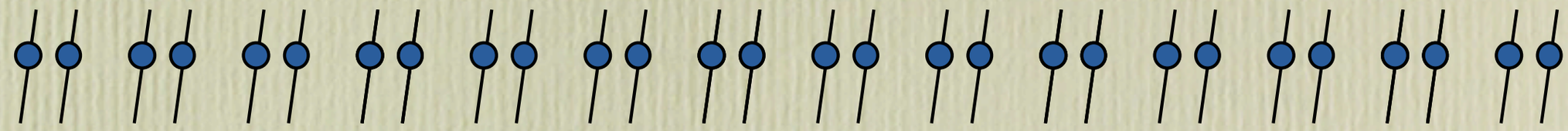
Harpending Lecture 5

Ashkenazi

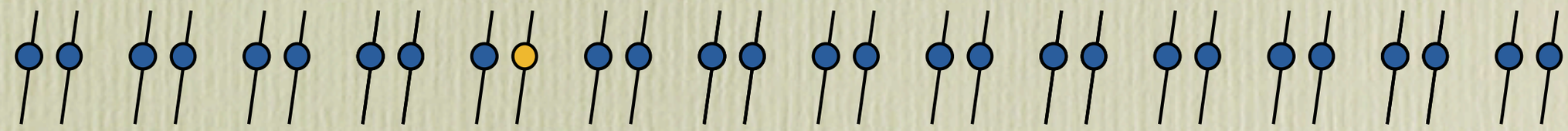
Balanced Polymorphism

- Carriers have higher fitness that either homozygote
- Often involve a broken version of a gene
- Sickle-Cell Anemia in the US Black population is a familiar example
- Often an evolutionary quick fix, eventually replaced by something better

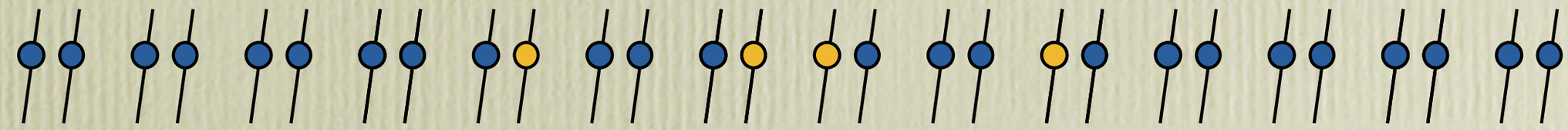
Population of 14 People, all making normal gene product



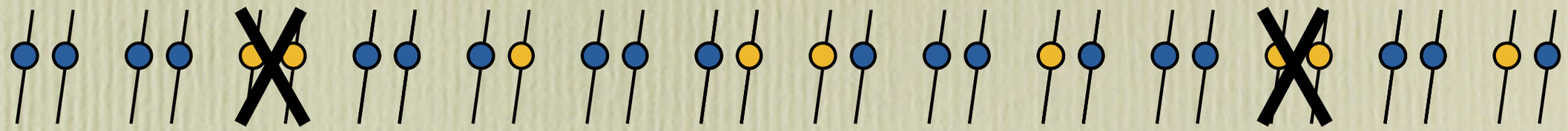
Mutation breaks a copy so carrier has higher fitness



