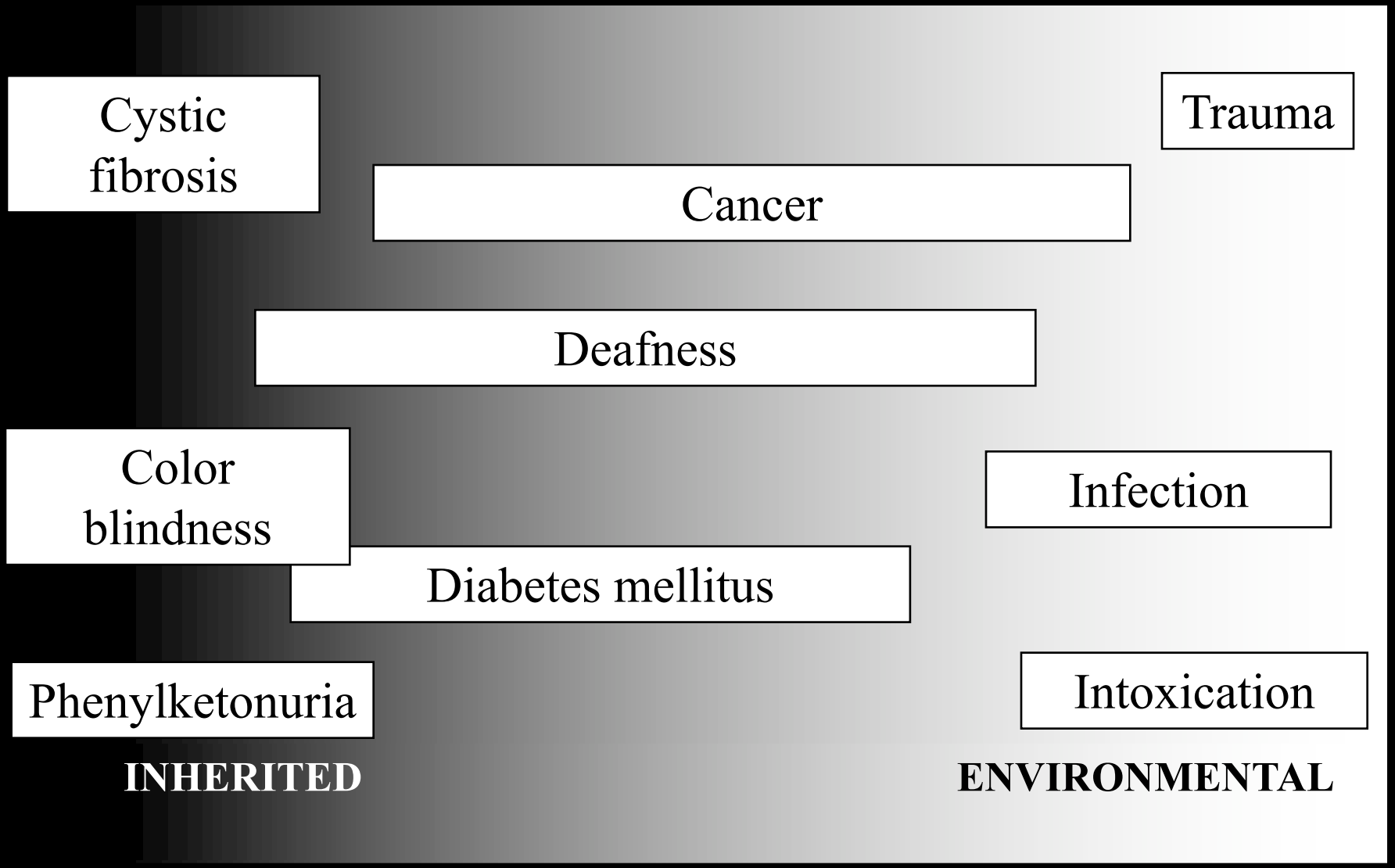
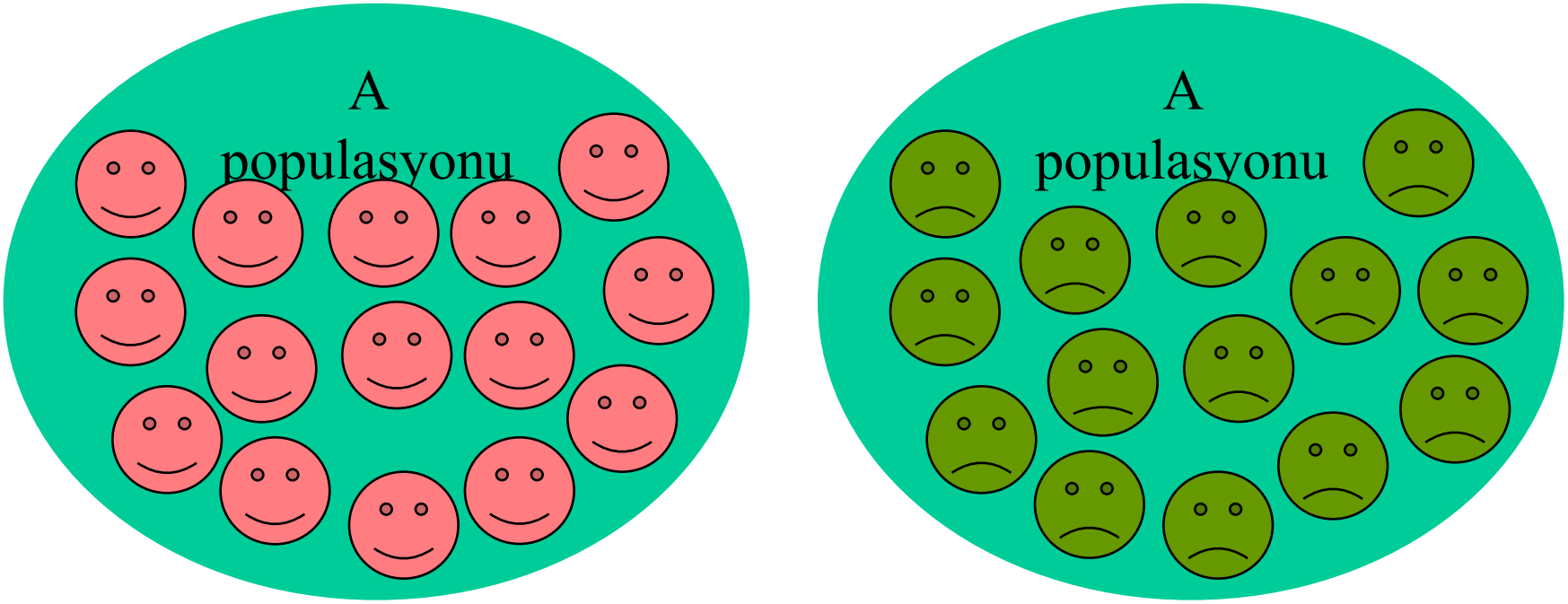
Ecogenetics and the role of genetics in personal response differences to environmental factors

