FITNESS GENES

GENETICS GUIDE · 2026

Hereditary Haemochromatosis

One of the most common inherited conditions in northern European populations — and one of the most commonly missed. Here is what the genetics mean, and how to turn a result into a useful conversation with your doctor.

1 in 3

of people with Celtic or northern European ancestry carry at least one copy of an HFE variant

4%

of FitnessGenes customers, carry two copies of the higher-risk group variants

2

blood tests establish whether iron is actually accumulating

A common condition, described long before it was understood.

People across Ireland, Scotland, and Wales identified an illness pattern centuries ago, long before its cause was understood. The condition is now formally called hereditary haemochromatosis, an inherited disorder where the body absorbs and retains more iron than necessary. While iron is vital and normally carefully controlled, excess iron can cause silent damage.

What makes it more problematic is not the severity but ordinariness. The early complaints are fatigue, poor concentration and joint pain: three of the most common presentations in general practice, and three of the hardest to attribute. So the condition is both one of the most prevalent inherited disorders and one of the most frequently missed diagnoses.

Inherited

The condition is inherited, and it is most common in people of Celtic and northern European descent. A result therefore carries information for close relatives as well as for the individual tested.

Gradual

Iron accumulates over years or decades, usually without symptoms. The timing of symptoms can vary widely between different people who carry the genetic variants.

Actionable

Once you know your genetics, there are two blood tests that will detect it, and the established treatment is the removal of blood at intervals. If identified early, the serious consequences are largely preventable.

WHY A GENETIC TESTING MATTERS

Many people feel fatigued. Standard dietary advice often focuses on preventing iron deficiency by recommending increased red meat intake, supplements if necessary, and pairing iron with vitamin C to enhance absorption. This guidance is generally appropriate for most people. However, for individuals prone to iron overload, following this advice can be the exact opposite of what they need.

Understanding your genetics early provides significant practical benefits. While sometimes it can diagnose conditions directly, it more often helps you identify the right health advice to follow, which blood tests to request, and which general advice might not apply to you.

A Celtic inheritance, carried around the world.

The risk variants behind hereditary haemochromatosis reach their highest frequencies in the formerly Celtic-speaking populations of Ireland, Scotland and Wales. Ancient DNA places the principal variant there at least 4,000 years ago. But those populations did not stay put: the great emigrations of the nineteenth and twentieth centuries carried that genetic legacy to North America, Australia and New Zealand — where it persists today, largely unrecognised.

1 in 10 people in parts of Northern Ireland are at risk of iron overload, on three years of cross-community screening by Haemochromatosis UK. Anywhere those communities settled in numbers, a comparable frequency travelled with them — the difference abroad is that almost no one is looking for it.

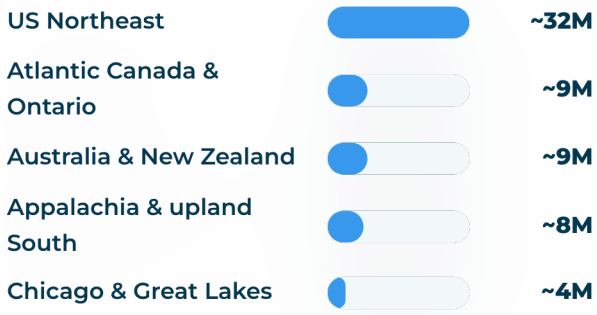
The emigration

Close to five million Irish people emigrated to the United States, alongside comparable Scottish movement to Canada, Australia and New Zealand. They left in family and community groups and frequently married within them for generations after arrival, which preserved the elevated variant frequency rather than diluting it.

Risk, therefore, is associated more with ancestry than with a passport. In these countries, the traces of that ancestry have mostly vanished from official records, as surnames were anglicised and census categories simplified into broad groups.

Where those populations concentrated

People reporting Irish or Scottish ancestry, by region, in national census data.



On the frequencies observed in the source populations, that scale implies several hundred thousand people carrying the major risk genotype outside Ireland and the UK — the substantial majority of them undiagnosed.

Why this matters outside these islands

Clinical awareness tracks the visibility of the condition rather than its prevalence. In Ireland and the UK it is a recognised differential for unexplained fatigue and joint pain; elsewhere it is often not considered at all, so the same genetics produce far later diagnosis.

