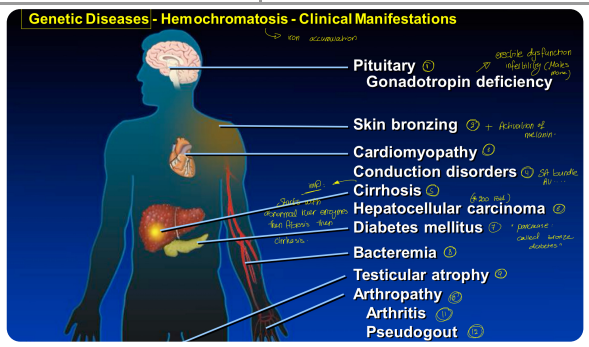
🧬 Genetic Diseases – Liver

🔷 Inherited Causes of Cirrhosis

- **a1– Antitrypsin deficiency**
- **Other genetic causes**
- **Cystic Fibrosis (CF)**
- **Wilson's disease**
- **Familial intrahepatic cholestasis**
- **Hemochromatosis**

Affected Age Group	Examples
👶 Newborns and Infants	CF, Wilson's, Familial cholestasis
👦 Adults	Hemochromatosis, a1-antitrypsin deficiency

🔷 Clinical Manifestations



2nd causes:

🔥 Iron Overload Disorders

- 1-Transfusion
- 2-Ineffective erythropoiesis
- 3-African iron overload (🥫 People who **drink beer from iron-rich cans** may also absorb excess **dietary iron**.)

🧪 **Note:** "Not all of these are primary (genetic). Some are secondary (acquired)."

🧬 Hemochromatosis – Overview

- Incidence is **population-dependent** → MC are caucasians.
- **Autosomal recessive** inheritance
- HFE gene mutations may be present
- Functional defect: **↑ iron absorption**
- Most common in **Caucasians**
- **Heterozygotes**: 1 in 12 one Gene
- **Homozygotes**: 1 in 400 2 Genes

"More than 90%" of Caucasian patients with genetic hemochromatosis have **HFE gene mutations**

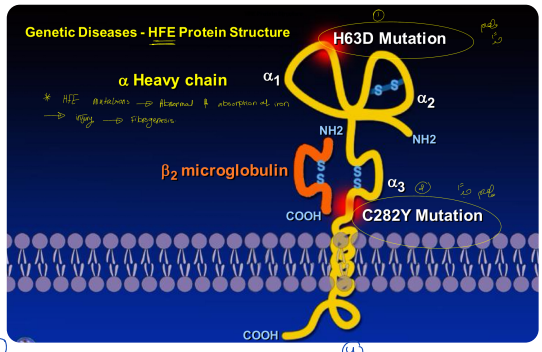
🧬 Genetic Diseases – Hemochromatosis

🔷 Frequency and Genetics

Genotype	Prevalence in Caucasians
Heterozygote (1 copy)	1 in 12
Homozygote (2 copies)	1 in 400

- The most common mutations:
- **C282Y mutation** → even more common
- **H63D mutation**

🧬 HFE Protein Structure



- The HFE protein interacts with:
- **Heavy chain** (1)
- **β2-microglobulin** (2)
- Domains: α1, α2, α3
- Mutations occur at:
- **C282Y**
- **H63D**
- Ends of the protein:
- **NH_2** (amino terminus)
- **COOH** (carboxy terminus)

🧪 **Effect of HFE mutations:**

🔶 **Abnormal iron absorption** (1) 🔶 **Tissue injury** (3) 🔶 **Fibrogenesis** (scarring of organs) (5) 🔶 **Defective intestinal epithelial protein** (4)

🔬 **Stages of Hemochromatosis**

1. **Iron overload without organ injury**
2. **Iron overload with organ injury but no symptoms**
3. **Iron overload with both organ injury and symptoms**

🧠 Symptoms appear late… often after **organ damage** like:

- Cirrhosis
- Heart failure
- Pancreatic fibrosis

⚖️ **Normal Iron Balance**

Process	Value
Ingested	10–20 mg/day
Absorbed	1–2 mg/day
Lost	1–2 mg/day (gut, skin, urine)
Menstruation	~30 mg/month (in women) Starts the disease at a late stage.

