# Hemochromatosis: A European Polymorphism

John McCullough
Kathleen Heath

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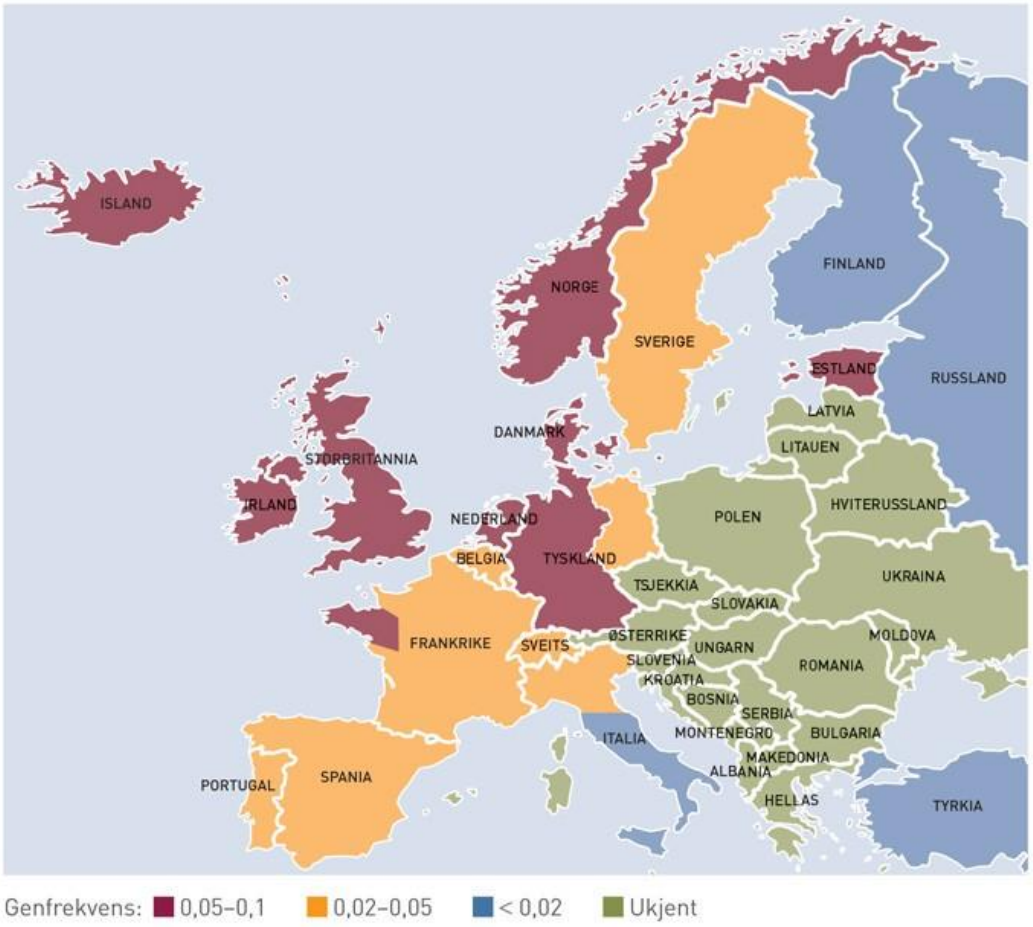
- Two basic causes
- Genetic – several loci
- Environmental
- Occasionally “lethal” esp. in males
- Variable geographic distribution – polymorphic!
- Gift from Darwin?

# Hemochromatosis in Europe



# How Does Evolution Work?

## Hardy-Weinberg Violations

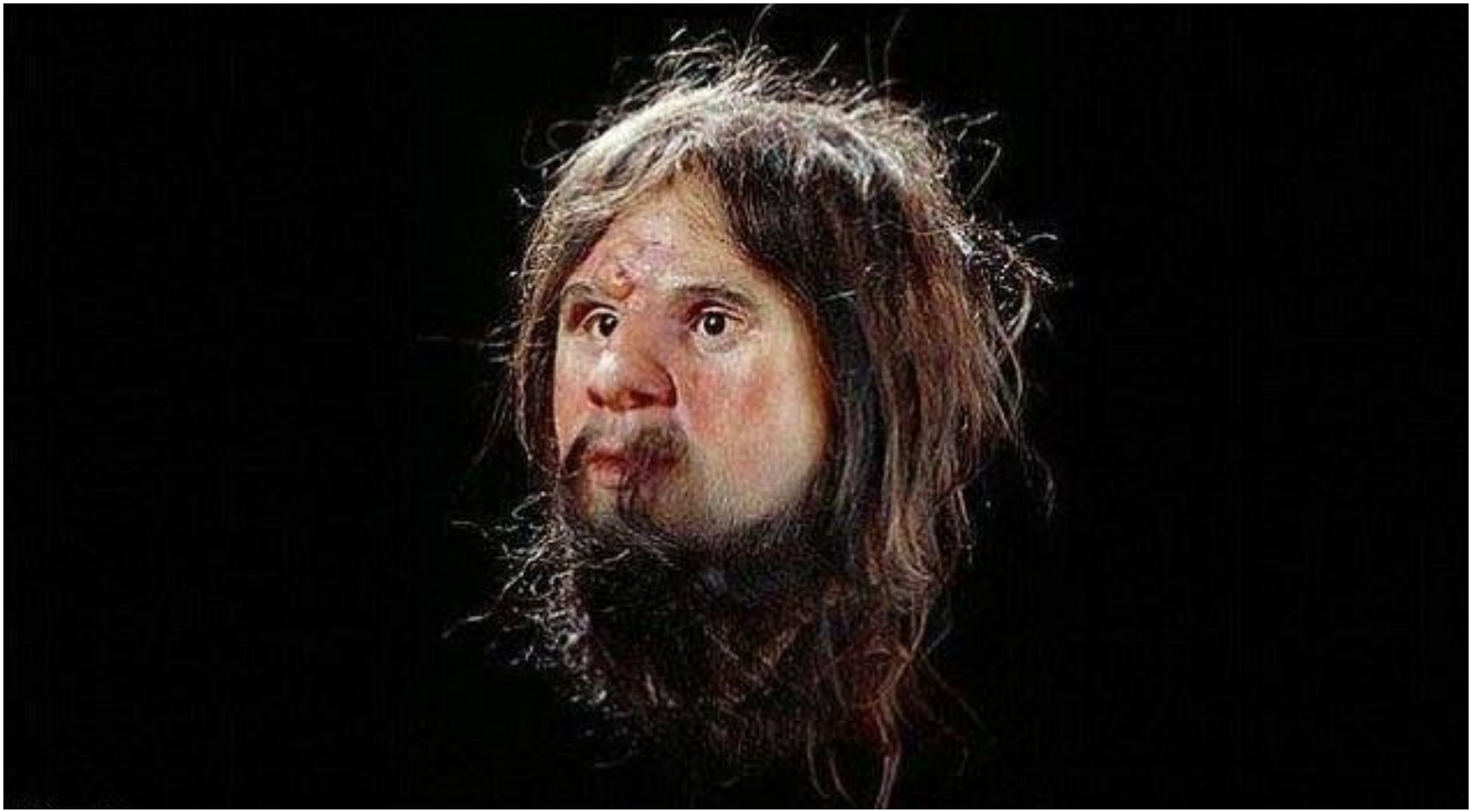
- Mutation
- Selection – natural or sexual
- Migration – in or out
- Drift – several mechanisms
- What Happened?

