Master in Cellular and Molecular Biology

Medical and Cancer Genetics course

MEDICAL GENETICS

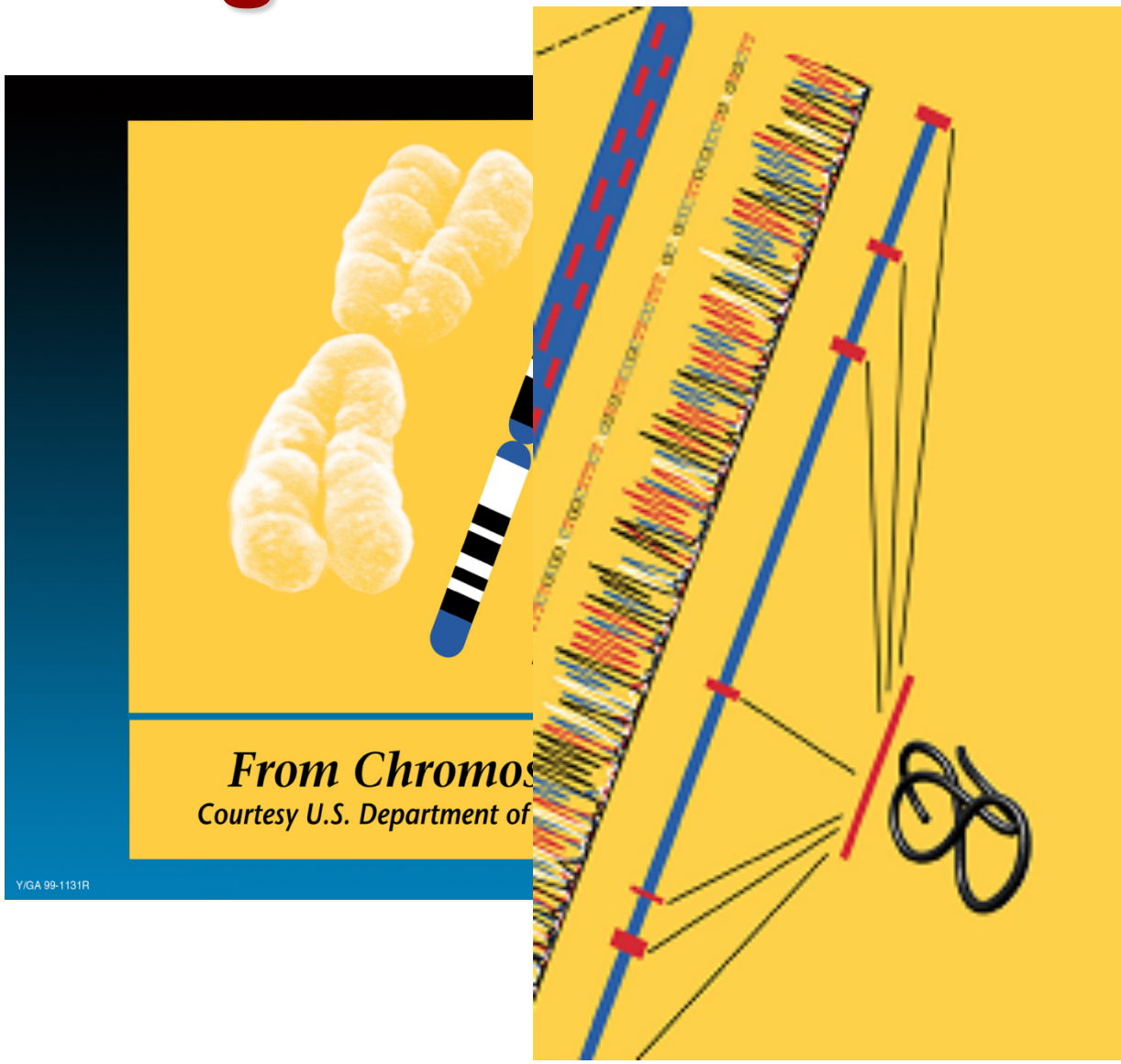
Teacher: Claudia Giachino

Lesson 4

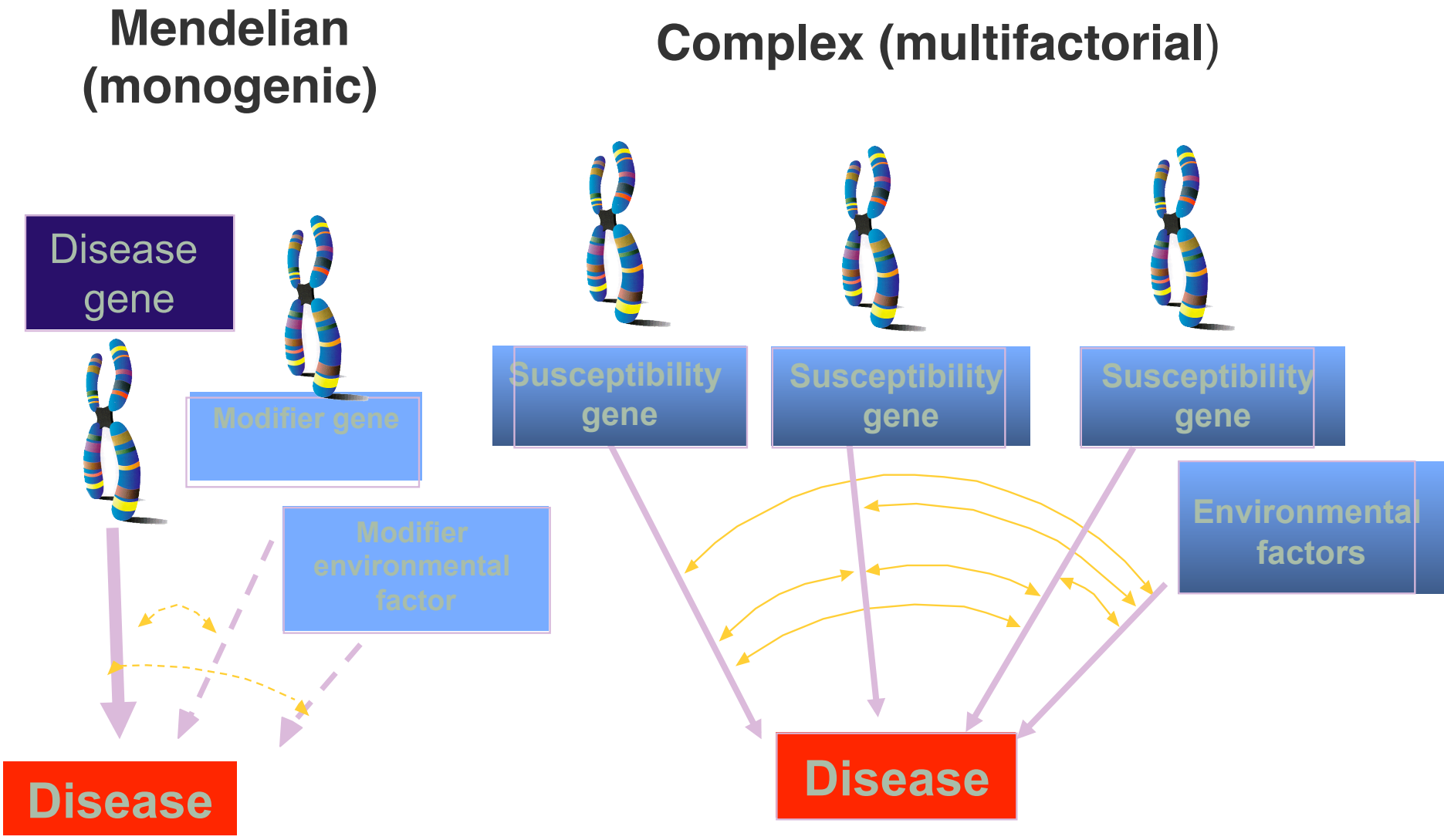
Complex diseases

What diseases are attributable to genetics?

- Monogenic or hereditary diseases
- Chromosomal diseases
- **Multifactorial or complex diseases**

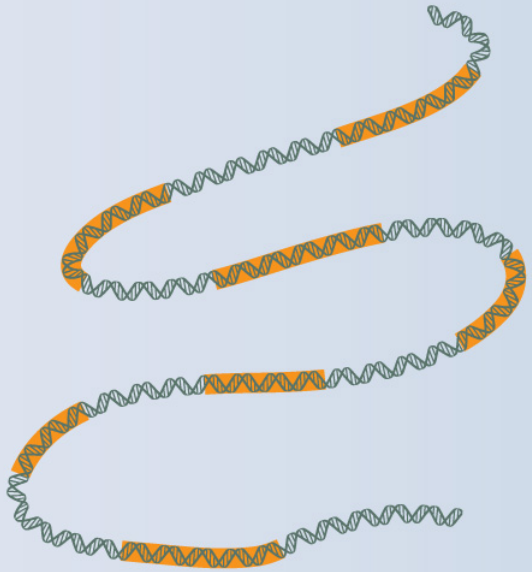


Hereditary diseases



Most traits result from the interaction of many genes and the environment

Multiple genes

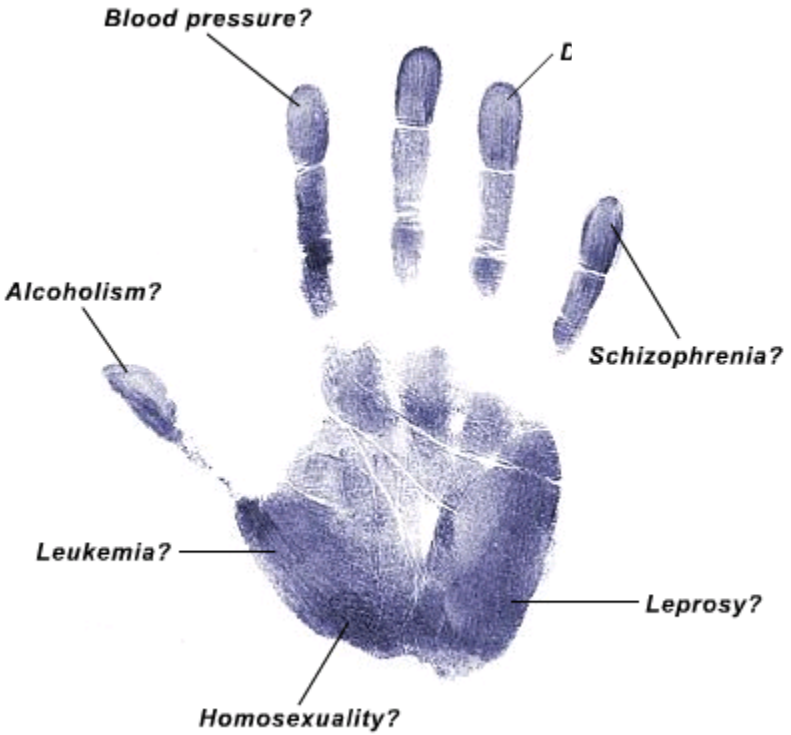


Complex Diseases:

- Cancer
- Asthma
- Diabetes
- Heart Disease

Environment factors

Not only diseases…



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Inheritance of finger pattern types in MZ and DZ twins

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ABSTRACT

Digital patterns of a sample on twins were analyzed to estimate the resemblance between monozygotic (MZ) and dizygotic (DZ) twins and to evaluate the mode of inheritance by the use of maximum likelihood based variance decomposition analysis. MZ twin resemblance of finger pattern types appears to be more pronounced than in DZ twins, which suggests the presence of genetic factors in the forming of fingertip patterns. The most parsimonious model shows twin resemblance in count of all three basic finger patterns on 10 fingers. It has significant dominant genetic variance component across all fingers. In the general model, the dominant genetic variance component proportion is similar for all fingertips (about 60%) and the sibling environmental variance is significantly nonzero, but the proportion between additive and dominant variance components was different. Application of genetic model fitting technique of segregation analyses clearly shows mode of inheritance. A dominant genetic variance component or a specific genetic system modifies the phenotypic expression of the fingertip patterns. The present study provided evidence of strong genetic component in finger pattern types and seems more informative compared to the earlier traditional method of correlation analysis.

Introduction

Studies of dermatoglyphic traits are particularly valuable with respect to developmental stability. The unique quality of these traits is that once formed at the end of the first and beginning of the

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NEWS & VIEW

EVOLUTIONARY BIOLOGY

Geography and skin colour

Jared Diamond

Human skin comes in many different shades. Recent studies of geographical differences in skin colo open up the subject scientifically by offering sophisticated accounts of the basis of this variation.

PERSPECTIVE

nature genetics

Implications of correlations between skin color and genetic ancestry for biomedical research

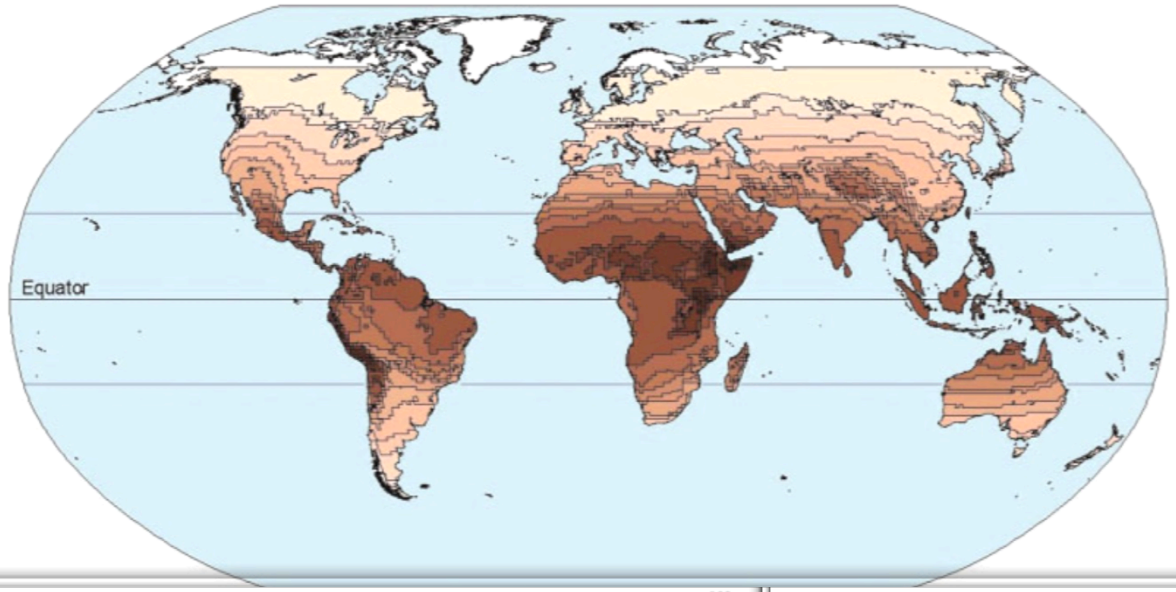
E J Parra[1], R A Kittles[2] & M D Shriver[3]

