

## TOPIC HIGHLIGHT

Nathan Subramaniam, PhD, Series Editor

# Non-HFE haemochromatosis

Daniel F Wallace, V Nathan Subramaniam

Daniel F Wallace, V Nathan Subramaniam, Membrane Transport Laboratory, The Queensland Institute of Medical Research, Brisbane, Queensland, Australia  
Correspondence to: Dr. V Nathan Subramaniam, Membrane Transport Laboratory, The Queensland Institute of Medical Research, 300 Herston Road, Herston, Brisbane, QLD 4006 Australia. [nathan.subramaniam@qimr.edu.au](mailto:nathan.subramaniam@qimr.edu.au)  
Telephone: + 617-3362-0179 Fax: + 617-3362-0191  
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## Abstract

Non-HFE hereditary haemochromatosis (HH) refers to a genetically heterogeneous group of iron overload disorders that are unlinked to mutations in the HFE gene. The four main types of non-HFE HH are caused by mutations in the *hemojuvelin*, *hepcidin*, *transferrin receptor 2* and *ferroportin* genes. Juvenile haemochromatosis is an autosomal recessive disorder and can be caused by mutations in either *hemojuvelin* or *hepcidin*. An adult onset form of HH similar to HFE-HH is caused by homozygosity for mutations in *transferrin receptor 2*. The autosomal dominant iron overload disorder ferroportin disease is caused by mutations in the iron exporter ferroportin. The clinical characteristics and molecular basis of the various types of non-HFE haemochromatosis are reviewed. The study of these disorders and the molecules involved has been invaluable in improving our understanding of the mechanisms involved in the regulation of iron metabolism.

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**Key words:** Haemochromatosis; Iron overload; Non-HFE; Juvenile haemochromatosis; Hemojuvelin; Heparin; Transferrin receptor 2; Ferroportin

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## INTRODUCTION

After the identification of the *HFE* gene in 1996<sup>[1]</sup> it became apparent that not all cases of haemochromatosis are caused by mutations in *HFE*. HFE-associated HH (HFE-HH) or type 1 HH is the most common form,

especially in populations of Northern European origin, where the C282Y mutation has a high allele frequency<sup>[2]</sup>. Haemochromatosis that is unrelated to mutations in the *HFE* gene are collectively referred to as non-HFE haemochromatosis. Non-HFE haemochromatosis occurs in populations world wide and makes up a larger proportion of HH cases in areas where the C282Y mutation is less common, such as Southern Europe<sup>[3]</sup> and Asia<sup>[4]</sup>. Non-HFE HH can be further differentiated according to the gene mutated. There are four main types of non-HFE HH. The molecules mutated in all forms of HH are related in pathways involved in the regulation of iron homeostasis. Heparin the central regulator of iron homeostasis and hemojuvelin are mutated in juvenile or type 2 HH<sup>[5,6]</sup>. Transferrin Receptor 2 is mutated in type 3 HH<sup>[7]</sup> and the iron exporter ferroportin is mutated in the autosomal dominant type 4 HH or ferroportin disease<sup>[8,9]</sup>. The genetic, clinical and laboratory features of the various types of HH are outlined in Table 1. This review will describe in detail the four main types of non-HFE HH and review the current literature in this area.

## JUVENILE HAEMOCHROMATOSIS (TYPE 2)

An early onset form of juvenile haemochromatosis (JH), distinct from the typical HFE-HH has been recognised for some time<sup>[10]</sup>. As with HFE-HH, JH or type 2 HH is an autosomal recessive disorder, and is characterised by elevated serum iron indices and iron deposition in parenchymal cells. JH usually presents before the age of 30 years and has a more rapid and severe course than HFE-HH. Unlike HFE-HH both sexes are affected equally<sup>[10]</sup>. Cardiomyopathy and hypogonadism are more prominent features of JH, hypogonadism being the most common symptom at presentation<sup>[11]</sup>. The rapid accumulation of iron in patients with JH can often be fatal, death usually resulting from heart failure<sup>[11]</sup>.

When the *HFE* gene was identified in 1996, it became apparent that JH was indeed a disorder genetically distinct from the typical HFE-HH. Linkage to the *HFE* gene region on chromosome 6 was ruled out, in a study utilising microsatellite markers in five Italian JH families<sup>[12]</sup>. This was followed by a genome wide search that identified linkage to the chromosome 1q21 region in nine JH families. Subsequently a subset of families who did not have linkage to 1q21 were found to have mutations in the *hepcidin* (*HAMP*) gene on chromosome 19<sup>[5]</sup>. This subset of JH has been termed type 2B HH and is described in more detail later. The chromosome 1 form of JH has been termed type 2A HH.