# Cheddar Man Burial
# 9100 BP - Mesolithic

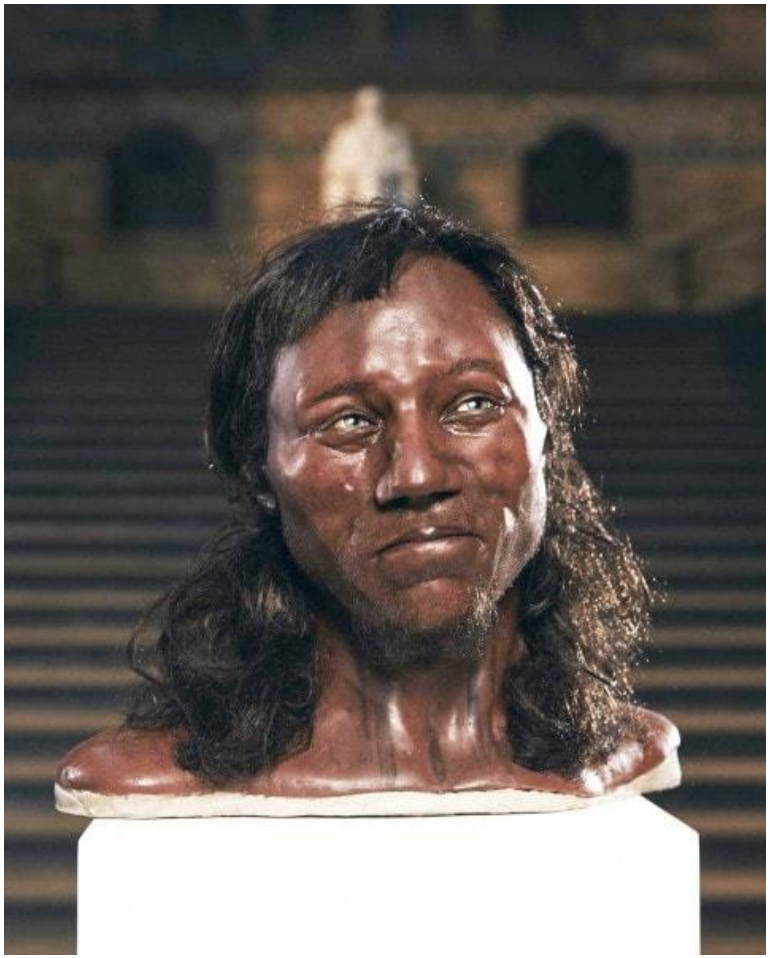
# Cheddar Man Skull

FIG. 2.—CHEDDAR MAN *NORMA FACIALIS.*

# Cheddar Man Reconstruction



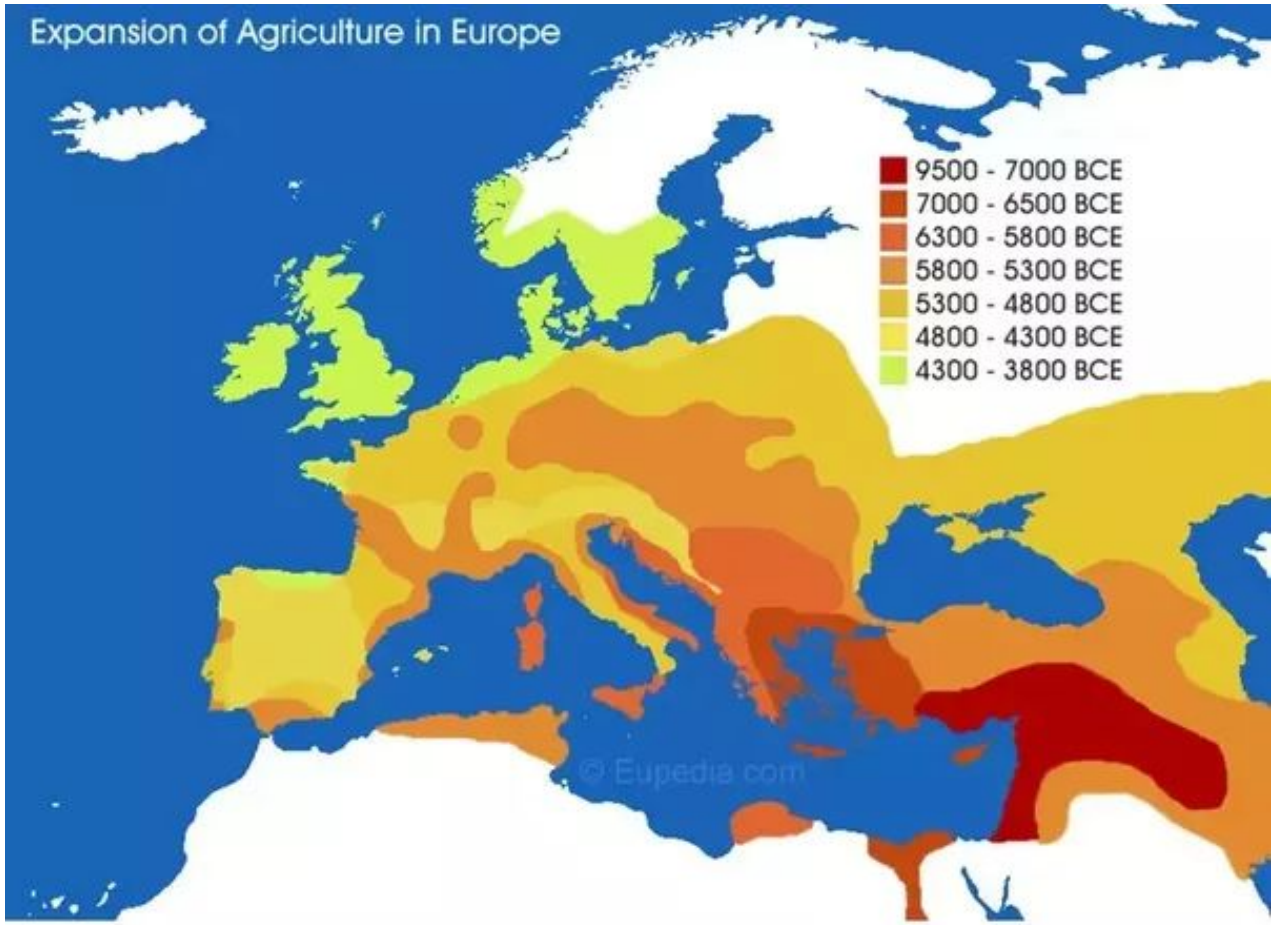
# New Cheddar Man



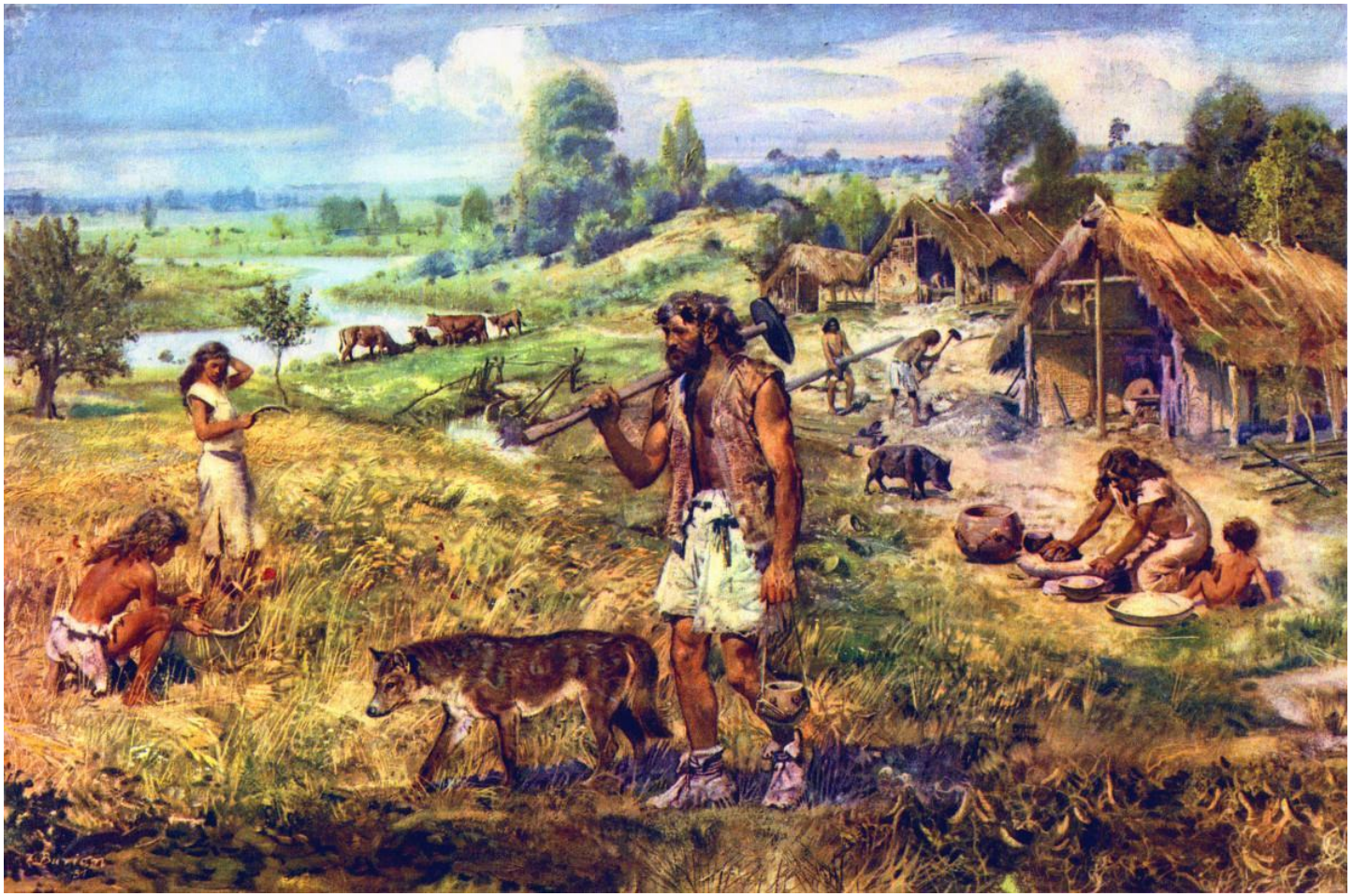
# East African Progenitors

# Cheddar & Britain First
# What Happened?

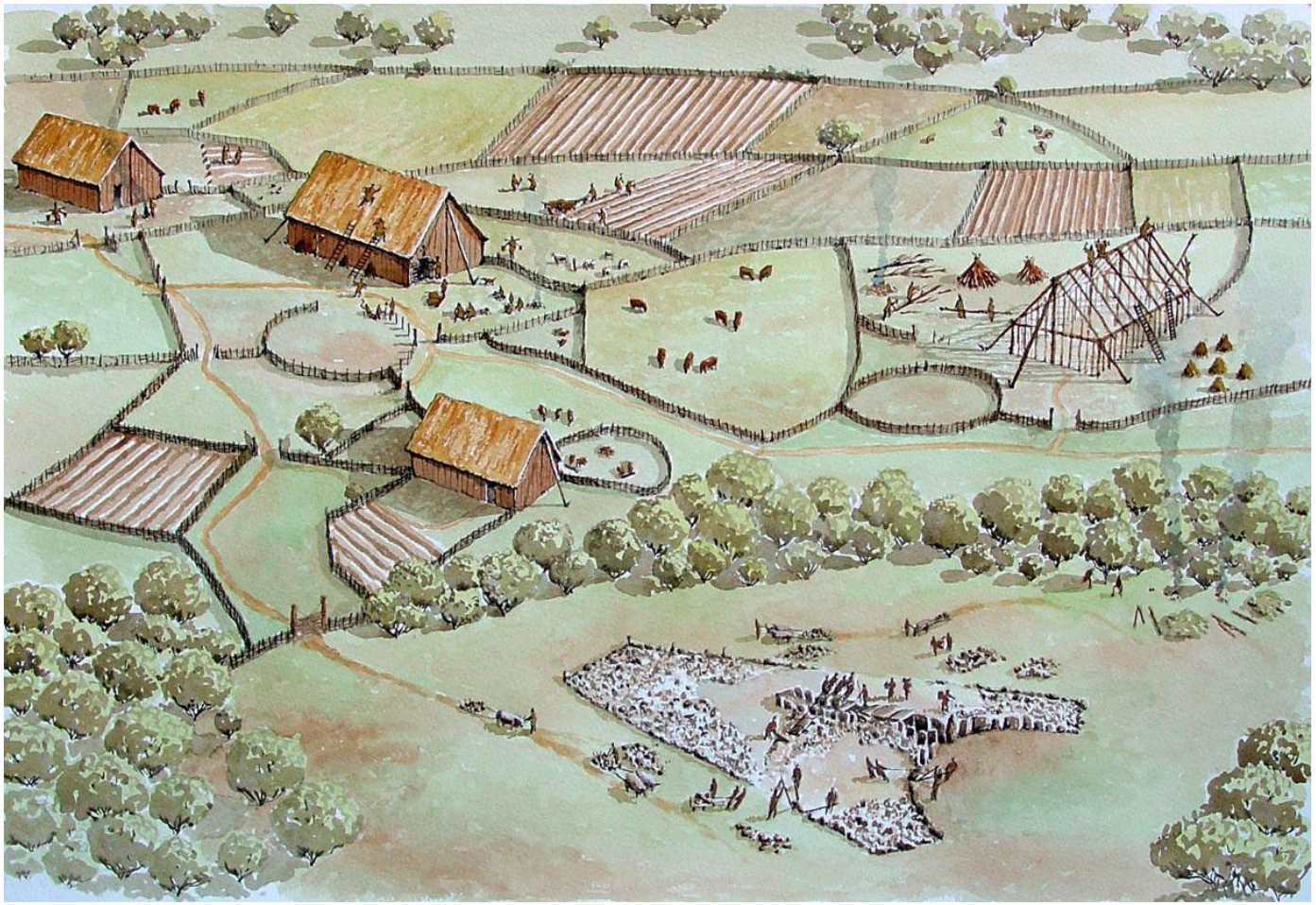
# Agriculture



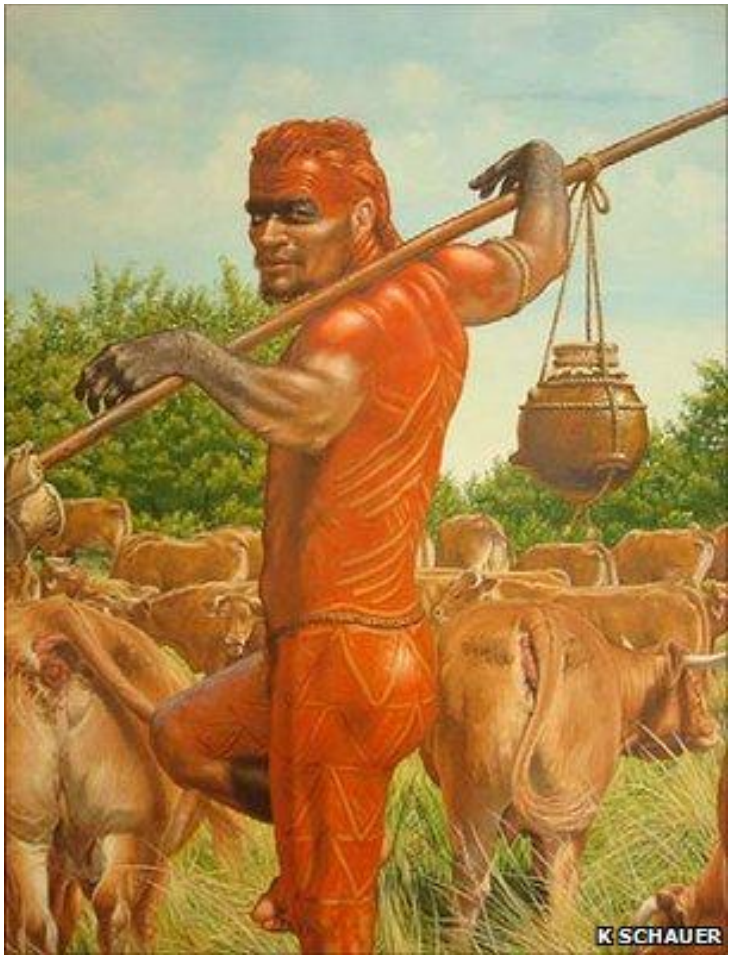
# Cropping of Grains



# Small Settlements



# Pastoralism, Especially Cattle in North



# Agriculture:
# Man's Greatest Mistake

- Shift in foods from high meat to low meat and high cereal crops
- Monocropping
- Impoverishment of food diversity in North
- Famine (1 year in 3 in Medieval Period)
- Reduced nutritional value in foods
- By Iron Age, larger settlements form
- What was the effect on health?  On genetics?

# HFE and Agriculture Link?

- Reduced Meat Intake – Seasonal??
- Thus reduced red meat iron intake
- Increased grain intake
- Whole grains -> incr. phytate capture

- Result is reduced iron intake.

# Skeletal Evidence?
# H & G to Agriculture

- Stature change?
- Porotic hyperostosis?
- Cribra orbitalia?
  (Data from Wittwer-Backofen and Tomo 2008)
- Early Neolithic is LinearBandKeramik Culture
- Late Neolithic is Corded Ware (Schnurkeramik) and Bell Beaker (Glockenbecherkeramik) Cultures

# Skeletal Evidence – Stature (cm)
## Central Europe

| | Males | | Females | |
|---|---|---|---|---|
| | N | Stature | N | Stature |
| E. Upper Paleo | 10 | 174.7 | 5 | 161.3 |
| L. Upper Paleo | 29 | 171.8 | 14 | 156.7 |
| Mesolithic | 124 | 167.2 | 104 | 155.9 |
| Neolithic (All) | 127 | 166.7 | 128 | 154.7 |
| E. Neolithic | 12 | 165.2 | 31 | 155.5 |
| L. Neolithic | 9 | 163.6 | 9 | 157.1 |

# Skeletal Evidence
# Paleopathology

- Porotic hyperostosis
- Cribra orbitalia
- Dental hypoplasia

- Data from Wittwer-Backofen and Tomo 2008

# Cribra Orbitalia

# Cribra Orbitalia

| – | Mesolithic | | E. Neolithic | |
|---|---|---|---|---|
| – | N | % | N | % |
| – Subadults | 6 | 0.0 | 55 | 60.0 |
| – Adults | 193 | 0.0 | 38 | 23.7 |

# Cribra cranii – Porotic hyperostosis

# Cribra Crania (Porotic Hyperostosis)

| | Mesolithic | | E. Neolithic | |
|---|---|---|---|---|
| | N | % | N | % |
| – Subadults | 6 | 0.0 | 52 | 3.9 |
| – Adults | 46 | 6.5 | 38 | 15.8 |

# Transverse Dental Hypoplasia

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| – | Mesolithic | | E. Neolithic | |