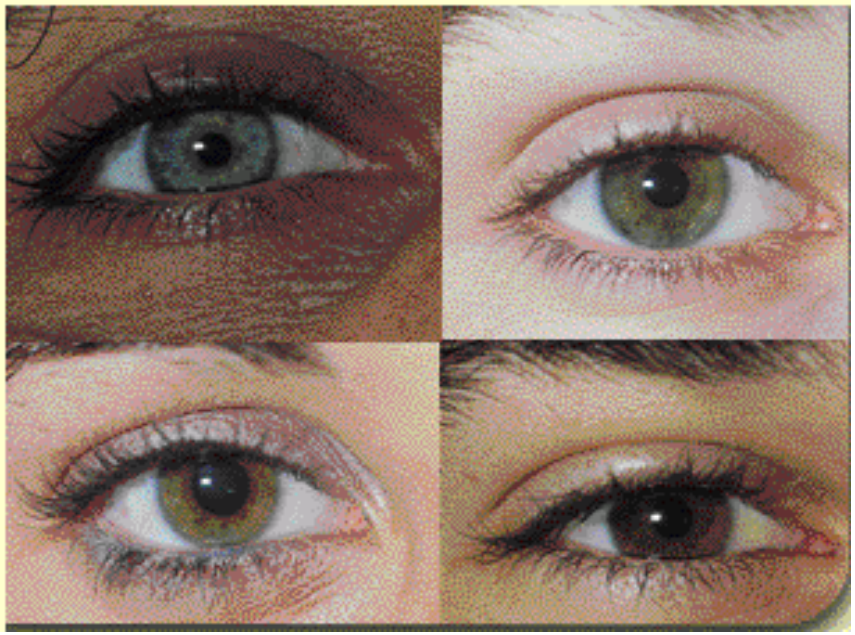
Skin pigmentation is a central element of most discussions on 'race' and genetics. Research on the genetic basis of population variation in this phenotype, which is important in mediating both social experiences and environmental exposures, is sparse. We studied the relationship between pigmentation and ancestry in five populations of mixed ancestry with a wide range of pigmentation and ancestral proportions (African Americans from Washington, DC; African Caribbeans living in England; Puerto Ricans from New York; Mexicans from Guerrero; and Hispanics from San Luis Valley). The strength of the relationship between skin color and ancestry was quite variable, with the correlations

among populations is important. To a large extent in the US, skin pigmentation is a proxy for 'race', on the basis of which racism has been manifested. Skin color can affect the level of discrimination a person experiences or the quality of medical care he or she receives. Differences in skin color among populations are commonly (and incorrectly) understood as an indication of deeper biological differences among populations. Pigmentation genes are unlike the bulk of the genetic variation among populations and can, and should, be used to help educate the general public about the distribution of genetic variation across the populations of the world and the lack of meaning of 'race' as a system of biological classification. Skin pigmentation is also of interest from the

of view. Melanin has a key physiological role, mediat-
f ultraviolet (UV) radiation reaching the dermal capil-
ore influencing the rate of UV-induced photolysis and
of compounds that function in many physiological
; skin pigmentation is useful as a model phenotype for
ixture mapping studies and can and should be used to
ethods for assessing the biology and sociology of
.

igmentation, the melanin content of unexposed areas
olygenic trait that is relatively unaffected by environ-
igmentation varies markedly both within and between
ns (Fig. 1). Both dark- and light-skinned populations
st continents, and a strong correlation between latitude
is evident[2,3]. The differences in pigmentation observed
opulations are probably due to the action of natural
ift and sexual selection may have been important as
n levels, and their effects on vitamin D synthesis, pho-
unburn and skin cancer, are believed to be important
the evolution of skin pigmentation genes[3,4]. Despite
knowledge of the genes involved in the pigmentation
is known about the genetic basis of normal variation in
thin and among human populations. Because of the
ction (natural and sexual) has had in the evolution of
entation and other superficial traits, the variation of
among human populations is typically higher than the
across the genome. In humans, most genetic markers
relatively small differences between populations. The
genetic variance explained by differences between con-
r an 'average' marker, measured as F_{ST}, is typically only
l variance. In contrast, Relethford[5] estimated that 88%
nce in skin pigmentation is explained by differences
hic groups.





A Three–Single-Nucleotide Polymorphism Haplotype in Intron 1 of *OCA2* Explains Most Human Eye-Color Variation

David L. Duffy,* Grant W. Montgomery,* Wei Chen, Zhen Zhen Zhao, Lien Le, Michael R. James, Nicholas K. Hayward, Nicholas G. Martin, and Richard A. Sturm

We have previously shown that a quantitative-trait locus linked to the *OCA2* region of 15q accounts for 74% of variation in human eye color. We conducted additional genotyping to clarify the role of the *OCA2* locus in the inheritance of eye color and other pigmentary traits associated with skin-cancer risk in white populations. Fifty-eight synonymous and nonsynonymous exonic single-nucleotide polymorphisms (SNPs) and tagging SNPs were typed in a collection of 3,839 adolescent twins, their siblings, and their parents. The highest association for blue/nonblue eye color was found with three *OCA2* SNPs: *rs7495174* T/C, *rs6497268* G/T, and *rs11855019* T/C (P values of 1.02×10^{-63}, 1.57×10^{-56}, and 4.45×10^{-54}, respectively) in intron 1. These three SNPs are in one major haplotype block, with TGT representing 78.4% of alleles. The TGT/TGT diplotype found in 62.2% of samples was the major genotype seen to modify eye color, with a frequency of 0.905 in blue or green compared with only 0.095 in brown eye color. This genotype was also at highest frequency in subjects with light brown hair and was more frequent in fair and medium skin types, consistent with the TGT haplotype acting as a recessive modifier of lighter pigmentary phenotypes. Homozygotes for *rs11855019* C/C were predominantly without freckles and had lower mole counts. The minor population impact of the nonsynonymous coding-region polymorphisms Arg305Trp and Arg419Gln associated with nonblue eyes and the tight linkage of the major TGT haplotype within the intron 1 of *OCA2* with blue eye color and lighter hair and skin tones suggest that differences within the 5′ proximal regulatory control region of the *OCA2* gene alter expression or messenger RNA–transcript levels and may be responsible for these associations.

The pigmentary traits of skin, hair, and eye color combined with high levels of environmental UV exposure are potential modulators of individual risk for developing both melanoma and nonmelanoma skin cancer (NMSC).[1] The incidence rate of both NMSC and melanoma is greatest in fair-skinned, sun-sensitive individuals, which indicates the importance of the innate ability to respond to UV light through an increased synthesis of melanin, known as the "tanning response." The quantity and quality of melanin pigmentation is central to the photoprotection of both melanocytes and keratinocytes. The human melanocortin-1 receptor (MC1R [MIM 155555]) protein, expressed on the surface of melanocytes, is a key determinant of photosensitivity,[2,3] with variant alleles of this seven-transmembrane G-protein–coupled receptor, present at high frequency in white populations, linked to the high incidences of NMSC and melanoma.[4]

Other genes involved in melanin biogenesis modify the penetrance of MC1R variant alleles. The gene responsible for oculocutaneous albinism type II (*OCA2*), which encodes the P protein, is an integral melanosomal membrane protein with an 838-aa ORF that contains 12 transmembrane-spanning regions.[5] *OCA2* maps[6] to chromosome 15q11.2-q12 and is the human homologue of the mouse pink-eyed dilution gene (*p*) (Entrez Nucleotide accession number NM_000275).[7,8] Epistatic interactions between MC1R and the *OCA2* gene were first reported to contribute to skin pigmentation phenotypes in a Tibetan population.[9] *OCA2* transcription is induced following UV-B irradiation of skin,[10] and, together with MC1R, plays important roles in control of pigmentation.[11]

Polymorphisms in *OCA2* occur in different populations,[12] and this locus underlies the genetic linkage of blue/brown eye (BEY2/EYCL3 [MIM 227220]) and brown hair (HCL3 [MIM 601800]) to chromosome 15, as reported elsewhere.[13] Two *OCA2* coding-region variant alleles—Arg305Trp and Arg419Gln—were recently shown to be associated with brown and green/hazel eye colors, respectively,[14,15] and blue eye color has also been linked to this locus through use of microsatellite[16,17] and SNP[18] markers. Indeed, our genomewide linkage scan for eye color suggested that 74% of variation in eye color in Europeans could be attributed to a QTL linked to the *OCA2* region of chromosome 15q.[16]

To understand how alleles of the *OCA2* gene influence eye color and pigmentation associated with skin-cancer risk, we sequenced all *OCA2* exons encoding the P protein. To test for statistical association with pigmentary traits, we typed the exonic polymorphisms detected in our preliminary study combined with those reported in the literature and haplotype-tagging SNPs identified from the

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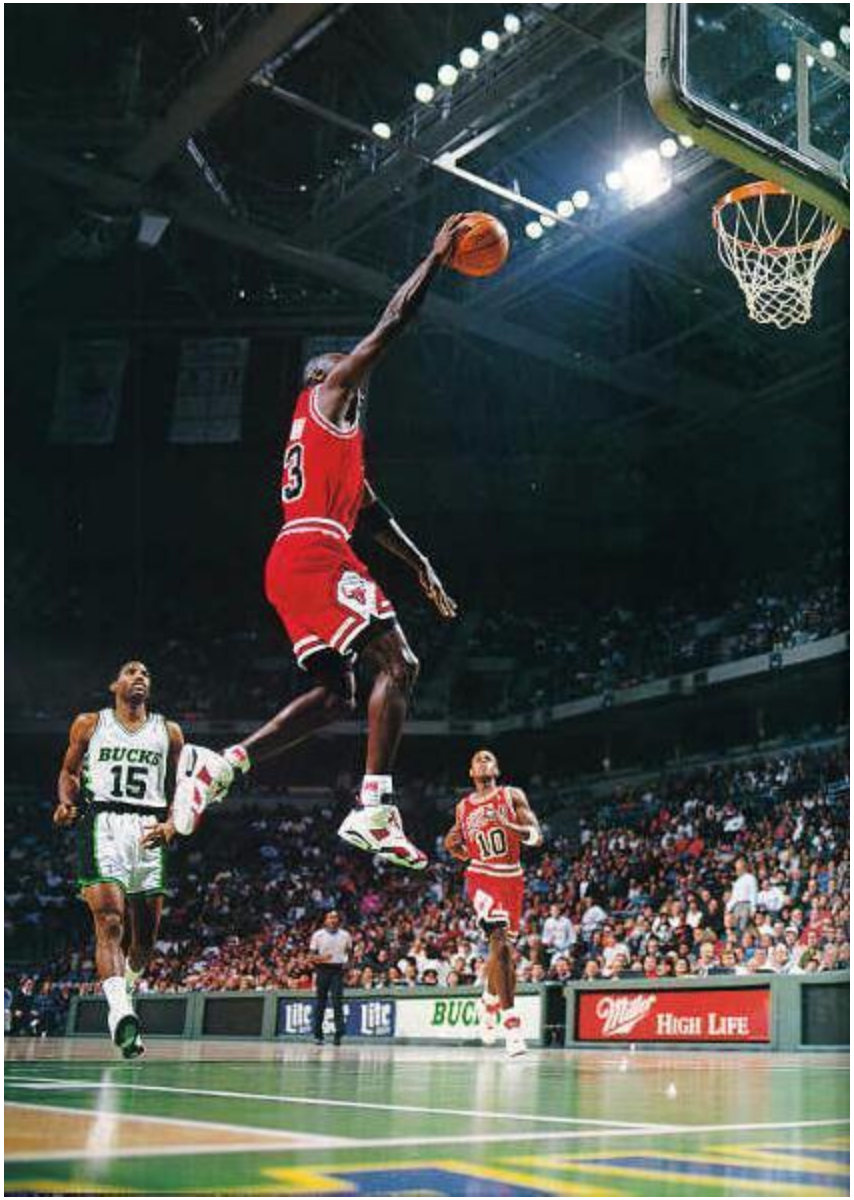

BUCKS
15
3
10
Miller
High Life


PHOTOGRAPHER 2003

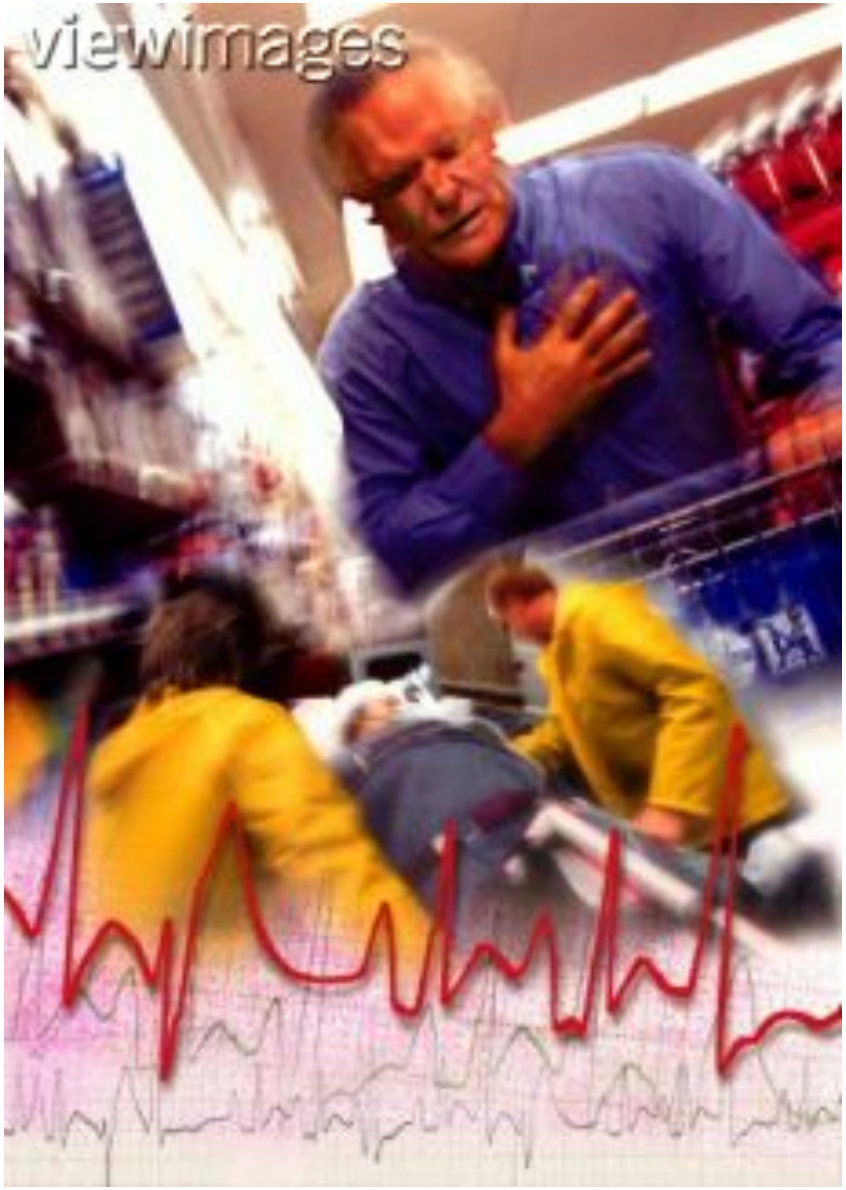
Florence Knapp, who was the world's oldest living person when she died at the age of 114, celebrates her 113th birthday. Genetics probably contributed to her long life; life spans of 90 and 100 are not uncommon in her family.

Complex diseases

- definition
- How you recognize them
- How you measure genetic susceptibility
- Genetic polymorphisms
- How you study them

Complex diseases

- Are common
- Often unknown etiology
- Multifactorial
  - Genetic factors
  - Environmental factors



Definition

Most of the features of an individual, like skin color, height, longevity does not follow the transmission characteristic of Mendelian genes, but is determined by multiple genes, which often interact with the environment.