🩸 **Iron Transport and Storage**

Component	Function
Transferrin	Carries 2 iron atoms in the plasma
Ferritin	Intracellular storage (thousands of Fe) inside BM.
Total body iron	≈ 4 grams
Storage locations	Liver, bone marrow, RBCs

🧬 **Genetic Diseases – Hemochromatosis**

🔷 **Phenotype Expression**

- More common in **men** than women
- Severity **increases with age**
- Correlates with:
- Amount of **dietary iron**
- Conditions like:
- **Chronic hemolysis**
- **Alcoholism**
- **Steatohepatitis**
- **Hepatitis C**

💡 **Why are women less affected early on?** Because of **menstrual blood loss** (iron depletion)

🔻 After **menopause**, women lose this protection 👴 Postmenopausal women are **more at risk** ⟶ usually at age of 50 and more

🧬 **Hereditary Forms of Iron Overload** Two types: HEF / non-HEF

Type	Description
HFE-related hereditary hemochromatosis	Most common, involves C282Y & H63D mutations
C282Y homozygosity	Major risk for clinical disease Diagnostic.
C282Y/H63D compound heterozygosity	Intermediate risk
Non-HFE hereditary hemochromatosis	Less common types not linked to HFE
Juvenile hemochromatosis	Presents early in life, more severe
Neonatal iron overload	Rare and severe, affects infants
Autosomal dominant form (Solomon Islands)	Extremely rare

🧪 **Causes of Iron Overload**

🔷 **Hereditary Causes**

🧬 Genetic mutations (like **C282Y**, **H63D**) 🧬 Juvenile or neonatal forms

🔷 **Acquired Causes**

🩸 **Iron-loading anemias** (require frequent transfusions):

- (1) **Thalassemia major**
- (2) **Sideroblastic anemia**
- (3) **Chronic hemolytic anemia**

🍖 **Dietary iron overload** 🍺 **Alcoholic liver disease** 🦠 **Hepatitis C** 🫒 **NAFLD** (Non-Alcoholic Fatty Liver Disease)

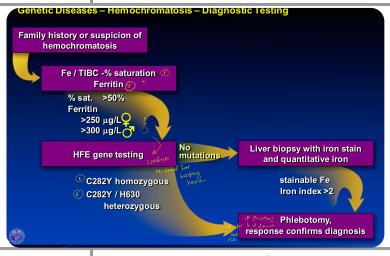
📌 "Acquired causes" result from **external sources** of iron or diseases, not from genetic defects.

Iron Measurement Values

All are high

Test	Normal Range	Hemochromatosis Range
Serum Iron (mg/dL)	60–180	180–300
Serum Iron (mmol/L)	11–32	32–54
Transferrin Saturation %	20–50%	55–100%
Ferritin – Males (ng/mL)	20–200	300–3000
Ferritin – Females (ng/mL)	15–150	250–3000
Liver Iron Stain	0 to 1+	3+ to 4+
Liver Iron Concentration	300–1500 mg/g dry weight	3000–30,000 mg/g dry weight
Liver Iron (mmol/g)	5–27	53–536
Iron Index = (Liver iron ÷ Age)	< 1.1	> 1.9

Diagnosis Criteria



- **Homozygous** for C282Y = diagnostic
- **Compound heterozygous** (C282Y + H63D) = possible risk
- Start with:
- **Serum iron**
- **TIBC**
- **Transferrin saturation**
- **Ferritin**
- **Liver iron (if needed)**

Test	Normal	Hemochromatosis
Iron (mg/dL)	60–180	>180
TIBC (mg/dL)	230–370	<300
Transferrin Saturation (%)	20–50	>50
Ferritin (ng/mL)	20–200	>300
Hepatic Iron (mg/g)	300–1500	>3000

Genetic Testing confirms diagnosis **Liver biopsy** can be done to assess iron quantitatively when needed