GENES vs ENVIRONMENT

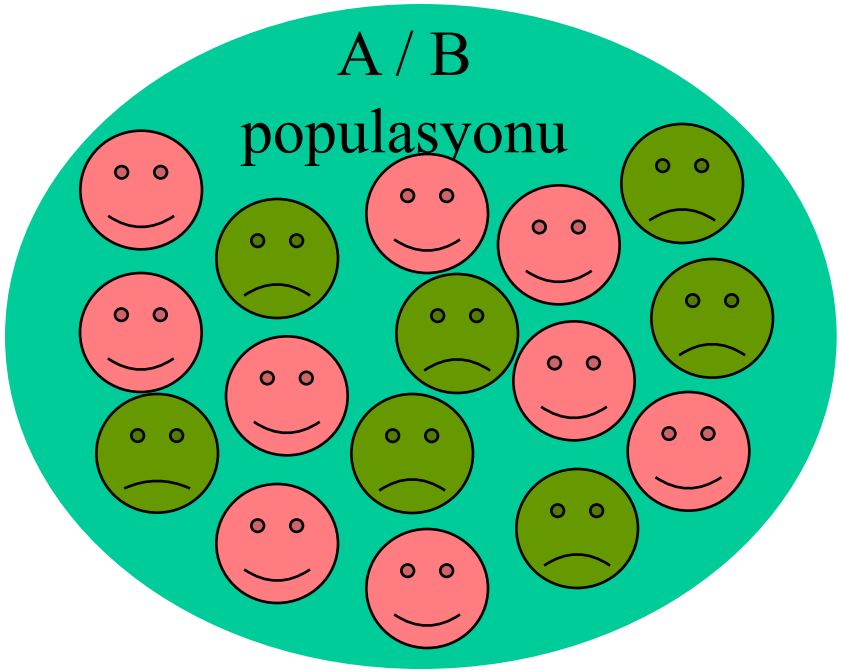


Population vs Environment Differences

- Same genetical background different environments



- Different genetical background same environment



Ecogenetics

It’s a branch of genetics that studies genetic traits related to the response to environmental substances. Or, a contraction of ecological genetics, the study of the relationship between a natural population and its genetic structure.

Examples to important polymorphisms that cause different responses to environmental conditions/affects

1. **Alpha 1-antityripsin (A1AT)** – a protease (peptidase) inhibitor, encoded by *SERPINA1*

   A1AT is produced in the liver,

   Protects the lungs from neutrophil elastase.

   A1AT total deficiency can severely cause inflamation in the respiratory system, pancreas and liver.