Multifactorial inheritance diseases is complex and difficult to predict because:

- you do not inherit the disease but the predisposition to illness;
- the disease is determined by a combination of genetic and environmental factors;
- although the predisposition is often necessary, many susceptible persons never get sick.

There are many diseases that are inherited as multifactorial character, including diabetes type 1 (diabetes mellitus or juvenile), celiac disease and systemic lupus erythematosus.

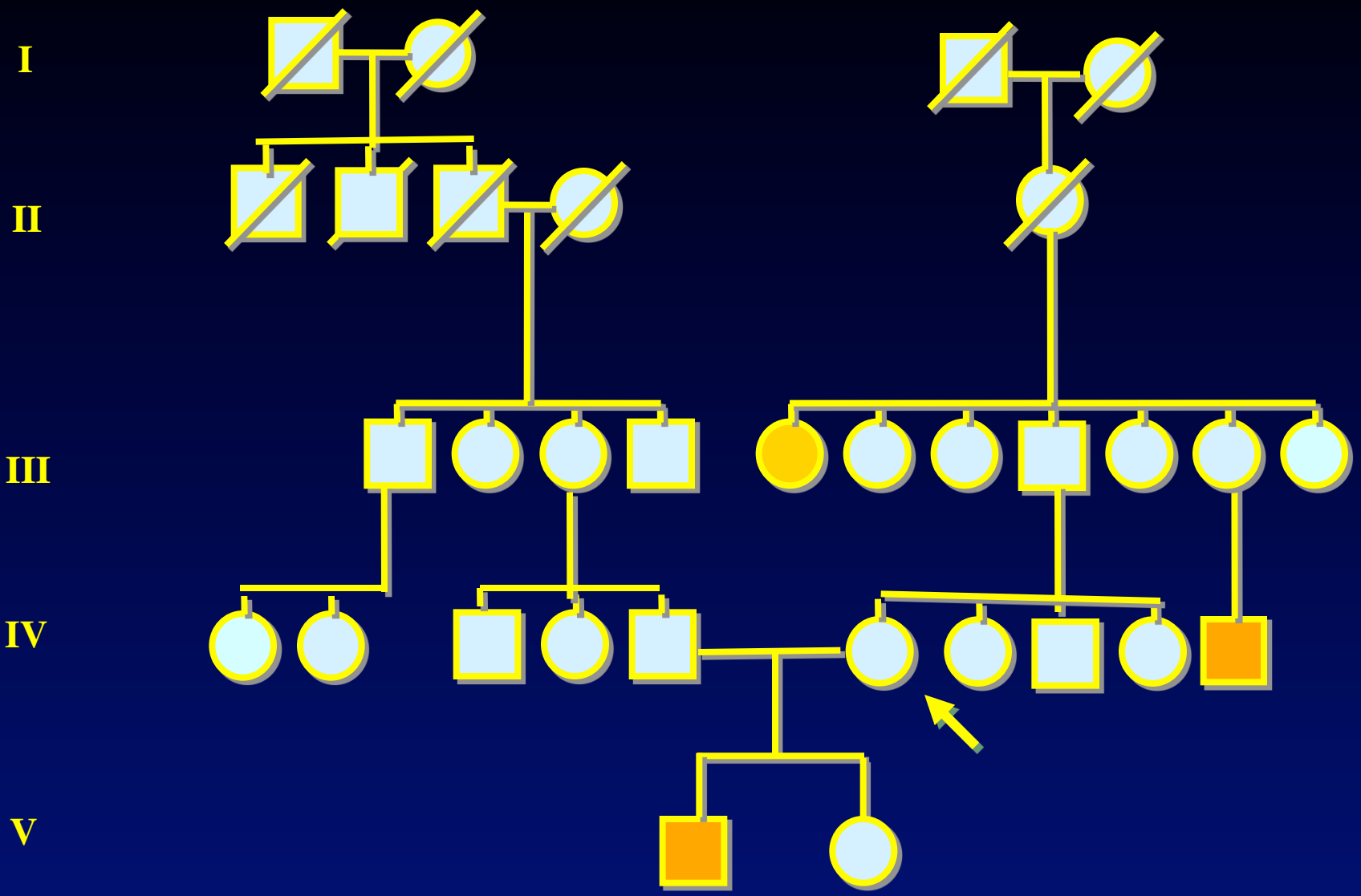
CHARACTERISTICS OF 'COMPLEX' TRAITS

- Highly variable phenotypes
- *Aggregate* but may not *segregate* in families
- Appear to be caused by multiple factors including environments
- Various types:
  - normal traits like weight
  - diseases like heart disease
- Includes many chronic, gradual or late onset diseases

Multifactorial Inheritance

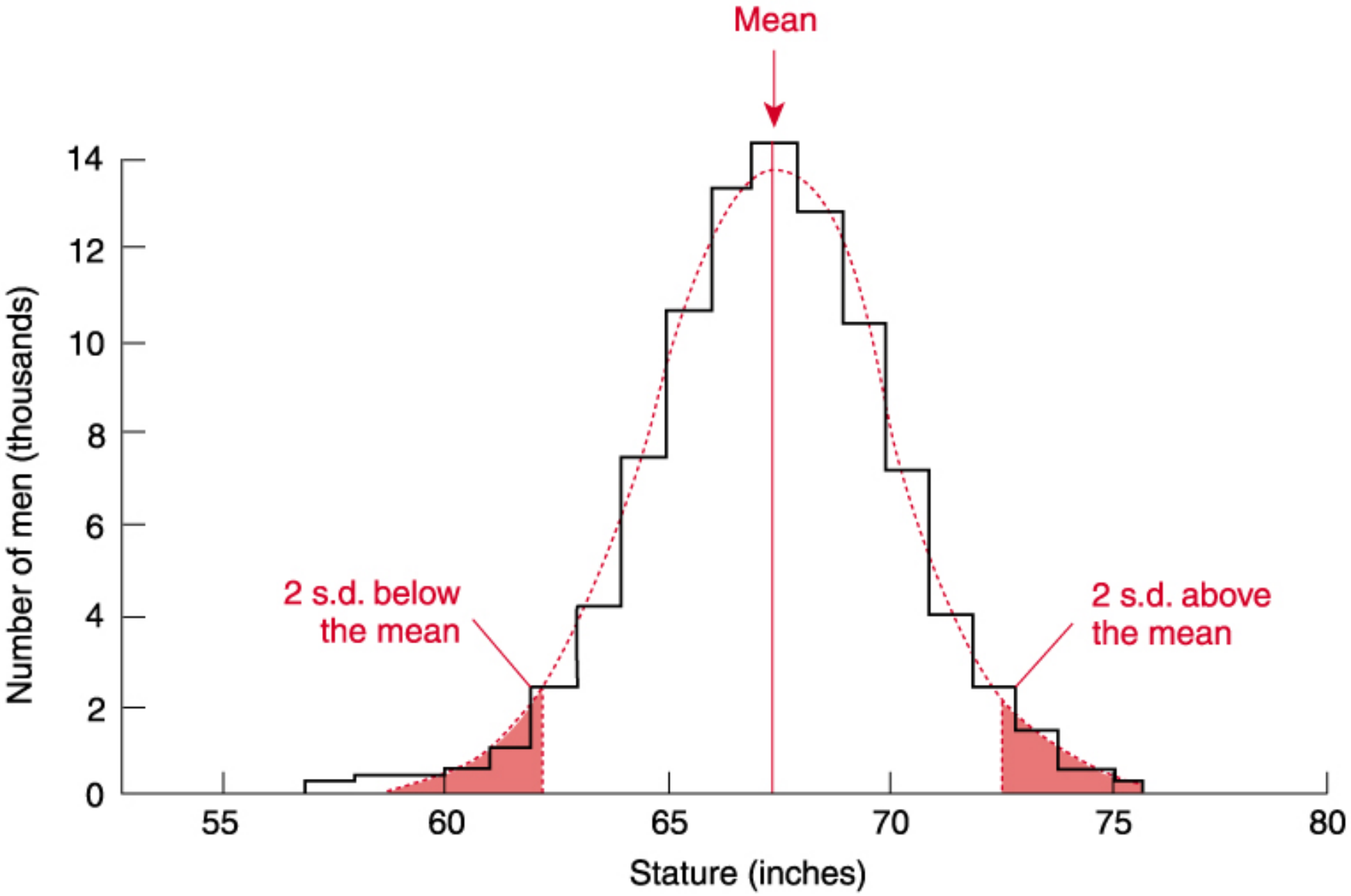
- tendency to recur in families
- does not follow Mendelian genetics
- combination of multiple genes and/or environmental factors

Recurrence of multifactorial diseases



SOME ‘COMPLEX’ TRAITS ARE QUANTITATIVE, LIKE BLOOD PRESSURE

OTHER ‘COMPLEX’ TRAITS ARE QUALITATIVE, SUCH AS HEART DISEASE DIABETES PARKINSON



Complex diseases

- definition
- **How you recognize them**
- How you measure genetic susceptibility
- Genetic polymorphisms
- How you study them

Frequency of Different Types of Genetic Diseases

Type	*Incidence at Birth (per 1,000)*	*Prevalence at Age 25 Years (per 1,000)*	*Population Prevalence (per 1,000)*
Diseases due to genome/ chromosome mutations	6	1.8	3.8
Disease due to single gene mutations	10	3.6	20
Disease with multifactorial inheritance	~50	~50	~600

Frequency of Different Types of Genetic Diseases

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Disease due to single gene mutations	10	3.6	20
Disease with multifactorial inheritance	**~50**	**~50**	**~600**

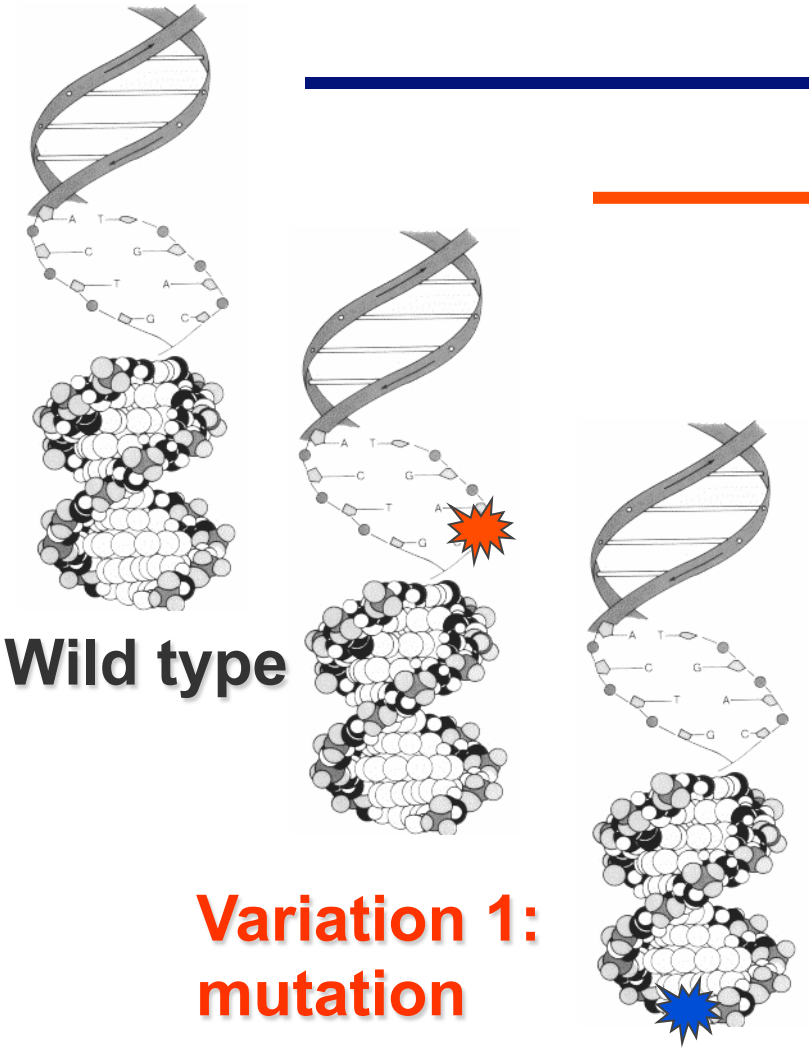
In multifactorial diseases are involved many genes, each with a different weight in determining the disease.

The genes involved in complex diseases are not mutated in the classical sense, but are polymorphic genes, or gene variants, very common in the general population, which may cause only minor quantitative differences (for instance in the synthesis of those proteins), but alone are not able to determine the disease.

Not completely known the reason of the preservation of these variants in the population, probably under certain environmental conditions they confer to holders a survival advantage compared to other individuals.

The combination of predisposing genes confers on individuals carrying only a risk, higher than that of the general population, when environmental conditions are permissive.

Genetics of complex diseases



Wild type

Variation 1: mutation

Variation 2: polymorphism

healthy

Monofactorial disease with some defect

healthy, but the protein could have different functional or biophysical properties: genetic susceptibility

1 individual in about 2000 develops DMT1

What is diabetes?

- Diabetes mellitus (DM) is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both.

- The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

- The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs.

Diabetes

- Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss.

- In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death.

- Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made.

Diabetes Long-term Effects

- The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction.

- People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.

Burden of Diabetes

- The development of diabetes is projected to reach pandemic proportions over the next10-20 years.
- International Diabetes Federation (IDF) data indicate that by the year 2025, the number of people affected will reach 333 million -90% of these people will have Type 2 diabetes.
- In most Western societies, the overall prevalence has reached 4-6%, and is as high as 10-12% among 60-70-year-old people.
- The annual health costs caused by diabetes and its complications account for around 6-12% of all health-care expenditure.

Types of Diabetes

- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
- Gestational Diabetes
- Other types:
  - LADA (
  - MODY (maturity-onset diabetes of youth)
  - Secondary Diabetes Mellitus

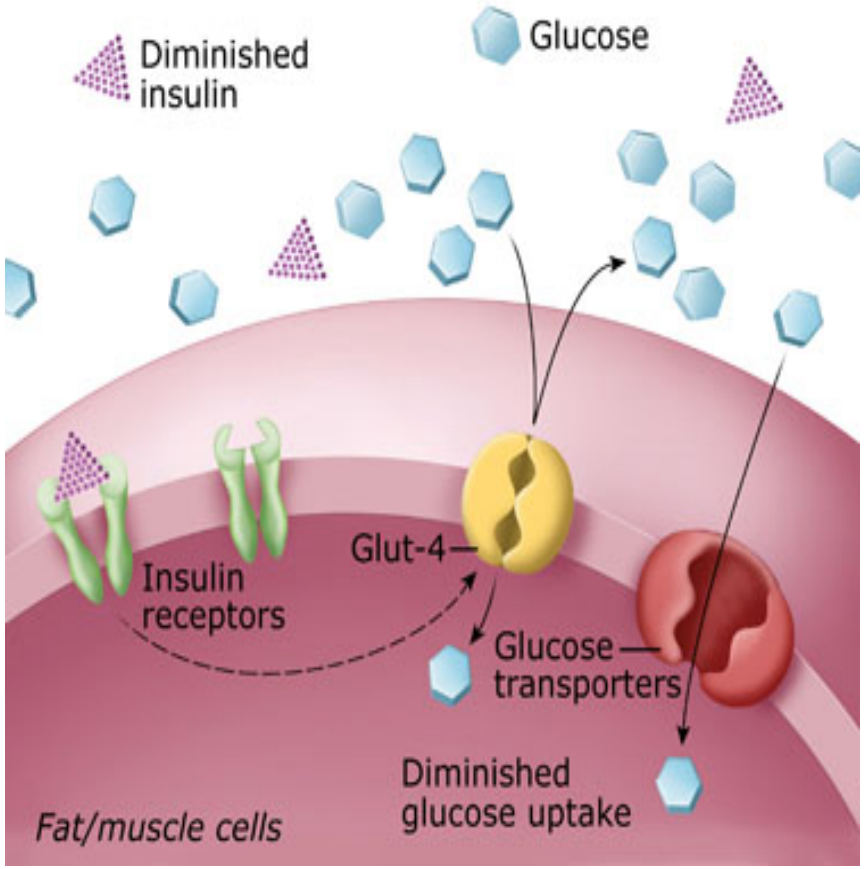
Type 1 diabetes

- Was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.
- Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose.
- This form of diabetes usually strikes children and young adults, although disease onset can occur at any age.
- Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.
- Risk factors for type 1 diabetes may include autoimmune, genetic, and environmental factors.

