

International Alliance of Haemochromatosis Associations (IAHA) Meeting and European Federation of Associations of Haemochromatosis Patients (EFAPH) Meeting

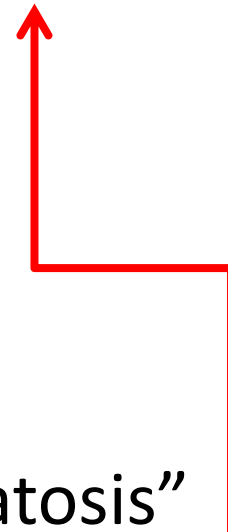
BioIron Affiliated Symposium

April 19th, 2013

University College, London

“Recent news on Haemochromatosis”

by: Graça Porto



Hereditary Hemochromatosis (HFE-related)

Definition*:

increased body iron stores associated with homozygosity for the HFE mutation p.Cys282Tyr, with or without clinical symptoms

Genetic Transmission:

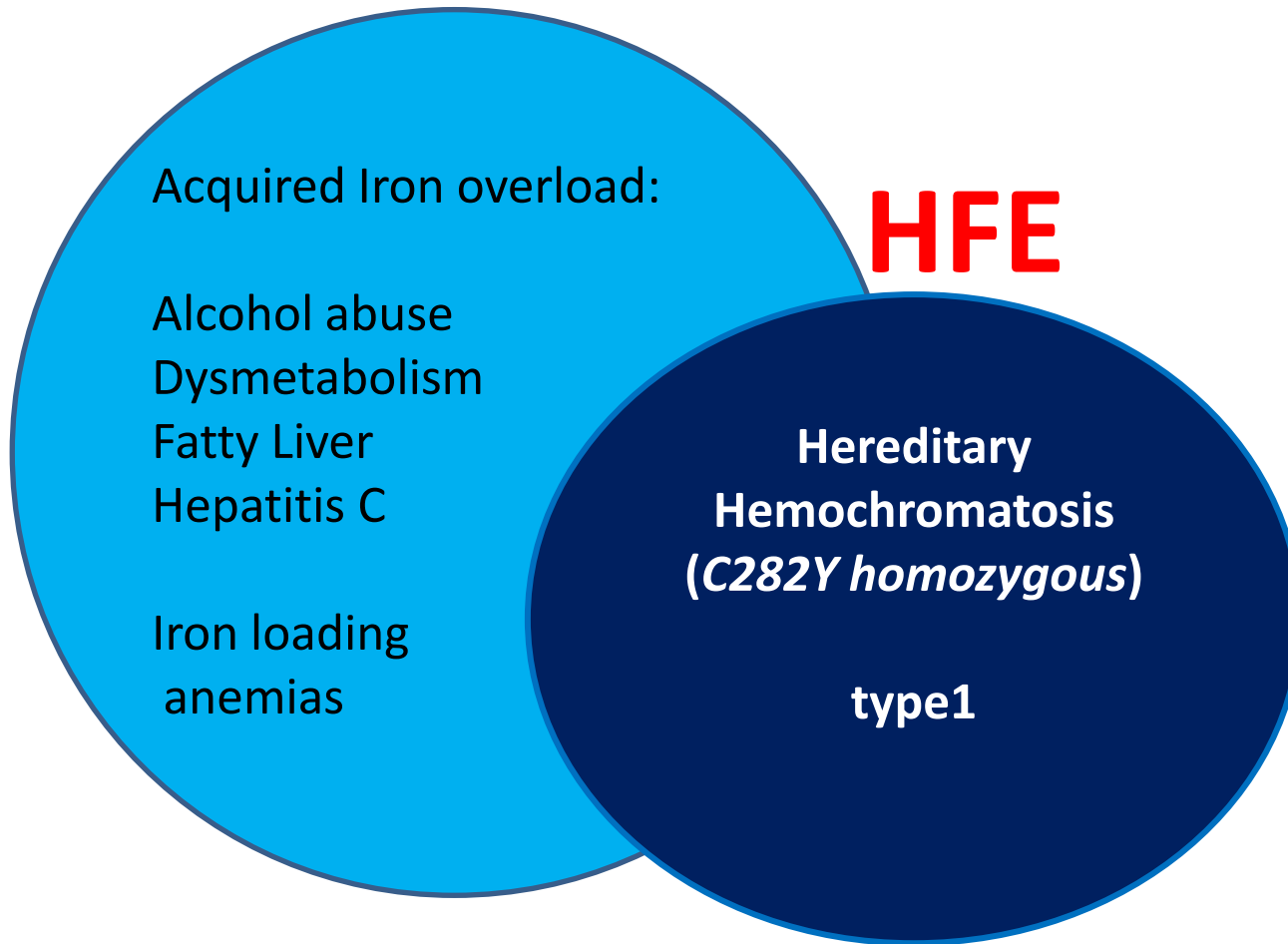
autosomal recessive mode

Epidemiology:

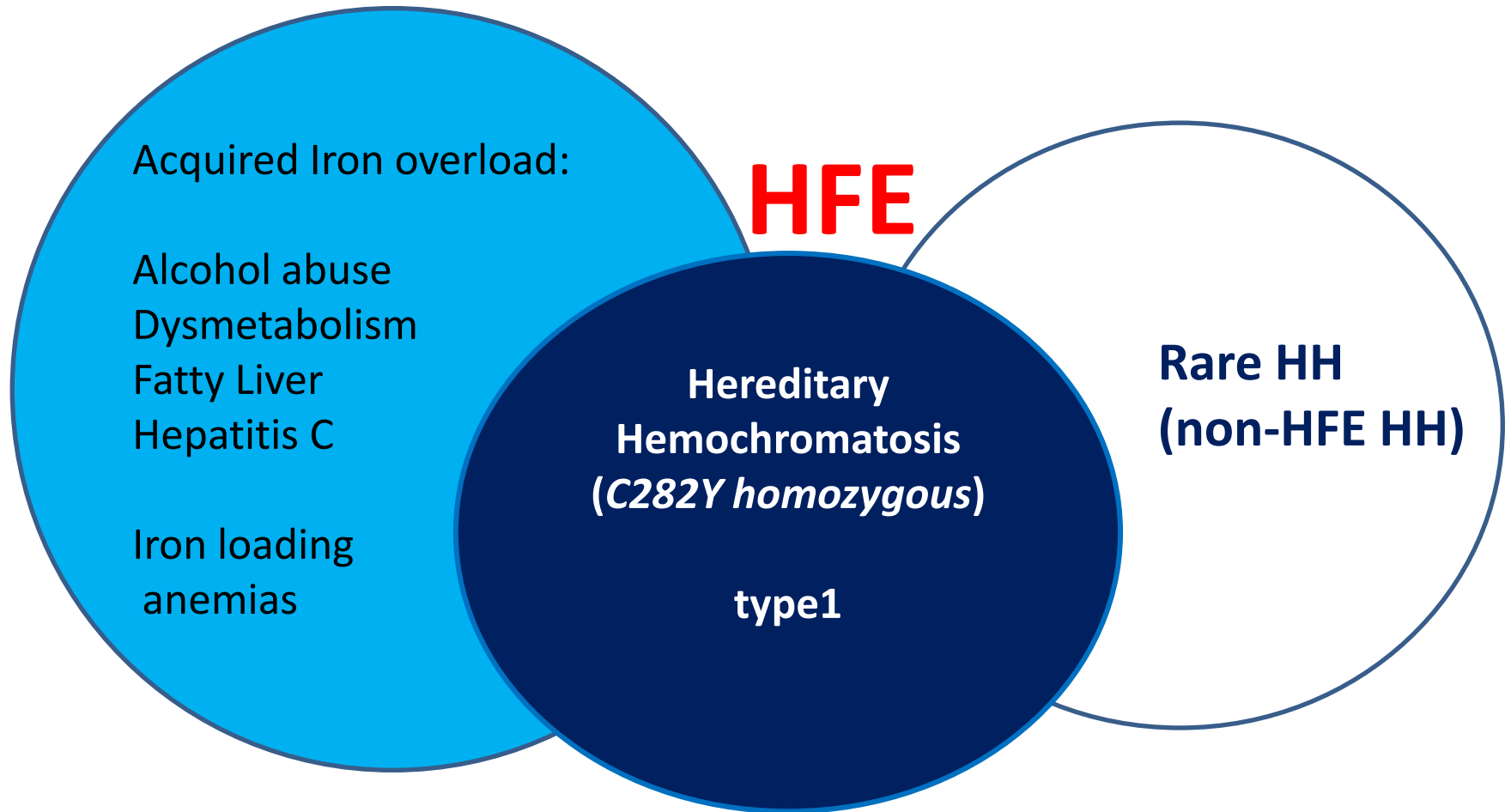
Affects predominantly males between 40 and 60 and is particularly common in people of Northern European descent where it may potentially affect 1 in every 200-300 individuals