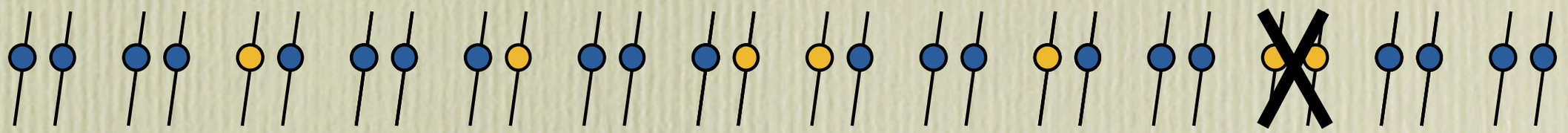
Broken version becomes more common



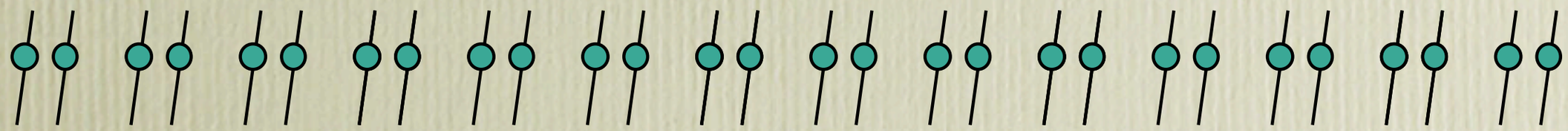
Two copies of broken version is fatal



A population "polymorphic equilibrium" is reached



Until the "right" mutation appears



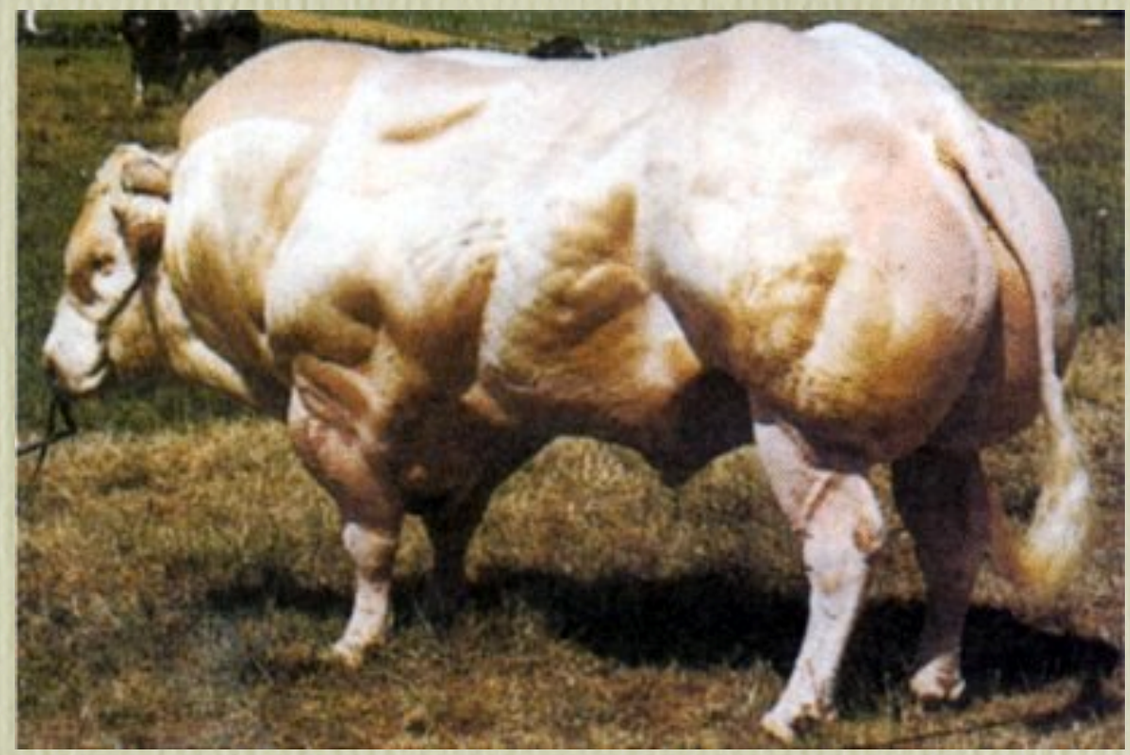
Twinning in Sheep

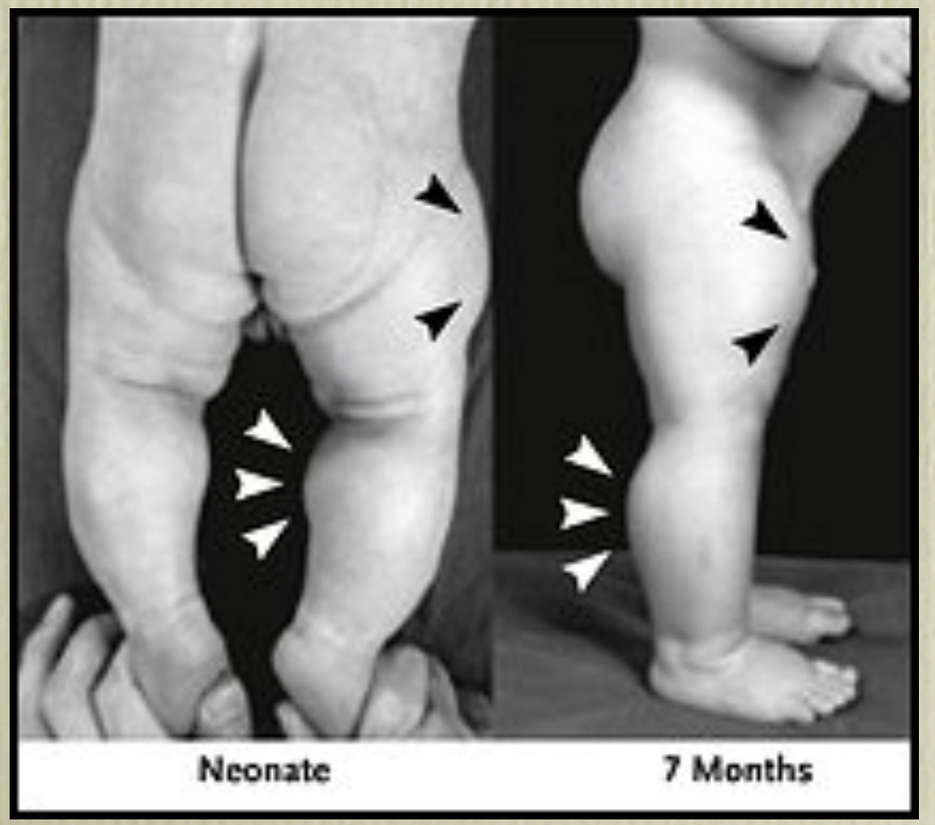
- BMP15 mutation in Inverdale: carriers twin, 2 copies cause sterility

