Prof.dr.Hans Van Vlierberghe
Maag-, Darm- en Leverziekten

Diagnostiek en behandeling van metabole leverziekten.

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Disclosures.

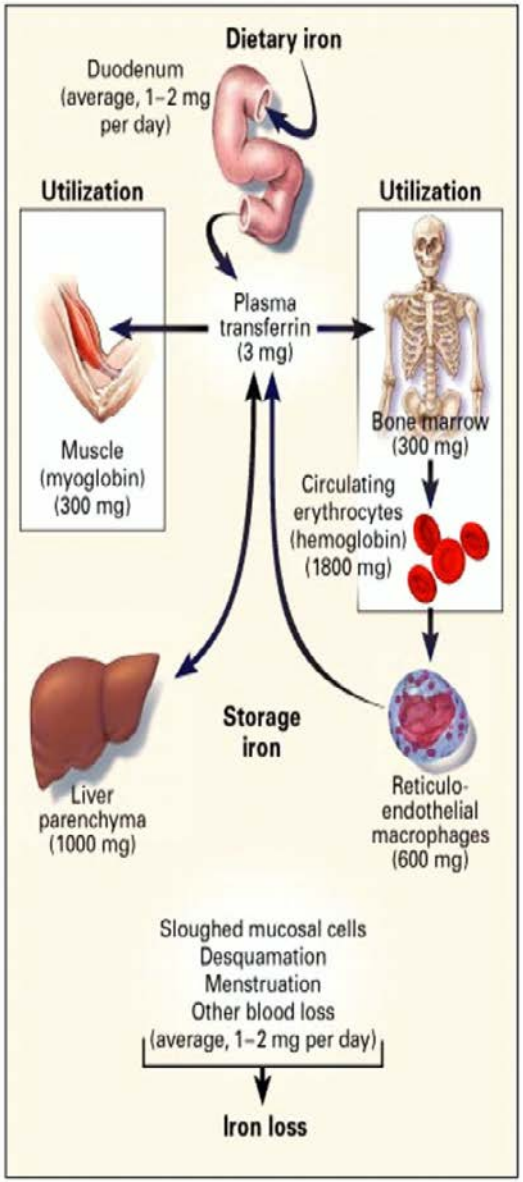
- Betaald door de Vlaamse overheid.
- Verder niets te melden.

- Hemochromatose
- Ziekte van Wilson
- Alfa 1 antitrypsine deficiëntie
- ….

Table 2. Classification of Iron Overload Syndromes

- Hereditary Hemochromatosis
  - *HFE*-related
    - C282Y/C282Y
    - C282Y/H63D
    - Other *HFE* mutations
  - Non–*HFE*-related
    - Hemojuvelin (*HJV*)
    - Transferrin receptor-2 (*TfR2*)
    - Ferroportin (*SLC40A1*)
    - Hepcidin (*HAMP*)
    - African iron overload
- Secondary Iron Overload
  - Iron-loading anemias
    - Thalassemia major
    - Sideroblastic
    - Chronic hemolytic anemia
    - Aplastic anemia
    - Pyruvate kinase deficiency
    - Pyridoxine-responsive anemia
  - Parenteral iron overload
    - Red blood cell transfusions
    - Iron–dextran injections
    - Long-term hemodialysis
  - Chronic liver disease
    - Porphyria cutanea tarda
    - Hepatitis C
    - Hepatitis B
    - Alcoholic liver disease
    - Nonalcoholic fatty liver disease
    - Following portocaval shunt
  - Dysmetabolic iron overload syndrome
- Miscellaneous
  - Neonatal iron overload
  - Aceruloplasminemia
  - Congenital atransferrinemia

Iron metabolism



- NEJM 1999;341:1986.

Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice

Gaël Nicolas*, Myriam Bennoun*, Isabelle Devaux†, Carole Beaumont†, Bernard Grandchamp†, Axel Kahn*,
and Sophie Vaulont*‡
*Institut National de la Santé et de la Recherche Médicale 129, Departement Genetique Developpement et Pathologie Moléculaire, Institut Cochin de Génétique Moléculaire.

PNAS,July 2001.

Molecule structure of human synthetic hepcidin-25

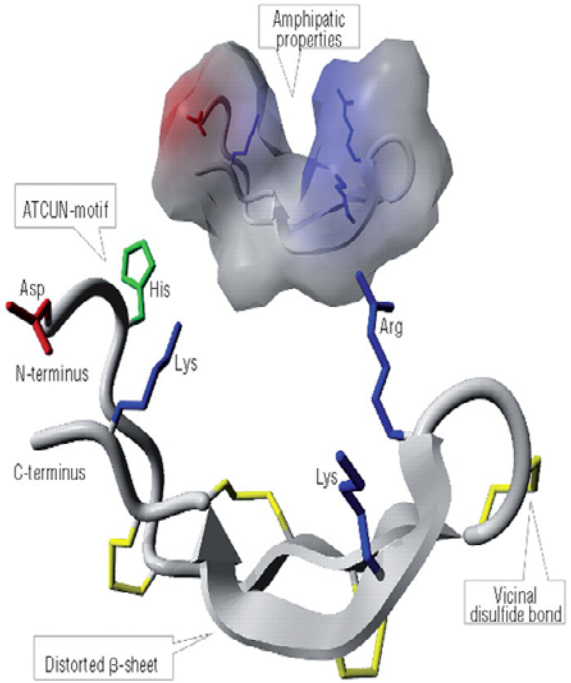
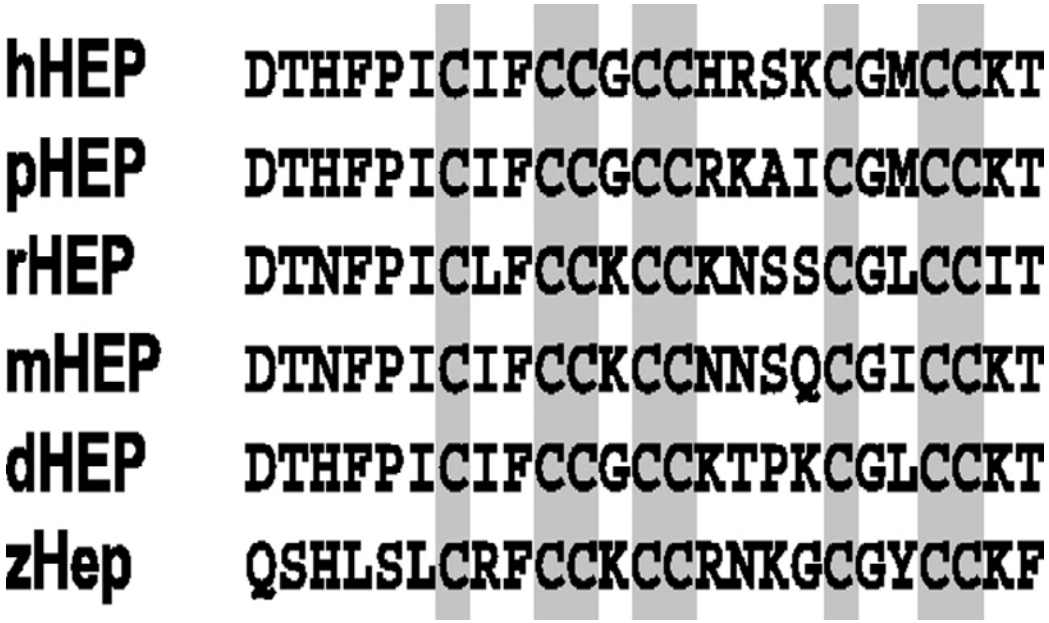