|---|---|---|---|---|
| – | N | % | N | % |
| – Subadults | 16 | 25.0 | 86 | 52.3 |
| – Adults | 62 | 45.5 | 44 | 63.6 |

# Porotic Hyperostosis
# Causes?

- Anemia by dietary deficiency
- Iron
- Ascorbic acid (Vit-C)
- Blood losses
- Parasites
- Hemoglobin dyscrasias

# Anemia

- A deficiency of red blood cells or hemoglobin on the surface of existing RBC's.
- Can also include hemoglobin dyscrasias.
- Major causes of anemia:
  - Inadequate iron intake (diet)
  - Excessive blood loss
  - Excessive RBC destruction (hemolysis)
  - Deficient or inadequate RBC production (hematopoesis)

# Anemia

- Many forms of anemia (diagnoses):
  - Pernicious anemia – inability to absorb Vit B-12
  - Hemolytic anemia – from breakdown of RBC's
  - Megaloblastic anemia – inhibition of DNA synthesis during hematopoesis – usually from lack of Vit B-12
  - Dietary iron deficiency

# Anemia

- Blood loss:
  - Hemorrhage
  - Menstruation
  - Pregnancy, childbirth
  - Warfare
  - Bar fights, etc.
  - Serious accidents

# Anemia

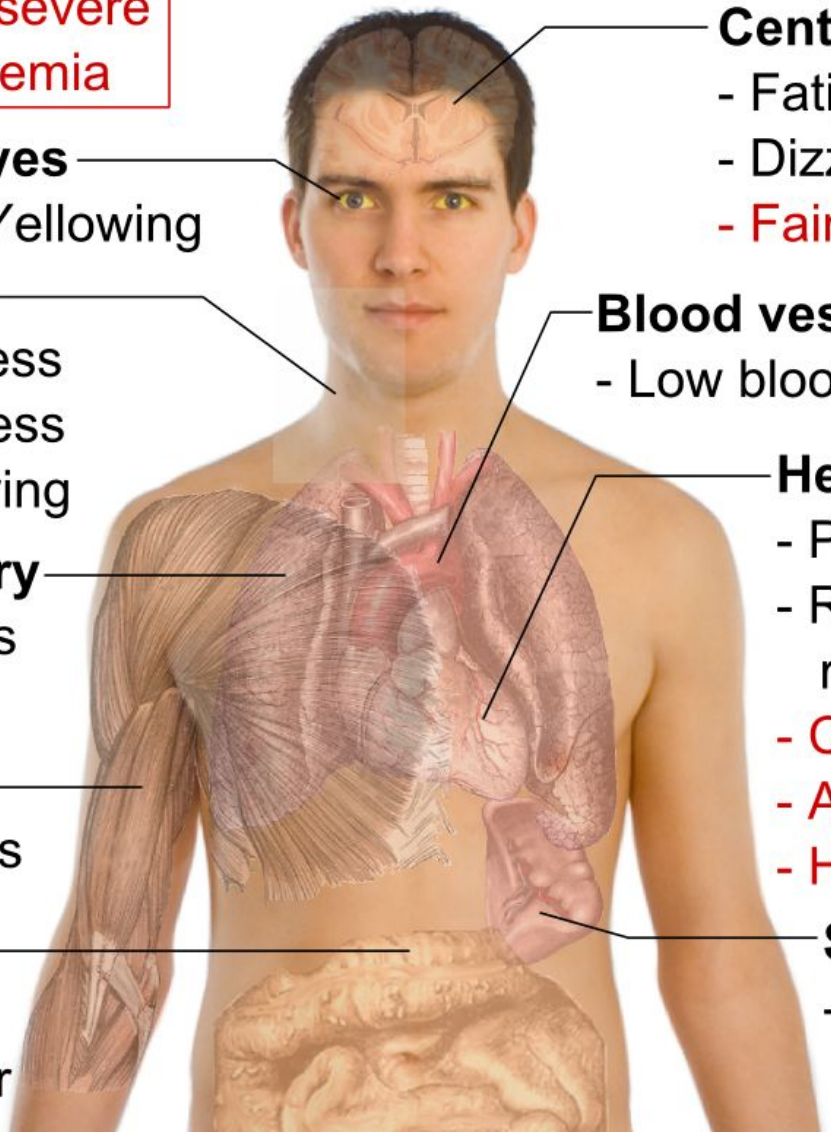
- Red Blood Cell Destruction (Hemolysis):
  - Malarial hemolysis, other blood parasites
  - Genetic basis for hemolysis
    - G-6-PD (Favism)
    - Beta thalassemia
    - Other Hemoglobinopathies – Hb-S, Hb-E, etc
  - Bacterial hemolysis
    - Steptococcus
    - Staphylococcus
    - Enterococcus

# Anemia

- Inadequate Red Blood Cell Production:
  - Inadequate iron intake
  - Inadequate Vitamin C (Ascorbic acid) intake
  - Inadequate Vitamin B-12 (Cobalamin) intake
  - Inadequate Folic Acid (Folate) intake

# Symptoms of Anemia

Red = In severe anemia



**Central**
- Fatigue
- Dizziness
- Fainting

**Eyes**
- Yellowing

**Skin**
- Paleness
- Coldness
- Yellowing

**Blood vessels**
- Low blood pressure

**Heart**
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack

**Respiratory**
- Shortness of breath

**Muscular**
- Weakness

**Intestinal**
- Changed stool color

**Spleen**
- Enlarge-ment

# How to Deal with Anemia?

- Niche Construction Theory (Laland & Brown, various):
  - Ecologically-stable organisms are “adapted”
  - When environment changes, culture or behavior responds first
  - If culture does not respond, genetic system must respond

# Man's Greatest Mistake

- Adoption of agriculture breaks human adaptation
- Result is anemia
- In Europe, culture does not respond (evidence of skeletons)
- Genetic system must respond – how?

