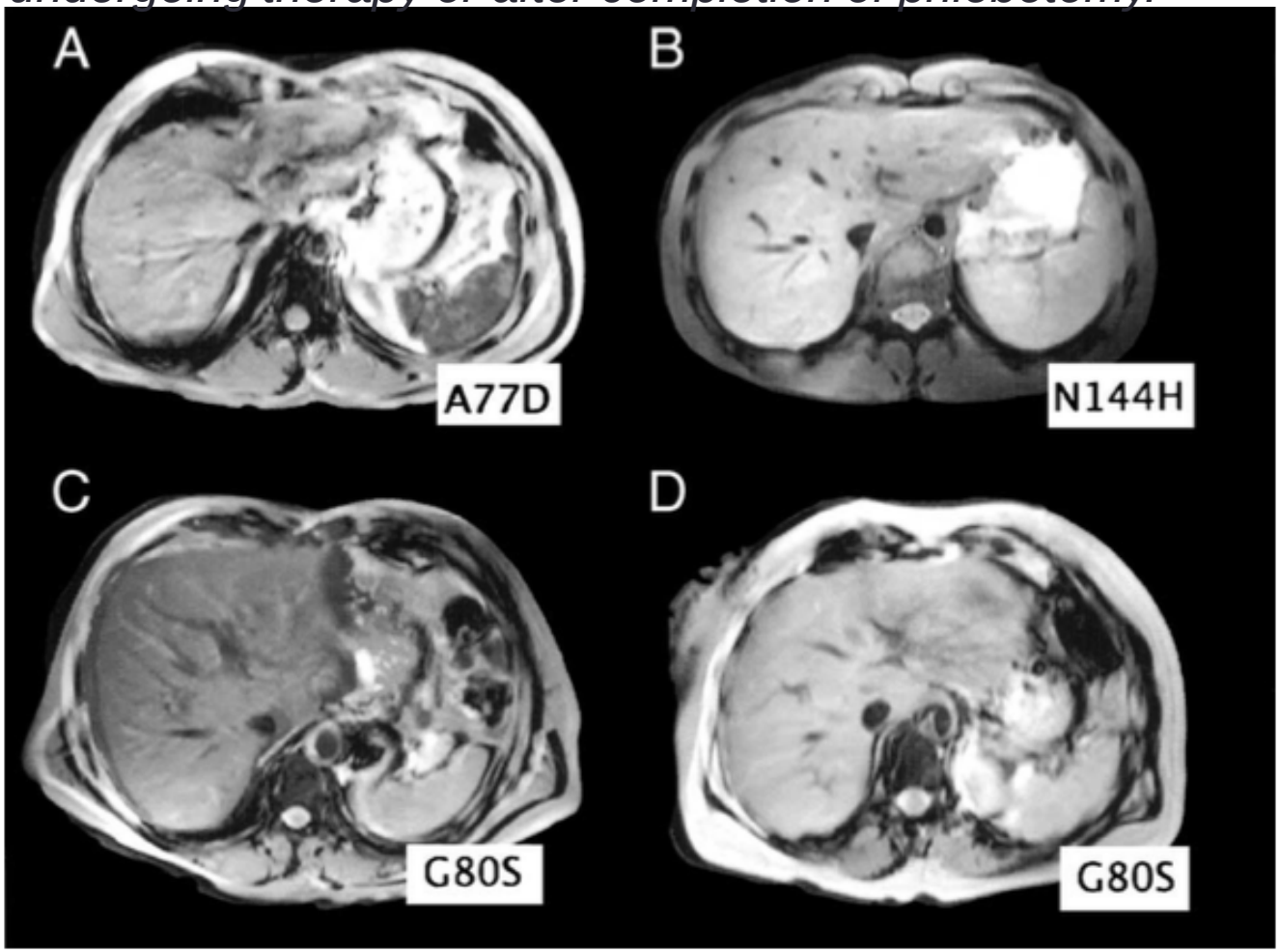
Magnetic Resonance Imaging is a **useful non-invasive diagnostic tool to suspect and categorize** the disease…

Magnetic resonance imaging from affected individuals.