- Different mutation in Hanna with same effect

- Booroola have similar mutation but in receptor

Myostatin





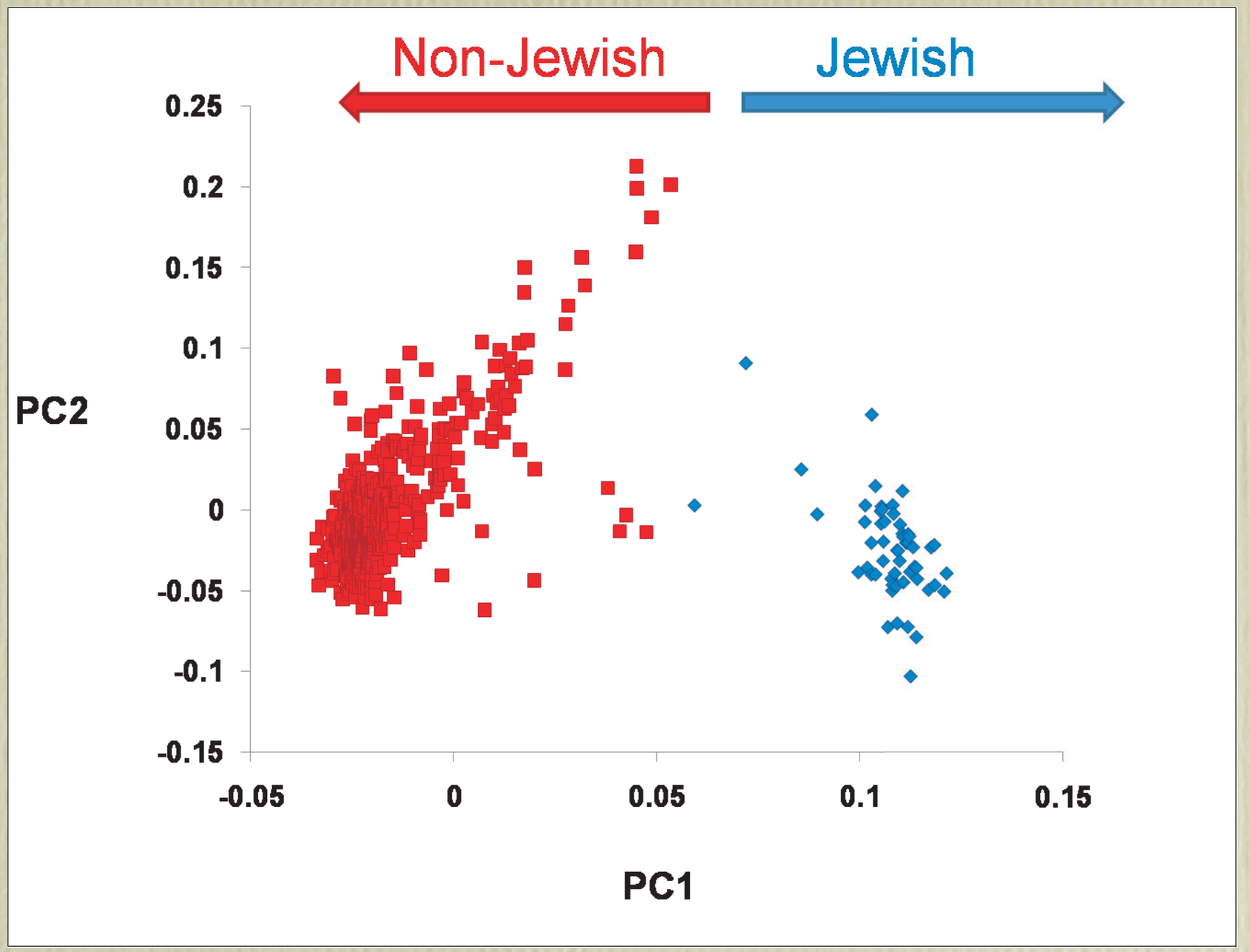
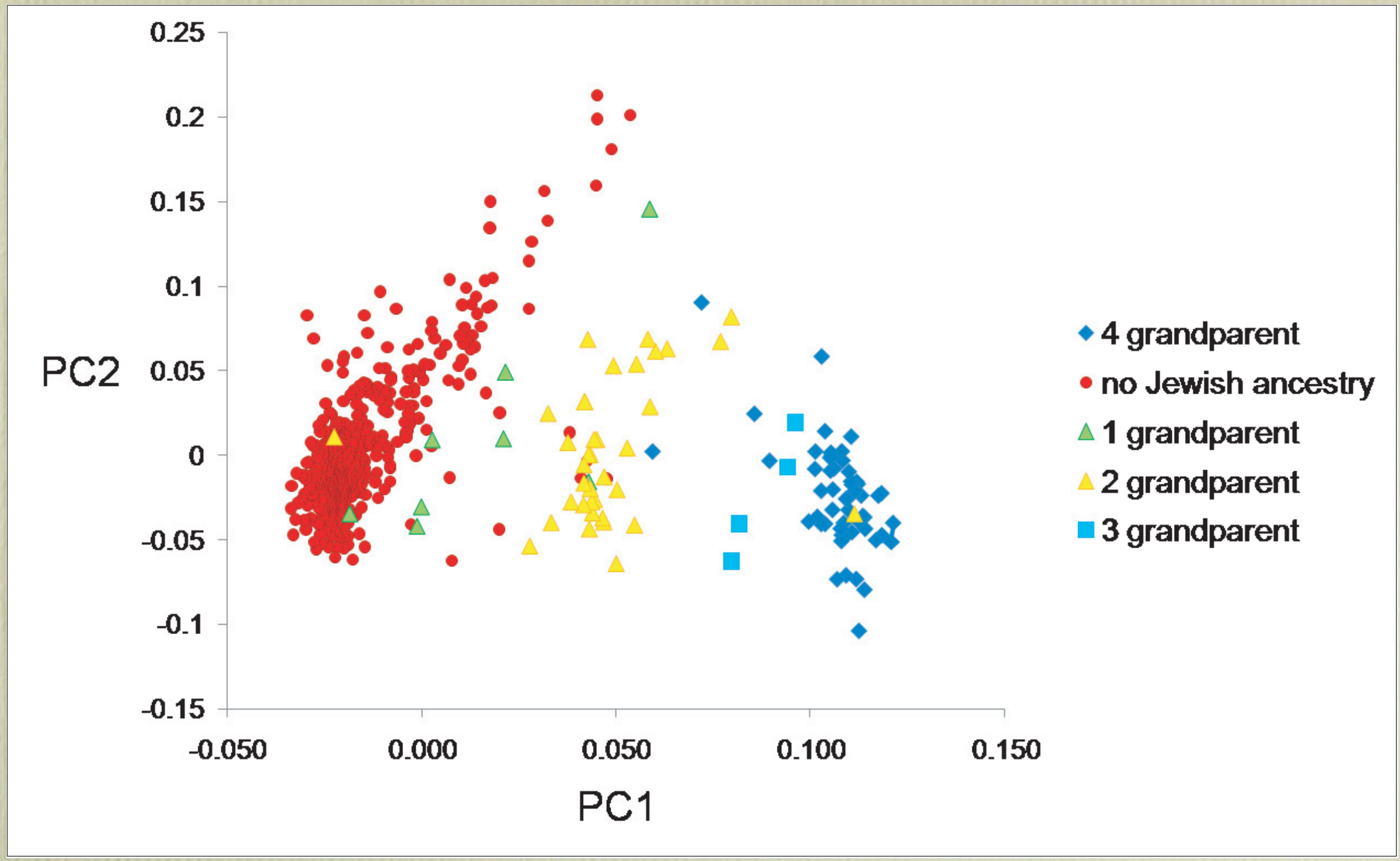