Figure 2. Molecule structure of human synthetic hepcidin-25. *Front*: overview of the structure of hepcidin-25. Distorted β-sheets are shown as grey arrows, and the peptide backbone is colored gray. The disulfide bonds are colored yellow, highlighting the position of an unusual vicinal bond between adjacent cysteines at the hairpin turn. Positive residues of Arginine (Arg)and Lysine (Lys) are pictured in blue, the negative residue of Aspartic acid (Asp) in red, and the Histidine containing amino terminal Cu^{2+}- Ni^{2+} (ATCUN)-binding motif in the N-terminal region is colored green. *Background*: hepcidin-25 molecule displayed with solvent accessible surface that illustrates the amphipathic structure of the molecule. The molecule is colored gray, except for the side-chains of positive (blue) and negative (red) residues. Molecular graphics created with YASARA[16] (*www.yasara.org*) and PovRay (*www.povray.org*), with coordinates and factors obtained from the Protein Data Bank (*www.rcsb.org*, PDB file code 1M4F).

Kemna, E. H.J.M. et al. Haematologica 2008;93:90-97

haematologica
the hematology journal

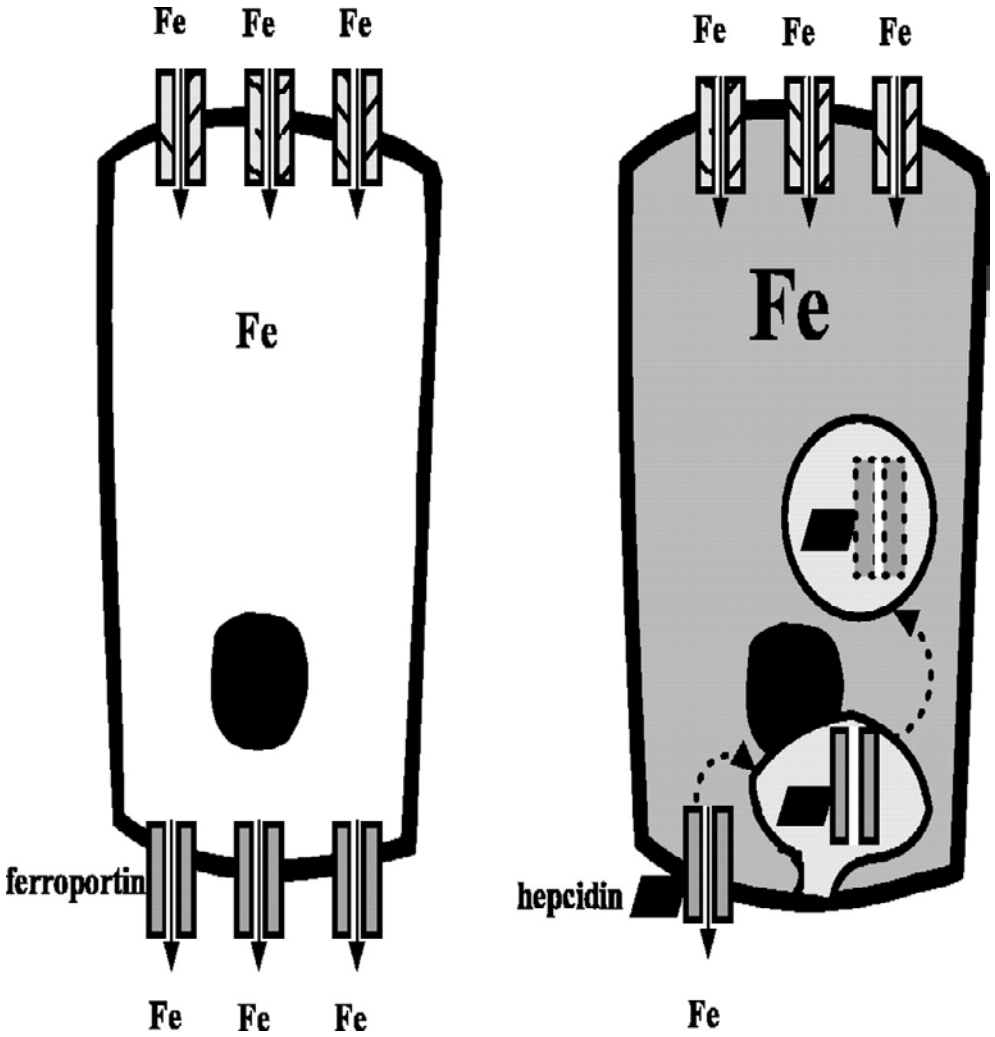
Sequences of verterbrate hepcidins



**Ganz, T. et al. Am J Physiol Gastrointest Liver Physiol 290: G199-G203 2006;
doi:10.1152/ajpgi.00412.2005**

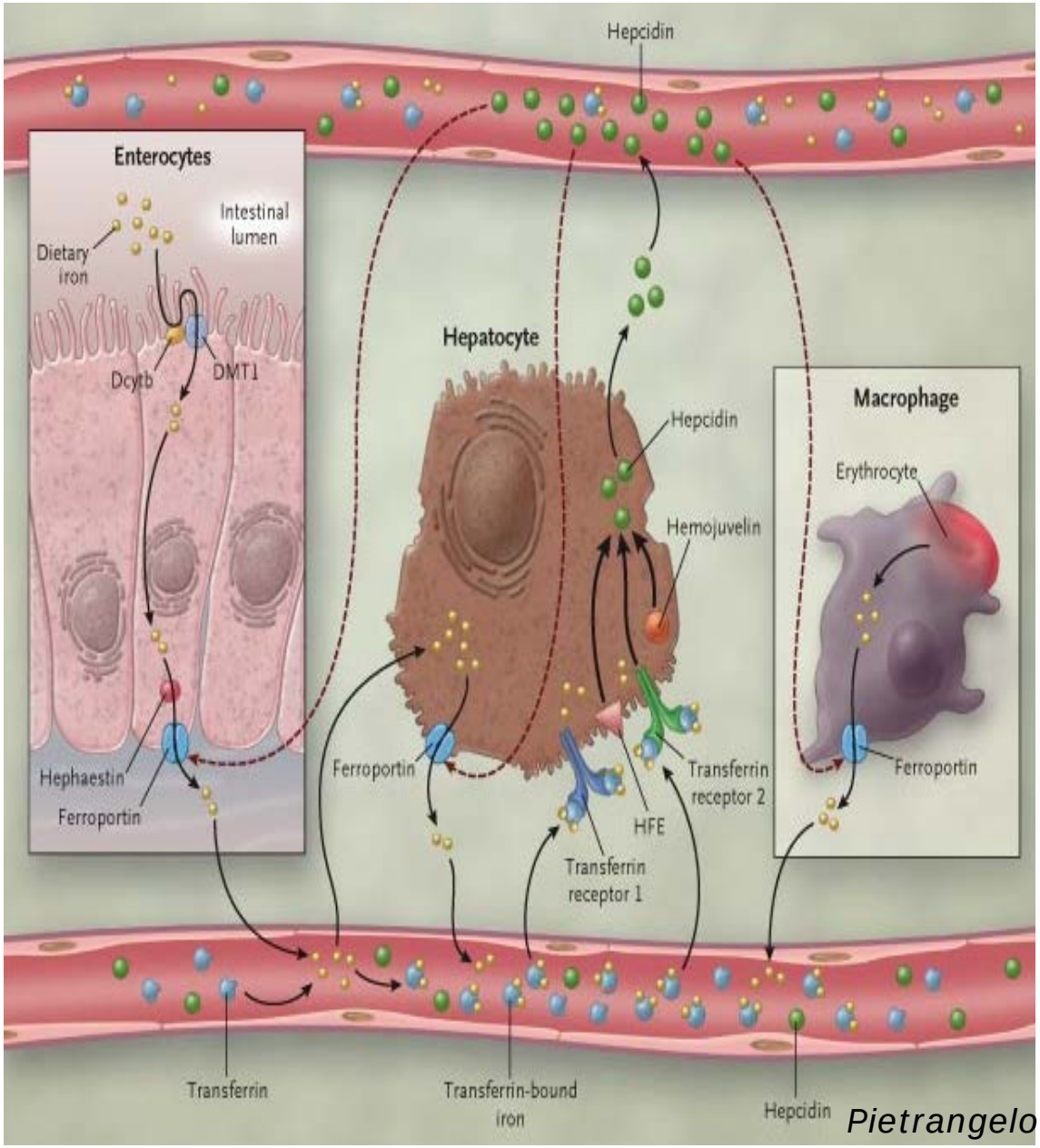
AJP - Gastrointestinal and Liver Physiology

Hepcidin regulates ferroportin expression on the basolateral membrane of enterocytes



Ganz, T. et al. Am J Physiol Gastrointest Liver Physiol 290: G199-G203 2006;
doi:10.1152/ajpgi.00412.2005

