Hereditary Hemochromatosis: Are We Ready for Population Screening?

Epidemiology

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Hereditary Hemochromatosis
textbook onset age 40 to 60 in men, less common and later onsets in women

widespread iron deposition

Fatigue, weakness, joint pain, abdominal pain
• Liver – cirrhosis and hepatocellular cancer
• Arthritis / arthropathy
• Diabetes

Less common
Susceptibility to infection, cardiomyopathy, arrhythmias, endocrine glands, erectile dysfunction, menstrual problems, Bronze skin
(e.g. Powell L et al, The Lancet 2016, Hollerer et al Haematologica 2017)

From: Hollerer et al Haematologica 2017
Genetic variants

Hereditary Haemochromatosis (HH - Type 1) predominantly occurs with European ancestries

**HFE mutations**
- 95% of HH is linked to p.C282Y homozygosity
- 5% p.C282Y/p.H63D
- *Plus some rare variants*

Higher prevalence in northern Europe
  - especially Ireland and the UK
But present across European ancestries
Prevalence in North America

*HFE* p.C282Y homozygosity (‘HMZ’)

HEIRS study: 99,711 participants across 5 North American Medical Centers
(Adams et al, NEJM, 2005)

White Americans – 1 in 227 people are C282Y homozygote p.(C282Y/C282Y)

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>White</td>
<td>0.44</td>
<td>0.42 to 0.47</td>
</tr>
<tr>
<td>Native American</td>
<td>0.11</td>
<td>0.06 to 0.20</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.027</td>
<td>0.022 to 0.032</td>
</tr>
<tr>
<td>Black</td>
<td>0.014</td>
<td>0.012 to 0.017</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>0.012</td>
<td>0.0043 to 0.032</td>
</tr>
<tr>
<td>Asian</td>
<td>0.000039</td>
<td>0.00015 to 0.00010</td>
</tr>
</tbody>
</table>
Biochemical ‘penetrance’: e.g. ferritin levels

C282Y partially inactivates control of iron absorption from the gut

Stages (of clinical progression):
1. Genetic risk only
2. Iron overload
3. Iron overload & early symptoms
4. Iron overload & organ damage

High risk for later stages in those with ferritin >1000µg/L

Ferritin and transferrin saturation at any one time - only moderately predictive


HFE Genotype

- Homozygotes “HMZ”
- Non-HMZ HFE mutations
- Wild Type (no HFE mutations)
Treatment

Phlebotomy effective at correcting iron overload
  Intensive initially
  Maintenance – 4 or 5 times per year
  \( \text{(maintenance blood can be used for transfusion for others)} \)

Good response
  • fatigue, weakness, abdominal pain
  • Liver fibrosis

Limited response
  • cirrhosis
  • arthritis
  • diabetes
  \( \text{so need to treat before this damage established} \)


Reduction in liver fibrosis after phlebotomy in group identified in family screening

7.5 fold reduction in fibrosis scores except in cirrhosis

(Powell L et al, Arch Internal Medicine, 2006)
US Preventive Services Task Force - HH report
Whitlock EP et al, Annals of Internal Medicine, 2006

HH Screening for primary care clinicians: *Review to February 2005*

Key questions:

1: What is the risk for developing clinical hemochromatosis in p.C282Y homozygotes?
2: Does early treatment reduce morbidity and mortality?
3: Can groups at risk be readily identified before genetic screening?

Noted insufficient data on precise penetrance and no RCTs of treatment

On ‘very small numbers’: 38% to 50% of C282Y HMZ develop iron overload cirrhosis (6.3%), diabetes (3.6%),
limited data on male and females separately, limited follow-up time

So: **supported family screening & testing of high risk symptomatic groups**
Penetrance to clinical diagnosis

**HFE p.C282Y homozygous mutation**

Wide range of estimates from clinical and smaller studies: 1% to 50%

Larger ‘community’ studies with genotyping:

- Low rates of associated disease, except in p.C282Y homozygote males with very high ferritin levels

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**Beutler et al Lancet 2002**: Kaiser Permanente health appraisal clinics, sample n=41,038, n=152 HMZ

*less than 1% of homozygotes develop frank clinical haemochromatosis*

i.e. full syndrome, after excluding prevalent cases

Liver problem or hepatitis: p.C282Y HMZ 8.1% vs 4.1% wild type OR 2.1 95% CI 1.1 to 4.0

**HEIRS study**: 5 North American centers, primary care patient sample n=99,711, n=299 HMZ


Higher prevalence chronic fatigue & metacarpophalangeal joint swelling with higher serum ferritin levels

**Healthiron study** (Allen et al, NEJM, 2008): population sample n=31,000 (203 HMZ) in Melbourne, Australia

Male p.C282Y homozygotes with serum ferritin level ≥1000 μg/L were more likely to report fatigue, use of arthritis medicine, and a history of liver disease