Table 1 Genetic, clinical and laboratory features of the various types of Hereditary Haemochromatosis

HH Type	Gene	Inheritance	Clinical features	Laboratory findings	Liver pathology	Functional consequences of mutations
1	<i>HFE</i>	Autosomal recessive	May include: fatigue, lethargy, arthropathy, skin pigmentation, liver damage, diabetes mellitus, endocrine dysfunction, cardiomyopathy, hypogonadotropic hypogonadism	↑ serum ferritin, ↑ transferrin saturation	Hepatocyte iron loading, fibrosis, cirrhosis	Impaired hepcidin regulation by iron, leading to increased intestinal iron absorption and release of iron from reticuloendothelial cells
2A	<i>Hemojuvelin (HJV)</i>	Autosomal recessive	As for HFE. Earlier onset (< 30 yr). Cardiomyopathy and hypogonadism more prevalent.	↑ serum ferritin, ↑ transferrin saturation	Hepatocyte iron loading, fibrosis, cirrhosis	Loss of hepcidin regulation, leading to increased intestinal iron absorption and release of iron from reticuloendothelial cells
2B	<i>Hepcidin (HAMP)</i>	Autosomal recessive	As for HFE. Earlier onset (< 30 yr). Cardiomyopathy and hypogonadism more prevalent.	↑ serum ferritin, ↑ transferrin saturation	Hepatocyte iron loading, fibrosis, cirrhosis	No/inactive hepcidin, leading to maximal iron absorption and release of iron from reticuloendothelial cells
3	<i>Transferrin Receptor 2 (TfR2)</i>	Autosomal recessive	As for HFE.	↑ serum ferritin, ↑ transferrin saturation	Hepatocyte iron loading, fibrosis, cirrhosis	Impaired hepcidin regulation by iron, leading to increased intestinal iron absorption and release of iron from reticuloendothelial cells
4	<i>Ferroportin (Fpn), SLC40A1, IREG1, MTP1</i>	Autosomal dominant	Typical presentation: as for HFE, except generally milder. May have mild anaemia and lower tolerance to venesection.  Atypical: as for HFE	↑ ↑ serum ferritin, normal transferrin saturation ↑ serum ferritin, ↑ transferrin saturation	Predominant Kupffer cell iron loading, fibrosis Predominant hepatocyte iron loading, fibrosis, cirrhosis	Reduced ferroportin iron transport ability, leading to accumulation of iron in reticuloendothelial cells Loss of ferroportin regulation by hepcidin, leading to increased intestinal iron absorption and release of iron from reticuloendothelial cells