AJP - Gastrointestinal and Liver Physiology



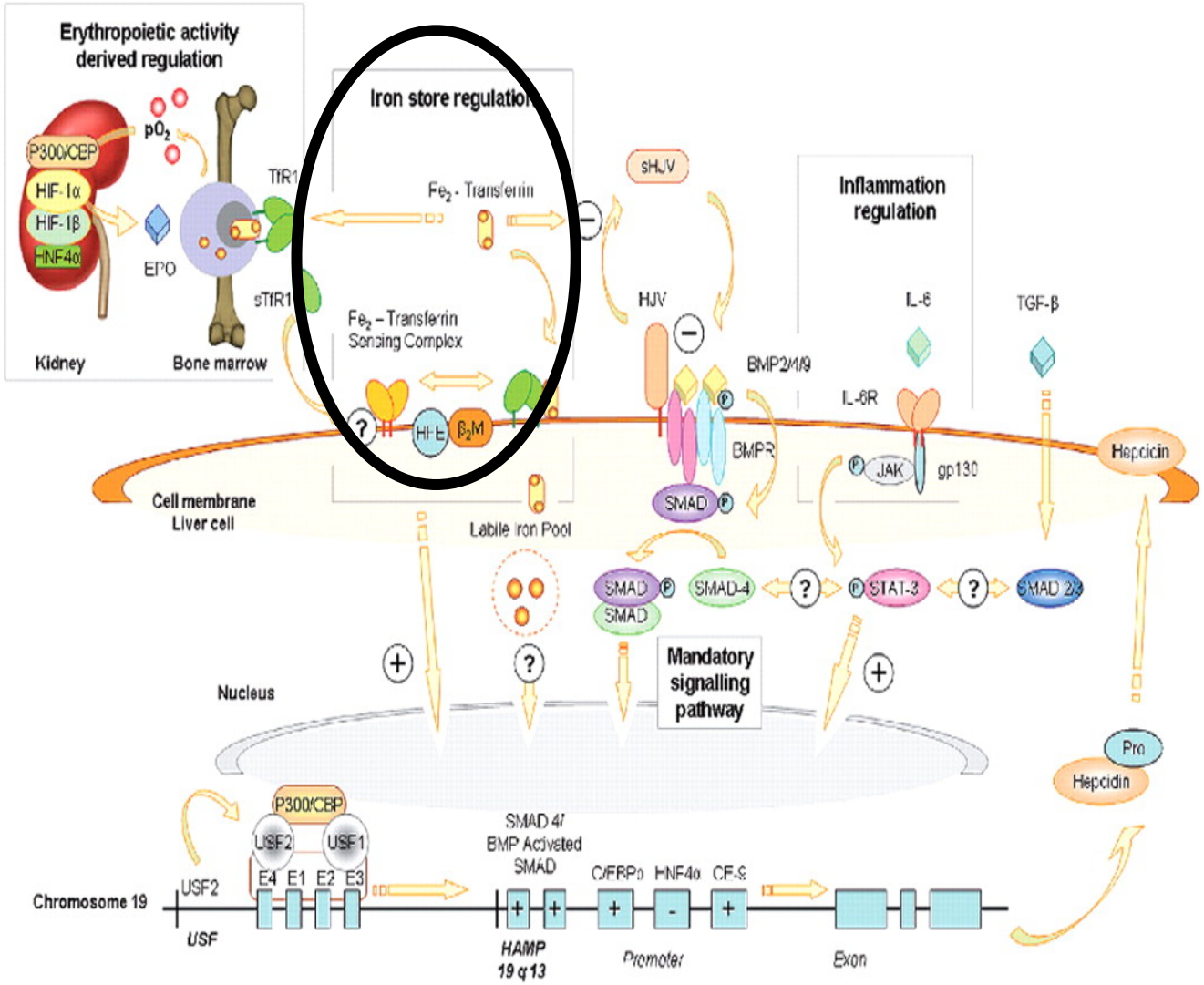
Pietrangelo NEJM 2004

Key points 1. Essentials on hepcidin

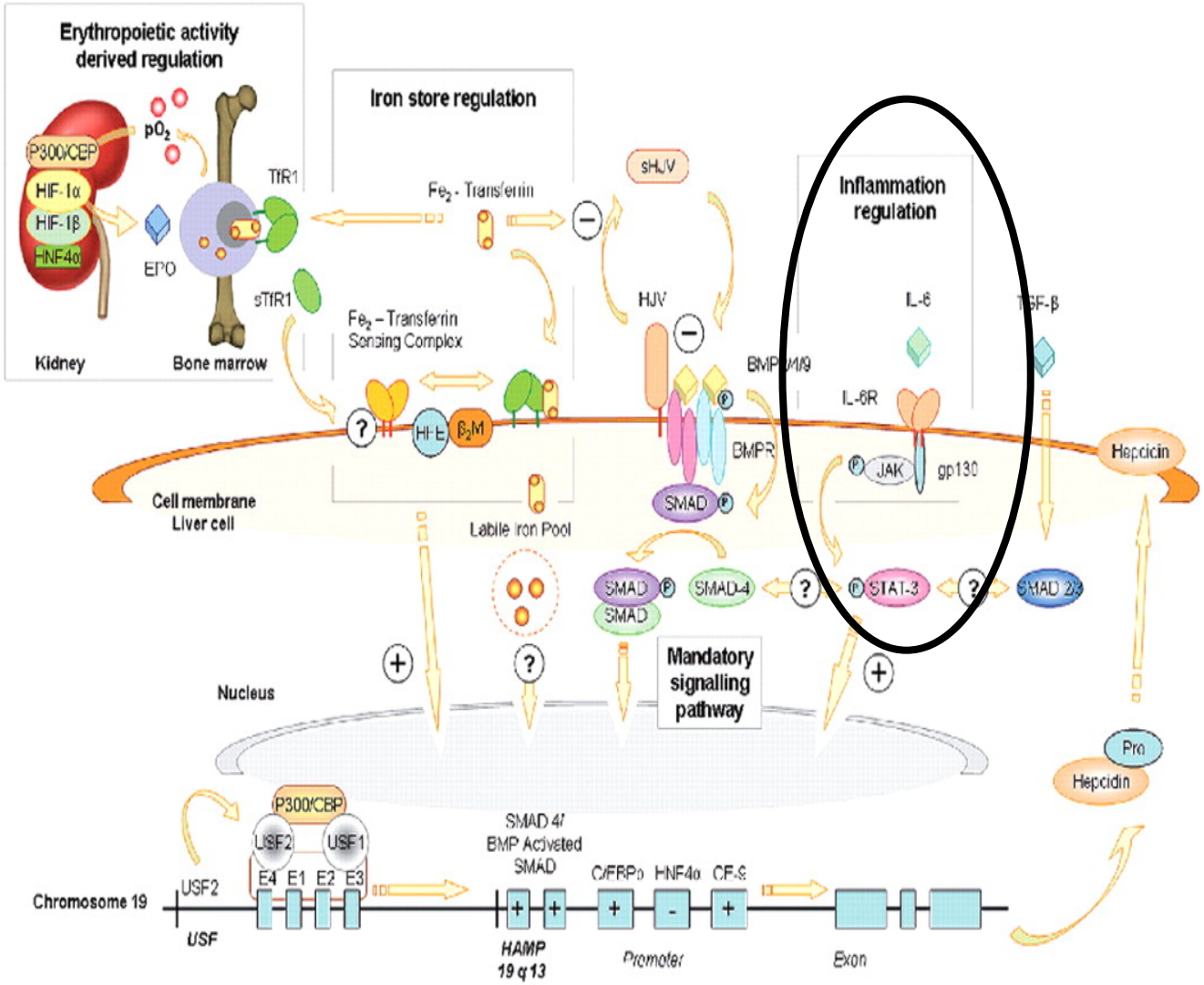
- Structure: 84 amino acid prepropeptide containing N-terminal 24 amino acid endoplasmic reticulum targeting signal sequence, and a 35 amino acid proregion with a consensus furin cleavage site followed by the C-terminal 25 amino acid bioactive iron-regulatory hormone
- Metabolism:
  - Synthesis: mainly in the hepatocytes
  - Serum concentration: 20–200 ng/ml
  - Excretion: kidney
- Regulation:
  - Stimulators: high serum/hepatic iron, inflammatory cytokines, bone morphogenetic proteins (BMPs), ER stress
  - Inhibitors: low serum/hepatic iron, anemia-hypoxia, bone-marrow derived factors (GDF15, TWSG1), erythropoietin
- Activity: N-terminus interacts with the iron-exporter ferroportin in macrophages, enterocytes, hepatocytes and placental cells and causes its internalization and degradation, leading to decreased cell iron efflux

GDF15: growth differentiation factor 15; TWSG1: twisted gastrulation protein homolog 1.

Model of pathways involved in hepcidin regulation



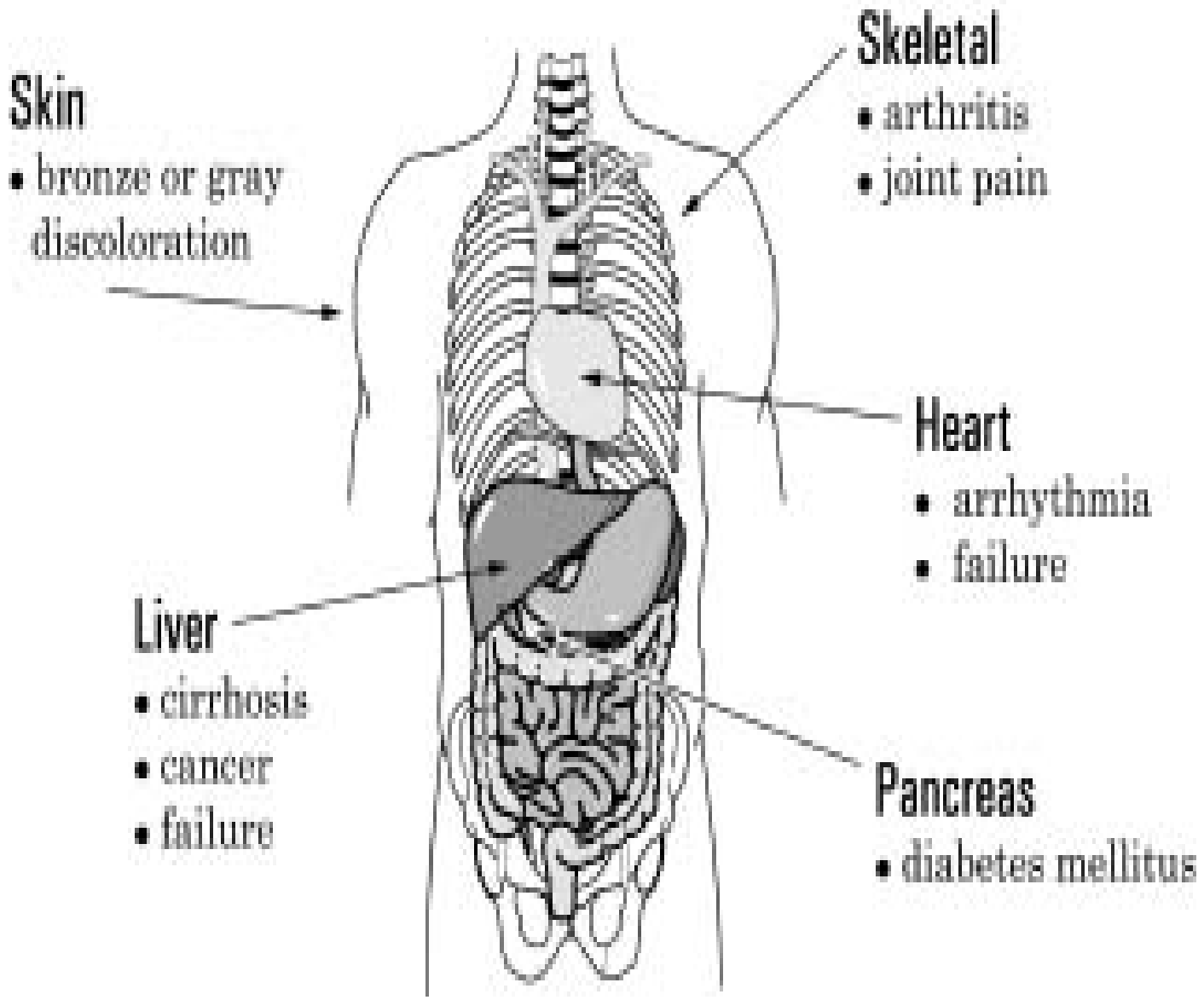
Model of pathways involved in hepcidin regulation