*EASLD Clinical Practice Guidelines for HFE Hemochromatosis. J Hepatol 2010; 53:3-22)

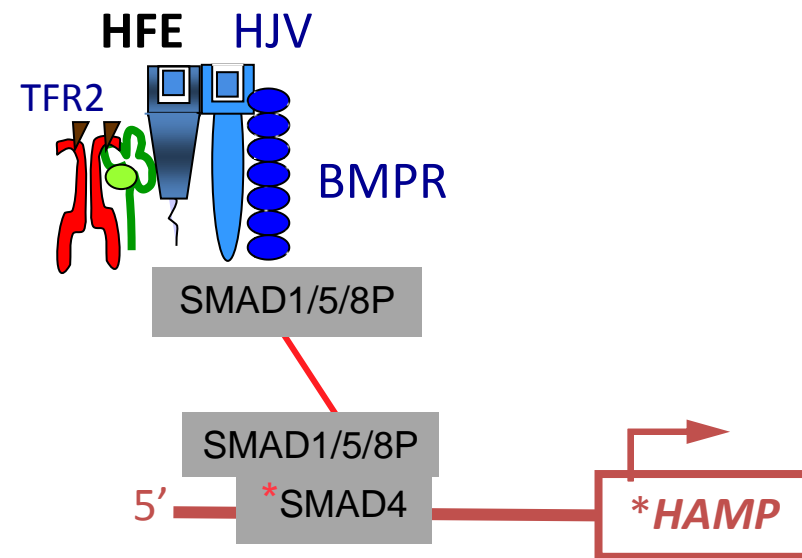
The Genetics of Hemochromatosis



The Genetics of Hemochromatosis



THE HEPCIDIN/FERROPORTIN REGULATION GENES



Disease type	Gene	Chromossome	Protein	Inheritance
Classic (type I)	HFE	6p	HFE	AR
Type IIA	HJV	1q	Hemojuvelin	AR
Type IIB	HAMP	19q	Hepcidin	AR
Type III	TfR2	7q	Transferin receptor 2	AR
Type IV	SCL40A1	2q	Ferroportin 1	AD

What would we like to know more?

Acquired Iron overload:

2. Are there novel treatment options for iron overload?

Iron loading anemias

Hereditary

3. Do we know the clinical evolution of HH patients in the “post-HFE” era?

Rare HH

1. Can we have a better idea about the epidemiology and natural history of Rare Hemochromatosis?

4. How are we approaching the question of penetrance?

Summary news:

1. The Genetic Diagnosis of Hemochromatosis
2. Novel therapeutic targets to treat iron overload
3. The natural history of HH
4. The search for disease modifiers

1. The Genetic Diagnosis of RARE hemochromatosis

Novel variants of non-HFE HH described:

Radio et al. (Sapienza University of Rome)

“TFR2 related hereditary hemochromatosis as a frequent cause of primary iron overload in central-southern Italy” (10 novel mutations in TFR2)

Majore et al. (Sapienza University of Rome)

“A novel frameshift mutation in a patient with Hereditary Hemochromatosis type 1”

Bignell et al. (Oxford University Hospital)

“Comprehensive genetic testing is required for patients with unexplained iron overload” (22 novel mutations and two large deletions in HFE2 and TFR2)

Pelusi et al. (University of Milano)

“Heterozygosity for novel HJV mutations”

Bardou-Jaquet et al. (University of Rennes)

“Seven new cases of type 3 hemochromatosis with eight previously undescribed TFR2 mutations emphasise the high variability of clinical presentation”

1. The Genetic Diagnosis of RARE hemochromatosis

Patricia Bignell (Oxford University Hospital)

“The use of **Next-Generation-Sequencing** to screen for mutations in 16 genes involved in iron homeostasis as an aid to genetic diagnosis for patients with iron overload or iron deficiency”

1. The Genetic Diagnosis of RARE hemochromatosis

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“The use of **Next-Generation-Sequencing** to screen for mutations in 16 genes involved in iron homeostasis as an aid to genetic diagnosis for patients with iron overload or iron deficiency”