Figure 1 Plot of PC1 scores for Jewish and non-Jewish subjects
PC1 scores for Jewish and non-Jewish subjects. The score on PC1 plotted against the score on PC2 for Jewish (blue) and non-Jewish (red) subjects.

A genome-wide genetic signature of Jewish ancestry perfectly separates individuals with and without full Jewish ancestry in a large random sample of European Americans Anna C Need, Dalia Kasperavičiūtė, Elizabeth T Cirulli and David B Goldstein. *Genome Biology* 2009.


0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
PC2
-0.050
0.000
0.050
0.100
0.150
PC1
4 grandparent
no Jewish ancestry
1 grandparent
2 grandparent
3 grandparent

Genetics and Jewish History

- Ashkenazi Jews roughly have about half Middle Eastern DNA, half European DNA
- The European contribution seems to be old, i.e. Roman
- Ashkenazi "appear" in history about the time of Charlemagne
- Ashkenazi origins are obscure

Ashkenazi Inherited Disorders

- Disorders are concentrated in a few clusters: All on the same page of a biochemistry textbook
- The mutant alleles are not old, several thousand years at most
- Hereditary disorders in Finland and Quebec do not cluster in pathways

Ashkenazi DNA Repair Cluster Disorders

BRCA1	breast cancer risk in heterozygotes, lethal in homozygotes	5.8 x 10-3	185delAG(66%), 5382insC(33%)
BRCA2	breast cancer risk in heterozygotes, lethal in homozygotes	5.55 x 10-3	6174delT(100%)
Fanconi anemia	average homozygote fitness of ~0.0	5.6 x 10-3	IVS4+4A (100%)
Bloom's syndrome	average homozygote fitness of ~0.0	4.7 x 10-3	2281 delta 6ins7 (100%)

Ashkenazi Sphingolipid Storage Disorders

Gaucher disease	Homozygote fitness of about 0.8?	2.8 x 10	84GG homozygotes are lethal, N370S is a milder mutation, with residual enzymatic activity: N370S (74%), 84GG (12%), L444P (3.9%), IVS2 (2.6%), V394L (2.6%)
Tay-Sachs	lethal	2.0 x 10	1278insTATC (85%), IVS12+1 (10%), G269S (4%)
Niemann-Pick	Lethal	6.25 x 10	Type A: R496L (43%), L302P (29%), fsP330 (25%) TypeB: R608P (?)
Mucolipidosis IV	Lethal	4.45x10	VS3-2A G (72%), 511del6434 (23%)

No Bottleneck in Ashkenazi History:
Relative Genetic Diversity

Mixed Europeans	Ashkenazi Jews	Yemeni Jews	Druze	Samaritans	Finns	Russians
1	0.96	0.95	0.99	0.83	0.92	0.96

IQ Test Scores

- Ashkenazi mean 112—115
- This is 0.75 to 1.00 SD's above European mean
- High verbal and math scores
- Visuospatial scores relatively low
- 3% of US population, 27% of US Nobel prizes, 25% of Turing awards
- Sephardic and Oriental Jews show no IQ elevation
- No one in classical world said that Jews were "smart"

Selection in Ashkenazi History

- Farmers in classical times
- European Jews entered a new niche as cities were restored after fall of western Roman Empire
- Money lenders first, later managers, tax farmers
- Were welcomed into Poland in thirteenth and fourteenth centuries
- Very successful ethnic group, population grew