Erfelijke hemochromatose

Historiek

- 1865 – Trousseau
  - “bronsdiabetes”
- 1889 – Von Recklinghausen
  - “haemochromatosis”
- 1935 – Sheldon
  - erfelijke aandoening
- 1976 - Simon et al.
  - autosomaal recessieve ziekte, gekoppeld aan korte arm chromosoom 6 (HLA-A3)
- 1996 - Feder et al.
  - identificatie causale gen: initieel *HLA-H*
  - huidige naam: *HFE* gen

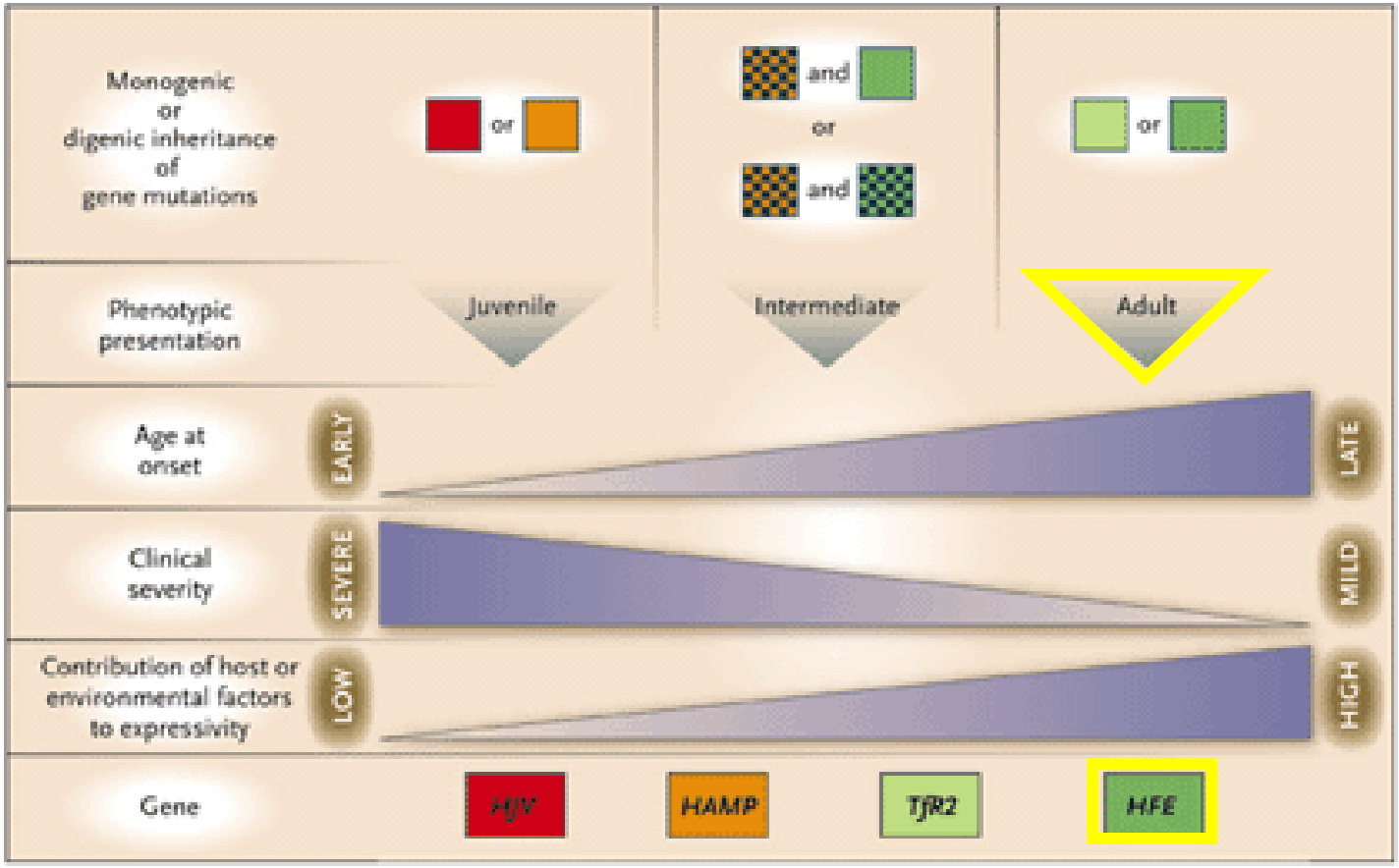

Skin
• bronze or gray discoloration
Skeletal
• arthritis
• joint pain
Heart
• arrhythmia
• failure
Liver
• cirrhosis
• cancer
• failure
Pancreas
• diabetes mellitus

HH type 1

- Variabele expressie

  - biochemische en klinische heterogeniteit

  - omgevingsfactoren, modifier genen => “multifactorieel”