# Man's Greatest Mistake Agriculture

- Adoption of agriculture breaks 800,000 years of human economic activity in Europe
- Cereal crops containing phytates are adopted
  - Wheat
  - Barley
  - Rye
  - Oats
- Hunting, fishing reduced or suspended, less game eaten
- Domestic stock are eaten, partially on a seasonal basis
- Dairying is adopted early on.

# Anemia – How come in Neolithic?

- Naugler – phytates?
- This presentation – dairying as well?
- Cold, wet North European climate?
- Reduced iron consumption from other domesticated foods?
- Some combination?

# Anemia – How come in Neolithic?

- Naugler – phytate hypothesis
  - Phytates – on seed coat or “skin”
  - Lock up minerals in diet, including iron

# Hunting Diet

- Red Deer
- Moose
- Elk
- Seal
- Clams, cockles
- Salmon
- Hazelnuts

# Horticultural Diet

- Whole wheat bread
- White bread
- Oatmeal
- Beef
- Goat
- Sheep
- Hazelnuts
- Whole milk
- Buttermilk
- Yogurt
- Ricotta cheese
- Mozzarella cheese
- Cottage cheese
- Butter

# Hemochromatosis

- HFE or HHC (Hereditary hemochromatosis) OMIM 235200
- 6p21.3; 6p22.2, autosomal “recessive”
- Increases absorption of iron in the lower intestine
- In extreme cases, leads to organ failure due to iron deposition in cells

# Hemochromatosis

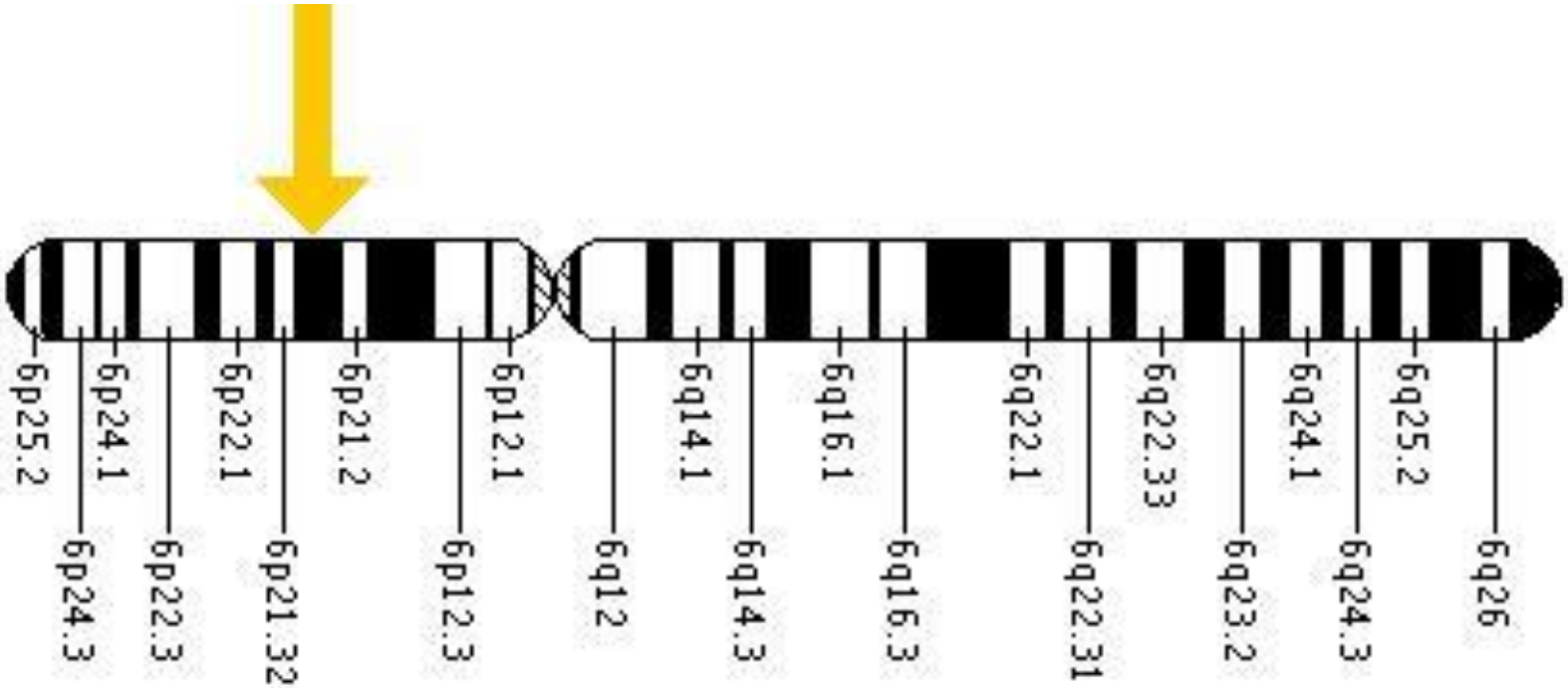
Inherited as an autosomal partial recessive

Located on short arm of $6^{th}$ chromosome

Mutation (C282Y) allows increased intake of iron

Cotrolling gene for interraction of transferrin and transferrin receptor?

# Hemochromatosis
# Chromosome 6



# Hemochromatosis

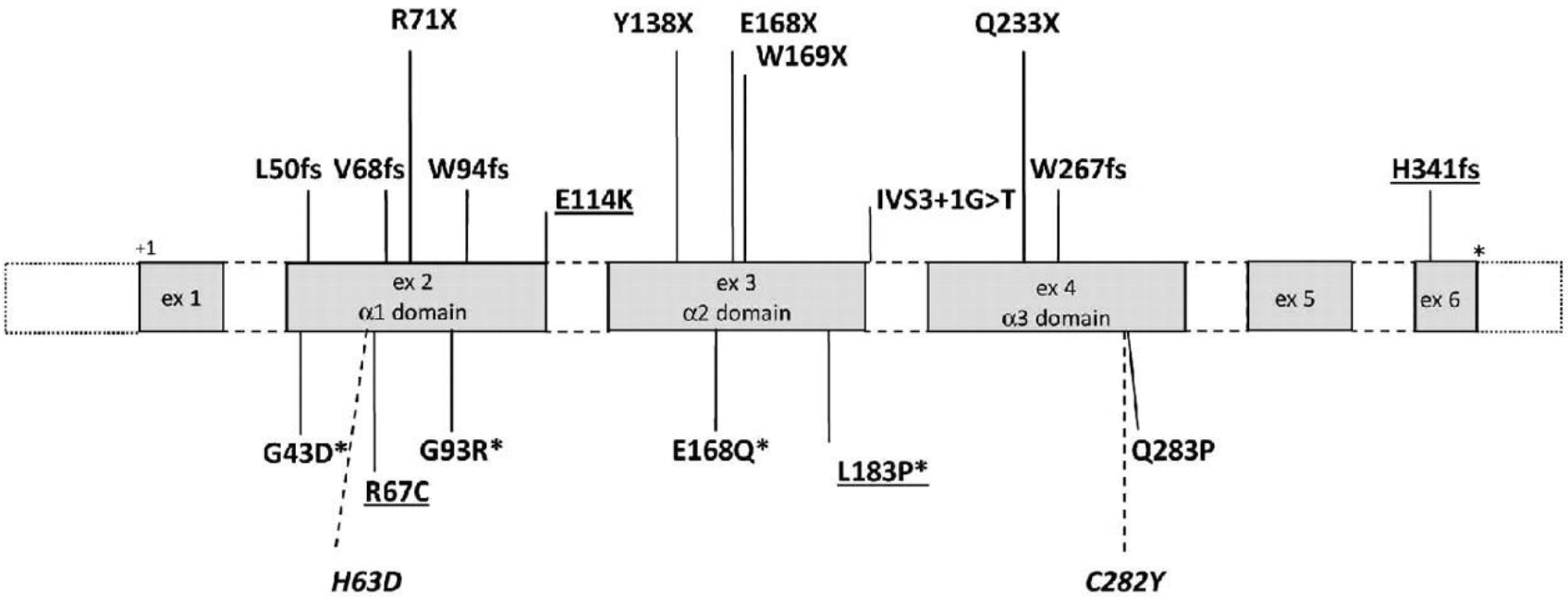
Three major mutated alleles:

- C282Y – most common in Northern Europe
- S63C - older, more widely, evenly dispersed
- H65D – less common, less known

C282Y allele found primarily in Northwest Europe and along coastline

Found in same geographical areas as LP

# HFE Mutations



# Hemochromatosis

- Variable % of C282Y homozygotes present with pathology
- C282Y homozygotes almost always have higher iron levels than “wt” homozygotes
- C282Y/wt heterozygotes have slightly elevated iron but do not present clinically
- H63D homozygotes not associated with HFE
- Double heterozygotes may present clinical symptoms

# Hemochromatosis

- Iron-retention disease
- Too much iron enters body
- No major release of iron except by bleeding
- Lethal in a small number of cases
  - Homozygous state
  - Double heterozygous state
- Affects men more than women