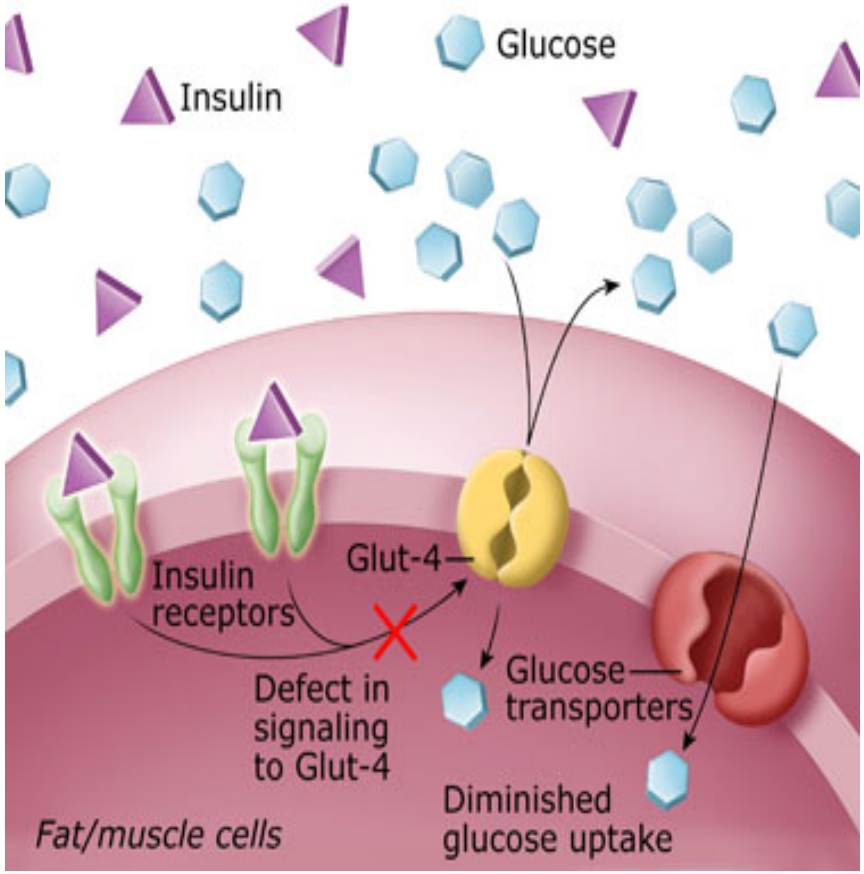
Type 2 diabetes

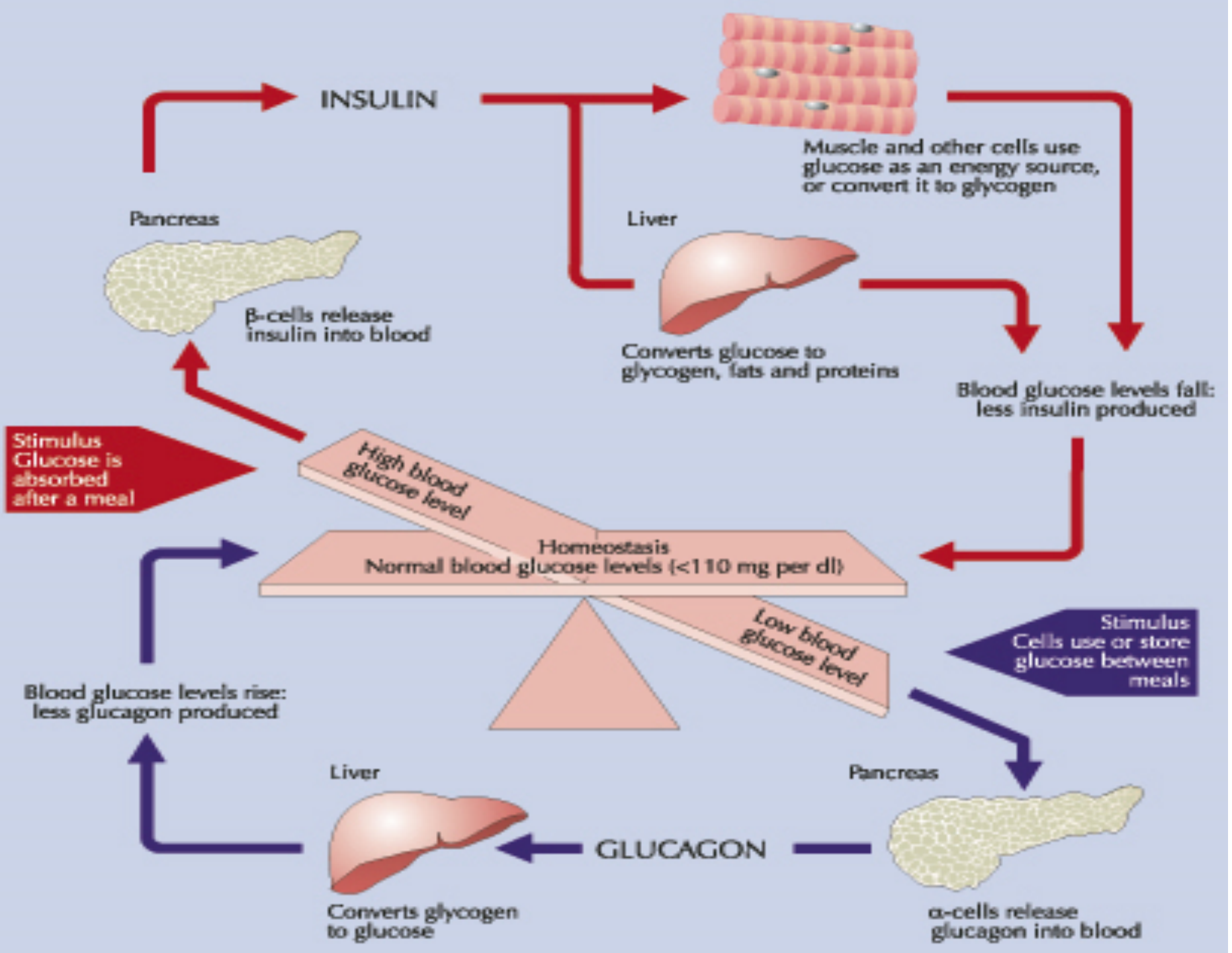
- **Was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes.**
- **Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes.**
- **It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin.**
- **Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.**
- **African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians or Other Pacific Islanders are at particularly high risk for type 2 diabetes.**
- **Type 2 diabetes is increasingly being diagnosed in children and adolescents.**

Type 1 Diabetes: Insufficient Insulin



Type 2 Diabetes: Insulin Resistance




INSULIN
Muscle and other cells use glucose as an energy source, or convert it to glycogen
Pancreas
β-cells release insulin into blood
Liver
Converts glucose to glycogen, fats and proteins
Blood glucose levels fall: less insulin produced
Stimulus Glucose is absorbed after a meal
High blood glucose level
Homeostasis
Normal blood glucose levels (<110 mg per dl)
Low blood glucose level
Stimulus Cells use or store glucose between meals
Blood glucose levels rise: less glucagon produced
Liver
GLUCAGON
Pancreas
Converts glycogen to glucose
α-cells release glucagon into blood

Diabetes mellitus type 1 (DMT1)

Diabetes mellitus type 1 is a form of diabetes that you configure as autoimmune disease characterized by the destruction of pancreatic beta cells (CD4 + and CD8 + T cells and macrophages infiltration in pancreatic islets) that usually leads to the insulin deficiency.

Manifests itself mainly in Scandinavia, in Sardinia and in several northern States of the USA, while in countries such as Japan or South of Europe the incidence is lower.

Regarding age of onset, in about half of cases younger than 20 years (for this in the past it was called "juvenile diabetes") and more frequently during puberty.

A worldwide incidence of 3% was calculated.

Management of DM

- The major components of the treatment of diabetes are:

A	• **Diet and Exercise**
B	• **Oral hypoglycaemic therapy**
C	• **Insulin Therapy**

A. Diet

- Diet is a basic part of management in every case. Treatment cannot be effective unless adequate attention is given to ensuring appropriate nutrition.

- **Dietary treatment should aim at:**
  - ensuring weight control
  - providing nutritional requirements
  - allowing good glycaemic control with blood glucose levels as close to normal as possible
  - correcting any associated blood lipid abnormalities

Exercise

- Physical activity promotes weight reduction and improves insulin sensitivity, thus lowering blood glucose levels.
- Together with dietary treatment, a programme of regular physical activity and exercise should be considered for each person. Such a programme must be tailored to the individual's health status and fitness.
- People should, however, be educated about the potential risk of hypoglycaemia and how to avoid it.

Insulin regimens

- The majority of patients will require more than one daily injection if good glycaemic control is to be achieved. However, a once-daily injection of an intermediate acting preparation may **be effectively used in some patients.**

- Twice-daily mixtures of short- and intermediate-acting insulin is a commonly used regimen.

- **In some cases, a mixture of short- and intermediate-acting insulin may be given in** the morning. Further doses of short-acting insulin are given before lunch and the evening meal and an evening dose of intermediate-acting insulin is given at bedtime.

- Other regimens based on the same principles may be used.

- A regimen of multiple injections of short-acting insulin before the main meals, with an appropriate dose of an intermediate-acting insulin given at bedtime, may be used, particularly when strict glycaemic control is mandatory.

Self-Care

- Patients should be educated to practice self-care. This allows the patient to assume responsibility and control of his / her own diabetes management. Self-care should include:

  - Blood glucose monitoring
  - Body weight monitoring
  - Foot-care
  - Personal hygiene
  - Healthy lifestyle/diet or physical activity
  - Identify targets for control
  - Stopping smoking

Diabetes mellitus type 1 (DMT1) - causes

The causes are a combination of factors concerning genetics, the environment and immunology. A genetic predisposition joins an immunological stimulus that, over time, leads to the destruction of pancreatic beta cells. When the percentage of beta cell loss achieves 80% you develop DMT1.

It is suspected that **environmental factors** initiate this form of disease, though there are no certain proofs. Viruses and nitrosurea compounds are possibly the responsible factors. A recent hypothesis considers molecular mimicry phenomena with antigens of *Mycobacterium avium*.

Chronic subclinical infections of the Mycobacterium, contracted in childhood, would result, in susceptible individuals, to autoimmune-type crossinteractions, as revealed by some recent studies.

Diabetes mellitus type 1 (DMT1) - causes

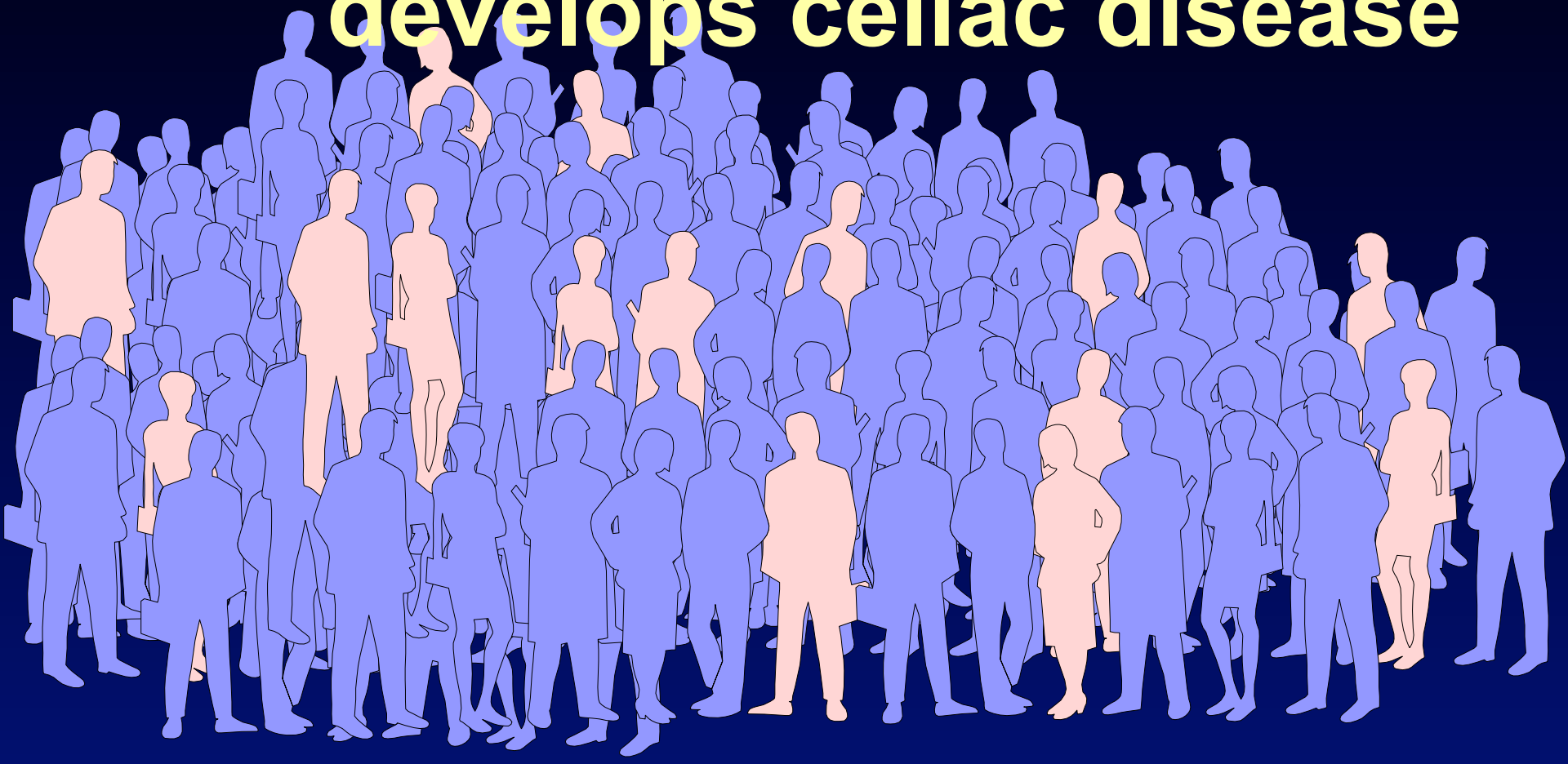
Genetic factors

There seems to be a correlation with particular combinations of HLA alleles.

