Associations with Haemochromatosis genetic variants

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Hereditary Haemochromatosis

Iron overload - reduced control of iron absorption
  fatigue, chronic pain
Arthritis – widespread, early
Diabetes
Liver – cirrhosis and cancer
  Early death – age 40+

Treatment: removing blood!
  but many diagnosed late, after irreversible damage

Ernest Hemingway working on “For Whom the Bell Tolls” 1939
HFE p.C282Y mutation
up to 1 in 150 of European ancestry have two copies of the mutation

UK Biobank:
allele frequency UKB = 7.3%: Alspac 7.9%, TwinsUK 6.9%

451,243 European descent (on genetics) aged 40 to 70 at baseline interview
N=2,890 C282Y homozygotes (‘HMZ’)
0.64% of population, or 1 in 156
approx. 350,000 people in the UK
0.68% in 10,500 Welsh blood donors (Jackson HA, BJH, 2001: no diagnosed HH)

14.3% C282Y heterozygous (ie one copy of the mutation)
15.1% in Welsh blood donor study

UKB baseline
HMZ disease associations

MEN: HFE C282Y HMZ versus ‘wild type’ i.e. those without C282Y mutation

<table>
<thead>
<tr>
<th>Baseline conditions</th>
<th>OR [95% CIs]</th>
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<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
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<tr>
<td>Liver disease (any)</td>
<td>4.30 [2.99, 6.18]</td>
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<tr>
<td>Osteoporosis</td>
<td>2.30 [1.49, 3.57]</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>2.23 [1.51, 3.30]</td>
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<tr>
<td>Osteoarthritis</td>
<td>2.01 [1.71, 2.36]</td>
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<tr>
<td>Pneumonia</td>
<td>1.62 [1.20, 2.19]</td>
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<tr>
<td>Diabetes (type 1 or 2)</td>
<td>1.52 [1.18, 1.98]</td>
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<tr>
<td>Atrial fibrillation</td>
<td>0.88 [0.60, 1.29]</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>0.76 [0.60, 0.95]</td>
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<tr>
<td>Frequent tiredness</td>
<td>1.16 [0.98, 1.38]</td>
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Associations less marked in women

Heterozygotes – little excess disease
incident diagnoses only
– hospital records to 2017

Males: HMZ versus wild type

Females –
Osteoarthritis HR=1.54 (1.11 to 2.15)

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

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
Clinical penetrance to haemochromatosis diagnosis

*HMZ penetrance estimates* <1% to 50%

**UK Biobank** (n=2890)

n=210 at baseline, n=321 incident diagnosed

**eMERGE 7 US Medical systems biobank** (n=98).

Gallego et al, Am J Human Genetics 2015
Comparison with full NHS records subset any haemochromatosis diagnosis

C282Y homozygotes — cumulative event plot
n=210 at baseline, n=321 incident diagnosed

Population representativeness check:
full population hospital records data
any diagnosed haemochromatosis
(subset) for England – all genotypes together, self-reported ‘white’,
same time periods and follow-up
aged 60 to 69 at ‘baseline’

Women – very similar rates
baseline and incident

Men
baseline – n=~45 extra diagnosed (in 145)
incident – very similar rates
Mortality by *HFE C282Y*

Heterozygotes HR = 0.99 (0.96 to 1.03)

**HMZ:** n=148 deaths  
HR= 1.22 (1.03 to 1.43)  \( p=0.02 \)  
versus wild type

(robust to removing HH diagnosed at baseline)
‘eradicating’ excess clinical morbidity

Male HMZ: 1.5% of frailty (in 60 to 70 year olds, Tamosauskaite et al, JGMS, 2019)

1.6% of hip replacements at baseline (all ages)

5.8% of incident liver cancers (all ages)

Criteria for screening

The condition: important problem, natural history - better understood thanks to UK Biobank!

The test: good screening test(s)

The intervention: effective intervention (if started early)

The screening programme: benefits outweigh harms, value for money

Implementation criteria: adequate staffing and facilities

Modifiers of penetrance

**Full clinical outcomes**

Brain & liver MRI

- *e.g. HFE C282Y & caudate iron levels*
  
  *Elliot LT et al, Nature, 2018*

DXA – joint images

Liver enzymes – see poster

iron overload signature – *clinical ‘pre-screener’*

- In full blood count
  
  *– extending Adris N, et al, 2019*
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Why so different from previous community studies?

**HFE C282Y homozygous in community samples:**

Welsh blood donors – mean age men 38  
*(Jackson HA, BJH, 2001: 10,500 donors, no diagnosed HH)*


HEIRS study: 5 North American hospitals  
~100,000 surveyed, but 299 C282Y homozygotes in analyses  
mean age 50

p.C282Y homozygotes had more liver disease in men, and higher prevalence of chronic fatigue and metacarpophalangeal joint swelling in p.C282Y homozygotes with higher serum ferritin levels.