## HEMOJUVELIN-ASSOCIATED HAEMOCHROMATOSIS (TYPE 2A)

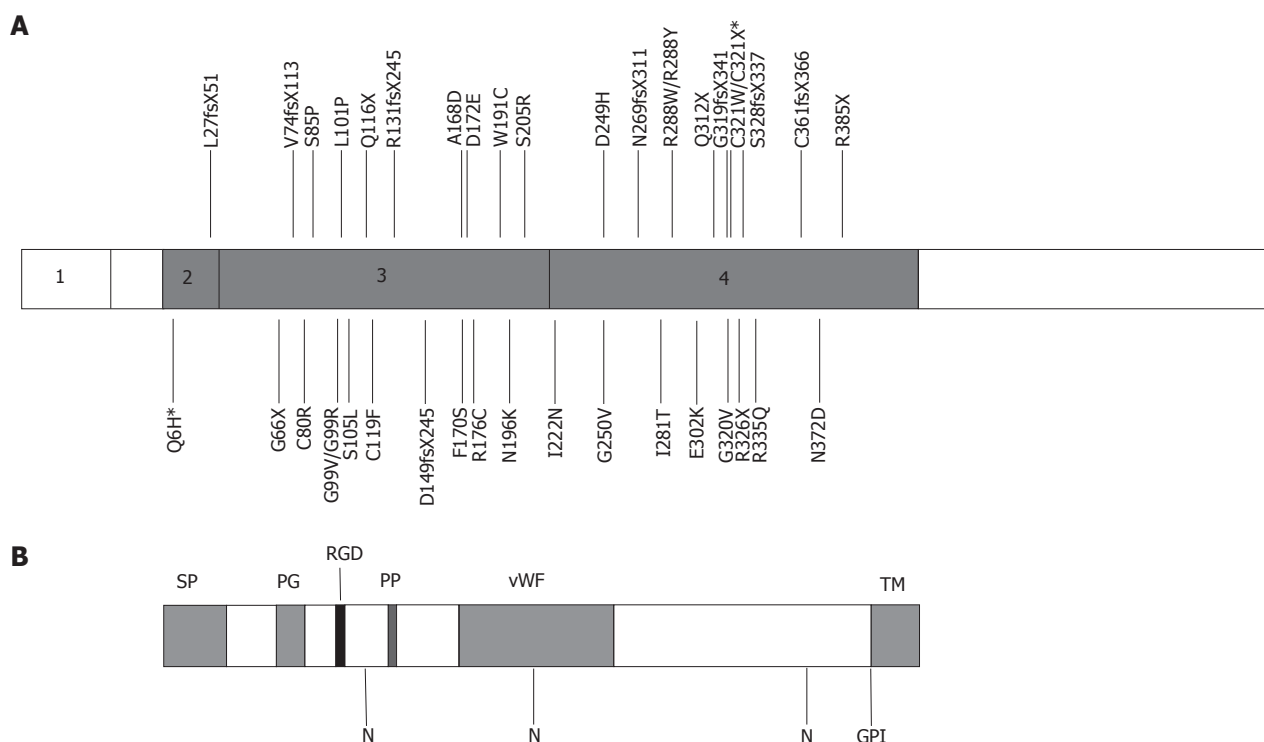
The gene responsible for the chromosome 1 form of JH was identified in 2004<sup>[6]</sup>. Fine mapping of the JH locus was performed in 12 JH families of Greek, Canadian and French origin. Sequencing of genes in this region revealed a novel gene that was mutated in all affected individuals<sup>[6]</sup>. The gene originally named *HFE2* encodes hemojuvelin (HJV), a protein with homology to the repulsive guidance molecule (RGM) family of proteins. Six mutations were initially identified in the affected individuals either in the homozygous or compound heterozygous state. One mutation G320V was present in nine of the 12 families<sup>[6]</sup>. Since the identification of *HJV*, numerous mutations have been identified in JH families worldwide<sup>[6,13-24]</sup>. An Italian study identified 16 more mutations among 34 JH patients from various European backgrounds<sup>[13]</sup>. Figure 1 illustrates the structure of hemojuvelin and position of disease-causing mutations. Most mutations are private and were detected in single families. A few have been detected in more than one population. One mutation in particular (G320V) is significantly more frequent and has been reported in JH patients in many populations<sup>[6,13,16-20,24]</sup>.

Patients with HJV-HH were shown to have low levels of urinary hepcidin<sup>[6]</sup>. This suggested that HJV may be involved in regulating hepcidin expression in response to iron. The generation of mouse knockouts confirmed that HJV was critical for the regulation of iron homeostasis and the induction of hepcidin<sup>[25,26]</sup>. Recent studies have suggested that HJV regulates hepcidin expression through signalling pathways involving bone morphogenic proteins (BMPs)<sup>[27]</sup>.

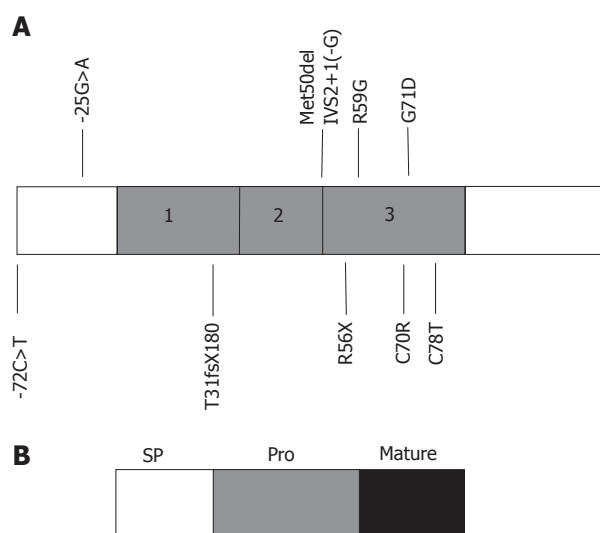
## HEPCIDIN-ASSOCIATED HAEMOCHROMATOSIS (TYPE 2B)

While most cases of juvenile haemochromatosis have been linked to a locus on the long arm of chromosome 1 (1q21) and mutations in *HJV*, a small number of families have been described with a JH-like disorder unlinked to 1q21<sup>[28]</sup>. This subset of patients was found to have mutations in the *hepcidin (HAMP)* gene. Two consanguineous families of Italian and Greek origin were originally reported with linkage to a region on chromosome 19, encompassing the region containing the *hepcidin* gene<sup>[5]</sup>. Homozygosity for mutations in the *hepcidin* coding sequence was detected in both families. One family harboured a one base pair deletion (93delG), causing a frameshift and an abnormal extended protein (T31fsX180). The other family carried a single base pair substitution (166C>T) causing the replacement of an arginine with a stop codon (R56X), in the predicted cleavage site for prohormone convertases. Both of these mutations severely affect the protein sequence and would result in the absence of any mature hepcidin peptide<sup>[5]</sup>.