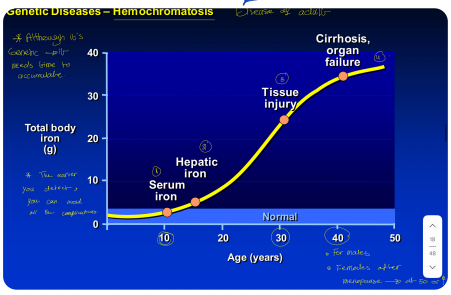
if you don't find anything helpful

Hemochromatosis – Iron Balance Over Time

How Iron Accumulates with Age

Age (Years)	Hepatic Iron (mg/g dry weight)	Serum Iron	Complications
0–20	Normal	Normal	None
30–40	Mild ↑	↑	Liver enzyme changes
50+	Marked ↑	High	Cirrhosis, organ failure

The **earlier** it is detected, the more **complications can be prevented**!



Who Should Be Tested?

Indications for HFE Genetic Testing:

- Family history of **hemochromatosis**
- Chronic liver disease
- Abnormal liver function tests
- Abnormal iron panel
- **Diabetes mellitus**
- **Arthropathy**
- **Heart disease**

Even without cirrhosis, suspect **hemochromatosis in young adults** with abnormal liver enzymes.

Interpretation of Ferritin Levels

Ferritin	Iron	Likely Diagnosis
High	High	Hemochromatosis
High	Low/normal	Acute liver injury / inflammation
Low	Low	Iron deficiency
Normal	Low	Chronic disease anemia

Hepatic Iron Index (HII)

HII = Liver iron (µmol/g) ÷ Age (years)

Index Range	Interpretation
< 1.1	Normal or non-HFE-related
> 1.9	Suggests Hemochromatosis

🩸 Phlebotomy – Treatment for Iron Overload

🔁 Induction Phase:

- **1 unit blood (≈250 mg Fe)**
- Weekly or biweekly
- Until **mild anemia** develops & Ferritin <50 ng/ml
- Monitor **Hemoglobin, Ferritin, Transferrin saturation**

🔄 Maintenance Phase:

- Once **Ferritin < 50 ng/mL** and
- **Transferrin saturation < 50%** → Switch to phlebotomy **every 2–3 months** → Continue monitoring

💡 Why Phlebotomy Works

Manifestation	Can it Improve?
Cardiac dysfunction	✅ Reversible
Glucose intolerance	✅ Reversible
Hepatomegaly	✅ Reversible
Skin pigmentation	✅ Reversible
Cirrhosis	❌ Irreversible
Hepatocellular carcinoma	❌ Irreversible risk
Arthropathy, Hypogonadism	❌ Often irreversible

✅ Early diagnosis = **Better survival** 📉 Delayed treatment = **Organ damage risk**

📊 Iron Depletion = Better Outcomes

Time	Cumulative Survival (%)
After 18 mo of phlebotomy	~100%
No treatment	↓ significantly

🧬 Hemochromatosis – Response to Phlebotomy

📈 Iron Lab Trends During Treatment

Time (months)	Serum Ferritin (ng/mL)	Transferrin Saturation (%)	Hemoglobin
0	High	High	Normal
4–12	↓↓	↓	↓ Slightly
20–28	Low-normal	Normal	Stable

🩸 Phlebotomy leads to:

- ↓ Serum ferritin
- ↓ Transferrin saturation
- Slight drop in hemoglobin (expected)

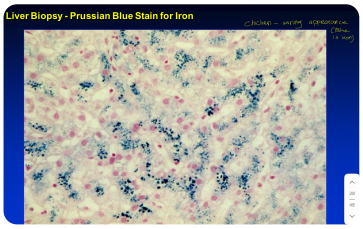
🔬 Liver Biopsy Findings

🔷 Trichrome Stain

- Stains **fibrosis (scarring)** in the liver

🔷 Prussian Blue Stain

- Stains **iron deposits blue**
- Classic "chicken-wire" appearance in hepatocytes
- Used to **quantify iron** in tissue