   Over 75 mutations are detected. Major alleles are M, S and Z

   PiMM: 100% (normal)

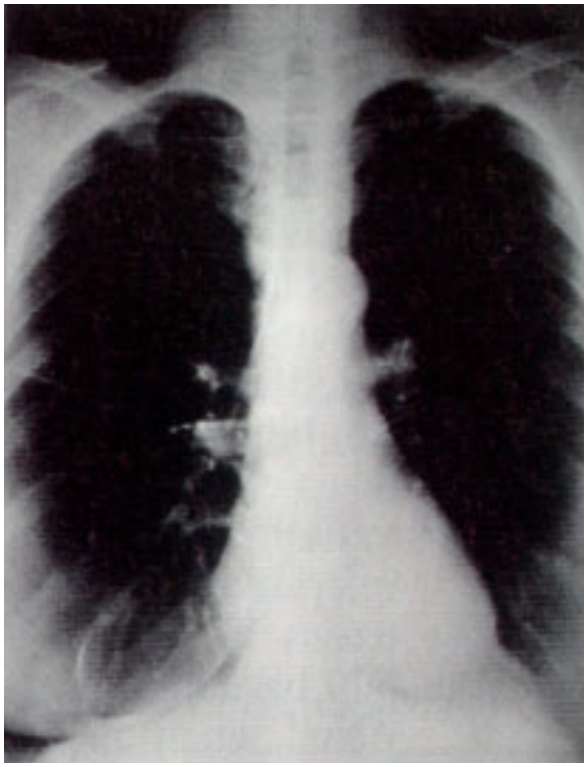
   PiMS: 80% of normal serum level of A1AT

   PiSS: 60% of normal serum level of A1AT

   PiMZ: 60% of normal serum level of A1AT

   PiSZ: 40% of normal serum level of A1AT (otherwise normal people may be effected by being exposed to cigarette smoke or air pollution)

   PiZZ: 10-15% (severe alpha-1 antitrypsin deficiency - disorder)



Emphysema due to alpha-1 antitrypsin deficiency.

Examples to important polymorphisms that cause different responses to environmental conditions/affects

2. **Lactase** – an enzyme that digest lactose (diary products – breat milk), encoded by *LCT*
   The primary lactase deficiency is caused by the the absence of lactase persistance allele.
   MCM6 gene helps control whether the *LCT* gene is turned on or off.

   Lactase production usually drops 90% during the first four years of life in humans, though the rate varies widely. This leads to lactose intolerance.

   Certain human populations have a mutation (on chromosome 2) which results in persistence of lactase activity (gain of function).

   Populations that are lactose intolerant lack this mutation.

   Analysis of the DNA of 94 ancient skeletons in Europe and Russia concluded that the mutation for lactose tolerance appeared about 4,300 years ago and spread throughout the European population.

Examples to important polymorphisms that cause different responses to environmental conditions/affects

Primary congenital alactasia, also called congenital lactase deficiency, is an extremely rare, autosomal recessive enzyme defect that prevents lactase expression from birth. People with congenital lactase deficiency cannot digest lactose from birth, so cannot digest breast milk. This genetic defect is characterized by a complete lack of lactase (alactasia).

Persistence of lactase in the intestine permits the "unnatural" continuation of milk ingestion throughout life, enhancing growth and development. One benefit is higher calcium intake, especially in northern climates where sun is insufficient to activate vitamin D.

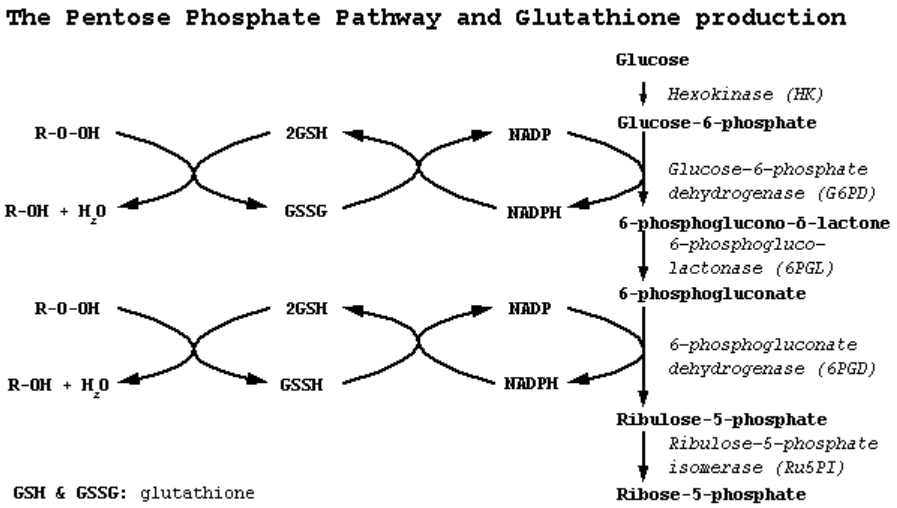
People without this mutation shut off lactase production and become "lactose malabsorbers"; they may become "lactose intolerant" with symptoms of excess gas (hydrogen) and diarrhea upon eating lactose-containing dairy products.