Where Irish, Scottish, Welsh or northern English ancestry is present in a family, awareness of this risk is warranted regardless of current country of residence.

Source-population genetic frequencies: Kerr et al., “The landscape of hereditary haemochromatosis risk and diagnosis across the British Isles and Ireland”, Nature Communications (2026). Screening prevalence: Haemochromatosis UK and FTI Consulting LLP (2025). Ancestry counts are approximate figures from national census data.

A regulator that does not switch off.

Iron absorption is normally tightly controlled. The hormone hepcidin suppresses iron uptake from the gut once your stores are adequate. In haemochromatosis, hepcidin activity is deficient, so you continue to absorb iron from food while white blood cells in the spleen release more into the bloodstream. Circulating and stored iron levels rise year on year.

Early disease is silent, often for decades. As iron accumulates, it is deposited in organs and tissues, where it generates reactive oxygen species and damages cells. The liver, heart, pancreas and joints bear the greatest burden.

01

Excess absorption

With hepcidin activity deficient, more dietary iron enters the body than it needs, and there is no signal to stop. Iron-rich foods, supplements and vitamin C all increase absorption.

02

Transport saturates

Transferrin, the protein that carries iron in the blood, becomes saturated. This is the earliest measurable sign — transferrin saturation rises before stores are substantially elevated.

03

Stores build

Ferritin rises as iron is deposited in the liver, heart, pancreas and joints. The burden is cumulative, so it reflects years of absorption rather than the current week.

04

Tissue damage

Deposited iron generates reactive oxygen species, injuring cells. If untreated, this leads to fibrosis and organ dysfunction — hepatic cirrhosis, cardiac disease, diabetes and arthropathy.

At stages 2 or 3, iron overload is manageable, and the organ damage of stage 4 is largely preventable.

Symptoms can resembles many conditions.

Since iron builds up gradually, early symptoms tend to be non-specific. Fatigue, difficulty concentrating, and joint pain are common complaints in general practice, but they are often difficult to link to a single cause. This contributes to hereditary haemochromatosis being both prevalent and frequently missed.

Persistent fatigue

Tiredness that rest does not resolve — usually the first thing people notice, and the easiest to explain away.

Brain fog

Impaired concentration and slower recall, often described as thinking through fog.

Joint pain

Frequently the hands, and often the second and third knuckles. Can appear well before other signs.

Abdominal discomfort

Vague pain or fullness in the upper right abdomen as iron is deposited in the liver.

Hormonal changes

Reduced libido, and in some cases changes to menstrual or erectile function, as the pituitary is affected.

Bronzed complexion

A darkening or grey-bronze cast to the skin in longer-standing overload.

When symptoms appear

In men

Symptoms typically emerge between **30 and 50**. With no regular route of iron loss, stores build steadily from early adulthood, so men present earlier and more often. Fatigue and joint pain are usually the first complaints, and alcohol intake accelerates both accumulation and liver risk.

In women

Onset usually occurs later, typically after menopause, since menstruation depletes iron during reproductive years. Pregnancy and breastfeeding also help protect iron levels. After this loss ceases, iron can build up quickly, making post-menopausal testing important even if previous results were normal.

WHY YOU SHOULD NOT WAIT FOR SYMPTOMS

Iron can accumulate for years before producing any detectable clinical sign. By the time symptoms are unmistakable, damage may already be established — so testing beats waiting.

Two variants, and the copies you carry.

Type 1 haemochromatosis — the predominant form in European populations — arises from variants in a single gene, HFE, identified in 1996. The HFE gene controls the levels of hepcidin, the master hormone controlling iron absorption. Inheritance is autosomal recessive: two copies are needed for the higher-risk picture, while a single copy makes you a carrier. **C282Y** is the principal contributor; **H63D** is milder, associated with smaller elevations in iron stores.