MRI

Magnetic resonance imaging from affected individuals undergoing therapy or after completion of phlebotomy.



…to monitor the **staus of iron depletion**, and gain insights on **natural history and management** of type 4 hemochromatosis.

Disease management: Ferroportin Disease (type 4a)

- No standardized therapeutic phlebotomy schedule.

- Although phlebotomy is an effective therapeutical tool, **in some individuals a weekly phlebotomy program is not tolerated**.
- With a less aggressive phlebotomy regimen, they can also be iron depleted, although a therapeutic target of ferritin <50 ng/ml should be avoided due to the risk of anemia.
- **Reports of liver and spleen iron depletion in presence of ferritin levels within the normal range** (< 200 ng/ml) has been described by MRI.
- **Reports of spleen and/or BM residual iron accumulation in well-treated patients with normal ferritin and LIC**.
- Discontinuation of phlebotomy treatment is followed by a **rapid rise of serum ferritin.**

Disease management: Ferroportin Disease (type 4a)

- *Endpoint* of therapeutic phlebotomy should be **at least the normalization of ferritin level**.
- *Maintenance (life-long)*: 2-4 phleb/year to keep **ferritin at least within the normal range.**
- **Tailored therapy** (degree of iron overload, tolerance, comorbidities…).
- **MRI may be helpful to monitor iron status.**
- **Surveillance for liver cancer.**
- **Iron chelation:**
  - Case report of therapy with *deferasirox 10 mg/kg/day for 9 months*, in a 15 y.o. female (P.Val162del); hepatic iron content was normalized *(Unal, Piperno et al, Journal Trace Elements 2015).*

Aceruloplasminemia

- Ceruloplasmin is a copper-containing **ferroxidase** that catalyzes the oxidation of ferrous to ferric iron, necessary for the release of iron to plasma transferrin.
- This activity of regulation of efficient iron efflux seems to involve the **stabilization of membrane Ferroportin**.

- The disease id caused by **mutations in Ceruloplasmin gene leading to the complete absence of CP ferroxidase activity.**

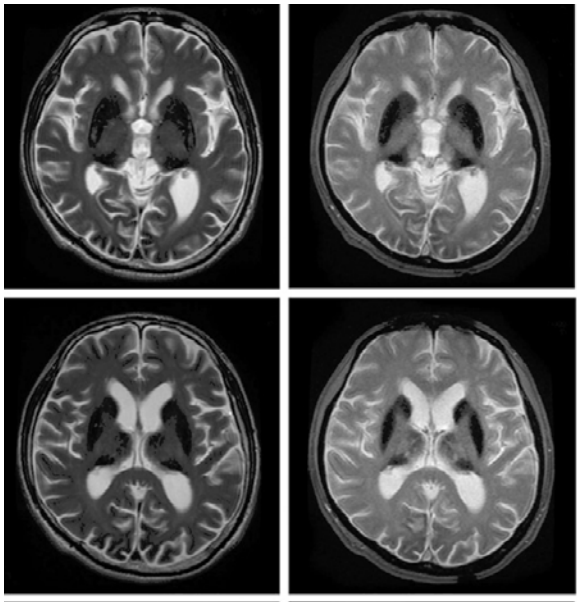
- **First description in Japan** (*Miyajima H, Nishimura Y, Mizoguchi K, Sakamoto M, Shimizu T, Honda N*. ***Familial apoceruloplasmin deficiency associated with blepharospasm and retinal degeneration. Neurology 1987***).