Pietrangelo NEJM 2004

HH type 1 of *HFE*-HH

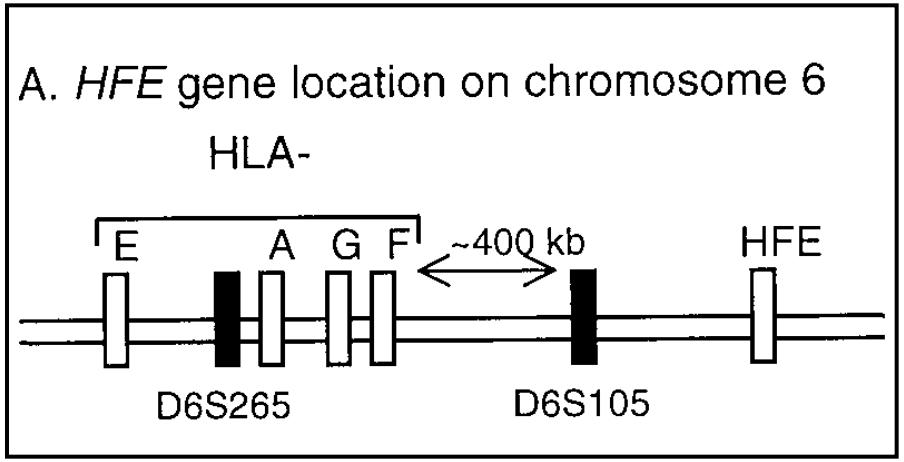
Gut, 1976, **17**, 332-334

Association of HLA-A3 and HLA-B14 antigens with idiopathic haemochromatosis

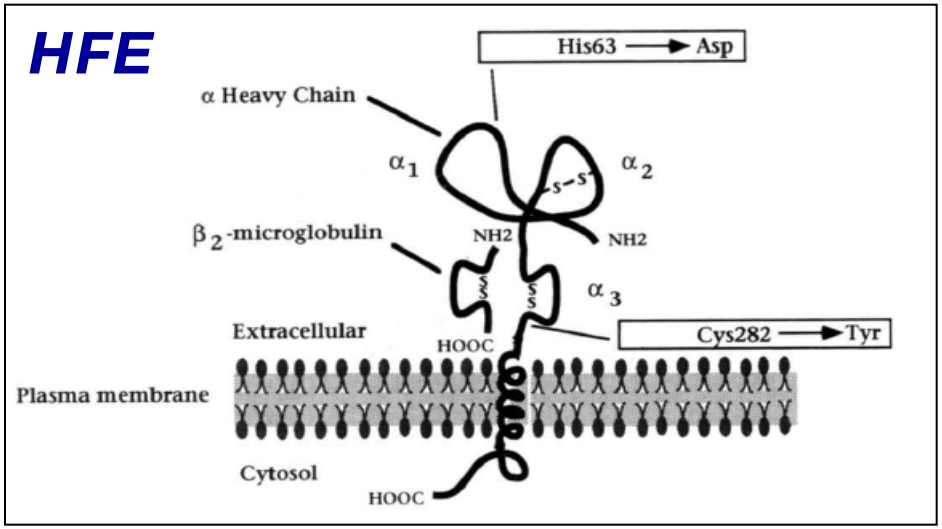
M. SIMON[1], M. BOUREL, R. FAUCHET, AND B. GENETET

From the Clinique Médicale A, Unité de Recherche U 49 (INSERM), and Centre Régional de Transfusion Sanguine, Hôpital Pontchaillou, Rennes, France

SUMMARY The frequency of HLA-A3 and HLA-B14 antigens was significantly higher in a series of 51 patients with idiopathic haemochromatosis than in a control group, being respectively 78·4 versus 27·0% and 25·5 versus 3·4%. This finding strongly supports the suggestion that idiopathic haemochromatosis is a genetic disease and suggests that the gene(s) responsible for the disease may be linked to the histocompatibility genes.



Simon et al. 1976



H63D

C282Y

Feder et al. 1996

Epidemiologie *HFE* mutaties

Table 1. Prevalence of *HFE* C282Y and H63D Genotypes According to Race or Ethnic Group.*

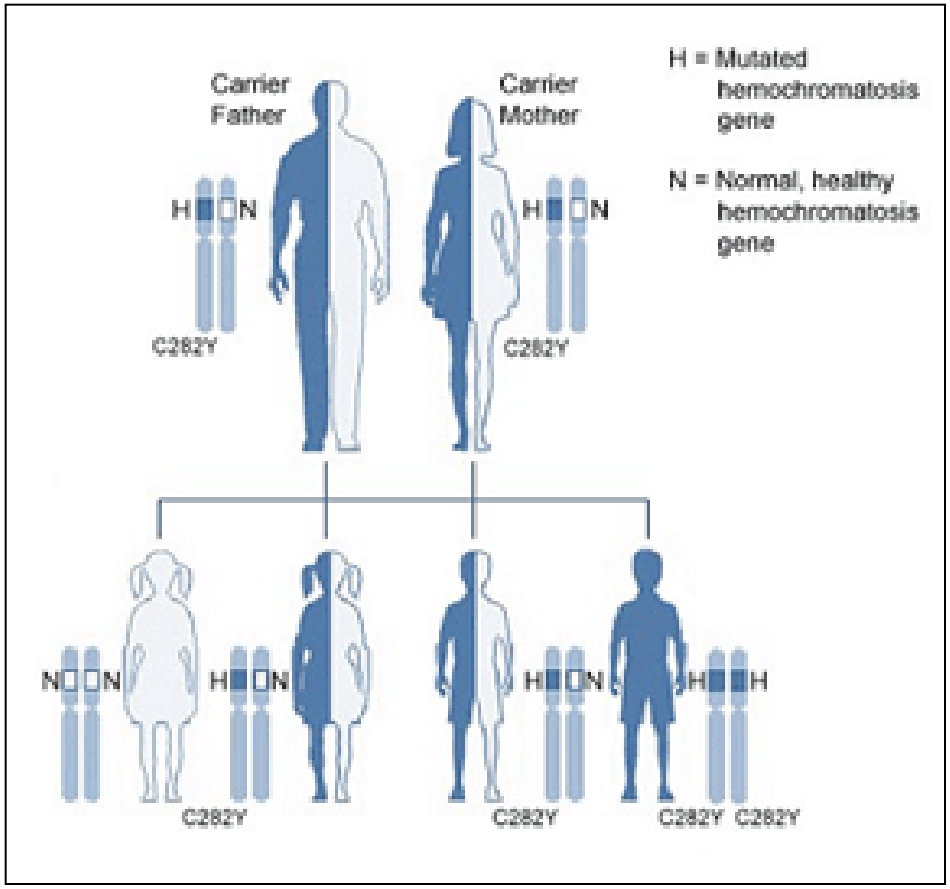
Race or Ethnic Group	Total No. of Participants	C282Y/C282Y		C282Y/H63D		H63D/H63D	
		No.	Prevalence (95% CI) %	No.	Prevalence (95% CI) %	No.	Prevalence (95% CI) %
White	44,082	281	0.44 (0.42–0.47)	908	2.0 (2.0–2.1)	1029	2.4 (2.3–2.4)
Native American	648	1	0.11 (0.061–0.20)	7	0.77 (0.56–1.1)	7	1.3 (0.98–1.8)
Hispanic	12,459	7	0.027 (0.022–0.032)	48	0.33 (0.30–0.37)	154	1.1 (0.98–1.1)
Black	27,124	4	0.014 (0.012–0.017)	35	0.071 (0.065–0.078)	30	0.089 (0.081–0.097)
Pacific Islander	698	0	0.012 (0.0043–0.032)	0	0.096 (0.055–0.17)	0	0.20 (0.12–0.32)
Asian	12,772	0	0.000039 (0.000015–0.00010)	0	0.0055 (0.0029–0.0093)	29	0.20 (0.17–0.22)
Multiple/unknown	1928	6	—	19	—	21	—
All	99,711	299	—	1017	—	1270	—