Genotype	C282Y	H63D	What it means
Non-carrier	0	0	No elevated risk attributable to these two variants.
Carrier (C282Y)	1	0	Accumulation is unusual. A 50% chance of passing the variant to each child.
Carrier (H63D)	0	1	Accumulation is unusual; the variant may still be transmitted.
Compound heterozygote	1	1	Modestly raised likelihood, typically mild. About 5% of diagnosed European cases.
H63D homozygote	0	2	Mildly raised stores in most. Genuine overload is uncommon and usually needs an additional factor.
C282Y homozygote	**2**	**0**	**The highest-risk genotype: 80–95% of diagnosed European cases; 1 in 200 among northern Europeans.**
Double homozygote	2	2	Extremely rare; high risk.

Genetic interpretation

- Two copies of C282Y do not constitute a diagnosis of haemochromatosis; they identify membership of the group in which the condition is most likely to develop.
- A substantial proportion of C282Y homozygotes never accumulate clinically significant quantities of iron.
- Sex, age, alcohol consumption, blood loss, diet and additional genetic factors all modify the expression of that risk.

The investigations, and what each one establishes.

Genetic analysis establishes predisposition; biochemical testing establishes whether iron is in fact accumulating. Two measures detect overload, one contributes to their calculation, and two provide the clinical context around them.

Investigation	What it measures	Typical reference range	Pattern consistent with iron overload
Transferrin saturation DETECTS OVERLOAD	The proportion of your iron-transport capacity that iron occupies, calculated from serum iron and total iron-binding capacity. The earliest and most sensitive indicator of excessive absorption — it rises before stores do.	Approximately 20–45%	Persistently above 45%; above 50% in men and 45% in women warrants investigation. A fasting morning sample is preferable, and one high result should be confirmed by repeat testing.
Serum ferritin DETECTS OVERLOAD	Iron held in storage, so it reflects the cumulative burden rather than the moment. It rises later than transferrin saturation and is the principal measure used to monitor treatment.	Approximately 30–300 µg/L (men); 15–200 µg/L (women)	Elevation above the sex-specific upper limit, particularly alongside raised transferrin saturation. Above 1,000 µg/L is linked to hepatic fibrosis risk and generally prompts specialist assessment.
Serum iron COMPONENT MEASURE	Iron currently circulating in the blood. Used to calculate transferrin saturation rather than assessed on its own.	Varies considerably; substantial diurnal and dietary variation	Interpreted only as a component of transferrin saturation, never in isolation.
ALT / AST CONTEXT	Liver function: transaminases that indicate injury to liver cells, and so whether the liver is already affected.	Laboratory-specific	Elevation alongside raised iron indices suggests hepatic involvement, and shapes how urgently a specialist opinion is needed.
Haemoglobin CONTEXT	Full blood count: oxygen-carrying capacity and red cell indices. Excludes other blood conditions and sets a baseline before venesection.	Laboratory-specific	Characteristically normal — a full blood count does not detect iron overload, and a normal result does not exclude it.

Reference ranges vary between laboratories, assays and patient sex; interpretation of any result belongs to the clinician who ordered it.

Four qualifications that change the reading.

The values on the previous page are patterns, not verdicts. Four qualifications materially affect how any individual set of results should be understood.

1. **Ferritin alone is not sufficient.** Ferritin is an acute-phase reactant, so it also rises with inflammation, infection, alcohol intake, hepatic steatosis, obesity and malignancy. An isolated elevation is a common finding and frequently benign; it is the combination of raised ferritin with persistently raised transferrin saturation that indicates genuine iron overload.

2. **Timing affects the result.** Transferrin saturation is subject to diurnal variation and is influenced by recent dietary intake. A fasting morning sample is preferable, and a single elevated result should be confirmed by repeat testing before any conclusion is drawn.

3. **Raised indices without a high-risk genotype still warrant investigation.** Iron overload is not exclusively genetic: excessive supplementation, repeated transfusions and alcohol-related liver disease all produce acquired haemochromatosis, and each merits assessment in its own right.

4. **A high-risk genotype with normal indices indicates monitoring, not treatment.** Normal results show that accumulation has not occurred to any significant degree. The appropriate response is a defined re-testing interval agreed with your clinician, since iron accumulates over years rather than months.

BRING THIS TO YOUR APPOINTMENT

Iron overload: what to ask your doctor.

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Your DNA result shows a predisposition to hereditary haemochromatosis. It is not a diagnosis. Two blood tests establish whether iron is actually accumulating.