*Hepcidin* mutations remain a rare cause of JH. However, since the first report, other cases and mutations have been described<sup>[5,29-37]</sup>. Mutations described in the *hepcidin* gene are shown in Figure 2. These include mutations affecting two of the eight highly conserved cysteine residues (C70R and C78T), important for the complex disulphide bonded structure of mature hepcidin<sup>[33-35]</sup>. A mutation in the 5'UTR of the *hepcidin* mRNA (-25G>A) has been described in two Portuguese families<sup>[36,37]</sup>. This mutation creates a new initiation codon upstream from the original



**Figure 1** Structure of human hemojuvelin and positions of mutations. **A:** The exon structure of human *hemojuvelin* is shown with positions of known mutations marked<sup>[16,13-24,30,39]</sup>. \*Q6H was found associated with C321X; **B:** Predicted structure of the full length HJV protein, showing the positions of structural domains and motifs. SP, signal peptide; PG, poly-glycine sequence; RGD, RGD motif; PP, poly-proline sequence; vWF, partial von Willebrand factor type D domain; N, potential N-linked glycosylation sites; GPI, GPI-attachment site; TM, transmembrane domain, cleaved after GPI attachment.



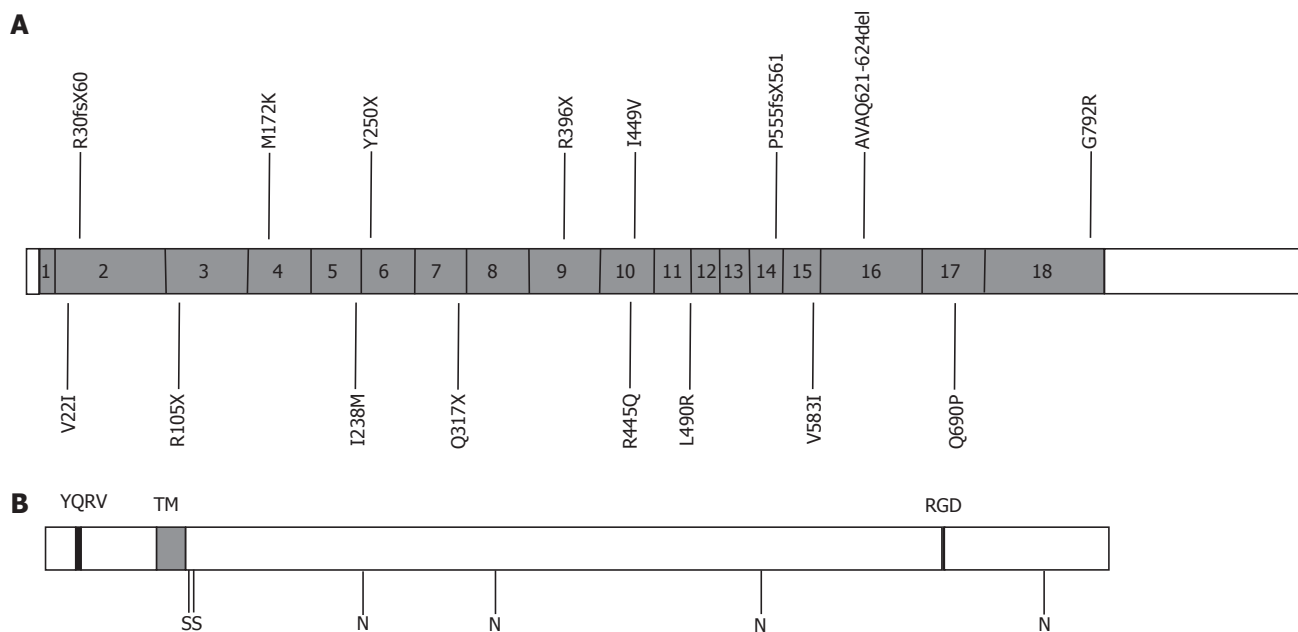
**Figure 2** Structure of human *hepcidin* and positions of mutations. **A:** The exon structure of human *hepcidin* is shown with positions of known mutations marked<sup>[5,29-37]</sup>. **B:** Predicted structure of the hepcidin peptide. SP, signal peptide; Pro, pro-region; Mature, 25 amino acid mature hepcidin peptide.