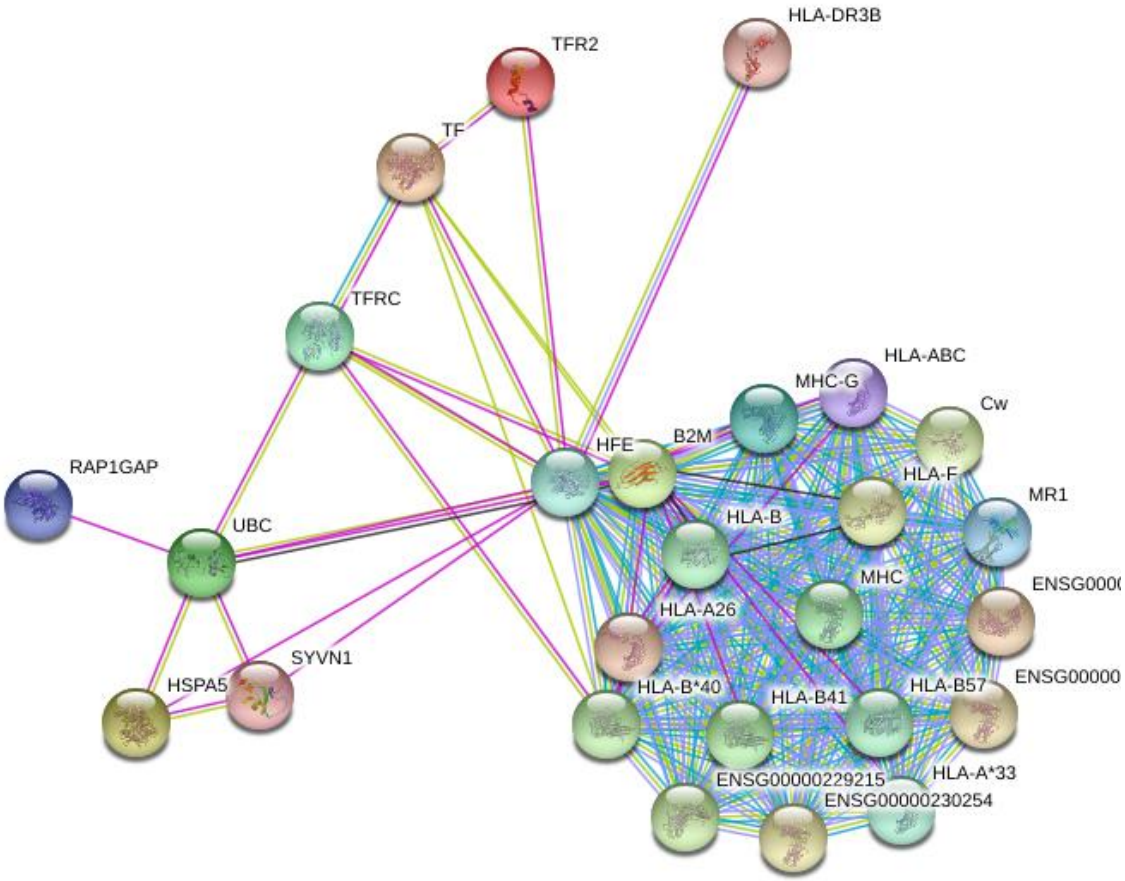
# Clinical Hemochromatosis

- Clinical symptoms:
  - Headaches
  - Joint pain
  - Bone pain
- Alcoholism is an accelerative factor
- Symptoms and sequelae appear in mid- to late life, especially in women; earlier in men?

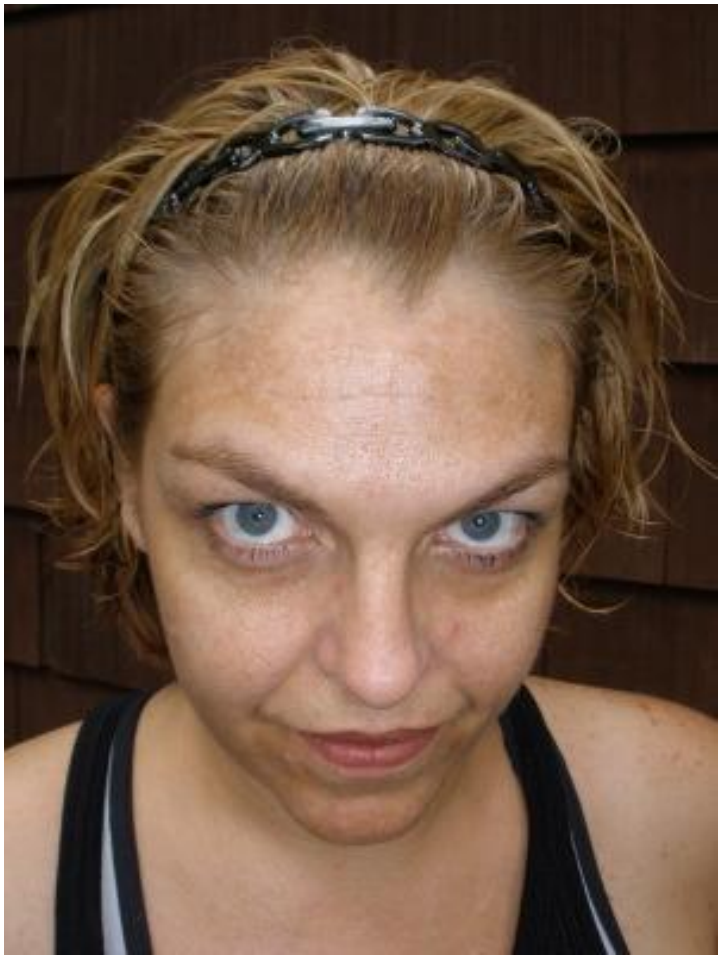
# Hemochromatosis

- Dangerous sequelae:
  - Hepatomegaly and cirrhosis of liver
  - Arthritis due to iron build-up in joints
  - Cardiomyopathy
  - Testicular failure and hypogonadism
  - Bronzing of face, other body parts
  - Splenomegaly
  - Diabetes (Pancreatic islet cell failure)

# HH Interactions



# Hemochromatosis



# Hemochromatosis

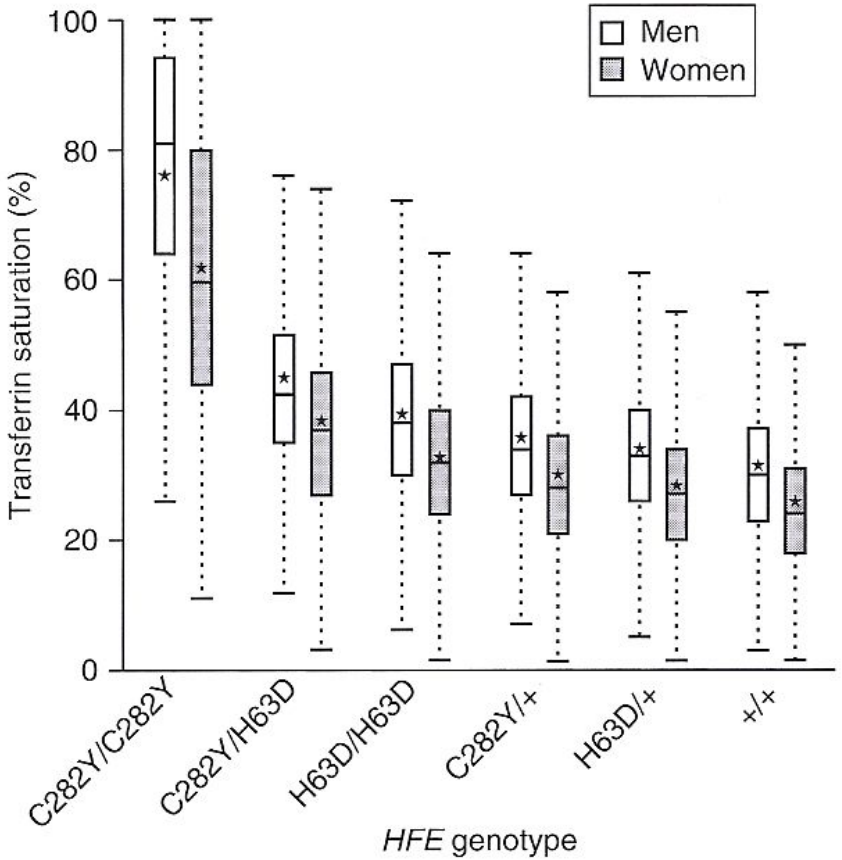
# Hemochromatosis

- Diagnosis:
  - Elevated serum ferritin, (usually] an intracellular protein that stores and retrieves iron)
  - Liver biopsy or MRI to assess cellular iron
  - Genetic analysis or familial history
  - Presence of sequelae  (above)

# Transferrin

- Plasma iron transport protein
- Produced in liver
- Found in plasma, bile
- On chromosome 3q21

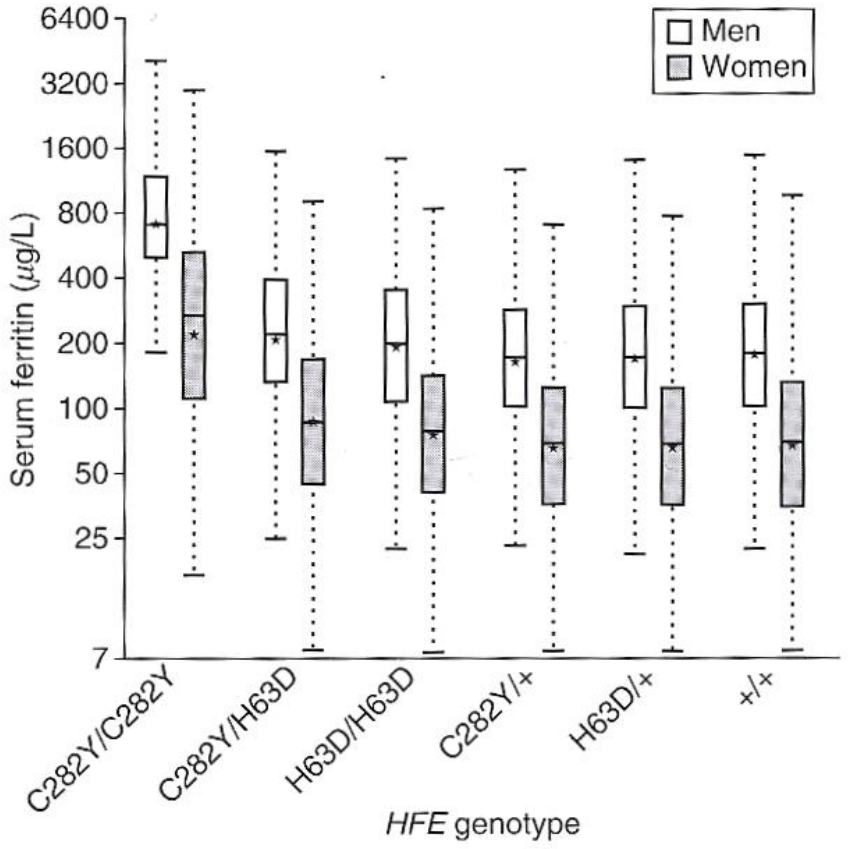
# Transferrin Saturation



# Serum Ferritin

- Forms nanocage for iron storage
- Found in hepatocytes (liver), macrophages (immune system), most other cells
- 2 subunits
  - Ferritin L-subunit – 9q13.3-q13.4
  - Ferritin H-subunit – 11q12-q13