- Very rare **autosomal recessive disease**
- The prevalence of aceruloplasminemia was estimated at 1/2,000,000 in Japan.
- Reports of aceruloplasminemia in Europe and USA

Miyajima H et al. Neurology 1987
Reviewed in Kono S, Inter Rev Neurobiol 2013 and Miyajima H, Neuropathology 2015

Aceruloplasminemia

- The diagnosis relies on demonstration of :
  - the **absence (or low levels) of serum CP (or ceruloplasmin with no ferroxidase activity**)
  - and some combination of the following: **low serum copper, low serum iron, mild anemia, high serum ferritin, high LIC**.
  - strongly **supported by characteristic MRI finding in brain and liver.**



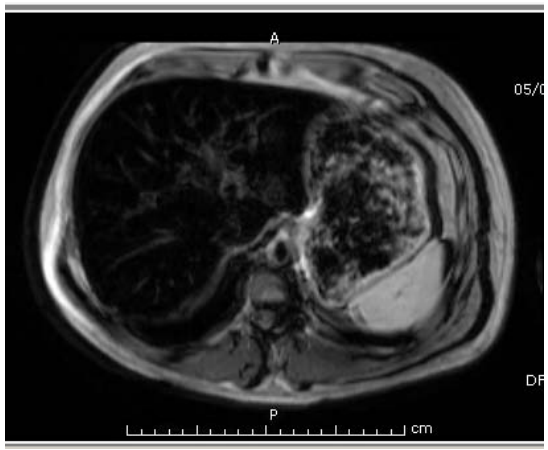
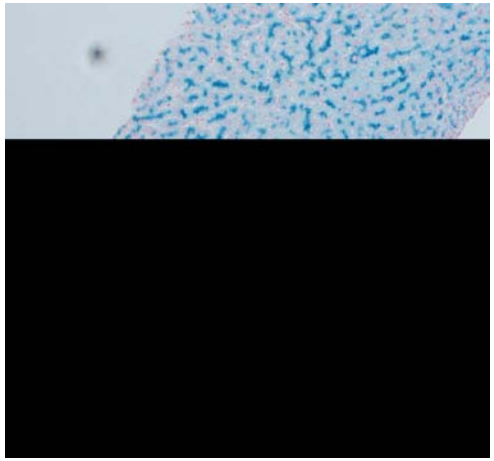


Table 6.1 The clinical characteristics of patients with aceruloplasminemia

Clinical manifestations in 71 patients with aceruloplasminemia
• Anemia (80%) • Retinal degeneration (76%) • Diabetes mellitus (70%) • Neurological symptoms (68%) **1.** Ataxia (71%): dysarthria > gait ataxia > limb ataxia **2.** Involuntary movement (64%): dystonia (blepharospasm, grimacing, neck dystonia) > chorea > tremors **3.** Parkinsonism (20%): rigidity > akinesia **4.** Cognitive dysfunction (60%): apathy > forgetfulness
Onset of clinical manifestations
• Diabetes mellitus: under 30 years old, 18%; 30–39 years old, 35%; 40–49 years old, 31%; over 50 years old, 16% • Neurological symptoms: under 40 years old, 7%; 40–49 years old, 38%; 50–59 years old, 42%; over 60 years old, 13%
Laboratory findings
• Undetectable serum ceruloplasmin • Elevated serum ferritin • Decreased serum iron, iron-refractory microcytic anemia • Low serum copper and normal urinary copper levels
MRI (magnetic resonance imaging) findings
• Low intensity on both T1- and T2-weighted MRI in the liver and the basal ganglia, including the caudate nucleus, putamen and pallidum, and the thalamus
Liver biopsy results
• Excess iron accumulation (>1000 μg/g dry weight) within hepatocytes and reticuloendothelial cells • Normal hepatic architecture and histology without cirrhosis or fibrosis • Normal copper accumulation