HLA alleles B8 or B15 increases about three times the risk of developing diabetes and combinations of alleles DR4-DQ8 and DR3-DQ2 occur in 90% of people with diabetes. However, the homozygous state does not further increase the risk.

Genetic etiology is still unclear: the index of concordance for identical twins with less than 40 years is less than 50%. Also there is no prevalence in vertical transmission.

1 individual in about 100 develops celiac disease



1 celiac sibling out of 20 (5%)
develops the same disease

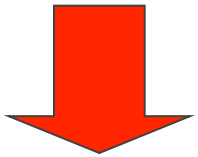
WHAT IS CELIAC DISEASE?

κοιλιακοσ, "those who suffer in the intestine", Celsus I century A.C

Celiac disease is an enteropathy dependent on gluten ingestion


wheat


rye



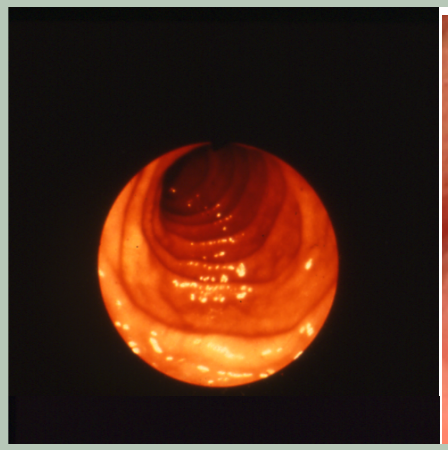
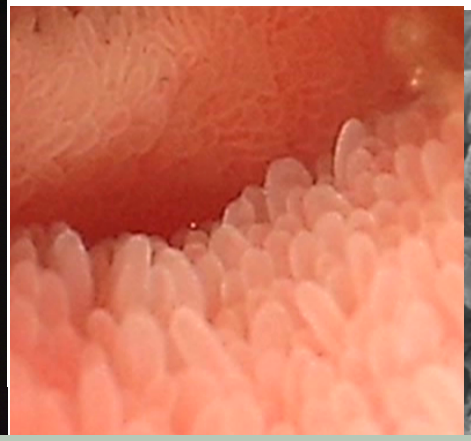

barley

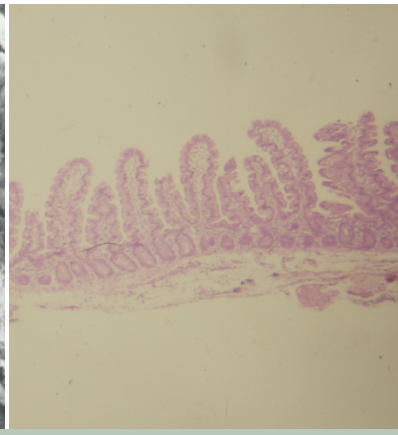

spelt

Intestinal villous atrophy resulting in malabsorption

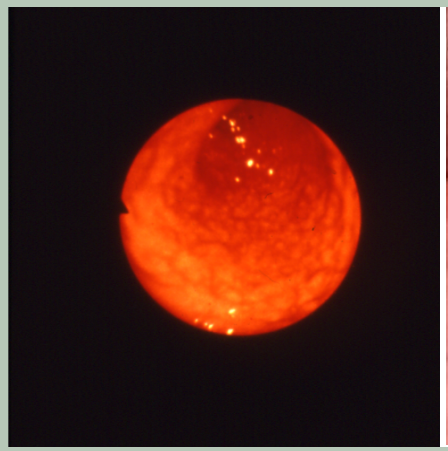
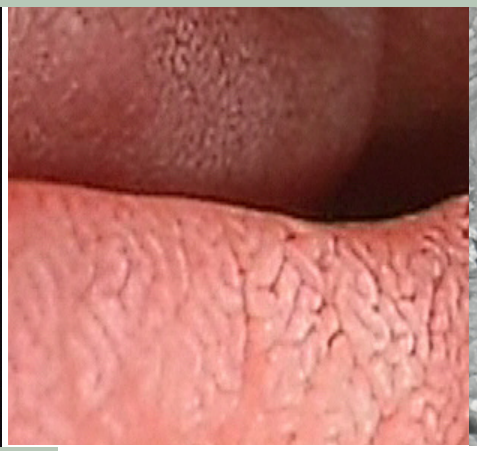
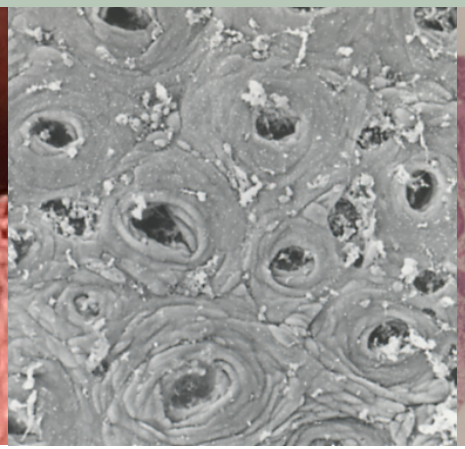
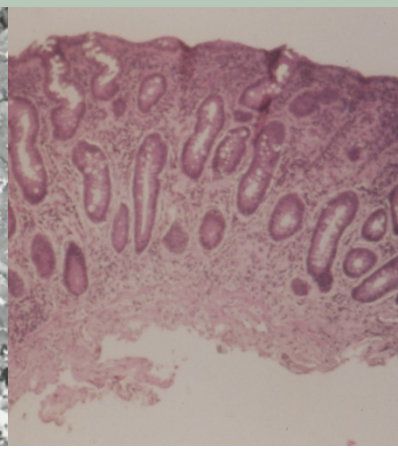
CD is characterised by a flattened mucosa, villous atrophy and crypt hyperplasia of the small intestine. In this slide are shown the endoscopic, electronic microscopy and histologic aspects of intestinal mucosa in a patient affected by coeliac disease and in a normal subject.

Normal



Coeliac

Clinical characteristics

- ***Classical form***

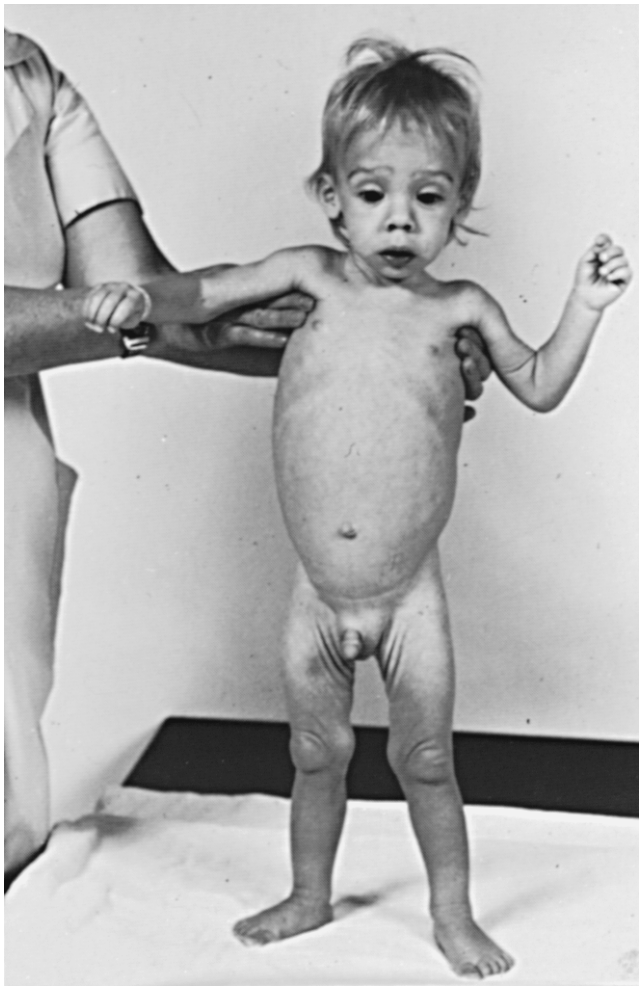
  diagnosed in young children is presented with intestinal symptoms such as chronic diarrhea, vomiting, poor appetite, bloating and steatorrhea. This causes malabsorption with consequent malnutrition, slowing growth and presence of anemia.

- ***atypical form***

  extraintestinal symptoms occur, also common to other diseases such as Dermatitis Herpetiformis, arthritis, arthralgia, osteoporosis, autoimmune hepatitis and many more.

- ***asymptomatic form***

  Identified only by screening programs

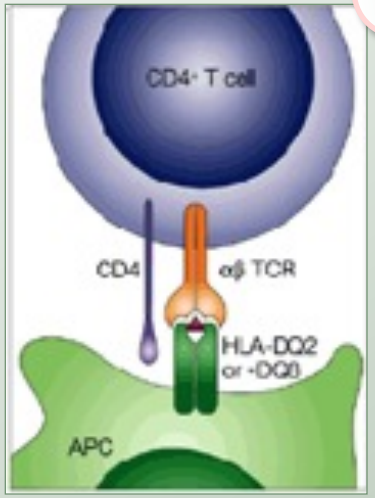


Gluten is not the sole cause of celiac disease

HLA-DQ2/8 necessary, but not sufficient (OR ~ 5)

wheat, barley, rye

+



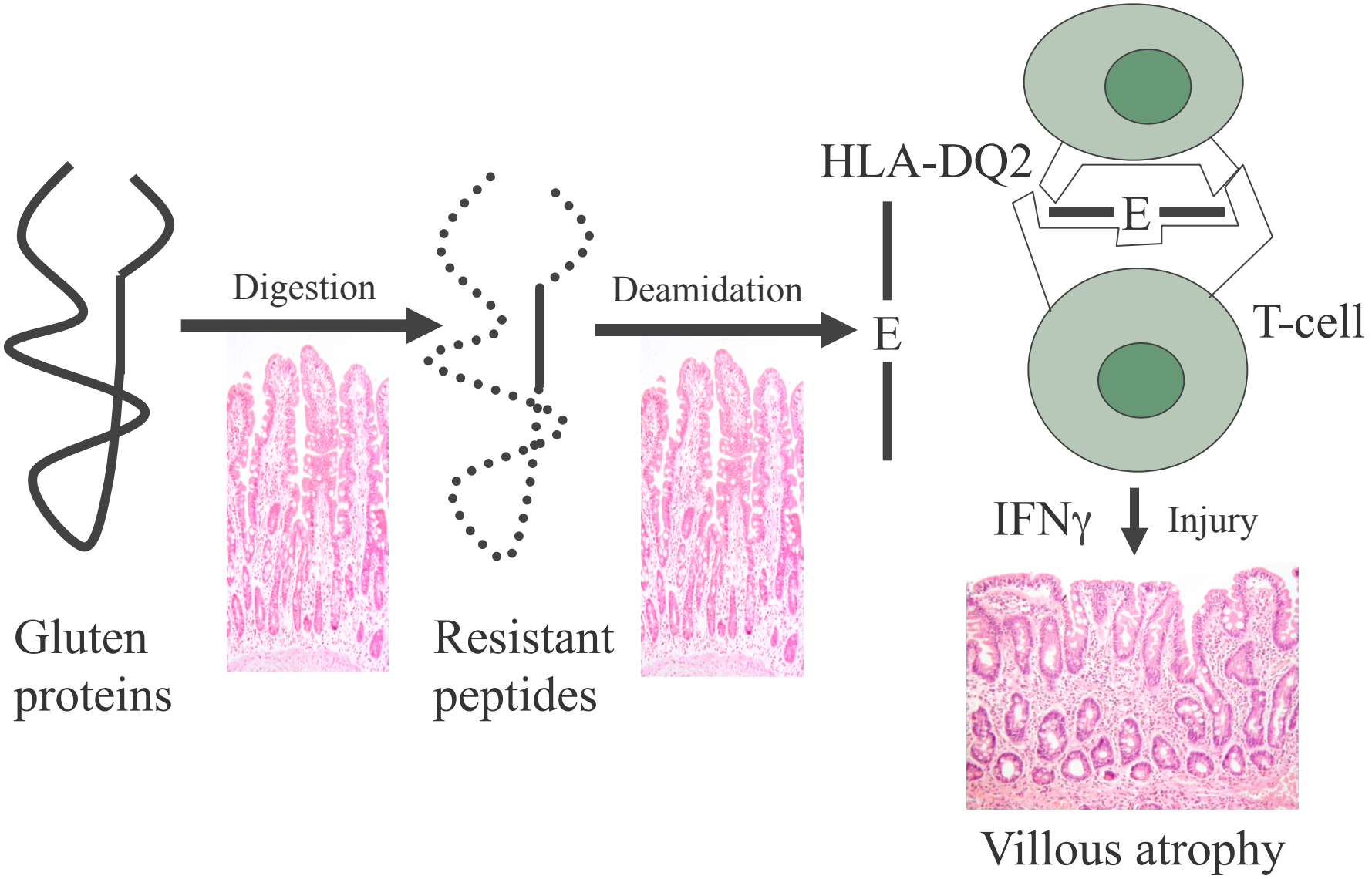
HLA DQ2/DQ8

+ Other non-HLA genes ⇒ Celiac Disease

Other env factors — 40% of heritability — 60% of heritability

CD is a multifactorial disorder. HLA plays a major role in CD. 95% of CD cases carry at least one of the risk molecules DQ2 and/or DQ8. But also 30-40% of the general population carry those risk alleles. Thus HLA is necessary but not sufficient. It is responsible for 40% of the genetic risk while the rest are shard among non-HLA genes.