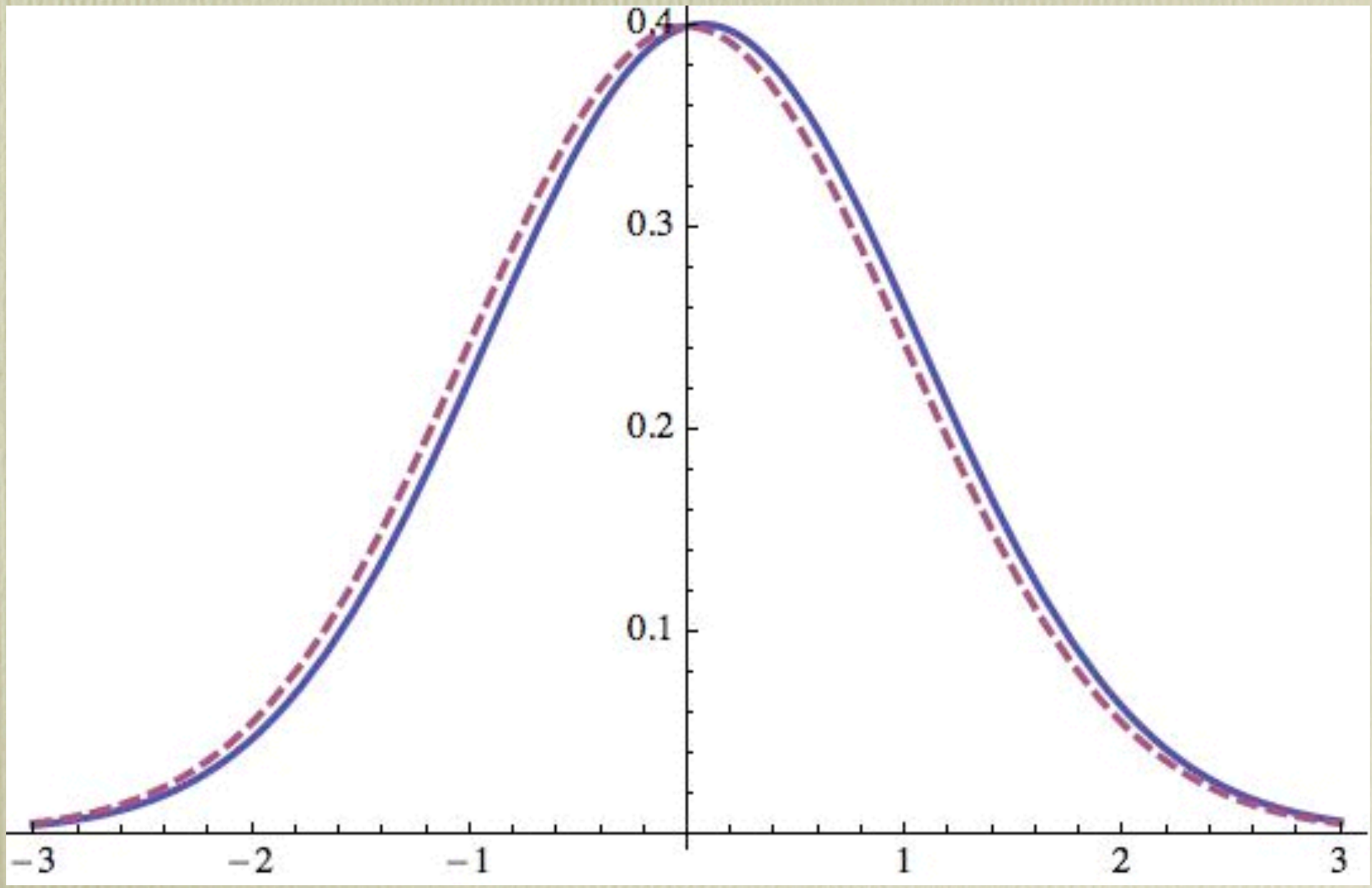

Main waves of migration
Cities with large Jewish communities
0
250 km
North Sea
Baltic Sea
Lithuania
Russia
Germany
Austria
Hungary
Mediterranean Sea
Adriatic Sea
Black Sea
Hamburg
Amsterdam
Poznan
Kalisz
Lodz
Radom
Kovno
Vilnius
Grodno
Bialystok
Brest-Litovsk
Pinsk
Lublin
Lutsk
Lemberg
Zhitomir
Ternopol
Krakow
Chernigov
Kharkov
Kiev
Kishinev
Crimea
Feodosiya
Rome
Konstantinopol
1096-1192
1012
1248
1159
1494
1348
1421
1495
1445
1350
1016
1016
1349-1360


The Pale
0
500 km
Baltic Sea
Prussia
Austria-Hungary
Romania
Black Sea
Russia
Moscow
Dvinsk
Vitebsk
Smolensk
Kovno
Vilno
Suwalki
Minsk
Mogilev
Grodno
Bobruysk
Gomel
Plock
Lomza
Bialystok
Warsaw
Siedlice
Pinsk
Kalisz
Lodz
Brest-Litovsk
Chernigov
Piotrkow
Radom
Lublin
Kielce
Zhitomir
Kiev
Poltava
Berdichev
Kremenchug
Ekaterinoslav
Kamenets-Podolsky
Elizavetgrad
Kherson
Odessa
Kishinev
Simferopol

Selection on a Quantitative Trait

- Response to selection is h^2s where h^2 is additive heritability and s is selection differential
  - For example is IQ heritability is 0.5 and if the mean IQ of parents is 1 point greater than the population mean, IQ will increase ½ point per generation, or 10 points in 500 years
- Strong selection for a trait that is not fitness itself has fitness costs
  - Five generations of selection for bristle number in Drosophila led to 20% to 35% loss in competitive ability

Selection on IQ (or anything)