Lactose Intolerance in different populations

Human Groups	Percent Intolerant	Allele Frequency
Swedish	2%	0.14
Europeans in Australia	4%	0.20
Swiss	10%	0.32
American Caucasians	12%	0.35
Finns	18%	0.42
African Tutsi	20%	0.45
African Fulani	23%	0.48
American Blacks	75%	0.87
Australian Aborigines	85%	0.92
African Bantu	89%	0.94
Chinese	93%	0.96
Thais	98%	0.99
American Indians	100%	1.00

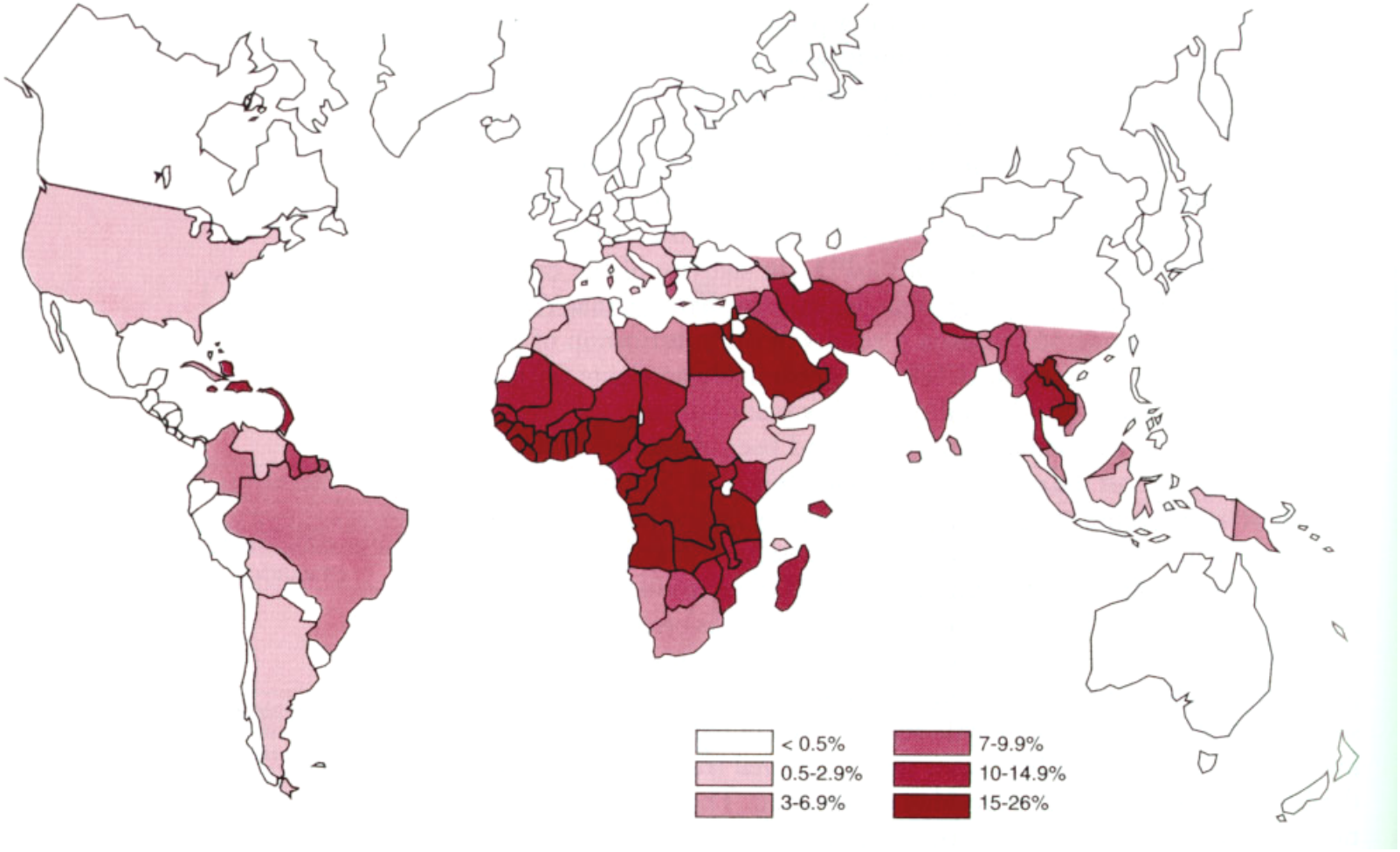
Examples to important polymorphisms that cause different responses to environmental conditions/affects

3. **Glucose-6-phosphate dehydrogenase** – an enzyme of pentose phosphate pathway. Functions to supply reducing energy to cells like erythrocytes which are subject to extensive oxidation by maintaining the level of the co-enzyme nicotinamide adenine dinucleotide phophate. NADPH in return maintains the level of glutathione which protects cells from hemolytic effects of hydrogen peroxide.



G6PD deficiency is very common worldwide, (400 million globally-30,000 deaths annually). It causes acute hemolytic anemia in the presence of simple infections, ingestion of fava beans, reaction with certain medicines, antibiotics, antipyretics and antimaliarals. Avoiding triggers is important.

Carriers of the G6PD deficiency alleles may be partially protected against malaria.