The Cause of Coeliac Disease



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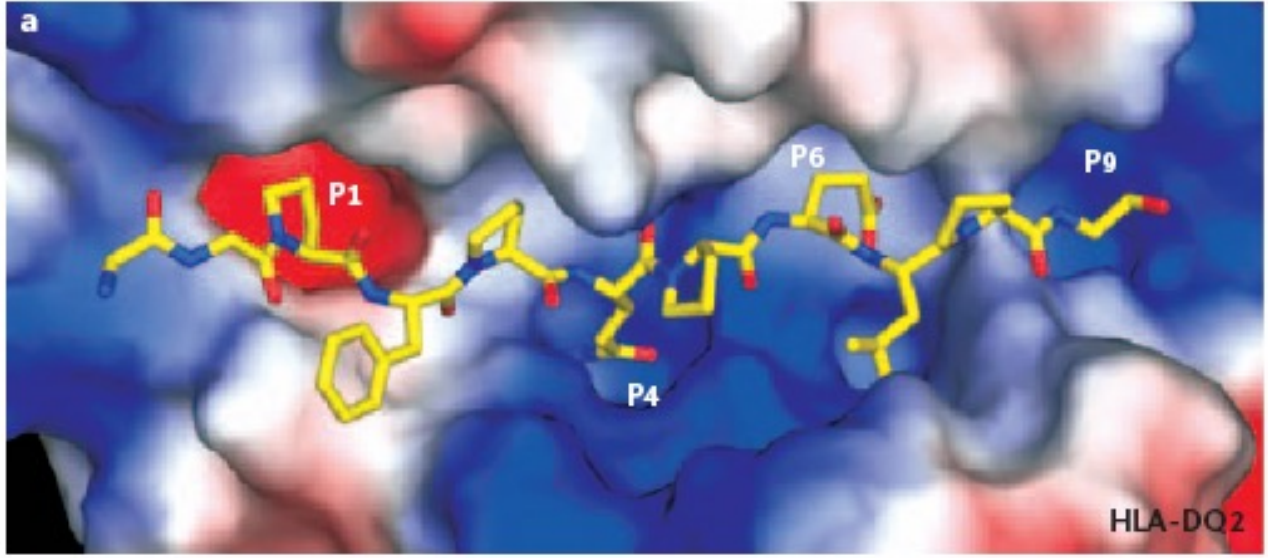
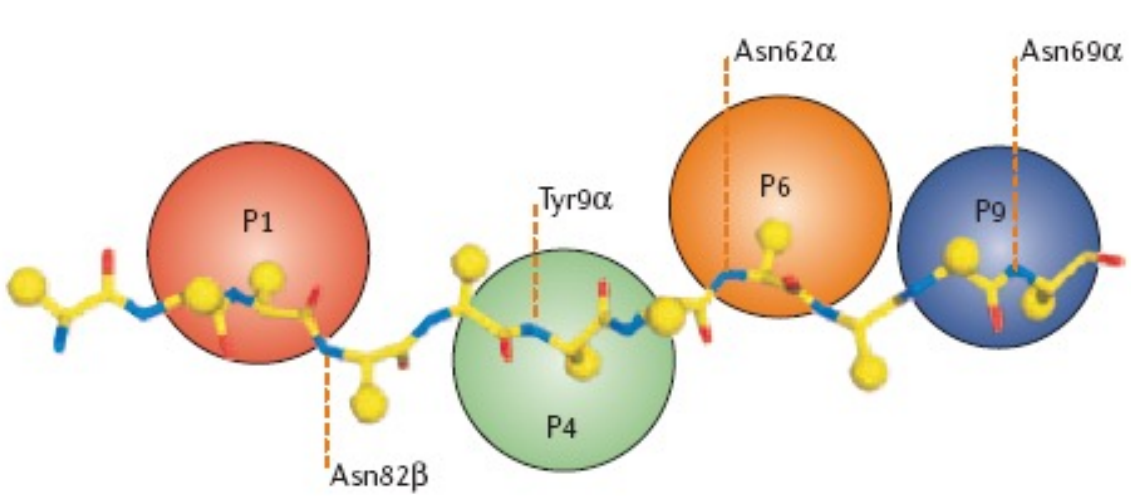
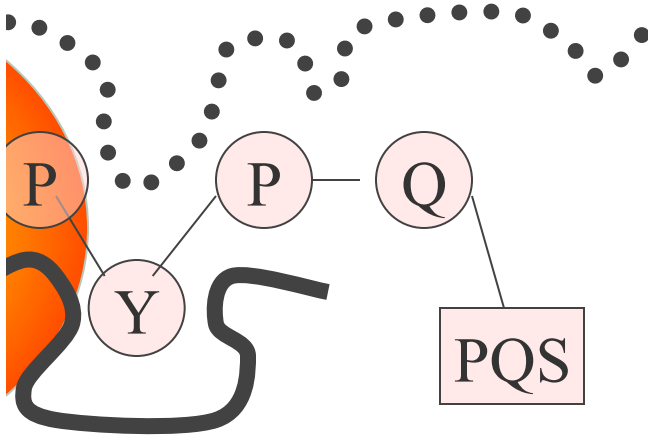






c

P1	P2	P3	P4	P5	P6	P7	P8	P9
Pro	X	Pro	Glu	Pro	Glu	Pro	Pro	Glu
Pro	Phe	Pro	Gln	Pro	Gln	Leu	Pro	Tyr
Pro	Phe	Pro	Gln	Pro	Glu	Leu	Pro	Tyr

ɔn RP et al Nat Med 2000
Hansen H. et al J Exp Med 2000

Systemic Lupus Erythematosus (SLE)

- Chronic multisystem inflammatory disease
- Associated with abnormalities of immune system
- Results from interactions among genetic, hormonal, environmental, and immunologic factors

Systemic Lupus Erythematosus (SLE) - causes

Lupus is a complex disease whose causes are known only in part. The cause is not unique, but as with all complex diseases there is a combination of genetic factors, environmental (and in this case also hormonal) factors, which come into play together in determining the disease.

The fact that Lupus can be found in several members of the same family indicates that its development has a genetic basis.

In addition, studies done on twins have shown how Lupus strikes mostly likely both identical twins than not identical twins.

However, as expected genes alone are not able to cause Lupus. Other factors must come into play, including the sun, stress, certain medications and infectious agents such as viruses.

Systemic Lupus Erythematosus

- Affects the
  - Skin
  - Joints
  - Serous membranes
  - Renal system
  - Hematologic system
  - Neurologic system

Systemic Lupus Erythematosus

- A variable disease
  - Chronic
  - Unpredictable
  - Characterized by exacerbations & remissions

Incidence

- SLE affects 2 to 8 persons per 100,000 in United States
- Most cases occur in women of childbearing years
- African, Asian, Hispanic, and Native Americans three times more likely to develop than whites

Etiology

- Etiology is unknown
- Most probable causes
  - Genetic influence
  - Hormones
  - Environmental factors
  - Certain medications

Pathophysiology

- Autoimmune reactions directed against constituents of cell nucleus, DNA
- Antibody response related to B and T cell hyperactivity

Systemic Lupus Erythematosus (SLE) - symptoms

The experience of each person with Lupus is different, although there are some characteristic signs that enable an accurate diagnosis. The symptoms can range from mild to severe.

The most common symptoms include pain or swelling in the joints, skin rash, fever without explanation, extreme fatigue.

The characteristic skin rash is localized at the level of the nose and cheeks and defined Butterfly Erythema. Other types of rash may affect the face, ears, arms, shoulders, chest and hands.

Other symptoms of Lupus include chest pain, hair loss, high sensitivity to sunlight, anemia, fingers and toes ranging from pale to purple-red color as a result of the stress and exposure to cold.

Clinical Manifestations

- Ranges from a relatively mild disorder to rapidly progressing, affecting many body systems
- Most commonly affects the skin/muscles, lining of lungs, heart, nervous tissue, and kidneys

Clinical Manifestations

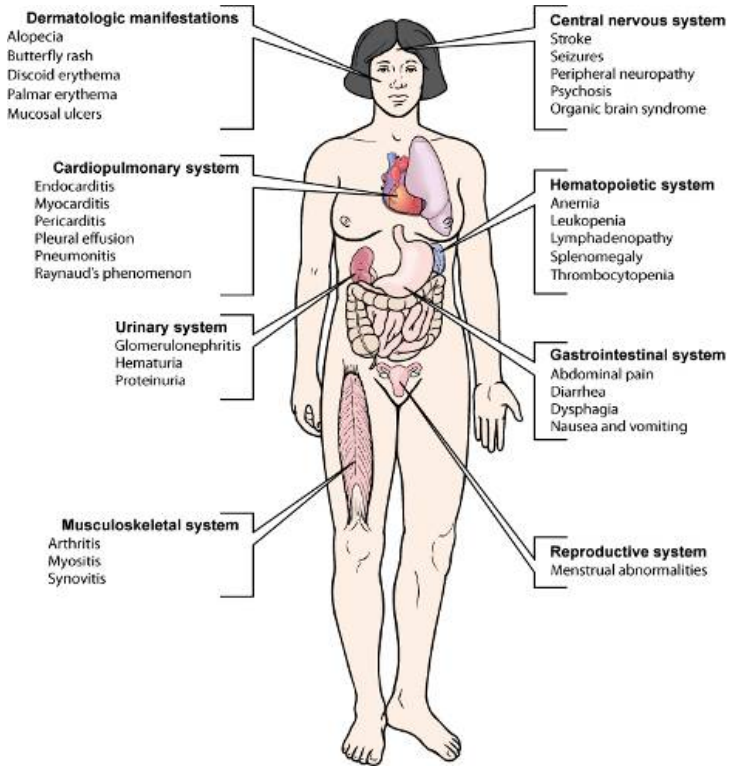


Fig 65-9

Clinical Manifestations

- Dermatologic
  - Cutaneous vascular lesions
  - Butterfly rash
  - Oral/nasopharyngeal ulcers
  - Alopecia

Dermatologic Manifestations

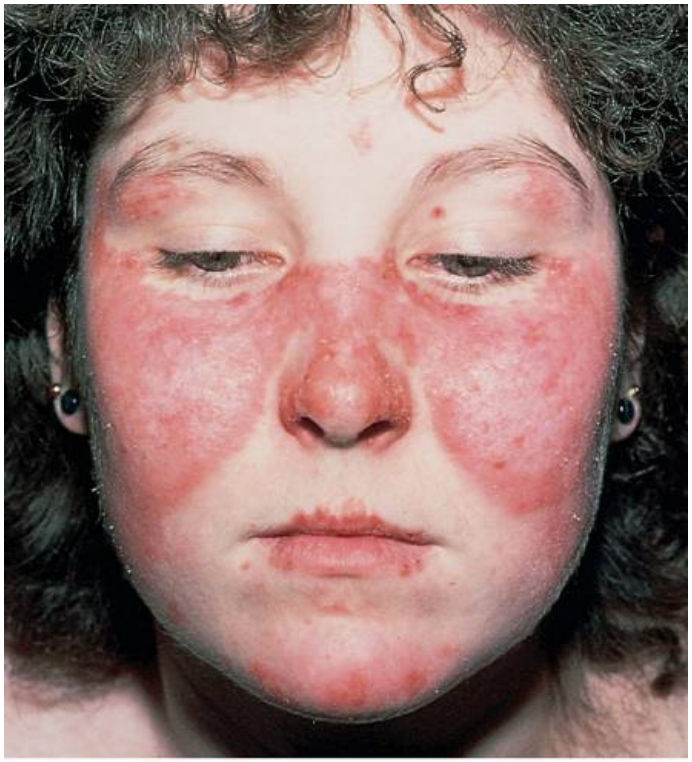


Fig 65-10

Clinical Manifestations

- Musculoskeletal
  - Polyarthralgia with morning stiffness
  - Arthritis
    - Swan neck fingers
    - Ulnar deviation
    - Subluxation with hyperlaxity of joints

Swan Neck Deformity

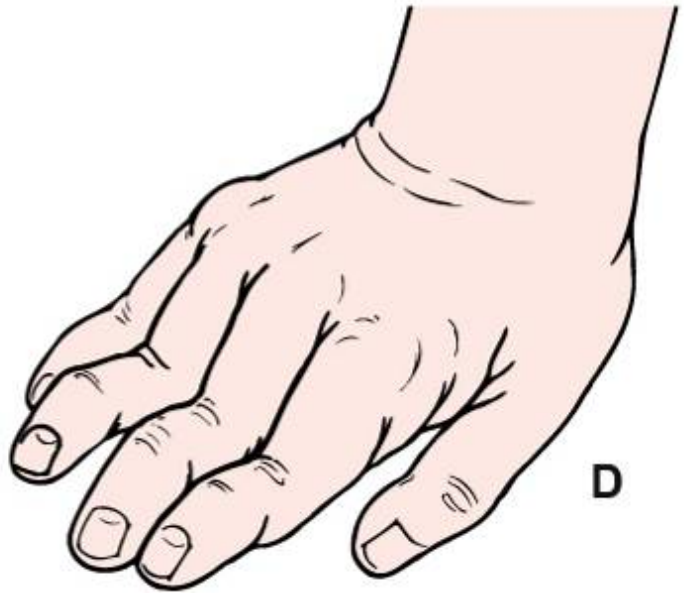


Fig. 65-4 D

Clinical Manifestations

- Cardiopulmonary
  - Tachypnea
  - Pleurisy
  - Dysrhythmias
  - Accelerated CAD
  - Pericarditis

Clinical Manifestations

- Renal
  - Lupus nephritis
    - Ranging from mild proteinuria to glomerulonephritis
    - Primary goal in treatment is slowing the progression

Clinical Manifestations

- Nervous system
  - Generalized/focal seizures
  - Peripheral neuropathy
  - Cognitive dysfunction
    - Disorientation
    - Memory deficits
    - Psychiatric symptoms

Clinical Manifestations

- Hematologic
  - Formation of antibodies against blood cells
  - Anemia
  - Leukopenia

Clinical Manifestations

- Hematologic (cont’d)
  - Thrombocytopenia
  - Coagulopathy
  - Anti-phospholipid antibody syndrome

Clinical Manifestations

- Infection
  - Increased susceptibility to infections
  - Fever should be considered serious
  - Infections such as pneumonia are a common cause of death

Systemic Lupus Erythematosus (SLE) - diagnosis

The diagnosis of Lupus can be difficult. There is no single test that allows the diagnosis of Lupus, which requires numerous laboratory tests.

The most useful test for the purpose of diagnosis is the determination of some auto-antibodies present in the blood. For example, the antinuclear antibody test is used for the detection of antibodies that react against the members of the patient's own cells. Most people with Lupus has positive antinuclear antibodies, although the positivity of these antibodies may be due to other causes such as infections, immunological disorders and occasionally can be seen even in healthy people.

In addition there are tests for certain types of antibodies that are more specific for Lupus, including the anti-DNA.
Your doctor may recommend a biopsy of the skin or of the kidney if these organs are affected by the disease.

Diagnostic Studies

- No specific test
- SLE is diagnosed primarily on criteria relating to patient history, physical examination, and laboratory findings

Diagnostic Studies

TABLE 65-14 Criteria for Diagnosis of Systemic Lupus Erythematosus*

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis: nonerosive, involvement of two or more joints characterized by tenderness, swelling, and effusion
- Serositis: pleuritis or pericarditis
- Renal disorder: persistent proteinuria or cellular casts in urine
- Neurologic disorder: seizures or psychosis
- Hematologic disorder: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
- Immunologic disorder: positive LE preparation; anti-DNA antibody or antibody to Sm nuclear antigen; or false-positive serologic tests for syphilis
- Antinuclear antibody

Diagnostic Studies

- Antinuclear antibodies
  - ANA and other antibodies indicate autoimmune disease
  - Anti-DNA and anti-Smith antibody tests most specific for SLE
  - LE prep can be positive with other rheumatoid diseases
  - ESR & CRP are indicative of inflammatory activity

Diagnostic Tests

- CBC for hematologic problems
- UA for lupus nephritis
- X-rays of affected joints
- Chest x-ray for pulmonary problems
- ECG for cardiac problems

Systemic Lupus Erythematosus (SLE) - treatment

Currently the effectiveness of therapy for Lupus has risen dramatically and the accomplishments are far superior to therapeutic failures.