*etc*
UK Biobank

500,000 volunteers
aged 40 to 70: baseline interview – 2006 to 2010
Assays: including liver enzymes, but no blood iron studies (so far)

Follow-up.....
hospital admission records, cancer registry, death certificates
GP records – recently released on ~250,000
MRI in a subset, including iron imaging

Consent – no individual feedback of genotypes: so results are under routine clinical care
**HFE p.C282Y prevalence in UKB**

451,243 European descent (on genetic clustering)

p.C282Y homozygotes (‘HMZ’): sample size=2,890

0.64% of population, or 1 in 156

Male HMZ 1294, Female 1596, mean age ~57 years

*Follow-up – now max 11 years, mean 8 years*

UK Biobank: C282Y allele frequency similar to other UK studies

UKB = 7.3%: Alspac (Bristol UK) 7.9%, TwinsUK 6.9%

0.68% in 10,500 Welsh blood donors (Jackson HA, BJH, 2001: no diagnosed HH)

(0.9 in Generation Scotland cohort, 0.88 in UKB)

approx. 350,000 people in the UK

UKB 14.3% C282Y heterozygous (i.e. one copy of the mutation)

15.1% in Welsh blood donor study

Prevalence data from Pilling L et al, BMJ, 2019
Age at hemochromatosis diagnosis (p.C282Y HMZ)

UK Biobank (usual care, n=2890)
- n=210 at baseline, n=321 incident diagnosed

Men | Women
---|---

eMERGE 7 US Medical systems biobank (n=98).
- Gallego et al, Am J Human Genetics 2015
UKB baseline associations, Men

Reported doctor diagnoses to study Nurse, or from inpatient hospital records back to 1997

Women p.C282Y HMZ osteoarthritis only:
OR 1.33 (CI 1.15 to 1.53)
Chronic pain & frailty
Older group (60 to 70 years) in UK Biobank, baseline

Chronic pain (3+ months)
Male p.C282Y HMZ: associations with hip, back, shoulder/neck

Sarcopenia (muscle weakness): \( \text{OR}=2.38: 1.80-3.13, p = 9.70 \times 10^{-10} \)
Frailty: \( \text{OR}=2.01: 1.45-2.80, p = 3.41 \times 10^{-05} \)
– based on weakness, fatigue and weight loss

p.C282Y HMZ women: Excess pain at ages 65 to 70:
chronic knee, hip and back pain.

From Tamosauskaite J et al, J Gerontology Medical Sciences 2019
incident diagnoses only: men
i.e.: minimising possible biased response to UKB

– hospital inpatient records to 2017

Males: HMZ versus wild type

Hazard Ratio (vs wild type)

0 2 4 6 8 10 12 14 16 18

Diabetes (type 1 & 2)
Osteoarthritis
Liver disease (any)
Liver cancer

Females –
Osteoarthritis HR=1.54 (1.11 to 2.15)

robust to excluding HH diagnoses at baseline
- also osteoarthritis and diabetes excluding liver disease (reducing hospital admission biases)

Adjusted for age, sex, 10 genetic principal components, assessment centre and chip. Removing related participants – little changed
Mortality by $HFE$ p.C282Y in UKB

Heterozygotes $HR = 0.99$ (0.96 to 1.03)
consistent with previous heterozygote evidence – no excess mortality.

HMZ: n=148 deaths
$HR = 1.22$ (95%CI 1.03 to 1.43) $p=0.02$ versus wild type

Lifetable ages 40 to 75:
Men: 1 in 23 additional HMZ men die by age 75
difference 4.4% i.e. HMZ=19.5% 95%CI 15.8 to 24
versus no HFE mutations =15.1% CI 14.7 to 15.5

Women: currently 1 in 38 additional deaths in HMZ
– not (yet) statistically significant

Adapted from Pilling L et al, BMJ, 2019 with longer follow-up:
original finding n=107 deaths in homozygotes,
published $HR =1.23$ (CI 1.01 to 1.48, $p=0.04$)
Epidemiology conclusions

1: **risk** for developing clinical hemochromatosis in p.C282Y homozygotes?
   - p.C282Y homozygotes do get substantial excess morbidity, some excess mortality (especially males)
   - Onsets at older ages common
   - Substantial pain and arthritis, in addition to liver disease

3: **readily identifiable before** genetic screening?
   - Many are not being diagnosed early under routine care (UKB, eMERGE)
   - Difficult to diagnose without routine testing
     - e.g. fatigue & arthritis common anyway

**Primary prevention** – population screening
**Secondary prevention** – clinical screening
Epidemiology acknowledgements

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