ATG. Measurement of urinary hepcidin in a patient homozygous for this mutation, suggests that steady state transcription of *hepcidin* from the original ATG codon does take place. But there is loss of upregulation of *hepcidin* transcription in response to iron<sup>[37]</sup>. In another study it was shown *in vitro* that the out of frame upstream initiation codon was functional and prevented normal transcription from the original ATG<sup>[38]</sup>.

## DIGENIC INHERITANCE AND MODIFIERS OF HFE

The remaining mutations in *hepcidin* have been detected in the heterozygous state in patients carrying *HFE* mutations. Merryweather-Clarke *et al*<sup>[29,30]</sup> described patients with haemochromatosis who carried mutations in both *HFE* and *hepcidin*. One patient carried a four base pair deletion in *HAMP* (Met50del IVS2+1(-G)) and had a JH-like phenotype. Another family carried the G71D mutation in combination with either heterozygous or homozygous C282Y, and adult-onset iron overload. This was the first description of iron overload due to digenic inheritance of mutations in two separate genes. Two studies have detected *hepcidin* mutations in large cohorts of patients with HFE-HH. Jacolot *et al* detected *HAMP* mutations in five individuals from a cohort of 392 C282Y homozygotes and found that these were among the more iron-loaded. In addition, four of 31 subjects with iron overload, but at least one chromosome lacking an *HFE* mutation also carried a *HAMP* mutation. This supports the concept that digenic inheritance of *HFE* and *HAMP* mutations can lead to iron overload. Biasiotto *et al*<sup>[30]</sup> also screened for *hepcidin* mutations in iron overload patients carrying the C282Y allele and detected sequence variations in some. They concluded that a novel substitution in the *hepcidin* promoter (-72C>T) may aggravate iron loading in patients with *HFE* mutations.

*HJV* mutations have also been detected in patients with HFE-HH. Two studies suggested that heterozygosity for *HJV* mutations may aggravate the phenotype in HFE-



**Figure 3** Structure of human transferrin receptor 2 (TfR2) and positions of mutations. **A:** The exon structure of human *TfR2* is shown with positions of known mutations marked<sup>[7,30,40-52]</sup>. The frameshift mutations R30fsX60 and P555fsX561 are also known as E60X and V561X respectively. G792R may be associated with R396X; **B:** Predicted structure of TfR2 protein. YQRV, endocytosis signal; TM, transmembrane domain; RGD, RGD motif; S, predicted interchain disulphide bonds; N, potential N-linked glycosylation sites.

HH<sup>[30,39]</sup>. Le Gac *et al.*<sup>[39]</sup> reported nine of 310 C282Y homozygous patients with additional *HJV* mutations. Eight of the nine patients appeared to have a more severe phenotype, suggesting that heterozygosity for mutations in *HJV* were having a modifying effect. A similar effect of *HJV* mutations was reported by Biasiotto *et al.*<sup>[30]</sup>, the N196K mutation being associated with abnormally high iron indices in a C282Y/H63D compound heterozygote. The effect of *HJV* mutations on phenotypic expression of HFE-HH is small, and has not been detected in all studies. Lee *et al.*<sup>[24]</sup> did not detect any *HJV* mutations in a group of 49 C282Y homozygotes. Wallace *et al.*<sup>[17]</sup> reported a G320V heterozygous relative of a JH patient, who was also a C282Y/H63D compound heterozygote, but with normal iron indices.