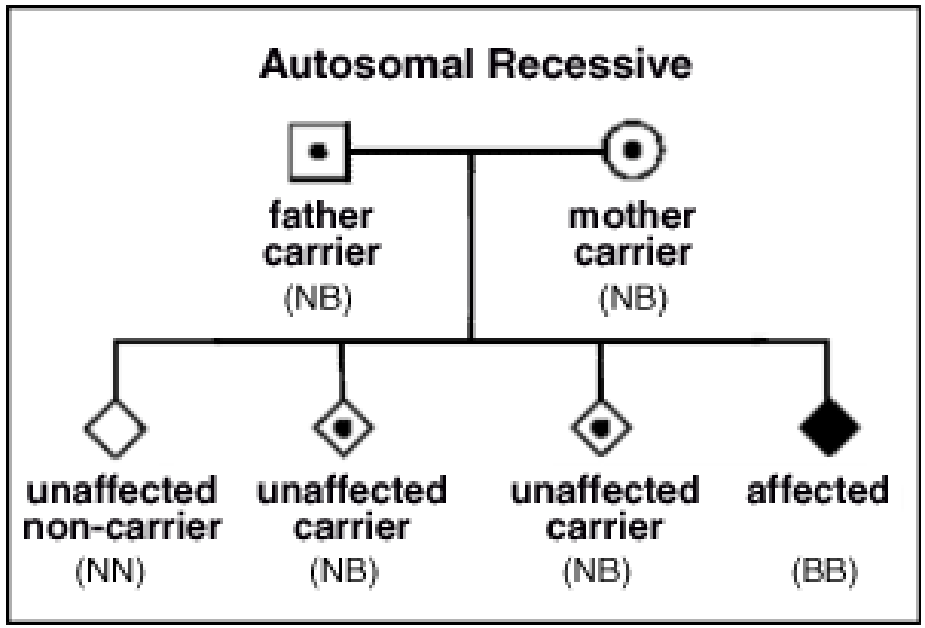
Race or Ethnic Group	Total No. of Participants	C282Y/+		H63D/+		+/+	
		No.	Prevalence (95% CI) %	No.	Prevalence (95% CI) %	No.	Prevalence (95% CI) %
White	44,082	4548	10 (10–11)	10,537	24 (24–24)	26,779	61 (60–61)
Native American	648	35	5.7 (4.2–7.7)	128	20 (17–22)	470	72 (69–76)
Hispanic	12,459	351	2.9 (2.6–3.2)	2199	18 (18–19)	9700	78 (77–78)
Black	27,124	605	2.3 (2.1–2.5)	1520	5.7 (5.4–6.0)	24,930	92 (92–92)
Pacific Islander	698	15	2.0 (1.2–3.4)	62	8.4 (6.6–11)	621	89 (87–91)
Asian	12,772	16	0.12 (0.074–0.19)	1070	8.4 (8.0–8.9)	11,657	91 (91–92)
Multiple/Unknown	1928	111	—	313	—	1458	—
All	99,711	5681	—	15,829	—	75,615	—

Pietrangelo NEJM 2004

Genetische counseling: wie testen ?

- Eerstegraadsverwanten indexpatient: afhankelijk van risico's
- Presymptomatisch in sibs: risico M/M is 25% als ouders beiden N/M (obligate dragers)



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Bosnia
Herz.
Bulgaria
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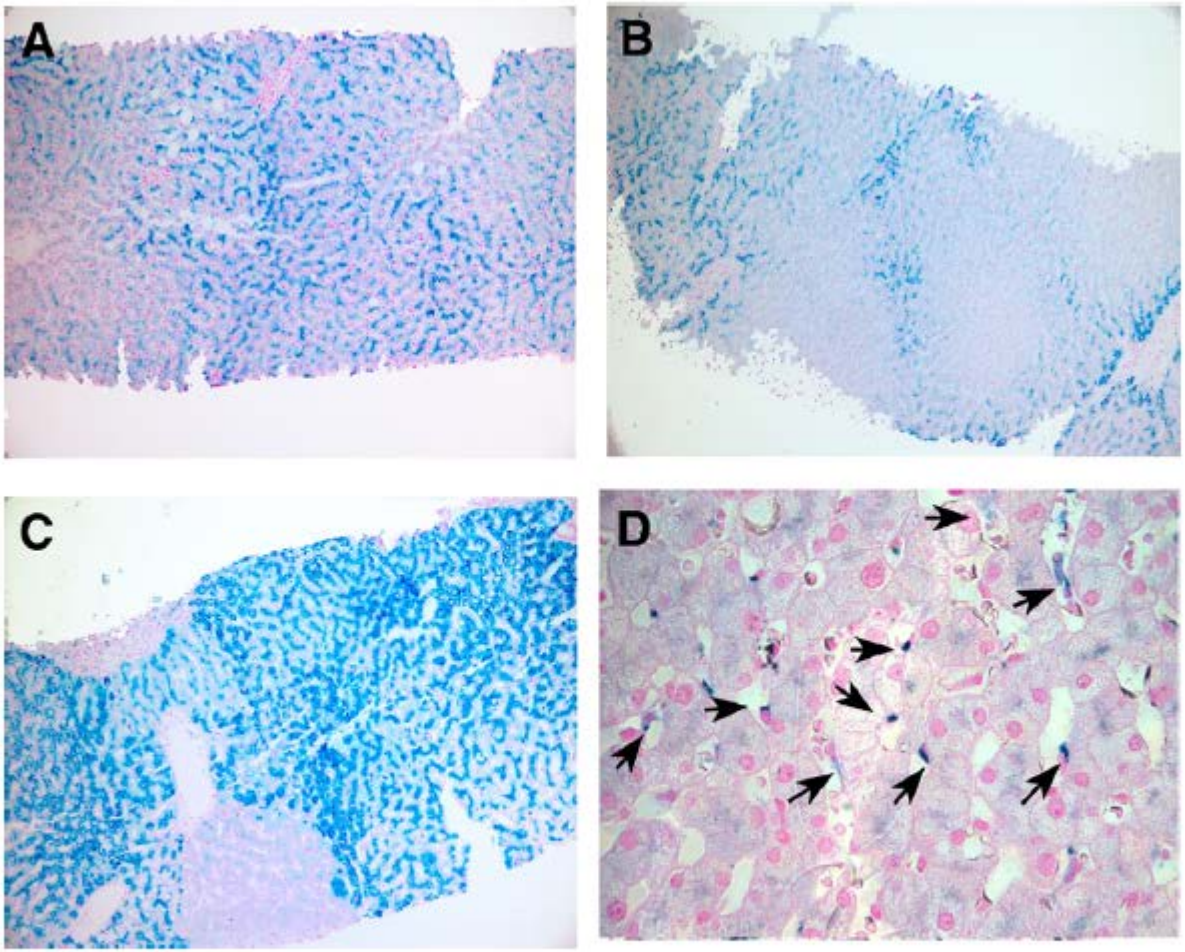
Mace.
Portugal
Albania
Spain
Italy
Greece