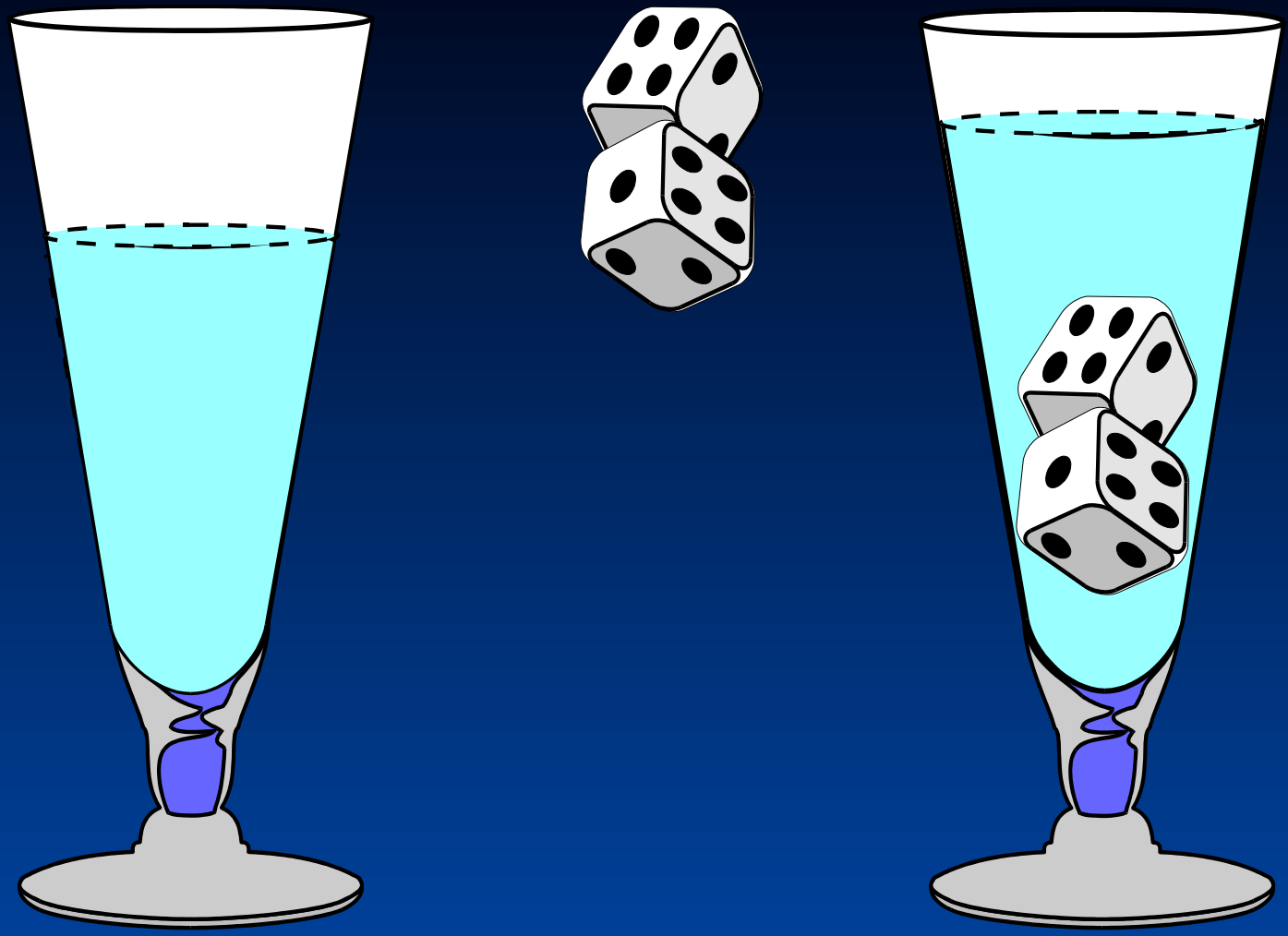
Several drugs are used to treat Lupus, which are administered according to the symptoms alleged by the patient. If the person has chest pain, joint pain or fever, are commonly used nonsteroidal anti inflammatory drugs (NSAIDs).

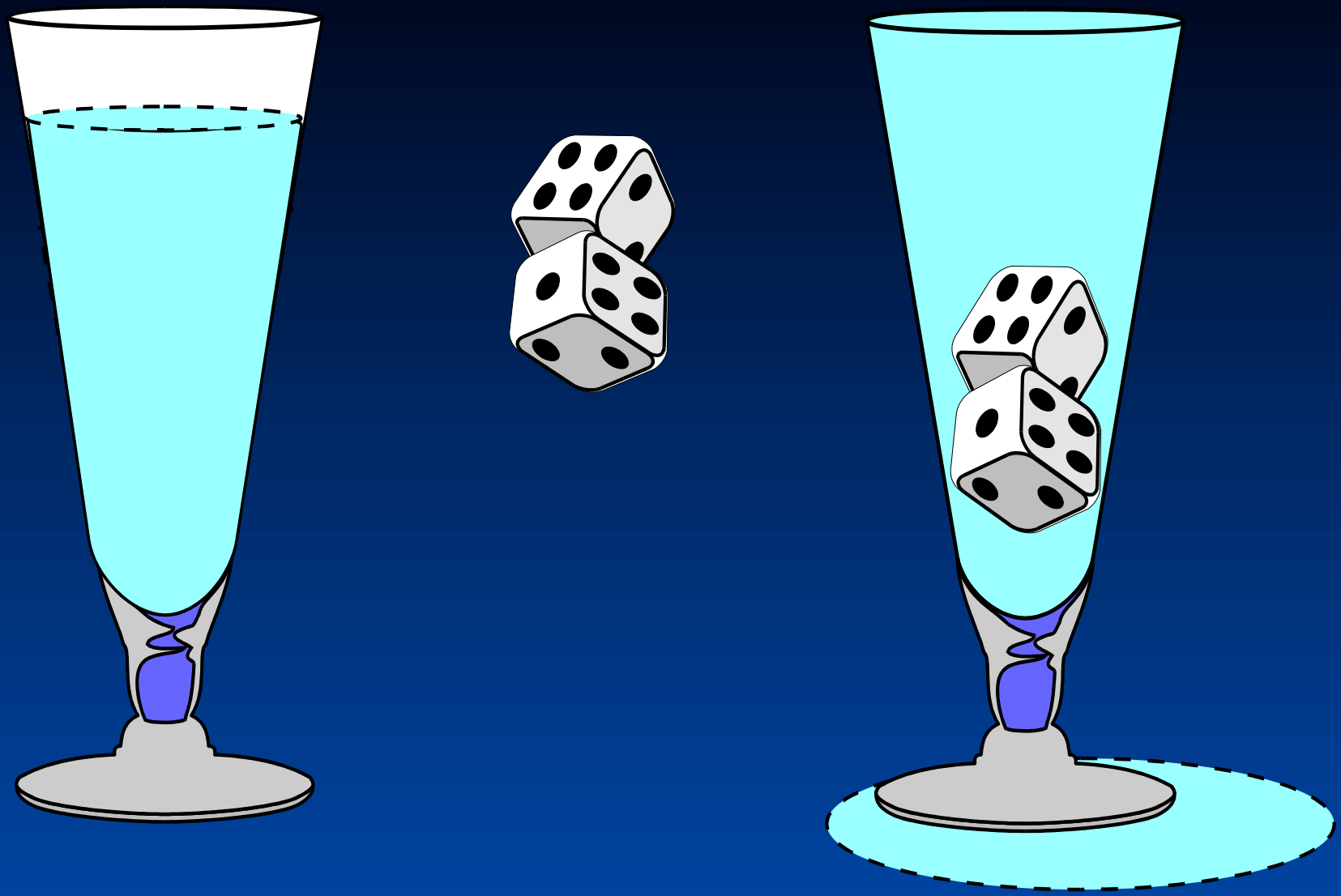
A new class of anti-inflammatory called COX-2 inhibitors (celecoxib, rofecoxib) has the same effect on pain and inflammation, but a lower risk of gastrointestinal side effects.

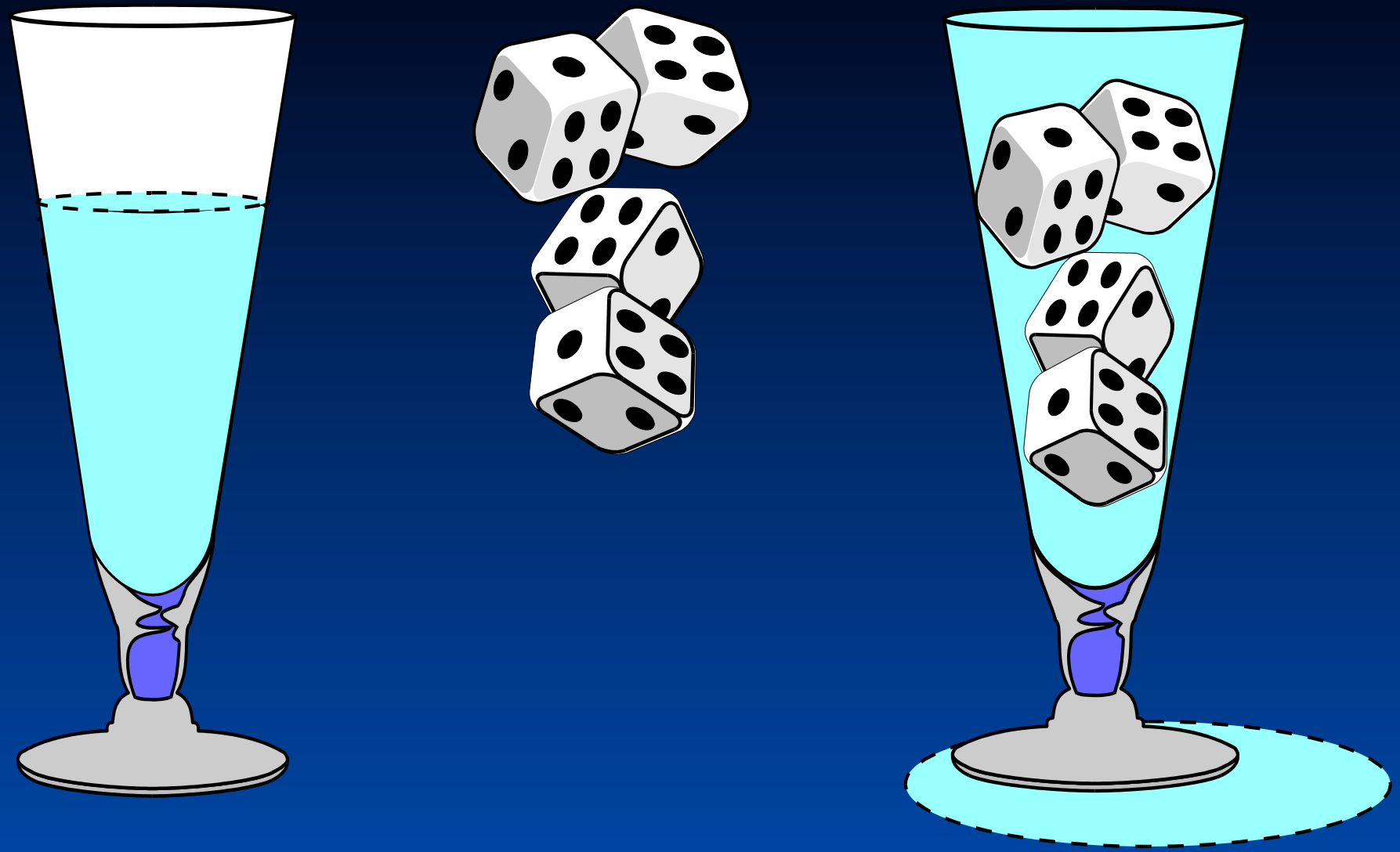
Antimalarial drugs are another group of medicines commonly used to treat Lupus. Is not completely clear what role they play in Lupus, but it is thought that they may have a regulatory effect in the immune response.

DISEASE EXAMPLES

Alzheimer's Disease
Autism
Arthritis
Asthma
Cancer
Diabetes: adult onset (type 2)
Diabetes: juvenile (type 1)
Hearing disorders
Heart disease, lipid disorders
Hypertension (blood pressure)
Obesity related disorders
Schizophrenia
Retinal degeneration (vision)