Daniele Manna (University of Verona)

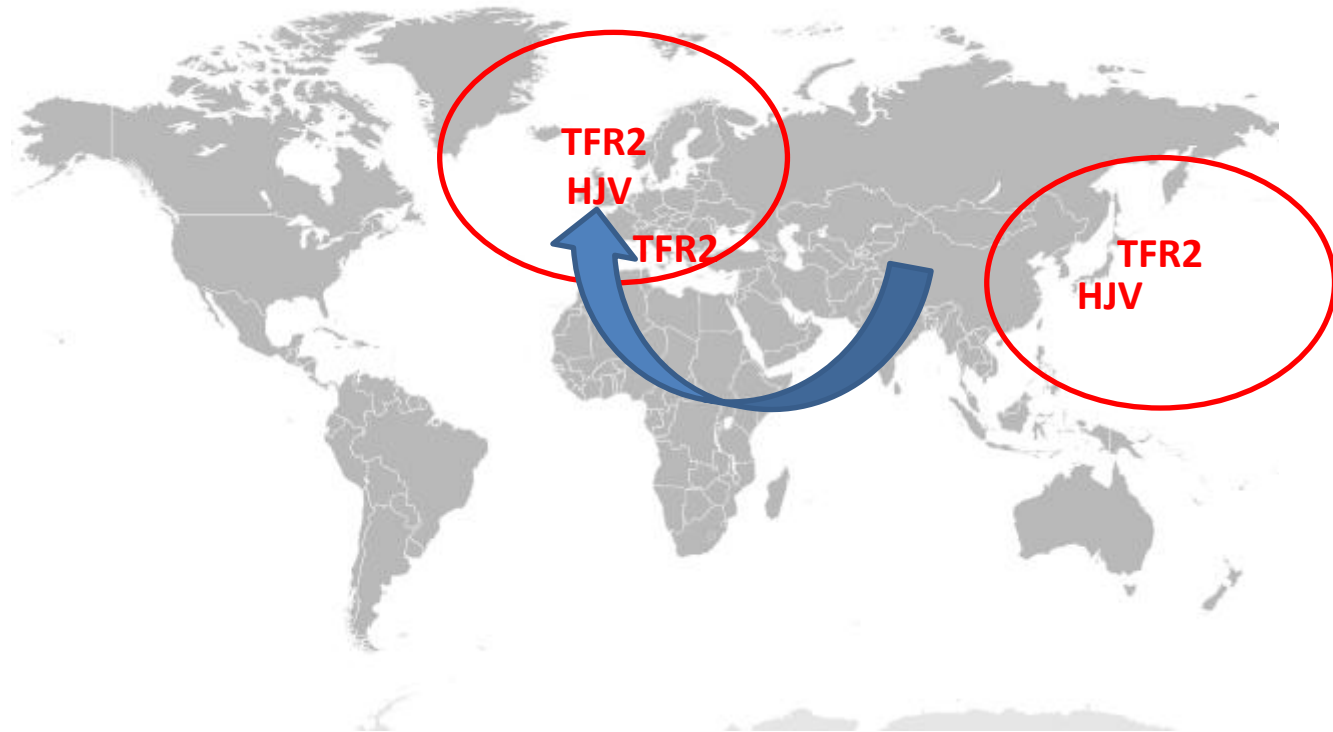
“Next generation targeted deep sequencing of hemochromatosis genes in iron overloaded patients: a pilot study”

Nathan Subramaniam (Queensland Institute of Medical Research)