Distribution of G6PD deficiency worldwide

Examples to important polymorphisms that cause different responses to environmental conditions/affects

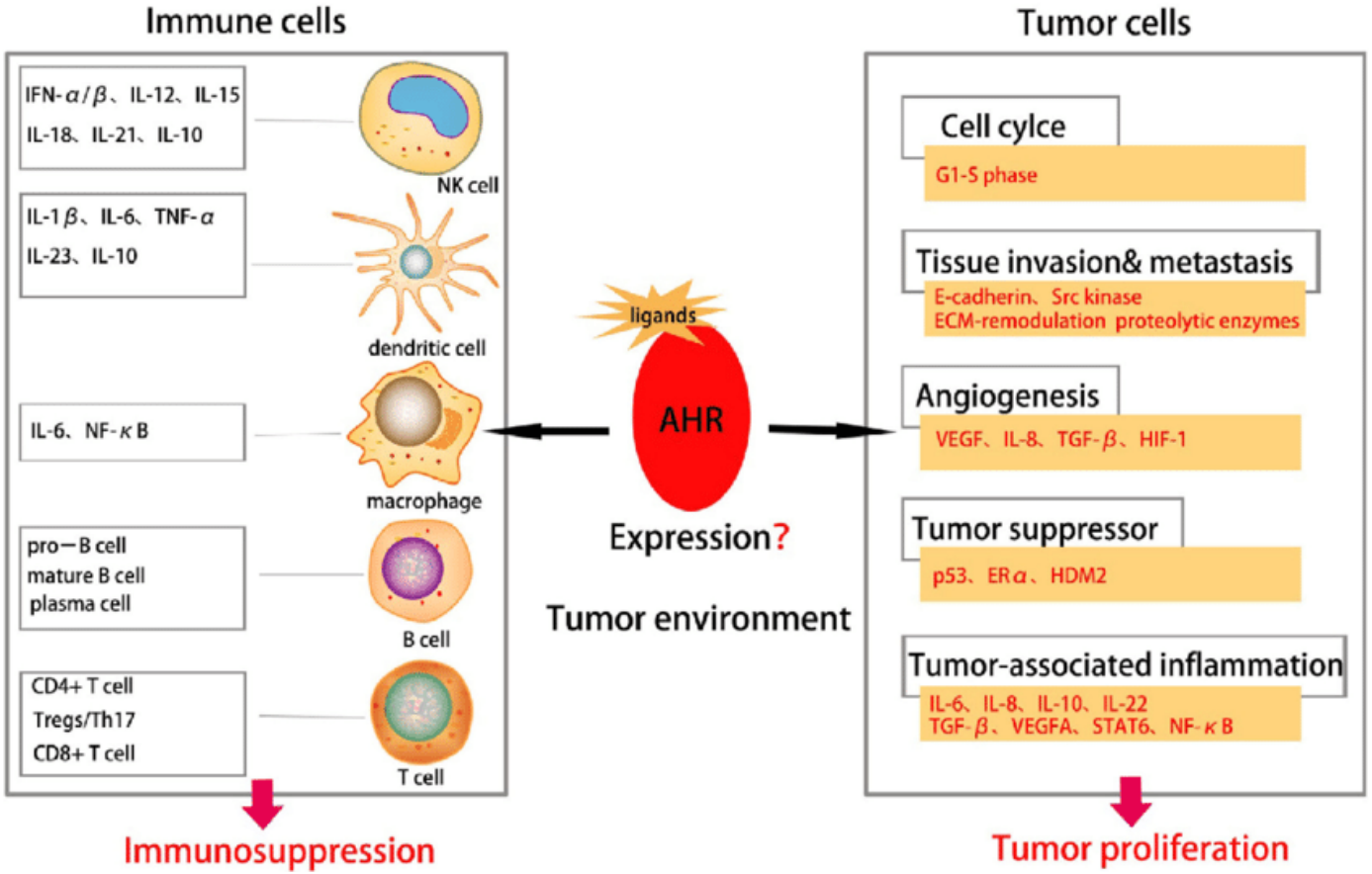
4. **Alcohol dehydrogenases** (**ADH**) - an effective method for eliminating both endogenous and exogenous formaldehyde was evolutionerly important and this capacity has conserved the ancestral ADH-3 through time.

   Alcohol intolerance is due to a genetic polymorphisms various enzymes in the pathway (eg. ALDH) This polymorphism is most often reported in Asian patients.