Aceruloplasminemia

Therapy

- Not standardized
- **Different protocol, with different drugs and time schedule:**
  - *Deferoxamine (with or without association to frozen plasma)*
    - Concerns on BBB crossing
    - Controverse results (brain MRI improvement or no results)
  - *Deferiprone*
    - BBB crossing
    - Controverse results (only one study, no improvements)
  - *Deferasirox*
    - No disease progression
    - Mild/moderate neurological improvement

Atransferrinemia-hypotransferrinemia

- **Transferrin** delivers iron to the erythorid precursors ➔ decreased hemoglobin synthesis ➔ increased intestinal absorption of iron that is efficiently imported by parenchymal cells

- The **disease** is:
  - associated to autosomal recessive mutations
  - extremely rare

- Most **patients** present with
  - **severe microcytic hypochromic anemia** at birth
  - **high serum ferritin and serum iron**
  - systemic **iron overload**

- **Therapy**
  - Patients appear to respond to a combined therapy (fresh frozen plasma and iron depletion via phlebotomy or chelation)

Heilmeyer L et al. DMW 1961, Hayashi A et al. A J Hum Genet 1993, Beutler E et al. Blood 2000, Kinsley AS et al Blood 2004, and others…

DMT1 deficiency

- **Divalent Metal transporter 1** (DMT1):
  - the protein that transport iron at the apical membrane of duodenal enterocyte
  - allows the iron exit from acidified endosomes

- The **disease** is:
  - associated to autosomal recessive mutations
  - extremely rare

- Most **patients** present with
  - severe **hypochromic anemia** at birth
  - increased transferrin saturation and **slightly elevated serum ferritin**
  - **marked hepatic iron overload**

- **Therapy**
  - Patients appear to respond to EPO

Mims MP et al. Blood 2005, Lam-Yuk-tesung S et a. BCMD 2006, beaumont C et al. Blood 2006, Iolascon A et al. Blood 2006, and others..

H-Ferritin related iron overload

- Members of a **Japanese family** with heterozygous mutation on the IRE motif of 5'-UTR

- Autosomal recessive
- **Hyperferritemia and concomitant iron overload**

Kato J et al. Am J Hum Genet 2001

- *Animal study*:
  - mice with ferritin H gene deletion: develop hemochromatosis
  - H-ferritin is required to limit iron efflux from intestinal cells in mice

Hereditary causes of hyperferritinemia

- **with iron overload**
  - Hereditary Hemochromatosis
  - Hereditary Iron-loading anemias (*Beta-Thalassemia syndromes, congenital sideroblastic anemia or dyserythropoietic anemias*)
  - Ferroportin diseases
  - Aceruloplasminemia
  - A/hypotransferrinemia
  - DMT1 deficiency
  - H-ferrtin related iron overload

- **without iron overload**
  - Hereditary Hyperferritinemia Cataract Syndrome
  - Benign-hyperferritinemia

Hereditary Hyperferritinemia-Cataract Syndrome

- In 1995 two groups in Italy and France independently discovered **families with hyperferritinemia of unexplained aetiology that co-segregated with autosomal-dominant cataract at young age.**

- Shortly thereafter both groups described the **molecular basis** of the disease: **mutations in the iron responsive element (IRE) of L-ferritin**

  ➔ reduction of the binding affinity of IRP to IRE

  ➔ **reduction of the negative control of L-ferritin synthesis** (uncontrolled and sustained ferritin translation)

  ➔ **increased serum ferritin levels (600-3000 ng/ml)** with normal serum iron and transferrin saturation.

Girelli et al. Br J Hematol 1995, Girelli et al. Blood 1995
Bonneau et al. J Med Genet 1995, Beaumont et al. Nat gen 1995

Hereditary Hyperferritinemia-Cataract Syndrome

- The expansion of ferritin (L-ferritin homopolymers and L-chain-rich heteropolymers) does not have major effects on cellular iron metabolism.