Costs of Rapid Selection

Drosophila: five generations of selection for bristle number cut fitness by 30%

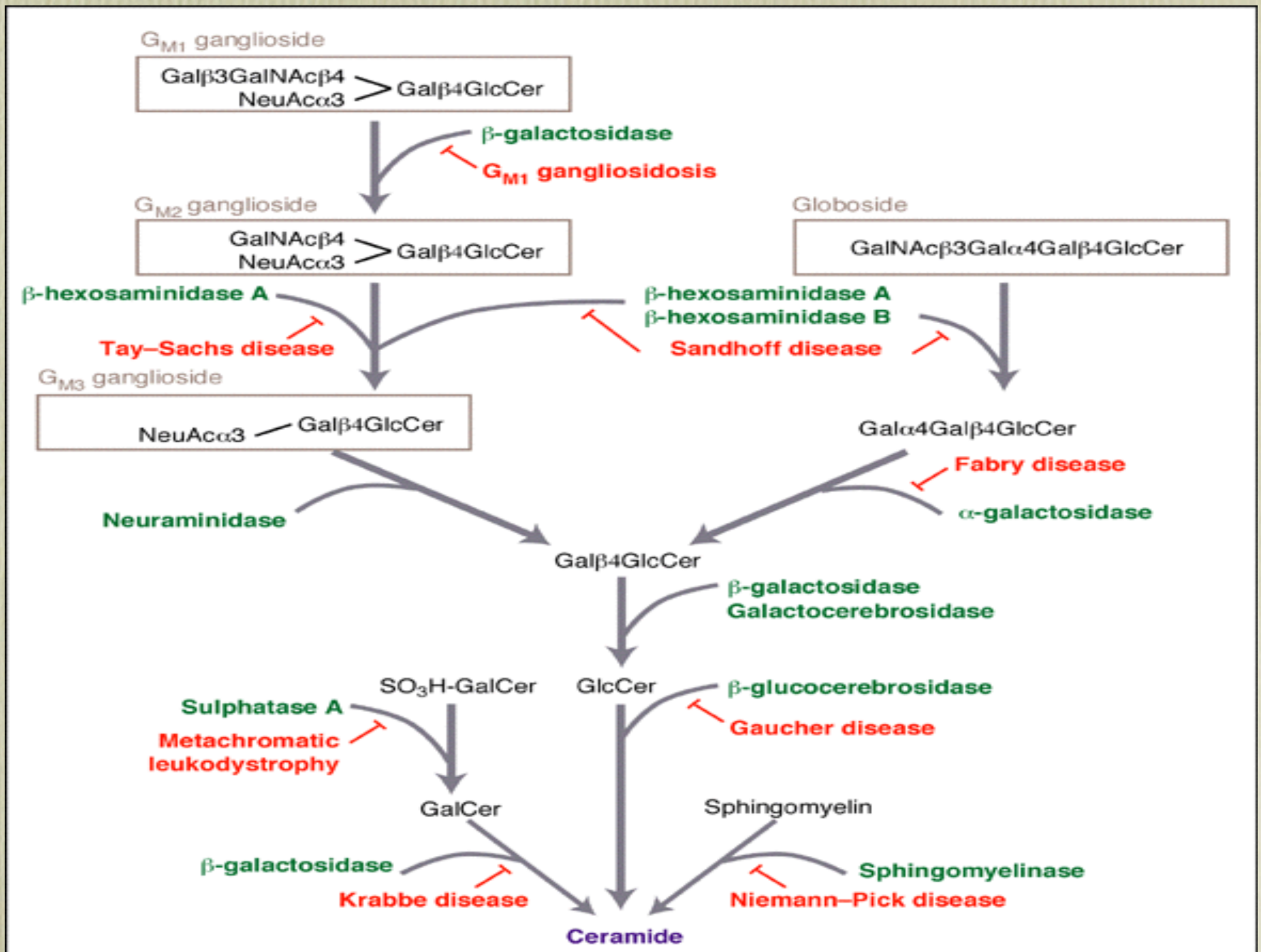
Sickle cell anemia the canonical human example: note hyperendemic P. falciparum only a few thousand years old

BMP15 mutation in Inverdale sheep: heterozygotes twin and triplet, homozygotes sterile

Hanna sheep have different mutation of BMP15 with same effects

Booroola sheep have mutation with similar effects in BMP15 receptor

Myostatin mutation in South Devon and Belgian Blue cattle increases muscle mass but calving difficulty in homozygotes, frequency of gene is 37%

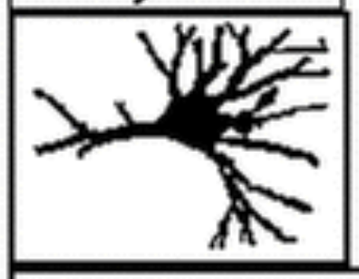


Catabolism of glycosphingolipids in humans: enzymes involved and enzyme-related diseases

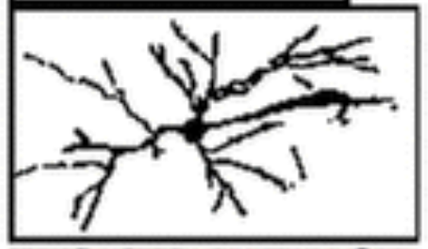
Morphological alterations in neurons in experimental and inherited GSL lysosomal diseases