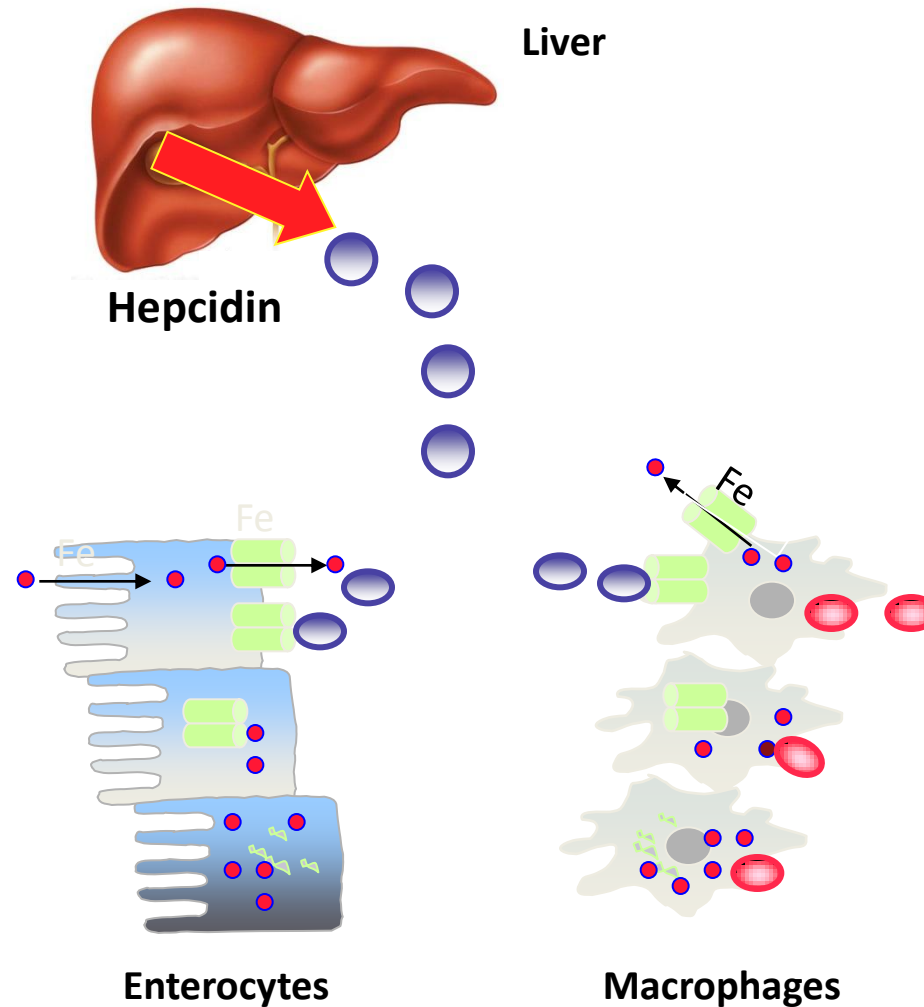
“Diagnosis of atypical iron disorders: clinical application of Next-Generation Sequencing”

1. The Genetic Diagnosis of RARE hemochromatosis

Increased detection **reveals increased population heterogeneity:**



2. Novel treatment options for iron overload?



2. Novel treatment options for iron overload?

The Hepcidin agonists:

Casu C, Gardenghi S, Nemeth E, Ganz T, MacDonald and Rivella S. “**Low dose minihepcidin peptide** causes improvement of anemia by increased erythropoietic efficiency in a **mouse model of thalassemia intermedia**”

Schmidt P, Toudjarska I, Sendamarai A, Racie T, Milstein S, Bettencourt B, Hettinger J, Brumcrot D, Butler J and Fleming M. “**RNAi targetting of TMPRSS6** decreases iron overload in a mouse model of hereditary hemochromatosis and meliorates anemia and iron overload in **murine β -thalassemia intermedia**”

Guo S, Casu C, Gardenghi S, Booten S, Aghajan M, Peralta R, Watt A, Freier S, Monia BP, Rivella S. “**Suppression of TMPRSS6** using antisense technology ameliorates hereditary hemochromatosis and **β -thalassemia in mice**”

Pre-Clinical Studies

3. The natural history of HH “post-HFE”

Edouard Bardou-Jacquet et al. (University of Rennes)

“Survival and causes of death in a cohort of 1086 treated C282Y HFE homozygous patients”

Previous reports on survival and causes of death in HH: “a selection bias for late diagnosis”

The results:

1. No difference in the overall mortality relative to the normal control population
2. Increased mortality in patients with very severe iron overload (mostly liver cancer)
3. Lower cardiovascular and extra-hepatic cancer in patients with mild iron overload

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Is this specific for HFE-related? Is this related with phlebotomy treatment in general?

