Haemochromatosis: An Australian Perspective

Lawrie W. Powell, MD, PhD

The Queensland Institute of Medical Research and The University of Queensland, Brisbane Australia.
Idiopathic Haemochromatosis in Menstruating Women
The Lancet 1964, 284, 555-7

A Family Study, Including the Use of Diethylene, Triamine Penta-acetic Acid

H. M. LLOYD, D.M. Oxon., Ph.D. Lond., M.R.C.P., READER IN MEDICINE
L. W. POWELL, M.B. Queensland, M.R.A.C.P., TEACHING REGISTRAR,
MEDICAL PROFESSORIAL UNIT, UNIVERSITY OF QUEENSLAND
M. J. THOMAS, B.Sc. Lond., OF THE DEPARTMENT OF PATHOLOGY
BRISBANE HOSPITAL, BRISBANE, AUSTRALIA
HFE Haemochromatosis
HFE Haemochromatosis
HC - Cirrhosis
Subject C.H. Cirrhosis
Subject C.H. Biopsy 13 years later
# Prevalence of Inherited Liver Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Homozygote Frequency</th>
<th>Gene Frequency</th>
<th>Heterozygote Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemochromatosis</td>
<td>1:200</td>
<td>1:14</td>
<td>1:10</td>
</tr>
<tr>
<td>α₁AT Deficiency</td>
<td>1:1600</td>
<td>1:40</td>
<td>1:20</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1:2500</td>
<td>1:50</td>
<td>1:25</td>
</tr>
<tr>
<td>Wilson's Disease</td>
<td>1:30,000</td>
<td>1:170</td>
<td>1:85</td>
</tr>
</tbody>
</table>
Stages in the Evolution of HC

1. Genetic predisposition
2. Iron overload (2-5 g) but no symptoms
3. Iron overload with early symptoms (lethargy, arthropathy)
4. Iron overload with organ damage especially cirrhosis
Criteria for Established Haemochromatosis

- Stainable hepatic iron grade 3 or 4
- Hepatic iron concentration $> 80 \, \mu\text{M/g (dw)}$
- Hepatic iron index (hepatic iron concentration/age) $> 1.9$
- $>5g$ iron removed by phlebotomy
- HFE HHC confirmed by C282Y/H63D testing
Regulation of Iron Absorption

Villus -> Fe Absorption -> Ferroportin

Iron Stores
TfR2
HFE
Liver

Hepcidin

Crypts
HFE controls hepcidin expression

Bridle et al. 2003 *Lancet* 361:669-673
1. (Hereditary) Haemochromatosis (HC)

**HFE-associated HC (HFE 1)**
- C282Y homozygosity
- C282Y/H63D compound heterozygosity

**“Non-HFE associated HC” or HFE 2 - 4**
- Hemojuvelin mutation (HFE2A) (Juv. HC)
- Hepcidin (Hamp)(HFE2B) (Juvenile HC)
- Mutated transferrin receptor 2 (HFE3)
- Mutated ferroportin 1 gene (HFE4A and 4B)
FERROPORTIN DISEASE in a family of Asian heritage and reclassification of the G80S mutation

McDonald C, Wallace D, Ostini L, Bell S, Demediuk B, Subramaniam VN.
The natural history and disease burden of HH

1 in 200 N.Europeans C282Y +/+ 

Biochemical Expression 75%

50%

25%

Iron overload related disease

ALT
Arthritis
Cirrhosis
HCC

28% 1%
5.6% 1.9%

(Cirrhosis)

Incomplete Expression of HH

- C282Y +/+ is necessary but not sufficient for expression of the disease

*Beutler 2005*
International Consortium

- NIH funded collaborative study – USA 4 Centres, Canada, Brisbane and Melbourne
- 692 YY subjects – only males with low alcohol intake – 35 high and 13 low expressers
- Genome sequencing – 10,337 genes tested
- \textit{GNPAT} significant \( (p = 0.033) \)
- \textit{GNPAT} in 16/22 high v 0/13 low expressers
- Functional studies…
International Consortium

• Functional studies
  – HepG2 cells – siRNA – based kd of *GNPAT*
    - *HAMP* significantly reduced
• The siRNA-based knockdown of *GNPAT* >17-fold decrease in mRNA expression of hepcidin

**Conclusion:** *GNPAT* associated with a high iron phenotype in HFE C282Y homozygotes and participates via hepcidin regulation

**Clinical relevance** is obvious
Summary

• HFE-HC is the most common inherited disease in Caucasians
• Numerous new iron transporters identified
• Non-HFE-HHC increasingly reported including the Asian Pacific Region.
• Role of HFE?
• Modifying genes ..... *GNPAT*?
Haemochromatosis – J.H. Sheldon 1934
“Haemochromatosis is, in spite of its implicit but unproved assumptions, the best name for the disease”
Iron as a Cofactor for Liver Disease

- Alcohol
- HBV
- HCV
- Porphyrias
- Iron
- Fat
Ferroportin Disease

• Classical disease
  – Mutation affects iron transport function.
  – Reduces iron export capacity.
  – Results in intracellular iron accumulation.

• Non-classical disease
  – Mutation prevents hepcidin binding.
  – Constitutive iron export.
  – Results in increased absorption and recycling.
Family of Vietnamese Origin

Family history of phenotypically diagnosed iron overload.

Iron parameters
  – High serum ferritin
  – High hepatic iron levels

• Liver function tests normal.
• Venesection was being poorly tolerated.

(McDonald, Wallace, Subramaniam. J. Hepatology)
Identification of genetic cause

- Ferroportin mutation causing Glycine to Serine change at amino acid 80 (G80S).

(McDonald, Wallace, Subramaniam. J. Hepatology)
G80S ferroportin fails to export iron
Why is this significant?

• Unable to mobilise iron stores after venesection.
  – Aggressive venesection is usually not tolerated.
  – Can result in anaemia.

• Specific diagnosis impacts patient care.
  – Requires more reserved approach to venesection.
  – Requires increased monitoring.

• 1st identification outside of Europe heritage.
Acknowledgments

• Membrane Transport Laboratory, QIMR
  – Dr. Daniel Wallace
  – Lesa Ostini
  – Denny Muslin
  – Patricia Lusby
  – Assoc. Prof. Nathan Subramaniam

• St. Vincent’s Hospital
  – Dr. Sally Bell
  – Dr. Barbara Demediuk

• Liver Research Centre, UQ School of Medicine

• Funding
  – NHMRC

In press: C. McDonald et al. G80S-linked Ferroportin disease: Classical ferroportin disease in an Asian family and reclassification of the mutant as iron transport defective. Journal of Hepatology