- L-ferritin deposition in the ocular lens causes **bilateral cataract** (pulverulent aspect) **at an early age**

- **Autosomic dominant** transmission
- Heterogeneous mutations (>30)

- The **clinical severity** (serum ferritin and visual impairent) **correlate with the type of mutation.**

Levi S et al. Blood 1998 and review in Millonig et al. Human Genomic 2010

Hereditary Hyperferritinemia-Cataract Syndrome

***Suspect case*:**

- Constantly high levels of serum ferritin
- Familial cataract and/or familial hyperferritinemia
- No signs of iron overload, liver disease or hematological disease (normal CBC, serum iron, transaminases)
- No relevant clinical symptoms apart visual impairment, if any

Diagnosed case:

- Patients do not develop iron overload
- Liver biopsy not indicated
- The only clinical consequence is cataract

Review in Millonig et al. Human Genomic 2010

Benign Hyperferritinemia

- In 2009 from a French group it was reported a new mutation in the **coding region of L-ferritin** subunit that **co-segregated with hyperferritinemia at the heterozygous status.**

- The serum ferritin of the family members carrying the mutation ranged from 400 to 6000 ng/ml, with high percentage of ferritin glycosilation

- There was important fluctuations of the leves with the time or between individuals
- No reproducible symptoms could be identified;
- Only one of the probads had cataract.

- In 2012 two novel missense variants were associated with hyperferritinemia with hyperglicosilation.

Kannengiesser C et al. Haematologica 2009
Thurlow V et al. Ann Clin Biochem 2012

Gaucher disease

- Gaucher is a rare lysosomal disease characterized by large amount of lipid-storing macrophages.
- Evidence of **iron accumulation in Gaucher'cells and different tissues, associated with hyperferritinemia (hallmark of the disease).**
- There is a **focal iron overload**, **not primarily related to a genetic defect of the regulation of iron balance**, but secondary to another genetic disease.
- A **chronic low grade inflammation state can lead to high ferritin and high hepcidin** with subsequent trapping of ferritin and/or iron in macrophages.
- Severe anemia and splenectomy may favour the iron loading.

Reviewed in Regenboog M et a. Blood Reviews 2016

Mixed (genetic and acquired) causes of hyperferritinemia **with iron overload**

- **African (Bantu) siderosis**
  - alcoholic beverages, iron pots, genetic modifiers *(FPN)*
- **Porphyria cutanea tarda**
  - alcohol abuse, HCV, HIV, genetic modifiers *(HFE)*