### TRANSFERRIN RECEPTOR 2-ASSOCIATED HAEMOCHROMATOSIS (TYPE 3)

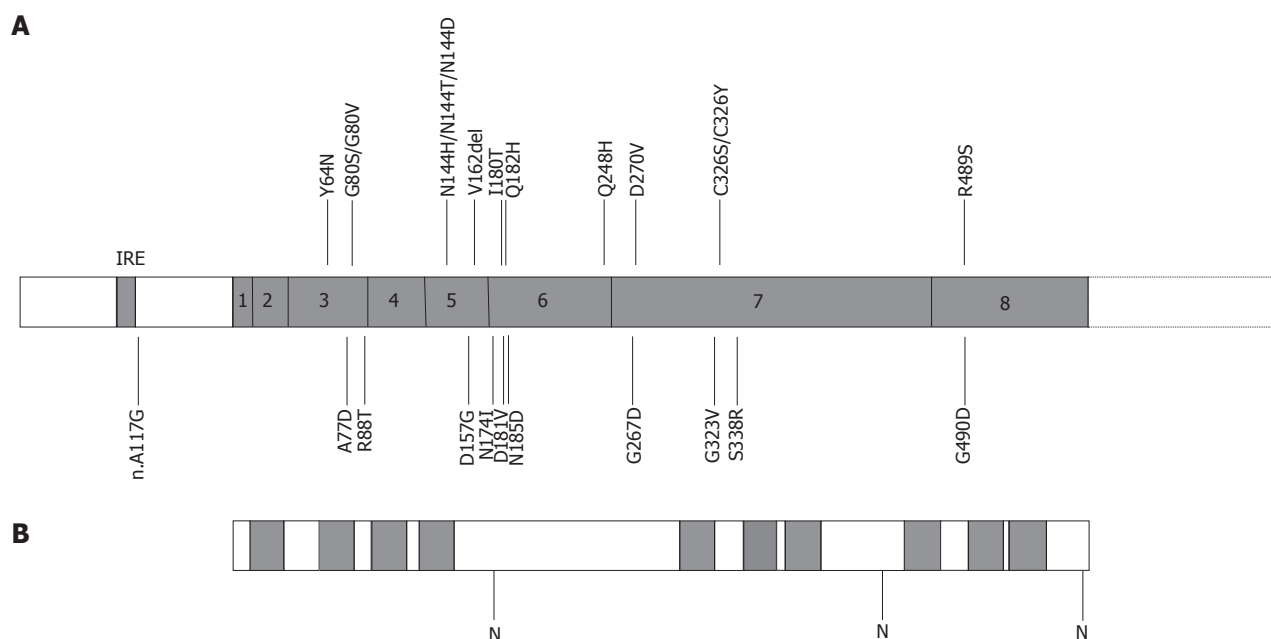
Transferrin Receptor 2 (TfR2)-HH was first described in 2000<sup>[7]</sup>. This was the first HH syndrome to be attributed to non-HFE mutations. Mutations in *TfR2* were first detected in six members of two Sicilian families. The defect was linked to a region on the long arm of chromosome 7 (7q22), and affected individuals were found to be homozygous for a nonsense mutation (Y250X) in *TfR2*<sup>[7]</sup>. Affected individuals had iron overload with a similar phenotype to HFE-HH. TfR2-HH is a rare condition; however, several mutations have been reported worldwide associated with haemochromatosis<sup>[7,30,40-52]</sup>. Mutations reported in *TfR2* are illustrated in Figure 3.

TfR2 is a homologue of the classical transferrin

receptor (TfR1)<sup>[53]</sup>, the molecule responsible for the uptake of transferrin-bound iron into cells. Unlike the ubiquitous expression of TfR1, TfR2 expression and activity is restricted almost exclusively to the liver<sup>[54]</sup>. Rather than being involved in the uptake of transferrin bound iron, it appears that the main function of TfR2 is as a sensor of iron levels and regulator of hepcidin. In both patients and animal models with TfR2-HH hepcidin levels are low in relation to iron stores<sup>[55-57]</sup>.

The clinical features of TfR2-HH resemble that found in HFE-HH. Onset is usually in adulthood and is associated with increased serum iron indices and iron accumulation in parenchymal cells. Clinical features reported in patients with TfR2-HH include abnormal liver function, liver fibrosis, cirrhosis, arthritis, diabetes, hypogonadism, cardiomyopathy and skin pigmentation<sup>[41,44]</sup>. All of these features are typical of HFE-HH. A direct comparison of phenotype between HFE-HH and TfR2-HH is difficult, due to the low prevalence of *TfR2* mutations and small number of reported cases. It appears, however, that TfR2-HH may have a more severe phenotype. Early onset of disease has been reported in a number of cases. Two adolescent siblings homozygous for the R105X mutation were reported with elevated transferrin saturation<sup>[51]</sup>. However, the serum ferritin in both cases was normal and liver biopsy was not performed. Two unrelated cases, presenting at ages 3 and 16 years were reported, homozygous for the Y250X mutation<sup>[40]</sup>. Both had raised serum iron, transferrin saturation and hepatic iron. The 16-year-old, who presented with fatigue, also had raised serum ferritin. Other cases suggestive of an earlier onset and more severe phenotype than HFE-HH have also been reported<sup>[42, 44]</sup>.





**Figure 4** Structure of human *ferroportin* and positions of mutations. **A:** The exon structure of human *ferroportin* is shown with positions of known mutations marked<sup>[8,9,60-85]</sup>. IRE, iron response element; **B:** Predicted structure of *ferroportin* protein. Predicted transmembrane domains are shaded; N, potential N-linked glycosylation sites.