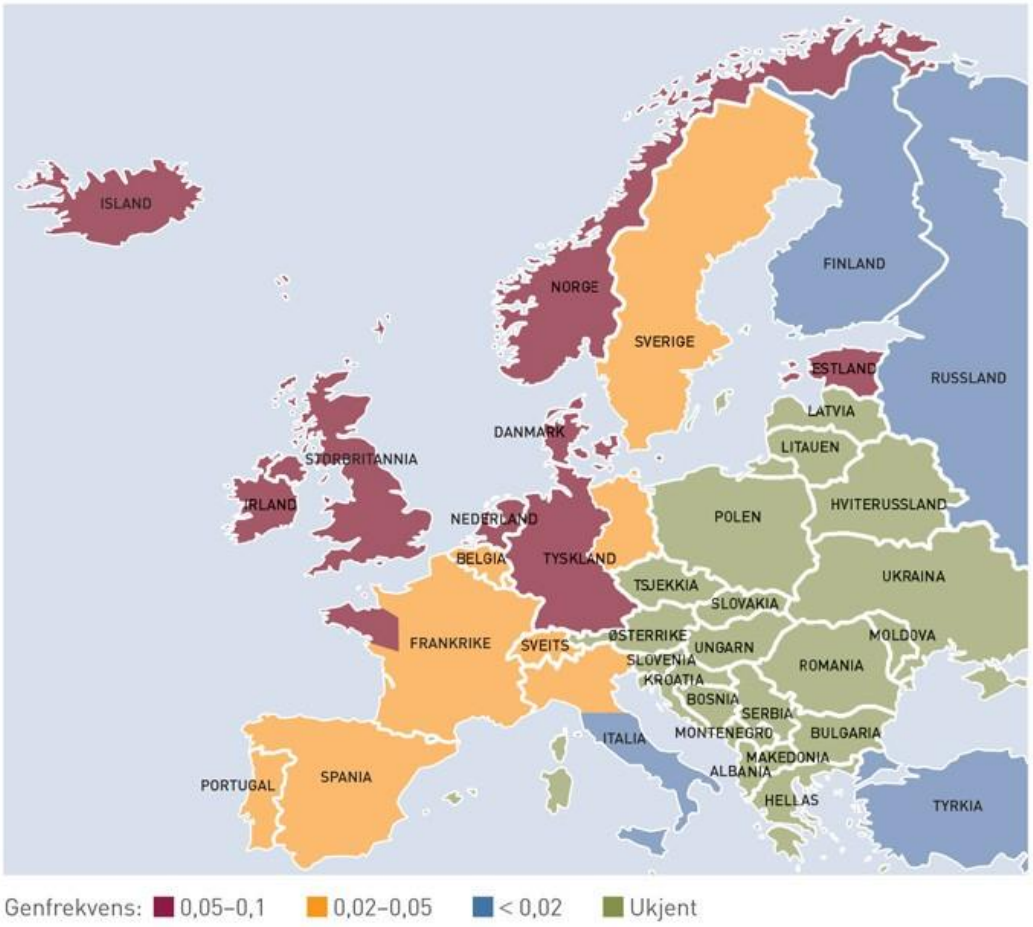
# Serum Ferritin Levels



# Hemochromatosis

- Found primarily in persons of NW European ancestry
  - Celtic
  - Scandinavian
  - Coastal populations
- Found in same geographical areas as LP – are they correlated?

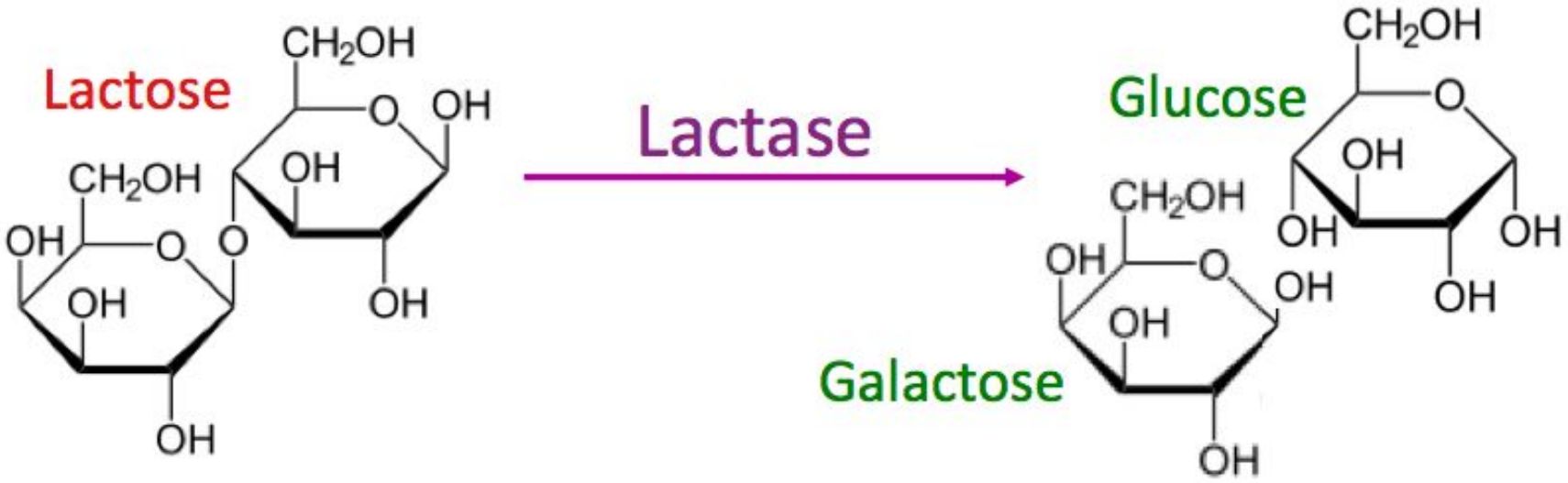
# Hemochromatosis



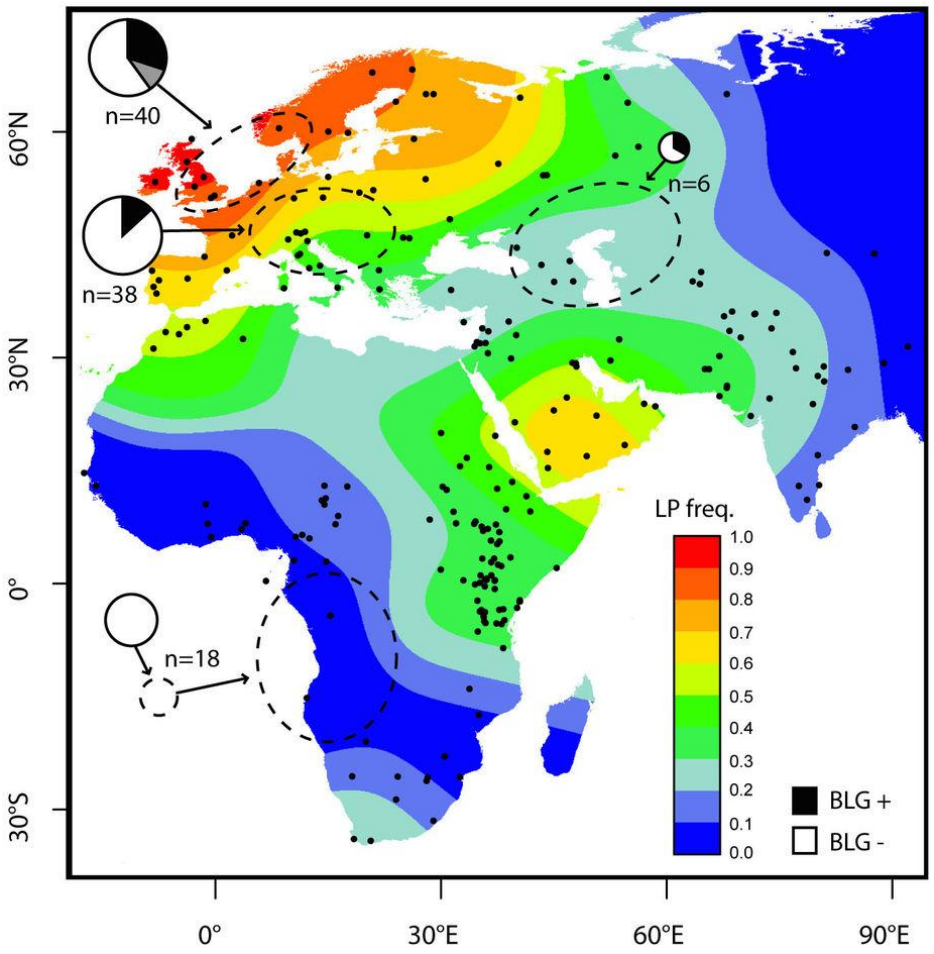
# Lactase Persistence

- Mammals feed young milk
- Lactose - a disaccharide
- Glucose
- Galactose
- Lactase enzyme
- Lactose intolerance