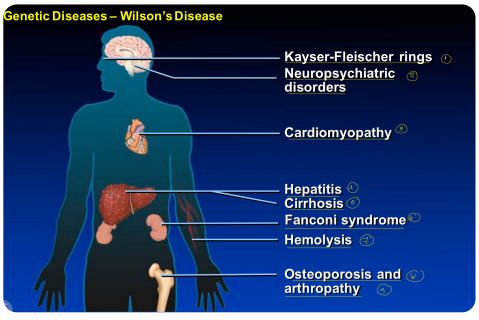
🧬 Genetic Diseases – Wilson's Disease

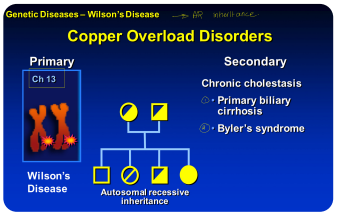
🧪 Pathophysiology

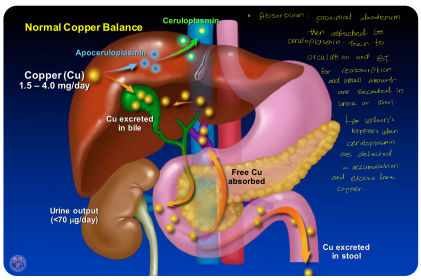
- Cause: **Copper accumulation** in tissues
- Mutation: **ATP7B gene defect** (on chromosome 13)
- Inheritance: **Autosomal recessive**

🧠 Affects:

- **Liver** – hepatitis, cirrhosis
- **Basal ganglia** – neuropsychiatric symptoms
- **Eyes** – Kayser-Fleischer rings
- **Kidney** – Fanconi syndrome







- **Heart** – Cardiomyopathy
- **Bones/joints** – Osteoporosis, arthropathy

🔁 Copper Overload – Mechanism

Normal Copper Metabolism	Wilson's Disease
Cu intake: 1.5–4.0 mg/day	↑ Accumulation of free copper
Cu bound to **ceruloplasmin**	Ceruloplasmin **↓ or defective**
Excess excreted in bile	↓ Bile excretion
Urine copper < 70 µg/day	Urine copper > 100 µg/day

🧪 Ceruloplasmin – Key Protein

- **Ceruloplasmin** = Blue alpha-2 globulin
- Binds copper **irreversibly**
- Normal serum level = **20–40 mg/dL**

Decreased ceruloplasmin decreases in:

Condition	Ceruloplasmin Level
1 Wilson's (homozygotes)	↓↓↓ (~95%)
2 Wilson's (heterozygotes)	↓ (~20%)
3 Menkes syndrome	↓
4 Nephrotic syndrome	↓
5 Hepatic failure	↓

🧬 Molecular Defect

- ATP7B gene codes for **P-type ATPase**
- Functions:
- Copper binding
- Channel/transport activity
- Excretion via bile
- Mutation = Copper builds up in:
- **Lysosomes**
- **Golgi**
- **Space of Disse**

➡️ Leads to **cellular stress and death**

🧬 Wilson's Disease – Indications for Testing

You should **suspect and test for Wilson's disease** in the following situations:

🔎 Clinical Scenario	💡 Why to Test for Wilson's
Liver disease in children, adolescents, or young adults	Copper accumulates early in life
Hemolysis with liver disease	Copper is toxic to RBCs
Neurological symptoms in young individuals	Tremor, gait changes, Parkinson-like signs
Psychiatric disorders in young people	Psychosis, depression, personality changes
Family history of Wilson's disease	Autosomal recessive inheritance
Kayser-Fleischer rings seen on slit-lamp exam	Classic sign of copper overload
Sunflower cataracts	Copper in the eye lens
Fanconi syndrome (renal tubular dysfunction)	Associated with copper toxicity
Low serum uric acid (hypouricemia)	Renal loss due to Fanconi
Unexplained acute liver failure in young patient	Wilson's is a major cause
Cryptogenic cirrhosis (unknown cause) in youth	Always rule out Wilson's
Indian Childhood Cirrhosis / PSC / PBC in young age	Overlaps in copper-related disease spectrum

🧠 **Golden Rule:** 👉 *"Any young patient with chronic hepatitis and abnormal liver enzymes — always think of Wilson's disease."*