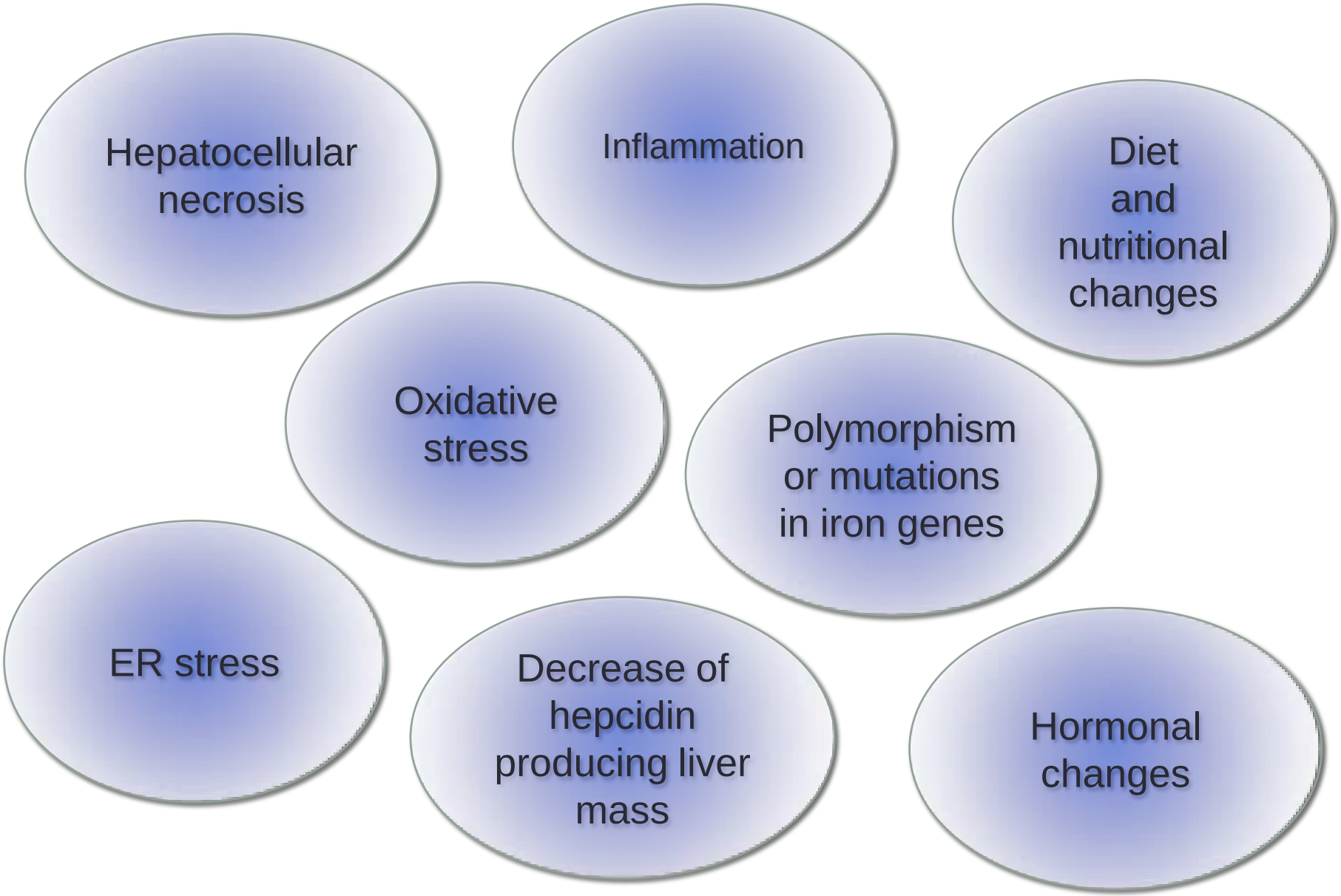
Acquired causes of hyperferritinemia

- **without true iron overload**
  - Infections
  - Immunological diseases
  - Inflammatory diseases
  - Autoimmune diseases
  - Cancer
  - Tissue injury or necrosis
  - Alcohol ingestions

