Haemochromatosis - The Evolution Of Understanding Of Iron Overload

26.3.13

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University College Dublin,
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HAEMOCHROMATOSIS

John Crowe
HEREDITARY HAEMOCHROMATOSIS

Hereditary Haemochromatosis is an inherited disorder of iron metabolism where excess dietary iron is absorbed leading to progressive iron loading of parenchymal cells in the liver, pancreas and heart. In it’s fully developed stage organ structure and function are impaired.

*European Consensus Statement 1999.*
FIRST MCP ARTHROPATHY
CHONDROCALCINOSIS
DIAGNOSIS

• FASTING TRANSFERRIN SATURATION >55%
• SERUM FERRITIN >300UG/L
• GENETIC SCREEN
• LIVER BIOPSY
LIVER BIOPSY-LOW POWER. PERL’S STAIN
LIVER BIOPSY INDICATIONS

- FERRITIN > 1000UG/L
- ABNORMAL LIVER FUNCTION TESTS
- AGE OVER 40
IMPORTANT EARLY PLAYERS

Prof Marcel Simon

Dr Liz Jazwinska

Prof Laurie Powell
Professor Ciaran McCarthy
HAEMOCHROMATOSIS GENETICS 1975-1992

**HLA antigens in haemochromatosis.**
Walters JM, Watt DW, Stevens FM, McCarthy CF.
Br Med J. 1975

**Histocompatibility antigens and haemochromatosis in Ireland.**

HLA-A3 and serum iron. A study in an Irish control population. Stevens FM, Fallon MG, McCarthy CF, Grimes H.
Tissue Antigens. 1983

Identification of four families with Hereditary Haemochromatosis showing discordance between HLA class 1 gene and gene locus.
A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis


Hereditary haemochromatosis (HH), which affects some 1 in 400 and has an estimated carrier frequency of 1 in 10 individuals of Northern European descent, results in multi-organ dysfunction caused by increased iron deposition, and is treatable if detected early. Using linkage-disequilibrium and full haplotype analysis, we have identified a 250-kilobase region more than 3 megabases telomeric of the major histocompatibility complex (MHC) that is identical-by-descent in 85% of patient chromosomes. Within this region, we have identified a gene related to the MHC class I family, termed HLA-H, containing two missense alterations. One of these is predicted to inactivate this class of proteins and was found homozygous in 83% of 178 patients. A role of this gene in haemochromatosis is supported by the frequency and nature of the major mutation and prior studies implicating MHC class I-like proteins in iron metabolism.
WILD TYPE HFE CRYSTAL
HFE CRYSTAL WITH C282Y MUTATION
HAEMOCHROMATOSIS IN IRELAND AND HFE

- ALLELE FREQUENCY 14%

- 93% OF HH PATIENTS C282Y HOMOZYGOOTES

FREQUENCIES OF C282Y AND H63D MUTATIONS IN 800 IRISH NEONATES

<table>
<thead>
<tr>
<th>Allele Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y ALLELE</td>
<td>10.7%</td>
</tr>
<tr>
<td>C282Y HOMOZYGOTE</td>
<td>1:86</td>
</tr>
<tr>
<td>C282Y HETEROZYGOTE</td>
<td>1:5</td>
</tr>
<tr>
<td>H63D ALLELE</td>
<td>15.4%</td>
</tr>
<tr>
<td>H63D HOMOZYGOTE</td>
<td>1:42</td>
</tr>
<tr>
<td>C282Y/H63D COMPOUND HETEROZYGOTE</td>
<td>1:60</td>
</tr>
</tbody>
</table>

TOTAL AT RISK OF IRON OVERLOAD 1:17

Valerie Byrnes et al. Genet Test. 2001

HEREDITARY HAEMOCHROMATOSIS
MOST COMMON RECESSIVE DISORDER IN CAUCASIANS

IRELAND HAS HIGHEST PREVALENCE IN THE WORLD

HOMOZYGOTE FREQUENCY 1:86
HETEROZYGOTE FREQUENCY 1:5
COMPOUND HETEROZYGOTE FREQUENCY 1:60

Valerie Byrnes et al. Genet Test. 2001

HEREDITARY HAEMOCHROMATOSIS
HEREDITARY HAEMOCHROMATOSIS
C282Y HOMOZYGOTES

HEREDITARY HAEMOCHROMATOSIS
TOTAL AT RISK

HEREDITARY HAEMOCHROMATOSIS
ALL ALLELES

HEREDITARY HAEMOCHROMATOSIS
CONCENTRATION OF HAEMOCHROMATOSIS IN NORTH WESTERN EUROPE
PENETRANCE

NO IRISH POPULATION STUDY TO DATE.