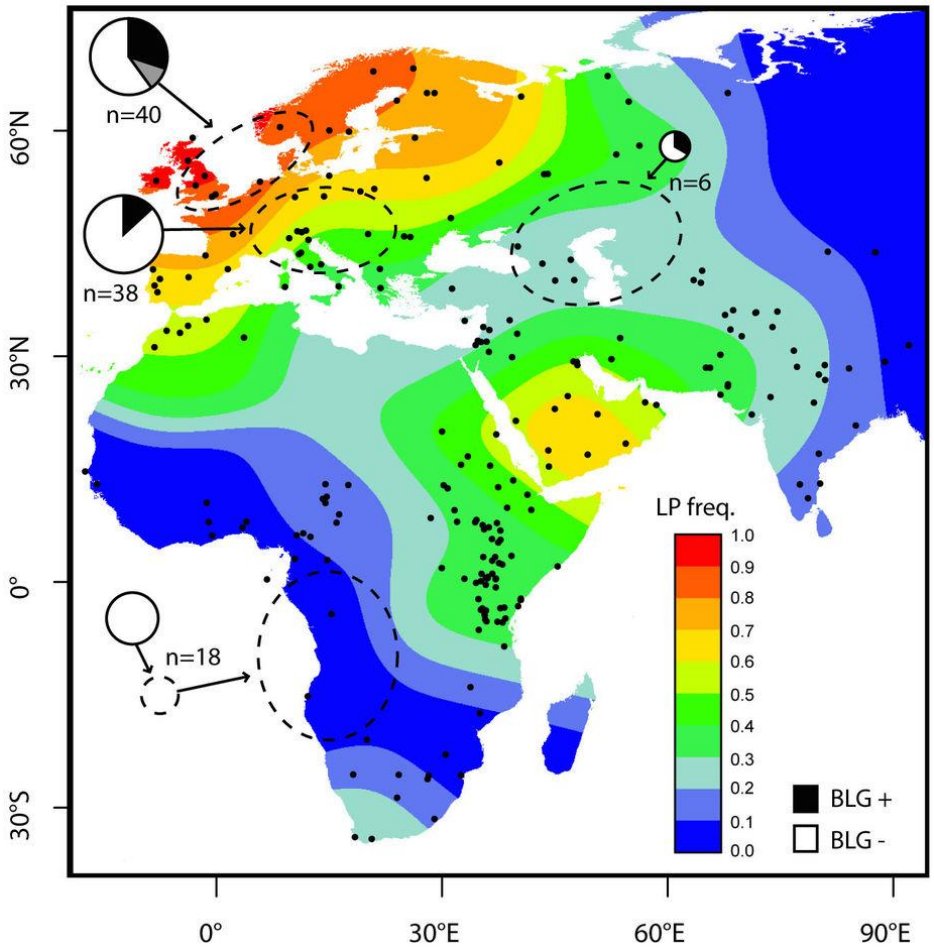
# Lactose

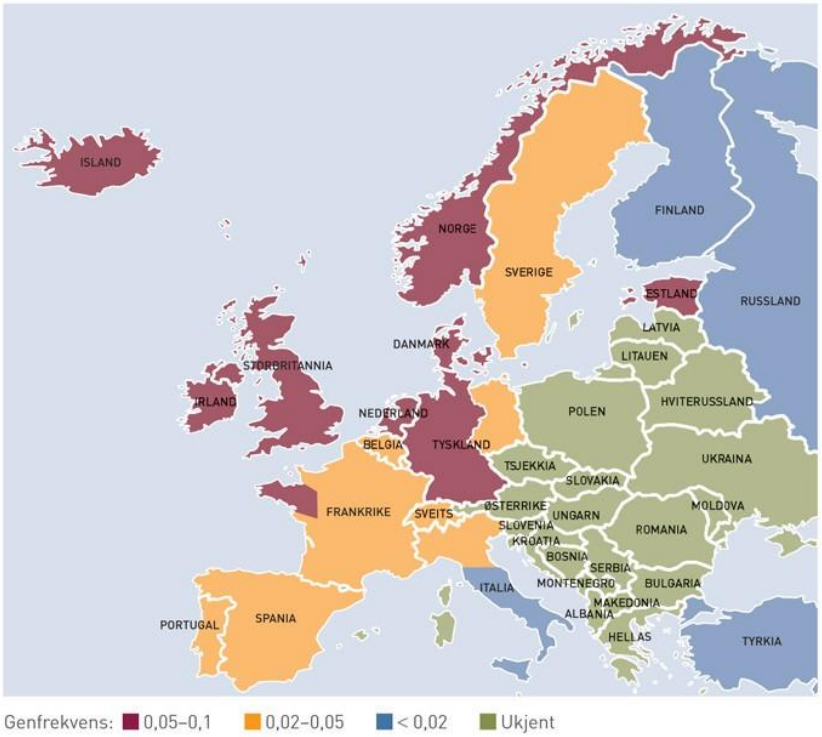


# Lactose Tolerance



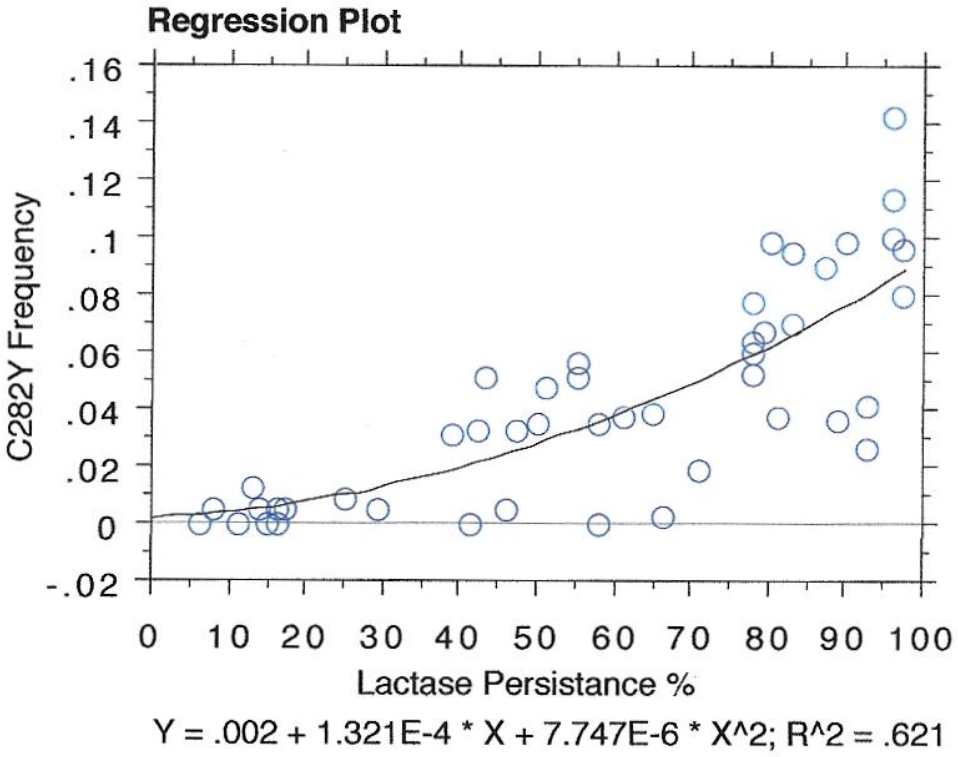
# LP and HFE


n=40
n=6
n=38
n=18
LP freq.
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
BLG +
BLG -
60°N
30°N
0°
30°S
0°
30°E
60°E
90°E


ISLAND
NORGE
SVERIGE
FINLAND
RUSSLAND
ESTLAND
LATVIA
LITAUEN
DANMARK
STORBRITANNIA
IRLAND
NEDERLAND
BELGIA
TYSKLAND
POLEN
HVITERUSSLAND
UKRAINA
TSJEKKIA
SLOVAKIA
FRANKRIKE
SVEITS
ØSTERRIKE
UNGARN
MOLDOVA
SLOVENIA
ROMANIA
KROATIA
BOSNIA
SERBIA
MONTENEGRO
BULGARIA
ITALIA
MAKEDONIA
ALBANIA
PORTUGAL
SPANIA
HELLAS
TYRKIA
Genfrekvens: 0,05–0,1
0,02–0,05
< 0,02
Ukjent

# Graph – LP Phenotype and HFE

## r = 0.788 (p<.001)



# LP and HFE

- Are the HFE allele and lactase persistence related in other ways?
  - Linked on same chromosome?
  - Common history?

# LP and HFE

Linked? No

- LP (OMIM 223100/601806) at 2q21.3
- HFE (OMIM 235200/613609) at 6p22.2

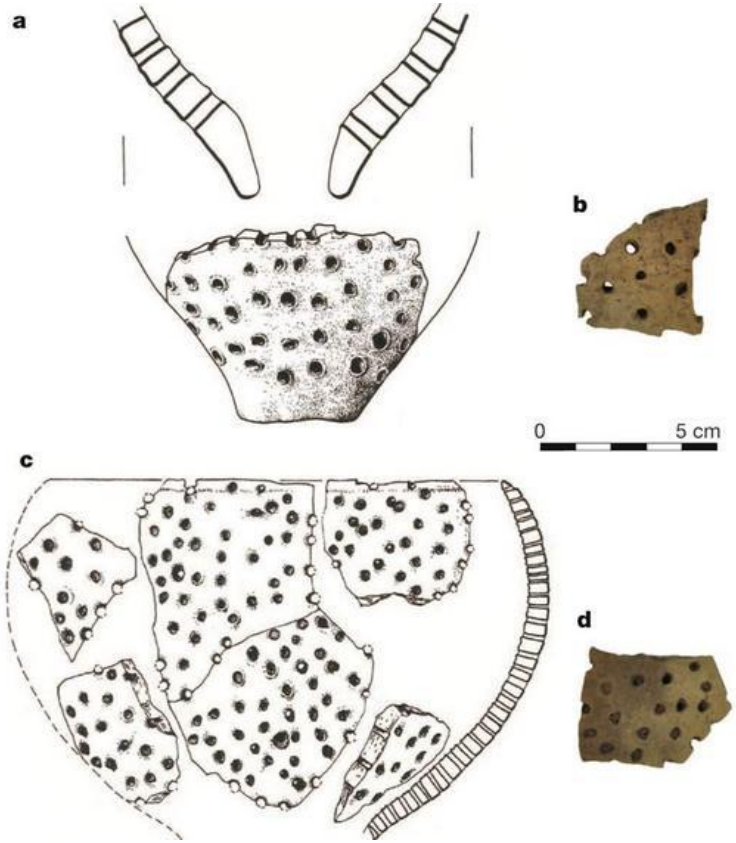
# LP and HFE

- Common History – Mutation Age?
  - LP (C/T(-13910)) mutation age:
    - 5-10,000 ya – Bersaglieri et al 2004
    - 5-12,000 ya - Enattah et al 2007
      - Second mutation event 1400 to 3000 ya
  - HFE mutation age:
    - ~4140 yrs ago (138 gens) – Toomajian et al 2003
    - ~1950 yrs ago (60-70 gens) – Milman and Pedersen 2003
    - <6000 yrs ago - Distante et al 2004

# Age of Dairying?

- Poland 7500 ya
- Anatolia 8000 ya
- England 6000 ya

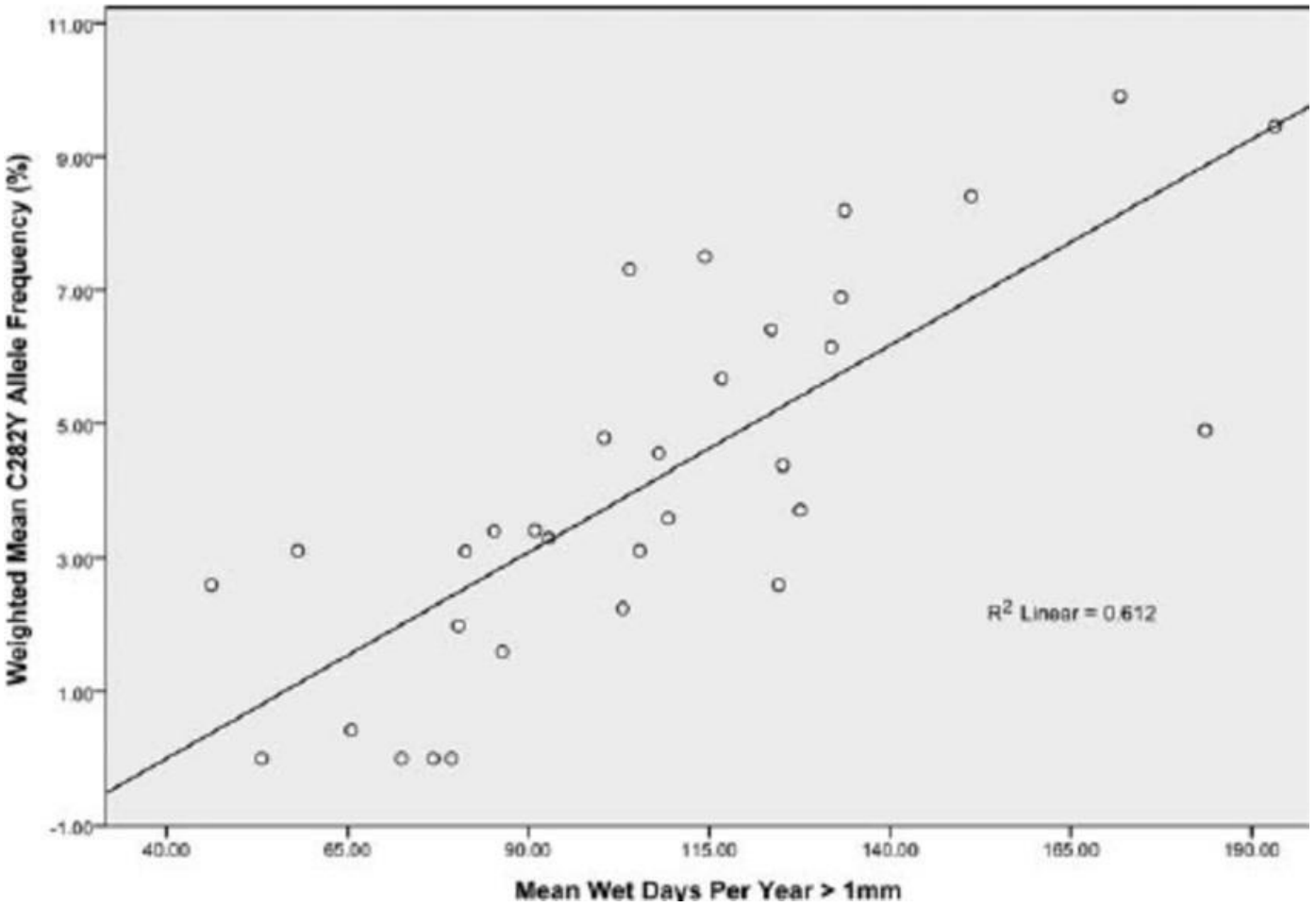
# Age of Dairying?
# Curd/Whey Sieves – LBK Culture