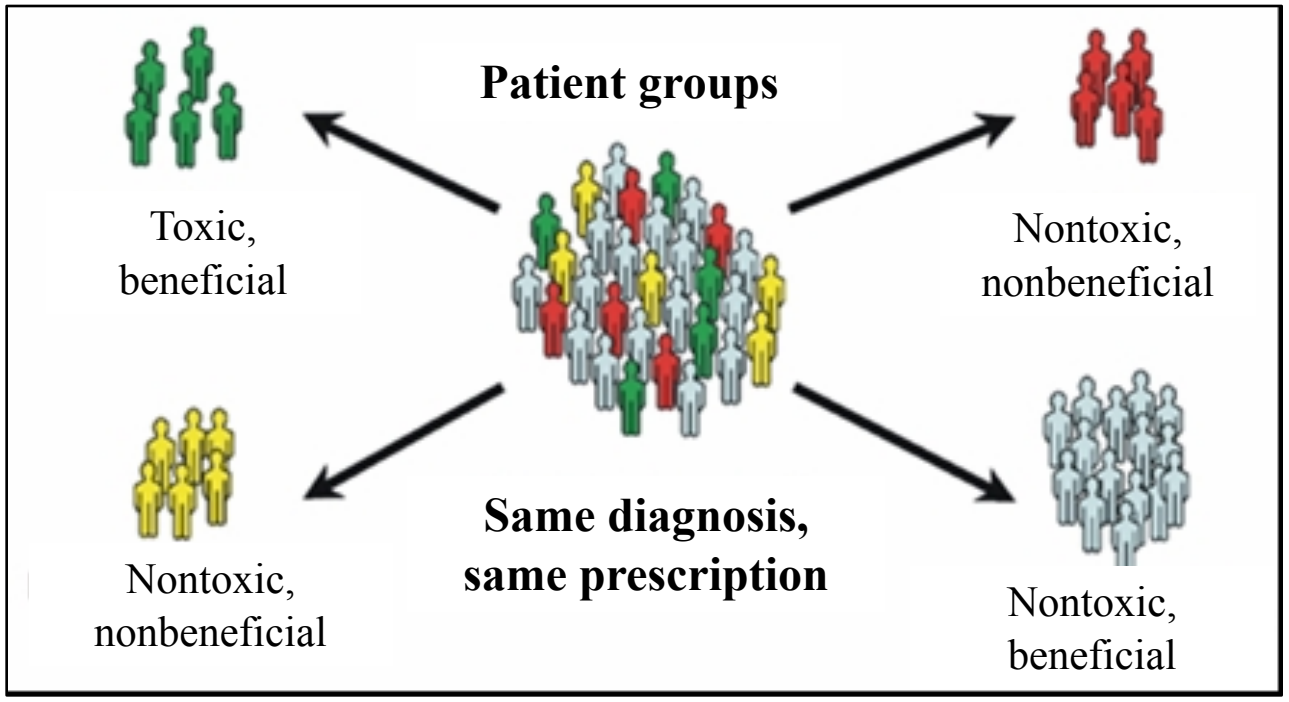
Examples to important polymorphisms that cause different responses to environmental conditions/affects

5. An **aromatic hydrocarbon** or **arene (aryl hyrocarbon)**

Arylhydrocarbon hydroxylase (AHH) – converts aromatic hydrocarbons to epoxides. Epoxy compounds. Most of them have carcinogenic effect.