• SURROGATE STUDY OF 209 C282Y HOMOZYGOTES DISCOVERED THROUGH FAMILY SCREENING.

• CORRESPONDS TO A POPULATION STUDY OF 17300 BASED ON A HOMOZYGOTE FREQUENCY OF 1:86.

• FATIGUE 46%, ARTHRALGIA 7% PIGMENTATION 8%

• TS >52% IN 51%. FERRITIN >300Uug/l IN 23%

• MODERATE TO SEVERE IRON STAINING 10%, FIBROSIS 42%, CIRRHOSIS 1%

Ferga Gleeson et al. Eur J Gastroenterol Hepatol 2004

HEREDITARY HAEMOCHROMATOSIS
PENETRANCE

- GENE FREQUENCY HIGH
- DISEASE FREQUENCY LOW
- POPULATION SCREENING NOT RECOMMENDED

HEREDITARY HAEMOCHROMATOSIS
POPULATION SCREENING-THE ALTERNATIVES

- PHYSICIAN EDUCATION
- PATIENT ADVOCACY ORGANISATIONS
- INCREASED PUBLIC AWARENESS
HAEMOCHROMATOSIS AWARENESS IN IRELAND

- HAEMOCHROMATOSIS ASSOCIATION
- MEDICAL LEADERSHIP
- SUPPORTIVE IRISH MEDIA
- INTERNET
Procedure for obtaining a small sample of blood from fingertip

1. Clean finger with steret provided.
2. Allow finger to dry.
3. Prick finger with the enclosed needle (see instructions below).
4. Fill 2 circles with blood.
5. Let card dry overnight at room temperature.
6. Write name and date of birth on card.
7. Place test strip into plastic bio hazard bag and then into special envelope provided.
8. Return to G.I. Laboratory, Centre For Liver Disease Mater Hospital, Dublin.
9. Dispose of used needle safely.
10. When more than one test is being returned, please use separate envelopes provided. If the test strips come in contact with each other, the result will be altered.

Instructions for use of Unistik (needle)

1. Push yellow tip into the body of Unistik until it clicks.
2. Twist off and discard the yellow tip.
3. Place platform end (i.e. the end where you have removed yellow tip) of Unistik firmly against finger and press top firing pad.
4. Massage the site to obtain blood flow, taking care not to squeeze too hard at the site.
5. The needle will always retract safely after use. Dispose of Unistik safely.
VENESECTION-WHEN TO START

- FERRITIN CONSISTENTLY > 450UG/L
VENESECTION

• REGULAR INTERVALS OR AS REQUIRED

• FERRITIN-HOW LOW SHOULD IT GO AND HOW HIGH CAN IT GO?
IRON ABSORPTION INCREASED BY 11-66% DURING VENESECTION

INCREASES OF 5-100% PERSISTED FOR UP TO 1 YEAR

Roger Williams et al. 1966. BMJ 2 78-81
RATE OF RISE IN SERUM FERRITIN PRE AND POST VENESECTION

DELTA SERUM FERRITIN
PRE VENESECTION
POST VENESECTION

\[ P = 0.022 \]

Eleanor Ryan et al. HEPATOLOGY 2003
MAINTENANCE OF IRON DEPLETION

AMERICAN IRON OVERLOAD ASSOCIATION:

- MAINTAIN FERRITIN < 50ug/l

BUT PHLEBOTOMY

- INCREASES DMT1 ACTIVITY
- INCREASES IRON ABSORPTION

SUIT THE BLOOD BANK!
## Real Time PCR: Duodenal DMT1 and IREG in Untreated and Treated HH

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HH Untreated</th>
<th>HH Treated</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN DMT1 [SD]</td>
<td>0.44[0.9]</td>
<td>1.9[2.3]</td>
<td>0.3[0.3]</td>
</tr>
<tr>
<td>MEAN IREG1 [SD]</td>
<td>0.7[0.5]</td>
<td>1.4[1.3]</td>
<td>0.79[0.4]</td>
</tr>
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BARRY KELLIHER et al. GUT 2004

HEREDITARY HAEMOCHROMATOSIS
MAINTENANCE VENESECTION - WHAT’S BEST?

