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Ferroportin Disease
(Haemochromatosis-type IV)
A Case Report

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Introduction: Haemochromatosis-type IV, the ferroportin disease, is characterized by an autosomal-dominant transmission and early iron accumulation in macrophages. It is caused by mutations in the transmembrane iron exporter protein ferroportin1 (SLC40A1 gene). In form A (classic), ferroportin loss of function mutants are unable to export iron from cells leading to cellular iron accumulation with decreased availability of iron for serum transferrin (TS). We present a Portuguese rare clinical case of HH-IV.

Table 1: Classification of the genetic forms of haemochromatosis

Disease	Type	Gene	Protein	Chromosome	Inheritance	Phenotype	OMIM* number
Haemochromatosis	1	*HFE*	HFE	6p	AR	classic	+235200
Juvenile haemochromatosis	2a	*HJV*	Haemojuvelin	1q	AR	juvenile	#602390
Juvenile haemochromatosis	2b	*HAMP*	Hepcidin	19q	AR	juvenile	#602390
Haemochromatosis	3	*TfR2*	TfR2	7q	AR	classic	#604720
Ferroportin disease	4	*SLC40A1*	Ferroportin	2q	AD	atypical (classic)	#606069

Clara Camaschella, Diagnosis and treatment of non-HFE-haemochromatosis.
OMIM* = On line Mendelian Inheritance in Man at http://www.ncbi.cnlm.nih.gov

Materials and Methods: A 42-year-old woman with hyperferritinemia and normal TS. Causes of hyperferritinemia (inflammation, chronic alcohol consumption, metabolic syndrome, cell necrosis, non-alcoholic fatty liver disease and aceruloplasminemia) were assessed. Liver iron, evaluated by magnetic resonance imaging (MRI) was carried out. Screening for mutation in HFE and SCL40A1 genes were performed by Sanger sequencing.
Therapy: weekly 450ml Therapeutic Phlebotomies (TP) until ferritin≤50ng/ml.

Results: Baseline/After 8 TP: Ferritin:708/262ng/ml; TS: 27/15%; MRI:85/35µmol/g; Hb:13,6/12,3g/dl. Hyperferritinemia comorbidities and common genetic mutations for haemochromatosis were negative. However, sequencing of the patient SLC40A1 gene has revealed the presence in heterozygosity of the variant c.238G>A; p.Gly80Ser.
Due to low tolerance to TP, we adopted smaller phlebotomies every three weeks.

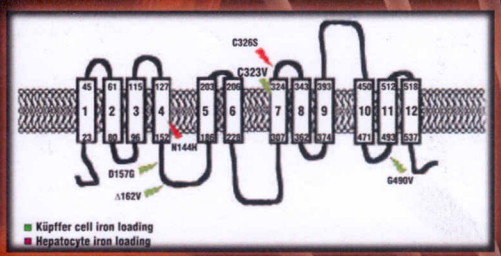


Figure 1. Predicted structure of ferroportin.
Fpn is a membrane protein with twelve predicted transmembrane domains. Several mutations in the Fpn gene have been reported. Mutations that lead to Kupffer cell iron loading are shown in green and those that lead to hepatocyte iron loading are shown in red.

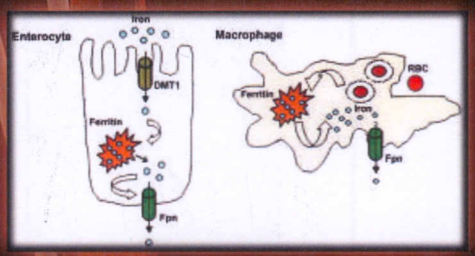
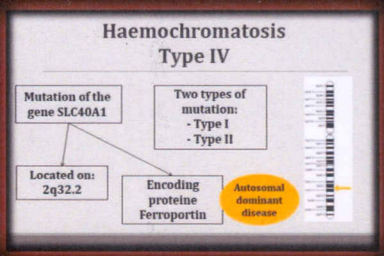


Figure 2. Schematic diagram of the location of ferroportin iron export in the enterocyte and the macrophage. Iron is transported into the enterocyte by DMT1 localized on the apical membrane.



Conclusion: This patient has a rare autosomal-dominant Ferroportin disease due to a mutated ferroportin which is predicted to be defective in iron cellular export. In agreement, she presents hyperferritinemia, with normal TS and liver iron overload. The genotype/phenotype association allowed to diagnosis this rare FD case. Although a mild form A, we decided to start TP. Her father also has been treated for iron overload.

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