# The Natural History of Ferroportin Disease – First Results of the International, Multicenter EASL non-HFE Registry

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EASL European Association for the Study of the Liver

non HFE registry

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## 1 INTRODUCTION

Ferroportin disease and hemochromatosis type 4 are phenotypically distinct diseases caused by heterozygous mutations in *SLC40A1*. Both traits are characterized by high serum ferritin and hepatic iron overload.

Transferrin saturation and splenic/macrophage iron overload distinguish ferroportin disease from hemochromatosis type 4. Prognosis and management of patients with *SLC40A1* mutations have been inferred from *HFE* associated hemochromatosis (type 1), despite distinct phenotypic presentation in the subgroup of patients with a ferroportin disease phenotype.

## 2 AIM

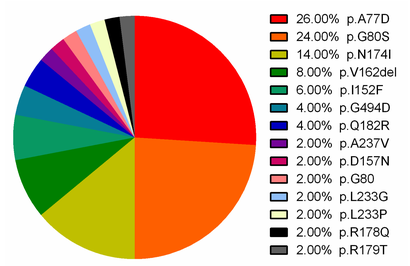
The aim of the present study was to define the clinical and biochemical characteristics and management of patients with *SLC40A1* mutations in comparison to *HFE* hemochromatosis.

## 3 METHOD

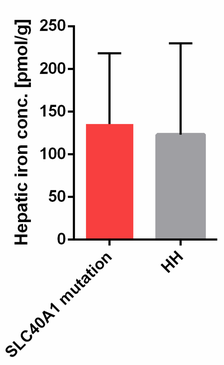
An online electronic case report form was set up to collect structured information on the clinical presentation, biochemistry, radiology, genetics and histology of patients with FPN disease. All participating centres obtained ethical approval for data entry.
Data were compared with an age and sex matched cohort of patients diagnosed with *HFE* hemochromatosis at the University Hospital Innsbruck.

## 4 RESULTS

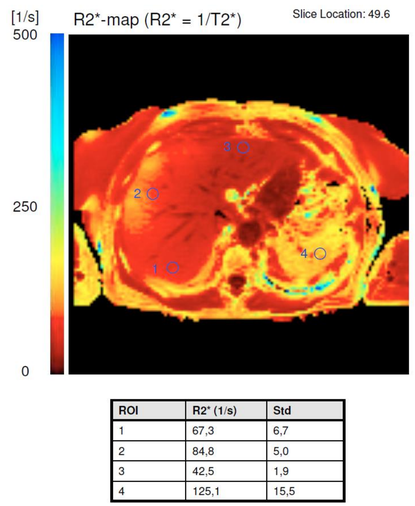
As of January 2019, 77 patients (41 female) with genetically confirmed ferroportin disease have been registered, representing the largest cohort of patients with disease-associated *SLC40A1* mutations.




*Reported SLC40A1 mutations.*




*Hepatic iron concentration determined by MRI in the ferroportin disease group as compared to the HFE hemochromatosis group (p = 0.405).*




| ROI | R2* (1/s) | Std |
|---|---|---|
| 1 | 67,3 | 6,7 |
| 2 | 84,8 | 5,0 |
| 3 | 42,5 | 1,9 |
| 4 | 125,1 | 15,5 |

*Hepatic and splenic iron overload indicated by increased R2* frequencies in the liver and spleen of a female patient with heterozygosity for the p.R178Q mutation in the SLC40A1 gene*

Seventeen different mutations were reported. Eleven percent of patients presented with a hemochromatosis type 4 phenotype.

Patients with ferroportin disease had significantly lower serum iron, ferritin, and transferrin saturation when compared with HFE hemochromatosis patients.

| | SLC40A1 mutation (Ferroportin disease & Hemochromatosis Type 4) | HFE Hemochromatosis | p |
|---|---|---|---|
| N (females) | 77 (41) | 91 (47) | 0.479) |
| Age at diagnosis [years] | 42.1 (±15.6) | 40.5 (±13.5) | 0.590 |
| Serum iron [µg/dL] | 74.2 (±46.1) | 34.9 (±9.8) | <0.001 |
| Ferritin [µg/L] | 798 (505.6-1284) | 427 (299.8-653) | <0.001 |
| Transferrin [mg/dL] | 216 (189-257) | 167 (157.2-195) | <0.001 |
| Transferrin saturation [%] | 28 (21.5-37.5) | 79 (60.5-84.5) | <0.001 |
| Transferrin saturation >50% | 11% | 89% | <0.001 |
| Liver iron content [µmol/g] | 135.5 (±82.7) | 123.2 (±107.1) | 0.405 |
| Median follow-up [years] | 9.7 (±4.4) | 7.6 (±5.6) | 0.042 |
| HCC incidence | 1.3% (1/77) | 1.1 % (1/91) | 1.000 |

*Demographic and biochemical parameters of patients with SLC40A1 mutations compared with a age and sex matched control cohort of HFE hemochromatosis patients.*

Five-year survival rate was 95.6% in HFE hemochromatosis patients as compared to 100 % in individuals with SLC40A1 mutations.

At follow-up no patient with an *SLC40A1* mutation had signs of end-stage liver disease.

One individual with an *SLC40A1* mutation developed a hepatocellular carcinoma and one patient developed cholangiocarcinoma. Non-alcoholic fatty liver disease was present in 7 *SLC40A1* patients.

In the *SLC40A1* group 45 % of patients (35/77) received regular phlebotomies (mean treatment duration 9.2 years, 0.85 phlebotomies per month).

## 5 CONCLUSIONS

Although serum ferritin indicates more severe iron overload in patients with *SLC40A1* mutations than in HFE associated hemochromatosis, both groups show comparable hepatic iron concentration. In contrast, lower serum iron and transferrin saturation are associated with better outcome in FPN disease, despite low rate of iron reduction therapy in patients with *SLC40A1* mutations.

## 7 REFERENCES

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Pietrangelo A. Ferroportin disease: pathogenesis, diagnosis and treatment. Haematologica 2017;102:1972-1984.

## 8 JOIN THE REGISTRY

Do you have data on patients with ferroportin disease? Would you like to join our effort to better understand this condition? Then join the non-HFE registry!

More information can be found at:

**www.non-hfe.com**

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