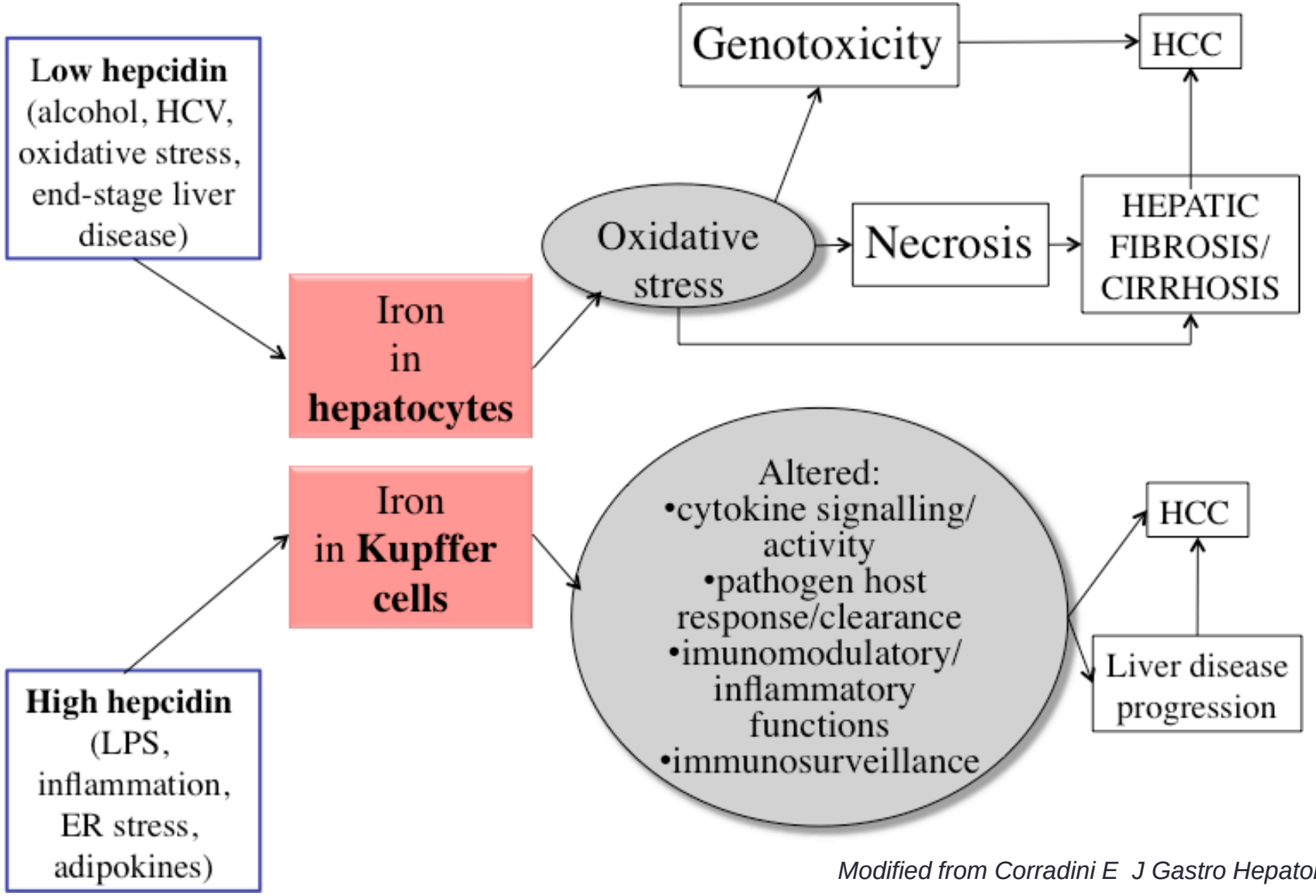
- ✓ Inflammatoty signals modulate ferritin expression
- ✓ Inflammatory signals increase hepcidin expression (iron misdistribution)
- ✓ Ferritin leakage from damaged cells
- ✓ Alcohol induce ferritin synthesis

- **with iron overload**
  - Acquired causes of bone marrow failure
  - Chronic liver diseases
  - Chronic alcohol abuse
  - NAFL and metabolic syndrome

Causes of iron status changes in chronic liver diseases



During the dynamic evolution of CLD diverse signals may modulate hepcidin expression in the opposite directions



Modified from Corradini E J Gastro Hepatol 2012

Alcohol-related hyperferritinemia and/or iron overload

- Alcohol increases the synthesis of ferritin
- Increased ability of desialylated transferrin to deliver iron to the liver
- Chronic hemolysis
- Ineffective erythopoiesis
- Alcohol consumption induce acute and chronic liver injury
- Alcohol **inhibits hepcidin transcription via oxidative stress**

Reviewed in Piperno Haematologica 1998
Harrison-Findik DD et al. J Biol Chem 2006
Bridle K et al. Alcohol Clin Exp Res 2006

Steatosis, iron and liver disease progression

- **The relationship between hepatic iron burden (and in particular the site of iron excess) and disease progression in NAFLD is controversial**.