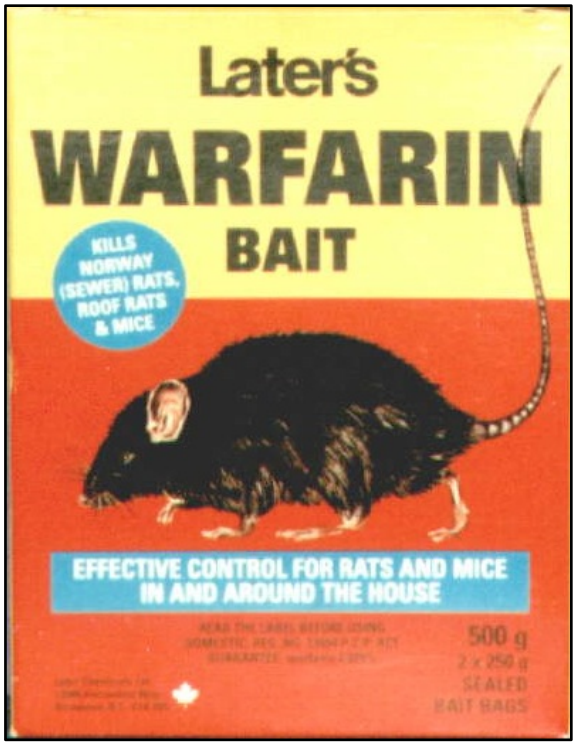
In response to medication



Warfarin

Anticoagulant,
Prevents the thrombosis

Warfarin
sold under the brand name **Coumadin**
among others

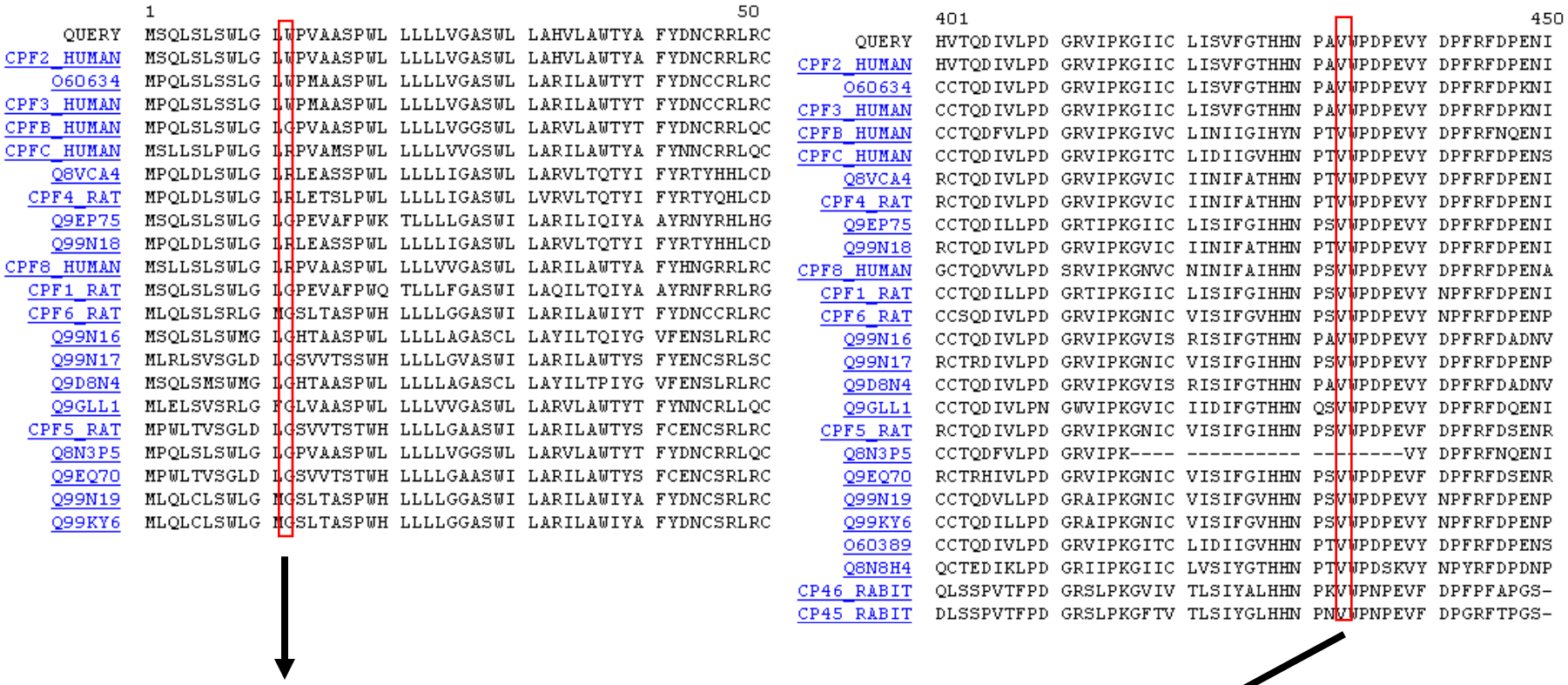


Warfarin mice poison
Inhibits vitamin K
Causes internal bleeding and death.

Optimal Dosing as an antigoagulant varies for people. Due to genetic polymorhism.

Genetic variants (VKORC1, CYP2C9)