Praktische aanpak van ijzer gerelateerde bevindingen

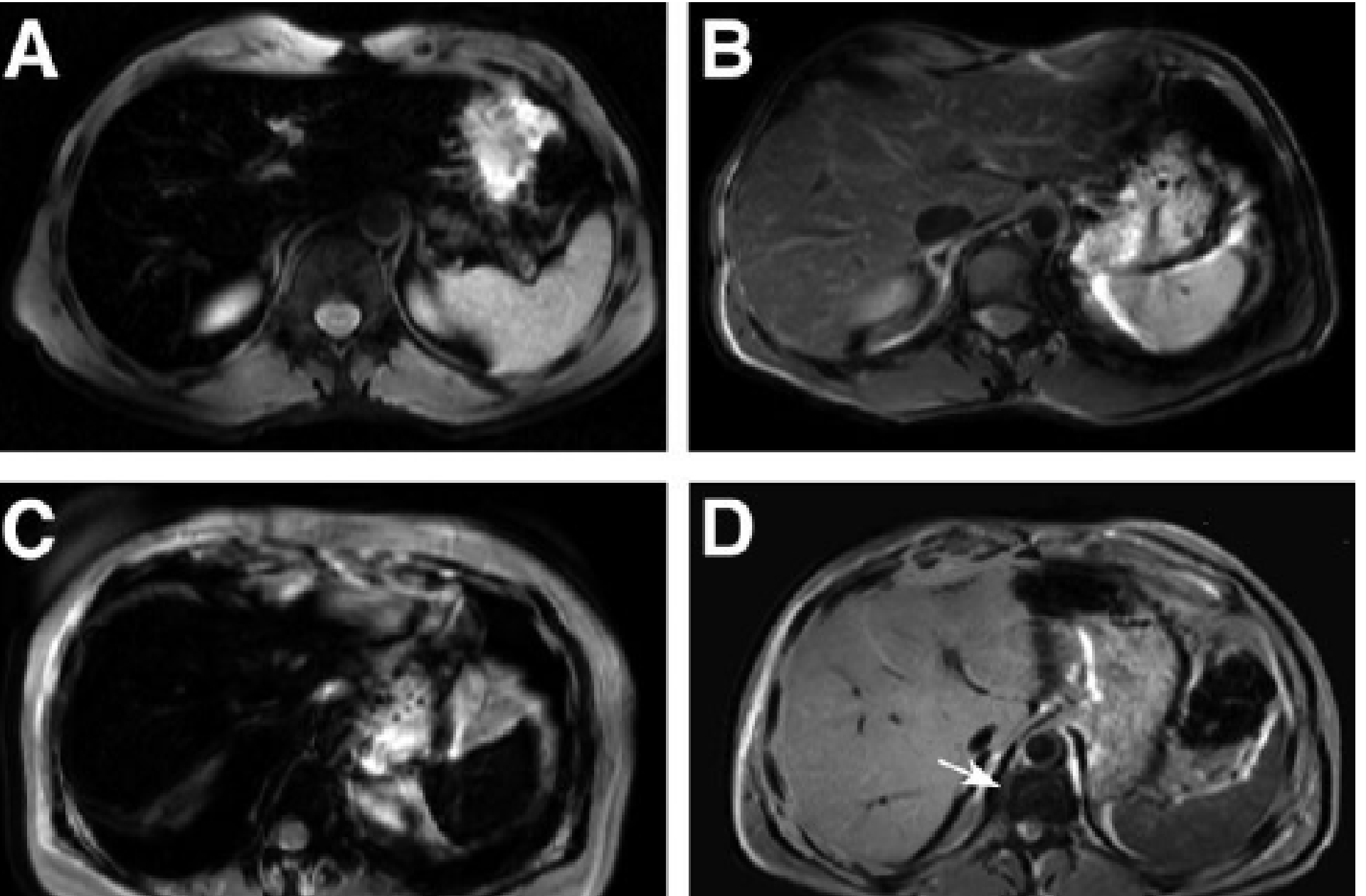


Supplementary Figure 1. Liver histology in patients with hemochromatosis. Perls' Prussian blue stain for iron. (*A*) HFE-related hemochromatosis is characterized by purely parenchymal iron overload that is heaviest in the periportal areas and less intense in the centrolobular areas. (*B*) TfR2-related hemochromatosis. The histopathologic picture is identical to HFE-related hemochromatosis with iron accumulation in periportal parenchymal cells. (*C*) HJV-related juvenile-onset hemochromatosis: massive pan-lobular parenchymal iron overload. (*D*) Classic ferroportin disease. Unlike the previous 3 cases, this liver displays iron overload that predominantly affects the Kupffer cells (*arrows*).

BEFORE
phlebotomy

AFTER
phlebotomy

- MRI



Behandeling

- Aderlatingen
- Chelatoren
- Erythrocytaferese

HFE Cys282Tyr Homozygotes With Serum Ferritin Concentrations Below 1000 μg/L Are at Low Risk of Hemochromatosis

Katrina J. Allen,[1,2,3] Nadine A. Bertalli,[1,4] Nicholas J. Osborne,[1,2,4] Clare C. Constantine,[4,5] Martin B. Delatycki,[1,2,6] Amy E. Nisselle,[1,2] Amanda J. Nicoll,[7] Dorota M. Gertig,[8] Christine E. McLaren,[5] Graham G. Giles,[9] John L. Hopper,[4] Gregory J. Anderson,[10] John K. Olynyk,[11,12] Lawrie W. Powell,[10,13] Lyle C. Gurrin,[4] and for the HealthIron Study Investigators*

Effects of treatment

Complication	Expected outcome
None	Prevention complications, N life expectancy
Weakness, fatigue	Resolution or improvement
Elevated liver tests	Resolution or improvement
Hepatomegaly	Resolution or improvement
Cirrhosis	No change
Arthropathy	Almost no improvement
Secondary hypogonadism	Resolution rare > 40y
Diabetes	Sometimes ↓ insulin need
Cardiomyopathy	Resolution rare
Hyperpigmentation	Resolution usually

Screening

- Familieleden
- Populatie
- Risicopopulatie

Casus

- Man 45 jaar.
- Ferritine 4000 ng/ml
- Ijzersaturatie 80%
- ALT: 55 IU/L

Casus

- Man 45 jaar.
- Ferritine 1000 ng/ml
- Ijzersaturatie 43%
- ALT: 55 IU/L

Casus

- Man 45 jaar.
- Ferritine 4000 ng/ml
- Ijzersaturatie 80%
- ALT: 3000 IU/L

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