Meganeurites in GM1 gangliosidosis

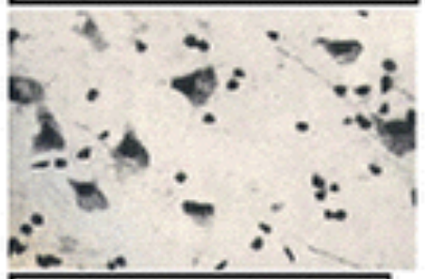
Meganeurites in GM2 gangliosidosis



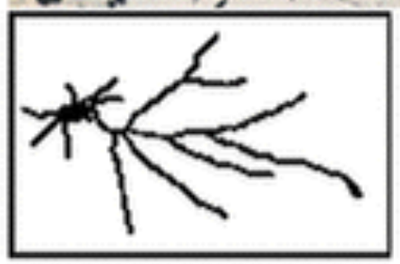
Meganeurites in Tay-Sachs-disease



Neuronal cell death in Gaucher disease

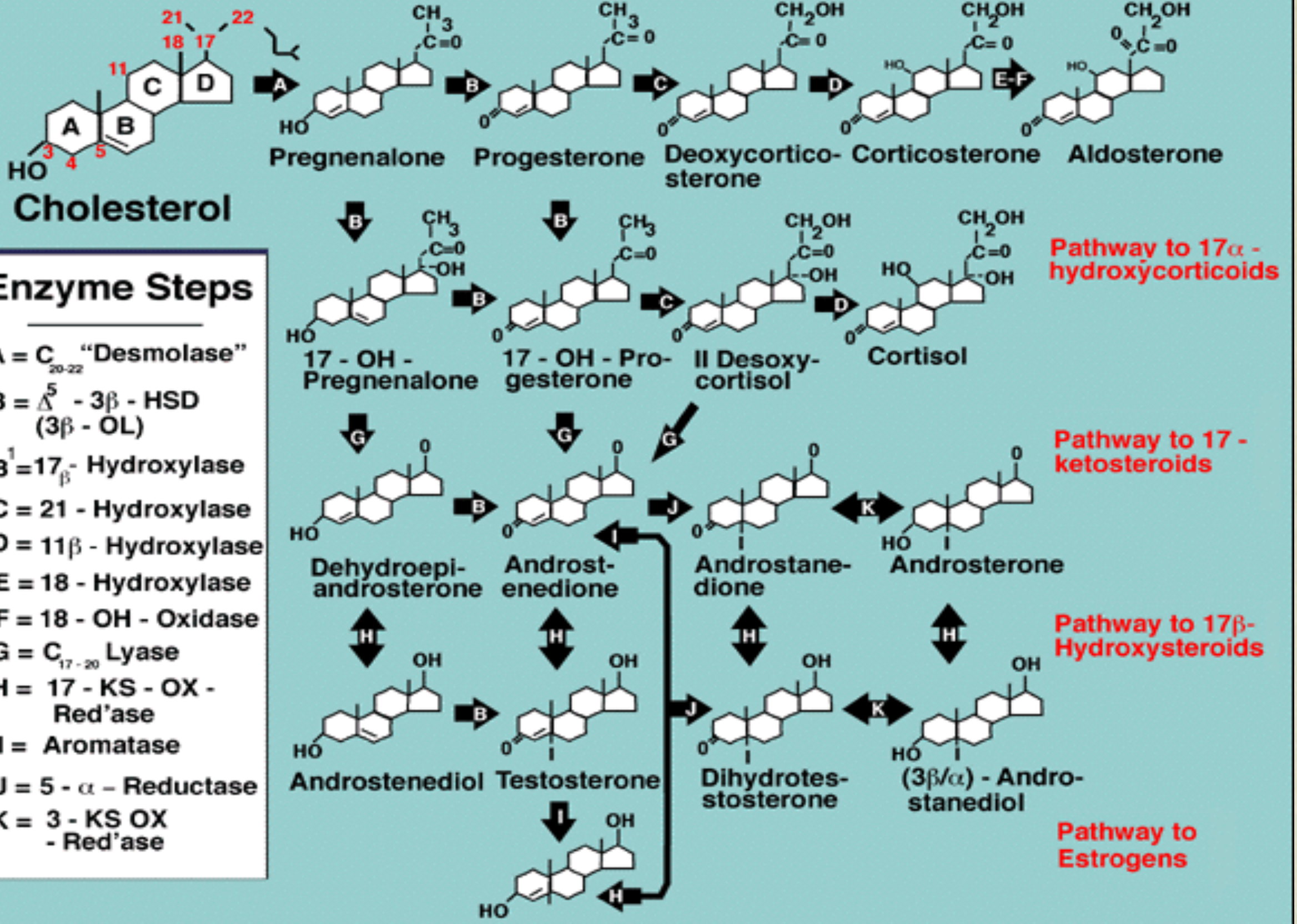


Increased axonal growth in experimental Gaucher disease



Congenital Adrenal Hyperplasia

- nonclassical
- very high gene frequency: almost 20%
- many reports of increased IQ


Cholesterol
Pregnenalone
Progesterone
Deoxycortico-sterone
Corticosterone
Aldosterone
17 - OH - Pregnenalone
17 - OH - Progesterone
II Desoxy-cortisol
Cortisol
Pathway to 17α - hydroxycorticoids
Dehydroepi-androsterone
Androst-enedione
Androstane-dione
Androsterone
Pathway to 17 - ketosteroids
Androstenediol
Testosterone
Dihydrotes-stosterone
(3β/α) - Andro-stanediol
Pathway to 17β- Hydroxysteroids
Pathway to Estrogens
Enzyme Steps
A = C20-22 "Desmolase"
B = Δ5 - 3β - HSD (3β - OL)
B1 = 17β - Hydroxylase
C = 21 - Hydroxylase
D = 11β - Hydroxylase
E = 18 - Hydroxylase
F = 18 - OH - Oxidase
G = C17 - 20 Lyase
H = 17 - KS - OX - Red'ase
I = Aromatase
J = 5 - α – Reductase
K = 3 - KS OX - Red'ase