Pietrangelo *et al*<sup>[52]</sup> recently reported an unusual family with both adult and juvenile onset haemochromatosis. Two siblings presented in their early twenties with features typical of JH. These included hypogonadotropic hypogonadism, cardiomyopathy and cirrhosis. Both were found to be homozygous for a mutation Q317X in *TfR2*. In addition compound heterozygosity for *HFE*-C282Y/H63D was also present. A brother who had a less severe adult onset phenotype was homozygous for the Q317X *TfR2* mutation, but had wild type *HFE* sequence. This is the first and only report of juvenile haemochromatosis due to mutations in two genes normally associated with adult-onset haemochromatosis<sup>[52]</sup>. This observation suggests that defects in either *HFE* or *TfR2* can be compensated to some extent by the other. Homozygosity for mutations in either one can lead to appreciable iron overload with onset normally in adulthood. The combination of mutations in both genes has an additive effect on iron loading, leading to an earlier onset and JH-like phenotype. Both *HFE* and *TfR2* are thought to regulate hepcidin expression in the liver through as yet unidentified signalling pathways. It is possible that *HFE* and *TfR2* work through either parallel or converging signalling pathways resulting in the induction of hepcidin. This would explain why the loss of one can be compensated to some extent by the other. The loss of both, however, would lead to complete loss of regulation of hepcidin by iron, as occurs in JH. Further studies will be needed to clarify the relationship between *HFE* and *TfR2*, and the signalling pathways they are involved in.

## FERROPORTIN DISEASE

Ferroportin disease differs from other genetic iron overload disorders in that it is inherited in an autosomal dominant pattern. An autosomal dominant form of

haemochromatosis was first reported in 1990, in a Melanesian pedigree from the Solomon Islands<sup>[58]</sup>. In a large 96 member pedigree, 31 of 81 members tested were affected in at least three generations. All affected individuals had raised transferrin saturation and serum ferritin levels. Liver biopsies in 19 individuals showed a pattern of iron staining consistent with *HFE*-HH, with iron present in hepatocytes and Kupffer cells. Some degree of fibrosis or cirrhosis was present in the majority of cases. This study was performed before the identification of the *HFE* gene; hence, analysis of *HFE* mutations could not be performed. However, linkage to the *HFE* locus on chromosome 6 was excluded, by HLA typing of affected and non-affected family members<sup>[58]</sup>. Another large pedigree with multiple affected individuals, but without pathogenic mutations in the *HFE* gene was described in 1999<sup>[59]</sup>. This Italian family consisted of 53 living members, with 15 affected across three generations. Linkage to the *HFE* region on chromosome 6 was excluded by typing of microsatellite markers.

Mutations in *ferroportin*, associated with autosomal dominant haemochromatosis were first described in 2001. An asparagine to histidine mutation (N144H) was identified in a large multi-generation family from the Netherlands<sup>[9]</sup>. At the same time an alanine to aspartate mutation (A77D) was reported in the large Italian pedigree described previously<sup>[8]</sup>. Since these first reports, many more *ferroportin* mutations have been described in association with autosomal dominant haemochromatosis<sup>[60-85]</sup>. Figure 4 shows the mutations reported in the literature to date. *Ferroportin* mutations have been reported in populations throughout the world. Most of the reported *ferroportin* mutations are private and restricted to single families. Some mutations, however, are more common and have been reported in diverse populations. The most prevalent is the deletion of one of a group of three valine residues

(V162del). This mutation has been reported in families from Australia, the UK, Italy, Greece, Sri Lanka and Austria<sup>[61-66]</sup>. It has been proposed that this mutation has occurred independently, several times, due to slippage mispairing in a repeat sequence. Other mutations reported in multiple populations include A77D (Italy and Australia)<sup>[8,60]</sup> and Q248H<sup>[75-79]</sup>. It is unclear whether Q248H is a mutation or polymorphism. It has been reported at high frequencies in African and African-American populations, in both controls and individuals with iron overload, where it can occur in the heterozygous or homozygous state. There is suggestive evidence that it may contribute to slightly higher serum ferritin levels<sup>[76-79]</sup>, but this effect is very small compared to other *ferroportin* mutants. There are three mutations affecting asparagine 144, suggesting that this residue is important for the functioning of ferroportin. In the original Dutch family reported by Njajou *et al*<sup>[9]</sup>, it was mutated to a histidine (N144H)<sup>[9]</sup>, in an Australian family to an aspartate (N144D)<sup>[71]</sup> and in a Solomon Island patient to a threonine (N144T)<sup>[67]</sup>. Whether this mutation is responsible for the autosomal dominant Solomon Island iron overload syndrome reported by Eason *et al*<sup>[58]</sup>, remains to be determined.