MY GENOTYPE (HFE)

C282Y copies			H63D copies		
0	1	2	0	1	2

Circle the number of copies. Two copies of C282Y is the highest-risk genotype.

FAMILY HISTORY TO MENTION

- ☐ Known haemochromatosis
- ☐ Liver disease or cirrhosis
- ☐ Early-onset arthritis
- ☐ Type 2 diabetes
- ☐ Heart failure or arrhythmia
- ☐ Northern European ancestry

THE TWO TESTS TO ASK FOR

Transferrin saturation — EARLIEST SIGNAL

The share of your iron-transport capacity that is currently occupied. It rises before stores do.

Usual range ~20–45%
Worth investigating persistently above 45%; above 50% in men, 45% in women

Best taken fasting, in the morning; repeat one high reading before drawing conclusions.

Serum ferritin — TOTAL BURDEN

How much iron is held in storage — the cumulative load, and the number used to track treatment.

Usual range ~30–300 µg/L men, 15–200 µg/L women
Worth investigating above your sex-specific limit; above 1,000 µg/L usually prompts specialist review

Ferritin also rises with inflammation, infection and alcohol. Raised ferritin *plus* raised transferrin saturation is the pattern that matters.

Suggested wording: “I have a genetic predisposition to hereditary haemochromatosis. Could I have a transferrin saturation and a serum ferritin measured, together with liver function tests, and could the numerical values be provided rather than an indication of ‘normal’?”

MY RESULTS OVER TIME

Date	Transferrin sat. %	Ferritin µg/L	ALT / AST	Next review / notes

DISEASE OVERVIEW

1. Brissot P, Pietrangelo A, Adams PC, de Graaff B, McLaren CE, Loreal O. Haemochromatosis. Nat Rev Dis Primers. 2018;4:18016. doi:10.1038/nrdp.2018.16. PMID: 29620054.

> **Value:** Authoritative disease primer covering the hepcidin–ferroportin axis, HFE C282Y and the rarer non-HFE forms (HAMP, HJV, TFR2, SLC40A1), diagnosis, phlebotomy, chelation and hepcidin supplementation as a future approach. Cited for the mechanism of iron accumulation and the framing of treatment.

CLINICAL GUIDELINES

2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022;77(2):479-502. doi:10.1016/j.jhep.2022.03.033. PMID: 35662478.

> **Value:** Current European guideline. Cited for sex-specific diagnostic thresholds (TSAT >45% with ferritin >200 µg/L in females; TSAT >50% with ferritin >300 µg/L in males and postmenopausal women in p.C282Y homozygotes), the requirement for hepatic iron overload on MRI or biopsy in non-C282Y genotypes, phlebotomy targets of ferritin <50 µg/L induction and <100 µg/L maintenance, and HCC surveillance in advanced fibrosis.

3. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol. 2019;114(8):1202-1218. doi:10.14309/ajg.0000000000000315. PMID: 31335359.

> **Value:** US guideline. Cited for genotype–phenotype correlations, ferritin <1,000 ng/mL at diagnosis as a marker of low advanced-fibrosis risk, MRI T2* replacing biopsy in most patients, and the differential for raised ferritin in non-C282Y homozygotes (NAFLD, alcoholic liver disease).

4. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(1):328-43. doi:10.1002/hep.24330. PMID: 21452290.

> **Value:** Earlier AASLD guideline, useful for historical diagnostic thresholds and as the reference point later guidance revises. Largely superseded for practice by references 2 and 3 — cite alongside them only where the revision of thresholds is itself the point.

CONTEMPORARY CLINICAL REVIEWS

5. Adams PC, Ryan JD. Diagnosis and Treatment of Hemochromatosis. Clin Gastroenterol Hepatol. 2025;23(9):1477-1485. doi:10.1016/j.cgh.2024.10.041. PMID: 39889898.

> **Value:** Recent narrative review focused on C282Y homozygotes. Cited for the antiquity of HFE variants — identified in North Western European human fossils over 4,000 years old and hypothesised to promote iron absorption as a survival benefit — for the complication set (arthritis, fibrosis, cirrhosis, primary liver cancer, diabetes), and for the argument for earlier diagnosis and treatment.