🧪 Clinical Features – Wilson's Disease

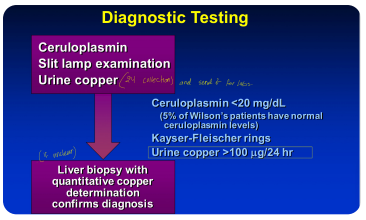
System	Presentation
Liver	Hepatitis, cirrhosis, acute failure
CNS	Parkinsonism, tremor, gait disturbance
Psychiatric	Depression, psychosis
Eye	Kayser-Fleischer rings, sunflower cataracts
Kidney	Fanconi syndrome, hypouricemia

🧬 Wilson's Disease – Diagnosis

🔎 Key Diagnostic Tests

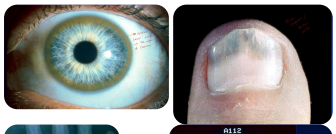
Test	Finding
Serum Ceruloplasmin	< 20 mg/dL (↓ in 95% of homozygotes)
24-hour Urine Copper	> 100 µg/day
Kayser-Fleischer rings	Seen on slit-lamp exam
Liver Biopsy	Hepatic copper > 250 µg/g dry weight
MRI Brain	Basal ganglia hyperintensity

⚠️ 5% of patients may have **normal ceruloplasmin** ⚠️ Liver biopsy is diagnostic when genetic testing is unclear



👁️ Kayser-Fleischer Rings

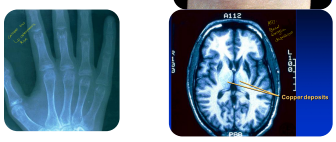
- Golden-brown deposits at the corneal edge
- Seen in **95%** of neuro-Wilson's cases
- Slit-lamp exam required to visualize

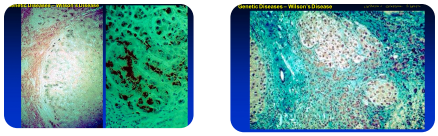


🧠 Brain MRI – Wilson's

- Shows **copper deposition** in:
- **Basal ganglia**
- **Thalamus**
- **Midbrain**
- Appearance: **Hyperintensity** (bright lesions)

📄 Also used to assess neurological severity





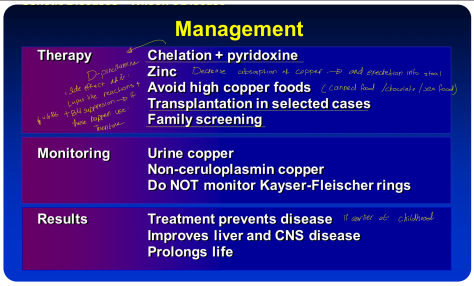
🧬 Wilson's Disease – Management

💊 Therapy

Treatment	Purpose
Chelation therapy	Removes copper from the body
D-penicillamine	Most common chelator
Trientine	Alternative if penicillamine not tolerated
Zinc	↓ GI copper absorption
Pyridoxine (B6)	Supplement with chelation
Liver transplant	In end-stage liver failure

🚫 Avoid:

- Shellfish
- Liver
- Chocolate
- Mushrooms
- Nuts
- **Canned food** (high in copper)



📋 Monitoring

- **Urine copper** (response to therapy)
- **Non-ceruloplasmin copper**
- Do **not** monitor Kayser-Fleischer rings as treatment indicator

📊 Hemochromatosis vs Wilson's Disease – Comparison Table

Feature	Hemochromatosis	Wilson's Disease
Inheritance	Autosomal Recessive	Autosomal Recessive
Metal Overloaded	Iron	Copper
Gene	HFE (C282Y, H63D)	ATP7B
Age of Onset	Adults (40–60 yrs)	Children/Young Adults
Ceruloplasmin	Normal	↓↓↓
Transferrin Saturation	↑↑ (>50%)	Normal
Ferritin	↑↑	May be elevated (due to liver injury)
Urine Metal	Not diagnostic	Copper > 100 µg/day
Eye Finding	None	Kayser-Fleischer rings
Organ Involvement	Liver, pancreas, heart, joints	Liver, brain, eyes, kidneys, joints
Biopsy Finding	Iron deposits (Prussian blue stain)	Copper buildup (rhodanine or biopsy test)
Treatment	Phlebotomy	Chelation + Zinc
Risk of HCC	Yes (in cirrhosis)	Yes (in advanced liver disease)