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New insights into iron homeostasis through the study of non-HFE hereditary haemochromatosis

Antonella Roetto PhD
Researcher
Clara Camaschella* MD
Professor
Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Azienda Ospedaliera San Luigi Gonzaga, Regione Gonzole, 10, 10043 Orbassano, Torino, Italy

Non-*HFE* haemochromatosis is a negative definition applied to all those haemochromatosis disorders that are unrelated to *HFE* mutations. Four genes are responsible for the distinct types of non-*HFE* haemochromatosis: hepcidin and hemojuvelin are the genes involved in type 2 or juvenile haemochromatosis, transferrin receptor 2 is involved in type 3 haemochromatosis, and ferroportin 1 is mutated in type 4, the atypical dominant form of primary iron overload. Molecular genetic studies of these conditions have greatly contributed to our understanding of the regulation of iron absorption. A milestone was the discovery that hepcidin, the key iron regulator in mice, is the gene mutated in the most severe, juvenile form of haemochromatosis. This finding indicates a fundamental role of hepcidin in inhibiting both iron absorption from duodenal cells and iron release from macrophages, and has opened up a new view of haemochromatosis as a disorder of hepcidin.

Key words: iron; haemochromatosis; *HFE*; hepcidin; hemojuvelin; transferrin receptor 2; ferroportin.

Hereditary haemochromatosis is the genetic disorder that results from the disruption of the mechanisms that regulate iron absorption, leading to progressive increase of total body iron and organ damage. The term haemochromatosis is often used to indicate the disease caused by the inactivation of the *HFE* gene. Non-*HFE* haemochromatosis is a negative definition introduced immediately after the discovery of the *HFE* gene and its mutations.[1] At that time it was shown that not all patients with clinical features of

* Corresponding author. Tel.: +39 011 902 6605/902 6837; Fax: +39 011 903 8636.
E-mail address: clara.camaschella@unito.it (C. Camaschella).

haemochromatosis were carriers of *HFE* mutations.[2] This was especially evident in patients of southern European ancestry.[2–5] The genetic background of this heterogeneous condition has been clarified in recent years, thanks to the study of multiplex or consanguineous families and using a classic positional candidate approach. From 1997, when it was demonstrated that the juvenile form of haemochromatosis (JH) was unlinked to chromosome 6p[6], until the recent cloning of the main juvenile haemochromatosis (JH) gene[7], several distinct genetic forms of haemochromatosis have been recognized. Now that the genetic background of non-*HFE* haemochromatosis has been fully elucidated[8], the negative definition 'non-*HFE* haemochromatosis' should be dismissed and each different disorder should be defined according to the gene mutated.

From the biological point of view, the study of non-*HFE* haemochromatosis patients has contributed important insights into the molecular mechanisms that operate to maintain the tight regulation of intestinal iron absorption and iron release from macrophages. This review will be focused on the genetics of haemochromatosis disorders unrelated to *HFE* and on the advances that their cognate gene discovery has contributed to our understanding of the regulation of iron homeostasis.

NOMENCLATURE AND CLASSIFICATION

The nomenclature of haemochromatosis is controversial. Haemochromatosis indicates the disease that results from iron loading; thus the term refers to the clinical complications due to iron toxicity in different organs, mainly the liver. The most common form, the first to be recognized, is HFE-related. According to *On Line Mendelian Inheritance in Man* (http://www.ncbi.nil.nih.gov/entrez/query.fcgi?db=OMIM), this classic form is called simply haemochromatosis or *HFE*-related haemochromatosis. The term *HFE* refers to the responsible HLA class I-like gene that in the original paper was called *HLA-H*.[1] The other forms of haemochromatosis are defined by numbers (type 2, type 3 and type 4), with an order that reflects their chronological recognition. Type 2 is also called 'juvenile haemochromatosis' (JH), since its distinctive feature is the early onset of clinical complications.[9] Type 2 is by itself heterogeneous, since it can result from mutations in two different genes: more commonly (type 2A) *HJV*, encoding hemojuvelin[7], and in a rare subset of patients (type 2B) *HAMP*, encoding hepcidin.[10] Type 3 haemochromatosis is characterized by *TFR2* mutations[11] and shows intermediate clinical features between classic type (*HFE*-related) and type 2. Finally, type 4 is a separate disorder due to mutations of *SCL40A1*, which encodes the iron exporter ferroportin 1.[12,13] It is also called 'ferroportin disease' since its genetic, biochemical, clinical and histological features are distinct from haemochromatosis.[14] A genetic classification of the different forms is reported in Table 1. The new term for each disorder could be *HFE*-related haemochromatosis, *TFR2*-related haemochromatosis, hepcidin- or hemojuvelin-related haemochromatosis, and ferroportin disease, respectively.

With the exception of ferroportin disease, clinical and histological features are similar in all these disorders. In all conditions inappropriately high intestinal iron absorption and rapid iron release from macrophages lead to increased saturation of circulating transferrin; this favours cellular iron uptake through the transferrin receptor mechanism and causes iron deposition, especially in hepatocytes. At the same time