6. Singh P, Millson C, Driver R. Hereditary haemochromatosis: A review. J R Coll Physicians Edinb. 2024;54(4):340-347. doi:10.1177/14782715241298724. PMID: 39523455.

> **Value:** UK clinical review. Cited for uninhibited intestinal iron absorption and deposition in liver, pituitary, pancreas and heart; variable biochemical and clinical penetrance in C282Y homozygotes; transient elastography to assess hepatic fibrosis; referral and non-HFE genetic testing for mutation-negative patients with MRI-visible liver iron loading; and venesection improving symptoms, fibrosis and mortality.

EPIDEMIOLOGY AND PENETRANCE

7. Kerr SM, Fletcher BS, Tzoneva G, Shuldiner AR, Gilbert E, Wilson JF. The landscape of hereditary haemochromatosis risk and diagnosis across the British Isles and Ireland. Nat Commun. 2026;17(1):716. doi:10.1038/s41467-025-65511-7. PMID: 41633988.

> **Value:** Population genetic and health-record study: risk across 29 regions in >400,000 subjects, and diagnosis prevalence in >63 million people in NHS England identifying 70,365 cases. Cited for regional variation (1/54–1/62 in Northwest Ireland and the Outer Hebrides, 1/117 mainland Scots, 1/212 southern England), white Irish prevalence 3.7× white British, 11-fold variation within white British (1/1,972 in parts of Kent to 1/177 in Liverpool), and under-diagnosis in Birmingham, Cumbria, Northumberland and Durham.

8. Pilling LC, Tamosauskaite J, Jones G, et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. BMJ. 2019;364:k5222. doi:10.1136/bmj.k5222. PMID: 30651232.

> **Value:** Cohort study of 451,243 participants of European descent including 2,890 p.C282Y homozygotes (~1 in 156). Cited for homozygote frequency, diagnosis in 21.7% of male and 9.8% of female homozygotes by end of follow-up, and raised odds in men of liver disease (OR 4.30), rheumatoid arthritis (2.23), osteoarthritis (2.01) and diabetes (1.53).

9. Lucas MR, Atkins JL, Pilling LC, Shearman JD, Melzer D. HFE genotypes, haemochromatosis diagnosis and clinical outcomes at age 80 years: a prospective cohort study in the UK Biobank. BMJ Open. 2024;14(3):e081926. doi:10.1136/bmjopen-2023-081926. PMID: 38479735.

> **Value:** Prospective cohort of 451,270 participants over a mean 13.3 years. Cited for lifetime penetrance — cumulative incidence of diagnosis by age 80 of 56.4% in male and 40.5% in female p.C282Y homozygotes — excess mortality in men (HR 1.29), joint replacement, liver disease, delirium and dementia with similar excess in those never diagnosed, and no excess incident outcomes in p.C282Y/p.H63D and p.H63D homozygotes. Draws on the same UK Biobank cohort as references 8 and 10; the three overlap substantially.

MODIFYING FACTORS

10. Pilling LC, Atkins JL, Melzer D. Genetic modifiers of penetrance to liver endpoints in HFE hemochromatosis: associations in a large community cohort. Hepatology. 2022;76(6):1735-1745. doi:10.1002/hep.32575. PMID: 35567766.

> **Value:** Analysis of 1,294 male and 1,596 female UK Biobank p.C282Y homozygotes — the same cohort as references 8 and 9. Cited for genotype alone being an incomplete predictor: a higher iron polygenic score raised fibrosis/cirrhosis risk in men (OR 4.90, 95% CI 1.63–14.73, top vs bottom quintile) plus liver cancer and osteoarthritis, with no robust association in female homozygotes or other genotypes.

11. Fletcher LM, Powell LW. Hemochromatosis and alcoholic liver disease. Alcohol. 2003;30(2):131-6. doi:10.1016/S0741-8329(03)00128-9. PMID: 12957297.

> **Value:** Review of three studies reporting cirrhosis roughly nine times more likely in haemochromatosis patients consuming >60 g alcohol daily, proposing shared oxidative stress and stellate cell activation as the mechanism. Cited for alcohol as a modifier and for the conclusion that added dietary iron is unwise in C282Y homozygotes.

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