# Cold Moisture as a Driver

- Cold/Moist Adaptation – Increase metabolism
- Increase metabolism – thyroxine
- Thyroxine production – iron required

# Cold Moisture?



# Vit $B_{12}$ and Anemia

- Cobalamin req for RBC production
- Dietary inadequacy at times
- Loss from parasite – Diphyllobothrium spp.
- Common in Europe – 5 million in 1970

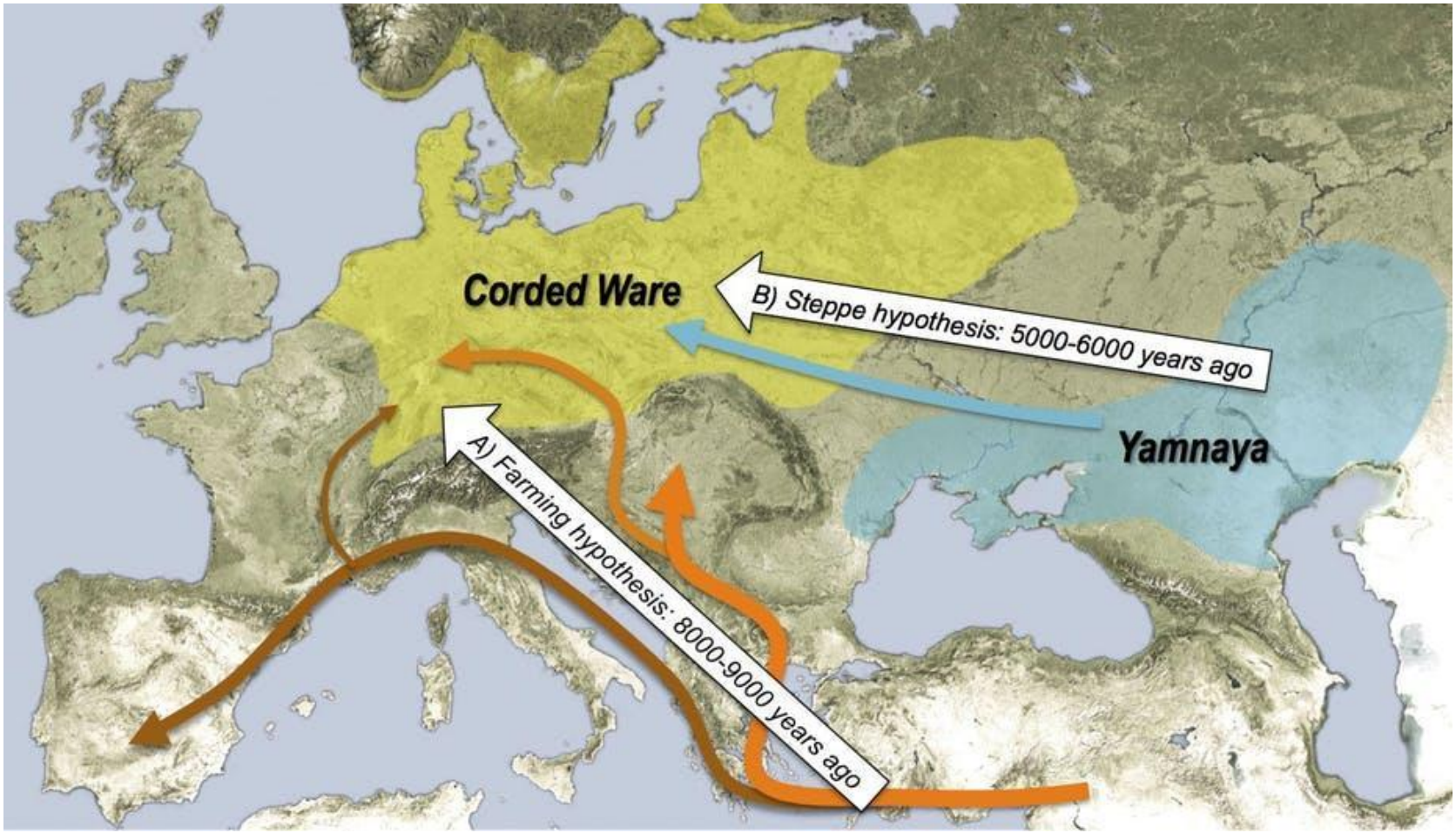
# A Rider on Another Sweep?

- Other loci closely-linked to 6p22.2, 6p21.3 include:
  - HLA-A, HLA-B – 6p21.3
  - HLA-C – 6p21.33
  - BMP6 – 6p24-p23
  - Tumor Necrosis Factor 6p21.3
  - Transient Neonatal Diabetes Mellitus I – 6p22.1, 6p24.2
  - Histone Gene Cluster 1 - 6p22.2
  - Gluten Sensitivity (HLA-DQ) – 6p21.32

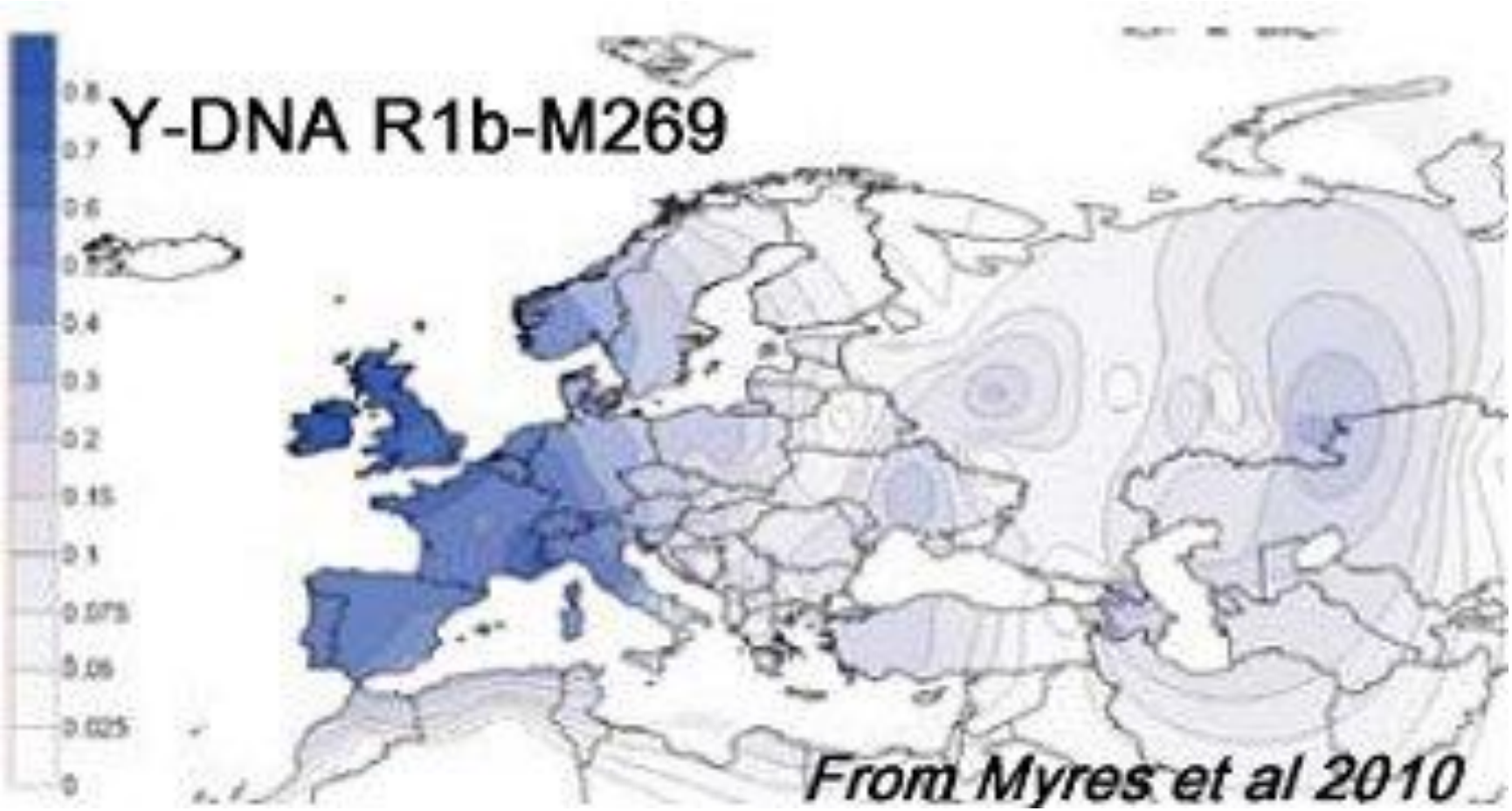
# Genetic Drift?

- Irish, British – Atlantic Modal Haplotype?
- R1b1a Y-chromosome
- Yamnaya Culture – Ukraine & Russia
- To Ireland With Love
- Indo-European languages spread

# Yamnaya – Bronze Age Intrusion



# Atlantic Modal Hyplotype – R1b



# Culture as Adaptation?
# Alcohol!

# Other Genetic Changes from Agriculture?

- Lactase Persistence
- Hemochromatosis
- Skin color
- Hair color
- PKU – Phenylketonuria?
- Others?

**A Balanced Meal!**

Vampire and friend should share their meals!