Underdiagnosed by how much? A decade of HFE gene tests in rural and metropolitan Queensland

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Hereditary Haemochromatosis

- common
- underdiagnosed
- potentially fatal
- easily treated
- preventable cause of chronic disease

- gene mutation
- excess iron
- iron overload
- organ damage

C282Y Homozygous

two copies of the C282Y mutation in the HFE gene

- liver damage
- skin changes
What we know

C282Y+/- (2 copies)

Medicare data

Elevated ferritin is not specific

One in 200 Caucasians

>500,000 tests

Elevated ferritin

90% other causes
- obesity
- diabetes
- metabolic syndrome
- alcohol consumption
  - liver disease
  - inflammation

10% true iron overload

Medicare data

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One in 200 Caucasians

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Elevated ferritin

90% other causes
- obesity
- diabetes
- metabolic syndrome
- alcohol consumption
  - liver disease
  - inflammation

10% true iron overload
What we don’t know

How many Australians?

Is detection working?

Do we need screening?

iron studies: current iron overload

gene test: future iron overload risk
<table>
<thead>
<tr>
<th>My research questions</th>
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<tbody>
<tr>
<td>1. Gap between observed &amp; expected</td>
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<tr>
<td><em>how many C282Y+/+ are undiagnosed?</em></td>
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<tr>
<td>2. Percentage of tests = C282Y+/+</td>
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<tr>
<td><em>how useful are current testing guidelines?</em></td>
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<td>3. Duplicate tests performed</td>
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<td><em>how much “waste” is there?</em></td>
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A decade of tests: 5519 results

**CQ**
- 2283 tests, 38660 people
- 66% male, mean age 49
- 5.9% of people had a test
- 146 pairs, 14 triplicates
- 0 quadruplicates
- 85.3% Caucasian

**BNE**
- 3236 tests, 83302 people
- 55% male, mean age 50
- 3.9% of people had a test
- 211 pairs, 20 triplicates
- 2 quadruplicates
- 77.9% Caucasian

CaSS | Pathology Queensland
A CLINICAL AND STATEWIDE SERVICE

Pathology.
Specialists in Private Pathology since the 1920s

Sullivan Nicolaides Pathology
### Genotype Frequencies

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prevalence</th>
<th>CQ</th>
<th>BNE</th>
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<tbody>
<tr>
<td><strong>Highest risk of iron overload</strong></td>
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<tr>
<td>C282Y +/+</td>
<td>0.5%</td>
<td>3.1%</td>
<td>5.4%</td>
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<tr>
<td><strong>Some risk of iron overload</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C282Y/H63D</td>
<td>2.0%</td>
<td>5.3%</td>
<td>6.6%</td>
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<tr>
<td><strong>Negligible risk of iron overload</strong></td>
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</tr>
<tr>
<td>1. H63D +/+</td>
<td>2.0%</td>
<td>3.7%</td>
<td>3.8%</td>
</tr>
<tr>
<td>2. C282Y carrier</td>
<td>12.5%</td>
<td>17.5%</td>
<td>17.5%</td>
</tr>
<tr>
<td>3. H63D carrier</td>
<td>25.0%</td>
<td>25.1%</td>
<td>23.1%</td>
</tr>
<tr>
<td>4. Wild type</td>
<td>58.0%</td>
<td>45.3%</td>
<td>43.6%</td>
</tr>
<tr>
<td><strong>Total 1+2+3+4</strong></td>
<td>91.6%</td>
<td>88.0%</td>
<td></td>
</tr>
</tbody>
</table>
C282Y+/+ results