- **BLOOD BANK** - 1-4 DONATIONS ANNUALLY
  IRON ABSORPTION CONTINUOUSLY UPREGULATED
  FACILITATES DONOR STATUS

- **HOSPITAL CLINIC** - VENESECTION ONLY WHEN
  FERRITIN > 300UG/L
  DIMINISHES UPREGULATION
  REDUCES CLINIC ATTENDANCE AND COST.
PROGRESSION OF HEPATIC IRON DEPLETION
PHLEBOTOMY AND DIETARY IRON

- 500ml BLOOD 200mg IRON
- 200 GLASSES OF WINE
- 37 BOWLS OF CEREAL
- 50 7oz CUTS OF BEEF
BEWARE OF CORNFLAKES

<table>
<thead>
<tr>
<th>Vitamin B&lt;sub&gt;6&lt;/sub&gt;</th>
<th>2.3mg 115%RDA</th>
<th>0.8mg 40%RDA</th>
</tr>
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For healthy blood, skin & nerves, and proper use of proteins.

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<th>Folic Acid</th>
<th>333µg 165%RDA</th>
<th>110µg 55%RDA</th>
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Essential for growing cells and healthy blood. Also important for healthy babies and a healthy heart.

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<th>1µg 100%RDA</th>
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Helps blood cells grow and develop, important for a healthy nervous system.

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<th>Iron</th>
<th>24.3mg 170%RDA</th>
<th>7.3mg 52%RDA</th>
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Helps the body’s use of oxygen, carrying it to all the cells of the body.
IRON HOMEOSTASIS

Enterocyte

Ferritin

Hepatocyte

BMPR I&II

TFR2

HFE

SMAD1/5/8

P

SMAD1/5/8

SMAD4

Hepcidin mRNA

FERGA GLEESON. EUR J GAST HEPATOL 2004
HAEMOCHROMATOSIS AND HEPATITIS C

HOW PARALLEL INTERESTS CAN CONVERGE UNEXPECTEDLY!
TREATING CHRONIC HEPATITIS C: THE FIRST 24 HOURS

- 31 PATIENTS WITH HCV GENOTYPE 1
- PEG INTERFERON AND RIBAVIRIN
- PROTEOMIC, GENOMIC AND VIRAL RESPONSES IN THE FIRST 24 HOURS
- SELDI-TOF, MICRO ARRAY, PCR AT 6 HOURLY INTERVALS FOR 24 HOURS

EMMA DEVITT ET AL. GASTROENTEROLOGY 2008, HEPATOLOGY 2008

HEREDITARY HAEMOCHROMATOSIS
**SELDI-TOF RESULTS**

**GENOTYPE 1**

16 PEAKS IDENTIFIED IN RESPONDERS

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<tr>
<td>1,966</td>
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**HEREDITARY HAEMOCHROMATOSIS**
WHAT WERE THE PEAKS?
MASS TO CHARGE RATIO OF PEAK 2193M/Z CONFORMED WITH **HEPCIDIN 20 ISOFORM**

FURTHER ANALYSIS REVEALED **HEPCIDIN 25 ISOFORM**

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**HEREDITARY HAEMOCHROMATOSIS**
THE FIRST 24 HOURS

Serum Hepcidin-25

PEG INTERFERON+RIBAVIRIN
THE FIRST 24 HOURS

Serum Hepcidin-25 and Iron

PEG INTERFERON+RIBAVIRIN
THE FIRST 24 HOURS

Serum Hepcidin-25, Iron and Viral Load

- Serum Iron
- HCV Viral load
- Serum Hepcidin-25

PEG INTERFERON+RIBAVIRIN

JOHN RYAN HEPATOLOGY 2012
HEPCIDIN INDUCTION AND HYPOFERRAEMIA

- MAY SIMPLY REFLECT AN INTERFERON RESPONSE EPI-PHENOMENON
- LOW IRON LEVELS MAY BE BIOMARKER OF IMMEDIATE INTERFERON RESPONSE
- IRON WITHDRAWAL MAY BE A POSSIBLE DIRECT ANTIVIRAL MECHANISM OF INTERFERON.

HEREDITARY HAEMOCHROMATOSIS
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LIVER CENTRE HH SERVICE

- 2 CONSULTANTS
- 1 SERVICE SpR
- 2 RESEARCH SpR [MD PhD]
- 3 SPECIALIST NURSES
- 3 POST DOC. SCIENTISTS
- PSYCHOLOGIST