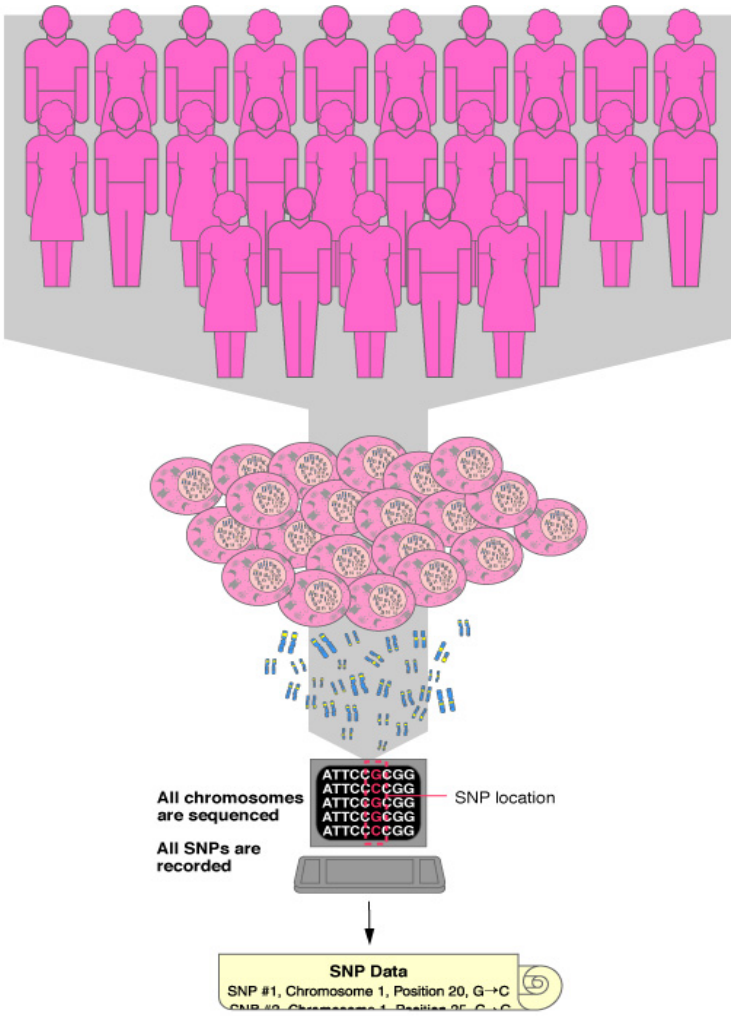
CYP4F2:cytochrome 450, subgroups

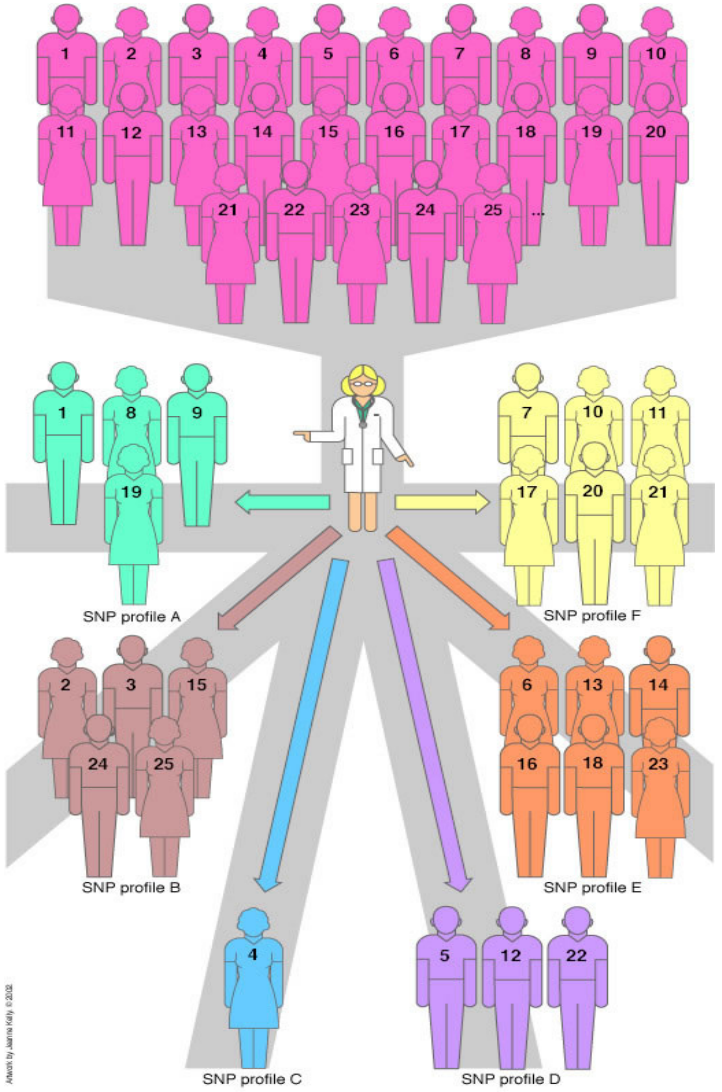


Trp (W) → Gly (G) Val (V) → Gly (G)

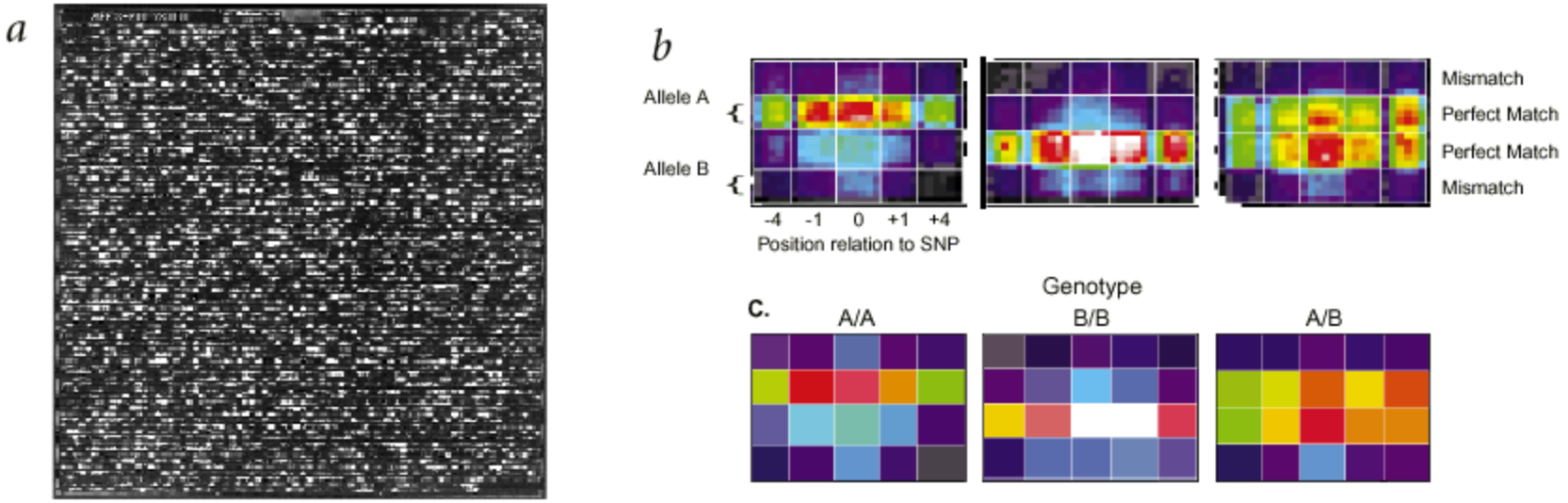
\+ Warfarin toleransı -

Population diffrences due to SNPs





SNP Genotyping



Microarray based high performance SNP studies

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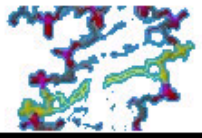
Single Nucleotide Polymorphism



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ANNOUNCEMENT

- NEW! dbSNP genotype data are now available on the web and on our FTP site (more info).
- ALERT! xml brief and submission format reports are dropped from ftp dump starting build 116. Please contact snp-admin with concerns.

Search by IDs

Note: rs# and ss# must be prefixed with "rs" or "ss", respectively (i.e. rs25, ss25)

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