CQ
n = 66
61% male
mean = 44.5

BNE
n = 157
51% male
mean = 45.3
My results for CQ

CQ 66 C282Y+/-, 61% male, mean age 44.5

1. 164 expected
2. 1 in 32 tests (3.1%) = C282Y+/-
3. Duplicates = 1 in 13

60% undiagnosed in CQ

gap = 98
**My results for BNE**

**BNE** 157 C282Y+/+, 51% male, mean age 45.3

1. **expected** 324

2. **observed** 157

3. gap = 167

52% undiagnosed in BNE

2. 1 in 19 tests (5.2%) = C282Y +/-  

3. Duplicates = 1 in 13
Existing methods…
- found less than half of expected C282Y+/
- found 6-10 times more C282Y +/- above natural frequency
- have a substantial problem with test duplication

CQ vs BNE – high ferritin?
- more % tests performed in CQ with less % C282Y+/

Suggestions to improve detection
- GPs – routinely ask about family history of haemochromatosis
  - check iron studies for people in their 30s, 40s and 50s
- patients – encourage family members to be tested
The next step...

1. Check iron studies with HFE result
   - do C282Y+/+ usually have elevated transferrin saturations?

2. Check request form clinical notes
   - testing relatives versus investigating elevated iron studies
More Information

Haemochromatosis Australia
www.haemochromatosis.org.au
derived GP Resources webpage
– clinical practice guidelines
– patient resources

Available online for free download:
Haemochromatosis tri-fold brochure
Haemochromatosis: Your Questions Answered

Health professionals can order resources
call Information Line or email
publications@haemochromatosis.org.au
Resources for General Practitioners

Haemochromatosis Awareness Week

Haemochromatosis Awareness Week 2012 will be observed from 13 - 19 August 2012.

There will be a series of free public haemochromatosis information sessions and seminars in Brisbane, Sydney, Perth, Adelaide, Sunshine Coast and Port Macquarie. Medical and allied health professionals are welcome to attend. For more details see our Meetings page.

Clinical Guidelines

HAEMOCHROMATOSIS (Third edition) 2007

Clinical guidelines for the diagnosis and management of haemochromatosis published by the Digestive Health Foundation (Gastroenterological Society of Australia).

Hereditary haemochromatosis

National Health and Medical Research Council

Genetic counselling and testing guidelines - GP Red Book

Extract from Guidelines for preventative activities in general practice, 7th edition, RACGP.

Diagnosis and Management of Haemochromatosis: 2011 Practice Guidelines (AASLD)

Clinical guidelines for the diagnosis and management of haemochromatosis published by the American Association for the Study of Liver Disease. July 2011

Management of HFE Haemochromatosis - European Association for the Study of the Liver


Hereditary Haemochromatosis: Diagnosis and Management from a GP Perspective

Paper published by the Irish College of General Practitioners, Quality in Practice Committee. 2009.
Elevated Serum Ferritin

1. Repeat serum ferritin
2. Assess history of iron supplementation (oral, IM, IV), blood transfusions, anaemia
3. Exclude iron loading anaemias (Hb, MCV, blood film)

Ferritin <1000 μg/L

- HFE genotype
  - HIGHEST RISK: C282Y homozygous
  - LOWER RISK: C282Y/H63D compound heterozygous
  - Hereditary Haemochromatosis
    - Keep looking
      - Comence venesection
        - Suitable for Blood Service Therapeutic Venesection program
  - C282Y carrier
    - No mutations
      - Keep looking
      - Examine elevated SF
      - Reduce alcohol intake then re-test
  - C282Y carrier
    - H63D homozygous
      - Examine elevated SF
      - Keep looking
      - Repeat ferritin

- Alcohol Intake
  - >20g daily
  - <20g daily

- Metabolic Syndrome, Obesity or Diabetes
  - Present
  - Absent

- Liver Disease
  - Present
  - Absent
  - eg: LFTs, HBsAg, HCV-Ab, ANA, AMA, SMA, AAT, copper, caeruloplasmin, liver ultrasound

- Malignancy, Infection or Inflammation
  - Present
  - Absent
  - eg ESR, CRP, ANA

- If no explanation is found, consider referral to gastroenterologist for assessment of hepatic iron (Ferriscan® MRI or liver biopsy)

Ferritin >1000 μg/L

- Refer to specialist gastroenterologist, haematologist or physician