The phenotypic features of most cases of ferroportin disease differ significantly from that of HFE-HH. The typical features are an early elevation in serum ferritin, with normal transferrin saturation, and iron accumulation preferentially in the Kupffer cells of the liver. With increasing age, iron stores increase, and iron is seen in hepatocytes as well as Kupffer cells, and the transferrin saturation can be elevated. In these cases liver damage is minimal, with fibrosis occurring in some individuals. Venesection therapy is not always tolerated, with anaemia developing, especially in early cases when the transferrin saturation is low. It is now apparent that some cases of ferroportin disease differ from this typical pattern. A second atypical phenotype has been proposed, with features that more closely resemble HFE-HH. Atypical features include an early rise in transferrin saturation, and iron accumulation preferentially in hepatocytes, with some Kupffer cell iron apparent in some cases. Venesection therapy in these cases is usually tolerated well, but liver damage would appear to be more prevalent, with two reports of cirrhosis<sup>[71,80]</sup>.

The heterogeneity of ferroportin disease has led to the suggestion that mutational differences account for the phenotypic variation observed in patients. In general each mutation can be classified as leading to either the typical or atypical ferroportin disease phenotype. It has been proposed that particular mutations affect the function of ferroportin in different ways. The *ferroportin* gene, also referred to as *IREG1*, *MTP1*, *SLC11A3* and *SLC40A1*, encodes a multiple transmembrane domain iron transporter, highly expressed in duodenum, liver and reticuloendothelial cells. It is responsible for iron transport across the basolateral surface of enterocytes into the blood and recycling of iron in the reticuloendothelial system. Mutations such as A77D and V162del lead to the typical phenotype of reticuloendothelial iron storage, with relatively low transferrin saturation. A non-functional

ferroportin molecule would be predicted to lead to this phenotype. Heterozygosity for a non-functional mutant would be predicted to lead to haploinsufficiency for ferroportin, with only half the amount of functional ferroportin present on the surface of cells at any one time. In the reticuloendothelial system, where the vast majority of daily iron turnover occurs, this would be predicted to cause a blockage in the release of iron back into the circulation. Hence, iron would accumulate in the reticuloendothelial macrophages, and serum iron concentrations would be relatively low. These low levels of circulating iron would in turn lead to an increase in iron absorption in the duodenum, possibly involving sensors in the liver, such as HFE and Tfr2 and signalling *via* the hepcidin pathway. The turnover of iron in the reticuloendothelial system far outweighs that in the duodenum. Hence, the ferroportin required to transport iron across the basolateral surface of enterocytes would probably be sufficient to transport more iron into the body, even if a non-functional mutant was present. Over a long period of time body iron stores would increase to a point where the capacity of the reticuloendothelial cells to store iron would be reached, and iron would accumulate in parenchymal cells such as hepatocytes. This is seen in advanced typical ferroportin disease and is usually accompanied by an increase in the transferrin saturation.

It was recently reported that ferroportin expression on the cell surface can be regulated by hepcidin<sup>[86]</sup>. It was shown that hepcidin could bind to ferroportin on the cell surface and induce its internalisation and degradation. In this way hepcidin could rapidly reduce iron absorption in the intestine and release of iron from the reticuloendothelial system, resulting in a reduction in serum iron. It has been proposed that the mutations which cause the atypical ferroportin disease phenotype affect the ability of hepcidin to internalise ferroportin. Failure to internalise would lead to a permanently “switched on” ferroportin molecule. This would lead to increased iron absorption in the duodenum and release from reticuloendothelial cells, resulting in high serum iron levels and storage of iron in parenchymal cells. Having a permanently “switched on” ferroportin molecule would effectively be the same as having hepcidin deficiency, as they both result in the same end point. This explains why the atypical form of ferroportin disease phenotypically resembles other forms of haemochromatosis, which all result from hepcidin deficiency.

## CONCLUSION

There are four main genes implicated in non-HFE haemochromatosis. Mutations in these genes occur in populations world wide and account for the majority of HH cases not linked to HFE. The study of these disorders has led to a greater understanding of how the body regulates iron homeostasis. All the genes implicated in the different forms of haemochromatosis are involved in the regulation and maintenance of iron homeostasis. Hepcidin is at the centre of the iron regulatory pathway. Its expression in the liver can be regulated by the activities of HFE, Tfr2 and HJV. Hepcidin itself can regulate the activity of the iron

exporter ferroportin. Mutations in any one of these genes can disrupt the regulation of iron homeostasis and lead to iron overload. Further study of these molecules, their relationships to each other, and signalling pathways they are involved in will further illuminate our understanding of iron metabolism and its regulation.

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