3. The natural history of HH “post-HFE”

Finkenstedt et al. (University of Innsbruck)

“Homozygosity for common HFE mutations is na independent predictor of improved survival in liver clinic patients”

Worse prognosis for non-C282Y homozygous patients(in a cohort of 3920 patients)

Valenti et a. (University of Milano)

“Effect of iron depletion on liver damage in non-alcoholic fatty liver disease”

Ellervik et al (University of Copenhagen)

“Total mortality by elevated ferritin concentration”

The Penetrance of Hemochromatosis

A novel approach: Deep sequencing of the full exome

Christine Mc Laren, et al. (University of California, Irvine)

“Identification of genes and variant alleles associated with iron overload in Hemochromatosis HFE C282Y homozygotes”

... “our results identify candidate genes for expanded studies that would examine their functional significance to iron absorption and metabolism”.

Conclusions

1. Recent advances in molecular biology methods, in particular the availability of Next-Generation targeted Sequencing and Whole Exome Sequencing are opening new avenues for a more effective genetic **diagnosis of rare forms** of hemochromatosis and to the identification of novel candidate **modifier genes**.
2. The first studies with **hepcidin agonists** in animal models confirm its efficacy as a treatment for systemic iron overload.
3. **Early diagnosis and treatment** of HH patients is associated with a lower mortality due to cardiovascular disease or extra-hepatic cancer, supporting the beneficial effect of sustained iron removal.



HOSPITAL SANTO ANTÓNIO



THANKS

The “time lapse” of the discoveries

THE FIRST “HINTS”

THE QUESTIONS WE WERE LOOKING FOR

Searching for the HH gene

1975

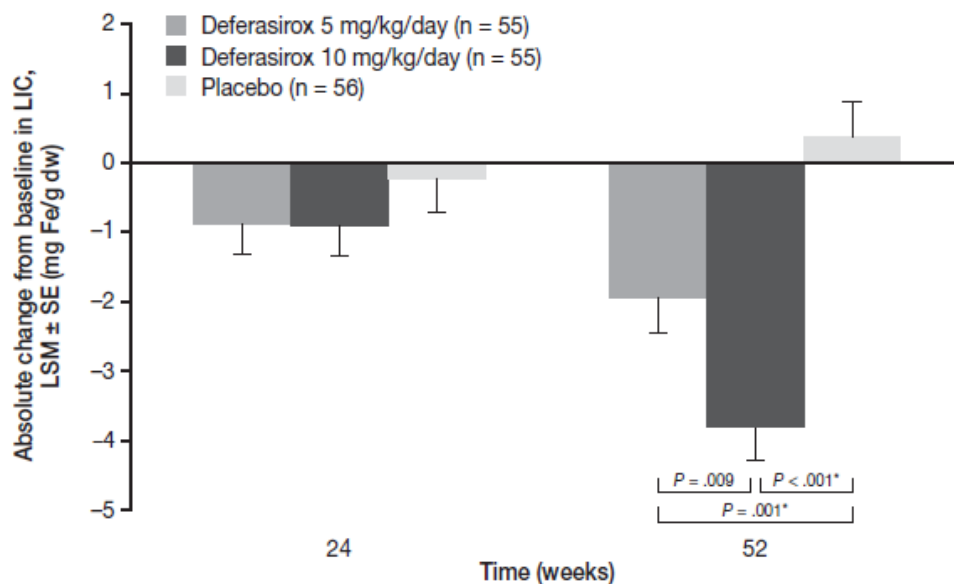
1996

**The HLA-A3
Association**
(Simon et al.
Nouv. Presse.
Med.4:1432

**The discovery of
the **HFE** gene**
(Feder et al. Nat
Genet.

Deferasirox significantly reduces iron overload in non-transfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study

Ali Taher, John Porter, Vip Viprakasit, Antonis Kattamis, Suporn Chuncharunee, Pranee Sutcharitchan, Noppadol Siritanaratkul, Renzo Galanello, Zeynep Karakas, Tomasz Lawniczek, Jacqueline Ros, Yiyun Zhang, Dany Habr and Maria Domenica Cappellini



4. Novel treatment options?

Nielsen P, Grosse R, Fisher R

“Efficacy of deferasirox in the treatment of severe iron overload in a patient with HFE-Haemochromatosis and β -Thalassemia minor”

BiolIron 2013, London April 14-18

The Penetrance of Hemochromatosis

... not all genetic modifiers have to be related to iron metabolism...

Nahon P, Sutton A, Pessayre D, Rufat P, Charnaux N, Trinchet JC, Beaugrand M, Deugnier Y.

Do genetic variations in antioxidant enzymes influence the course of hereditary hemochromatosis?

Antioxid Redox Signal. 2011 Jul 1;15(1):31-8.