- Increased serum ferritin with normal Tf-sat%:
  - frequently found in patients with hepatic steatosis
  - reflects iron overload only in those patients in whom it persists despite an appropriate diet

- Excessive iron accumulation:
  - not observed in the majority of patients with NAFLD
  - unlikely the main reason for progression to cirrhosis

- Ferritin is a risk factor for DM and may represent a marker of vascular damage in NAFL patients.

Bugianesi E et al. Hepatology 2004; Fargion S et al. Am J Gastroenterol 2001; Ferrannini E Lancet 2000; Younossi ZM et al Hepatology 1999; Valenti L et al. Am J Gastroenterol. 2007; Valenti L et al. Gastro 2010; Valenti L et al. NMCD 2011 Nelson JE et al. Hepatol 2011

Steatosis, iron and liver disease progression

- Phlebotomy improves **diabetes** in animal models.
- In healthy volunteers, blood donation improves insulin sensitivity and protects from **T2DM**.
- Iron-related IR is improved by phlebotomies in **NAFLD**.
- In a case-control study phlebotomy reduced IR more than lifestyle modifications in patients with **NAFLD and hyperferritinemia**.

Facchini FS et al. Gastro 2002; Fernandez-Real JM et al. Diabetes 2002; Piperno A et al. Liver Int. 2004; Sumida Y et al. Hepatol Res 2006; Valenti L et al. Am J Gastroenterol. 2007; Valenti L et al QJM 2011

Steatosis, iron and liver disease progression

- Liver sinusoidal iron overload may be associated with development of liver **cancer** in patients with **NASH-related cirrhosis.**

Sorrentino P et al. 2009. J Hepatol 2009

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
May 2015

The Impact of Phlebotomy in Nonalcoholic Fatty Liver Disease: A Prospective, Randomized, Controlled Trial

Leon A. Adams,[1,2] Darrell H. Crawford,[3,4] Katherine Stuart,[4] Michael J. House,[5] Timothy G. St. Pierre,[5] Malcolm Webb,[6] Helena L.I. Ching,[2] Jenny Kava,[7] Michael Bynevelt,[8] Gerry C. MacQuillan,[1,2] George Garas,[1,2] Oyekoya T. Ayonrinde,[7,9,10] Trevor A. Mori,[1] Kevin D. Croft,[1] Xianwa Niu,[1] Gary P. Jeffrey,[1,2] and John K. Olynyk[7,9,10]

Prospective RCT trial conducted in 74 patients with NAFLD, with a 6 months follow-up, **iron removal by way of venesection was not associated with any significant improvement in steatosis, liver injury, insulin sensitivity, measures of LPO**, or quality of life.
(No liver biopsy)

World Journal of Gastroenterology

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BRIEF ARTICLE

A randomized trial of iron depletion in patients with nonalcoholic fatty liver disease and hyperferritinemia

Luca Valenti, Anna Ludovica Fracanzani, Paola Dongiovanni, Serena Rovida, Raffaela Rametta, Erika Fatta, Edoardo Alessandro Pulixi, Marco Maggioni, Silvia Fargion

RCT trial on 38 **NAFLD (2/3 NASH) patients with hyperferritiemia** despite after 6 months of lifestyle changes, with a 2 years followup.
Iron depletion was associated with a higher rate of improvement of histological liver damage, with amelioration of liver enzymes.

Hyperferritinemia

- Can be of **genetic or acquired origin,** and

  - …. **not always represents iron overload**!

    (inflammatory, infectious or immunological diseases, malignancy, tissue injury such as massive liver necrosis, splenic and myocardial infaction, hereditary hyperferritinemia with/without cataract,...)

  - …. **in case of association with iron overload, the latter is not always systemic (= regional/focal)!**

    (chronic liver diseases, neurodegenerative disorders, Gaucher disease...)

  - …. **in cases of regional/focal iron excess, ferritin levels can be within the normal range**!

    (neurodegenerative disorders, Neuroferritinopathy, Friederich

Hyperferritinemia