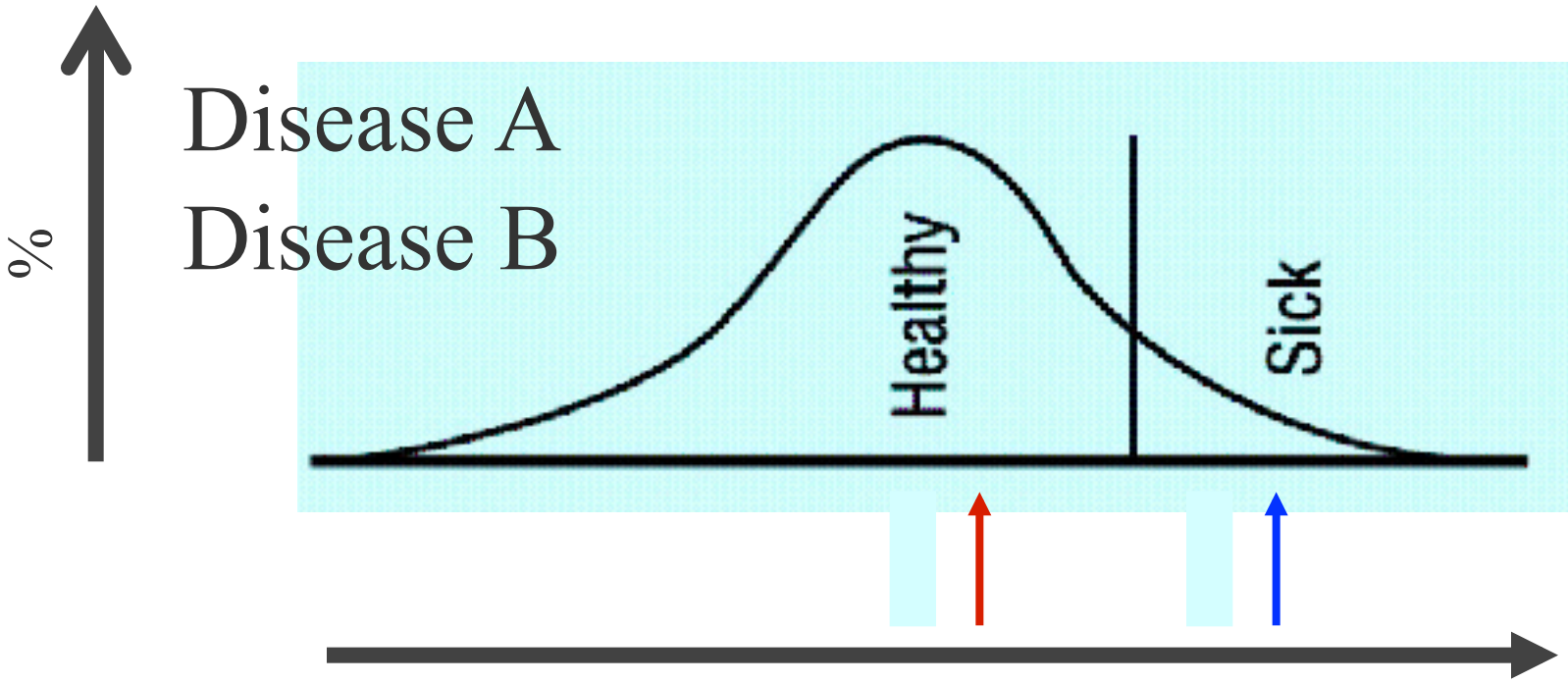


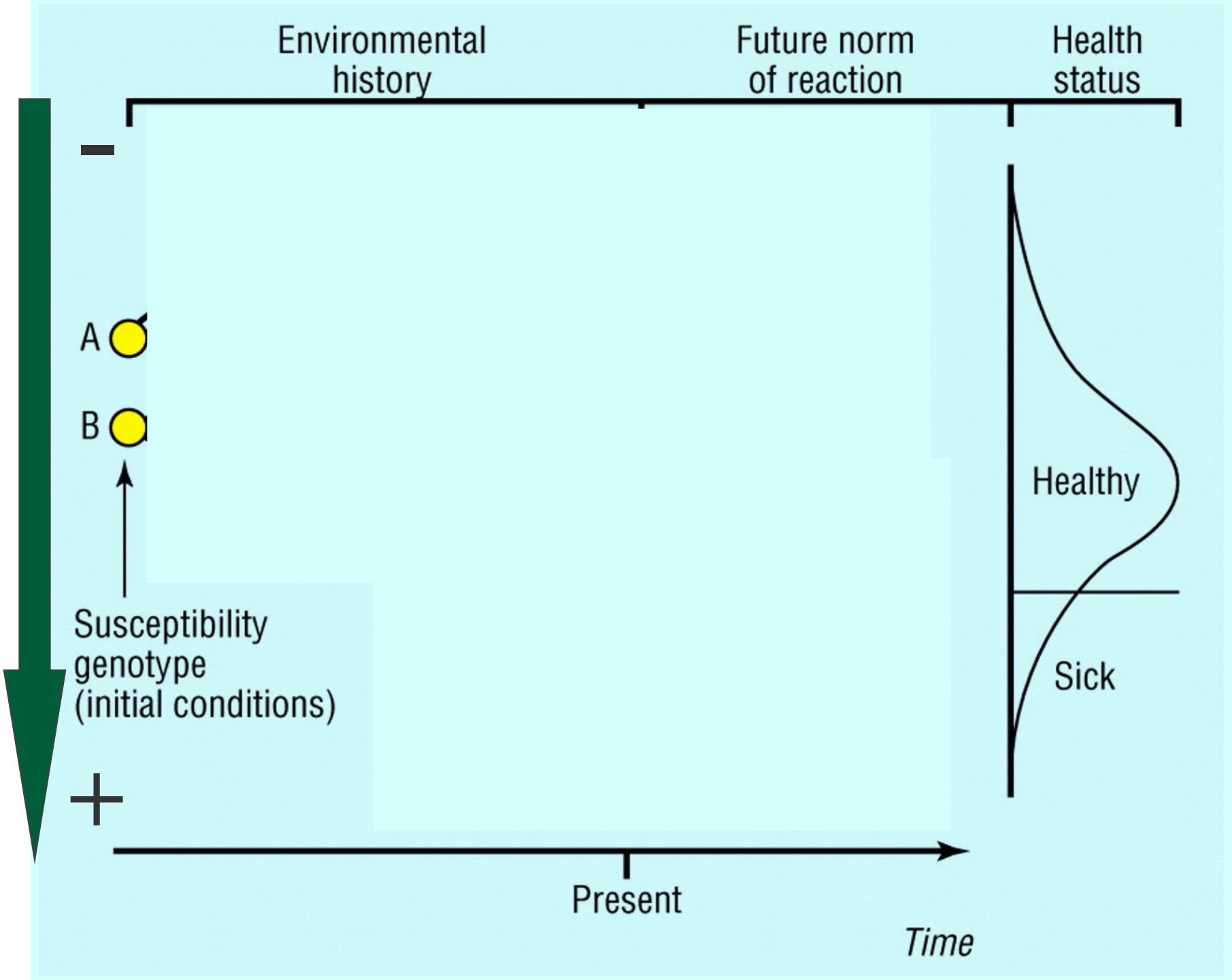


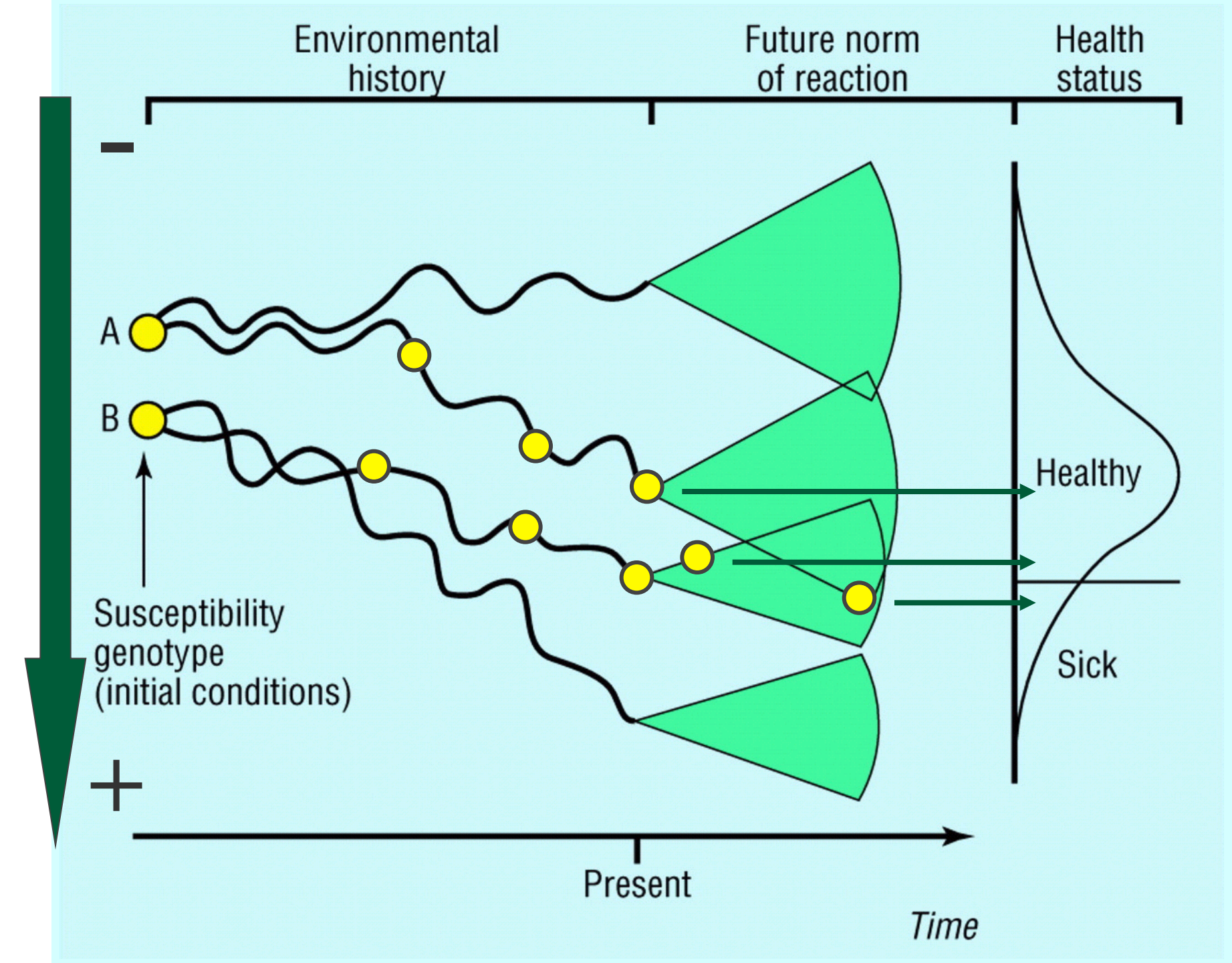
Complex diseases

- definition
- How you recognize them
- **How you measure genetic susceptibility**
- Genetic polymorphisms
- How you study them

Susceptibility to complex traits or diseases

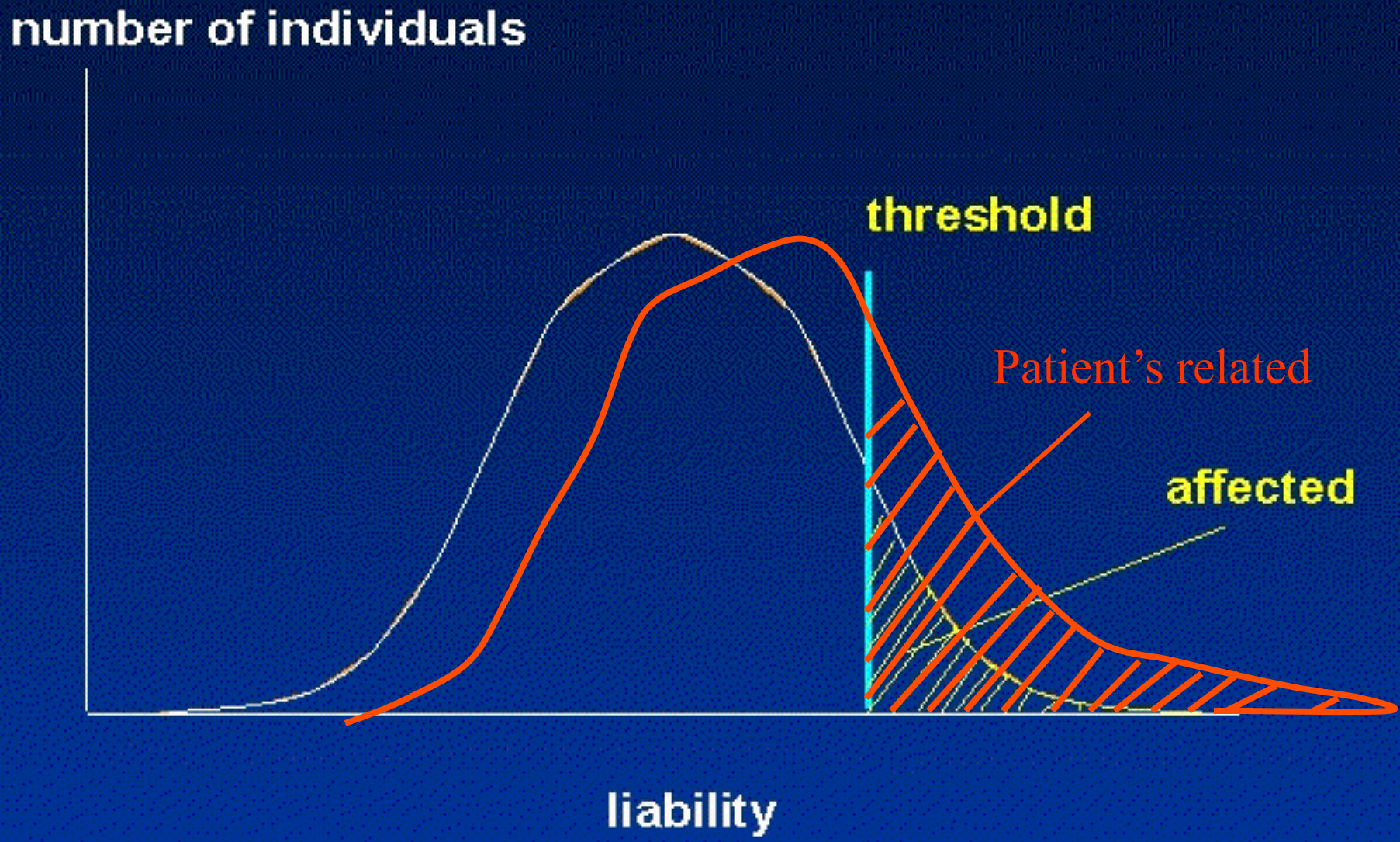



Environmental history
Future norm of reaction
Health status
A
B
Healthy
Sick
Susceptibility genotype (initial conditions)
Present
Time


Environmental history
Future norm of reaction
Health status
A
B
Susceptibility genotype (initial conditions)
Healthy
Sick
Present
Time

Theoretical model to explain the genetic control of multifactorial diseases.

In the general population, a number of individuals exceeds the threshold of susceptibility to a certain disease and as a result will be affected. First degree relatives of probands will present an averaged increased number of predisposing factors resulting in threshold exceedance by a higher proportion of individuals.


number of individuals
threshold
Patient's related
affected
liability

The role of genetic factors

- Familial aggregation can be measured by comparing the frequency of the disease in the relatives of an affected proband with its frequency (prevalence) in the general population.

- Relative risk ratio (λ_r) is defined as:

$$\lambda_r = \frac{\text{prevalence of disease in a relative “r” of an affected person}}{\text{population prevalence of the disease}}$$

- $\lambda_r = 1$ indicates that a relative of an affected is no more likely to develop a disease than any individual in the population.

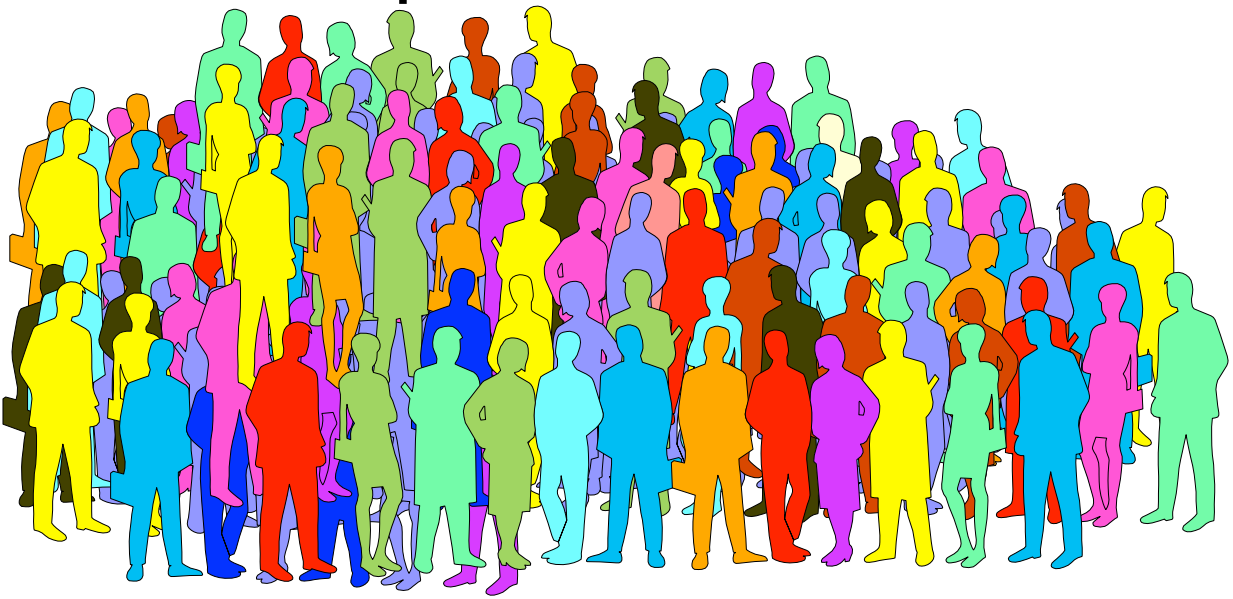
1 individuo ogni 100 circa
si ammala di celiachia

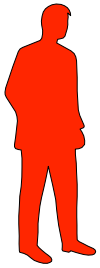
1 fratello di celiaco ogni 20 (5%) si ammala anche lui della stessa malattia

$\lambda_r = 5$

Anomaly	Population Incidence	Recurrence Risk in First Degree Relatives (%)
labbro leporino	1/1,000	4.9
dislocazione dell'anca congenita	1/1,000	3.5
stenosi del piloro	1,500	3.2
piede equino	1/1,000	2-8

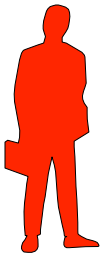
Popolazione sana





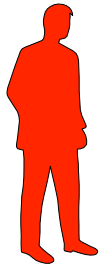
HLA
5/100

Popolazione malata



HLA
90/100

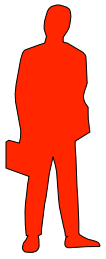
Popolazione sana



5/100

HLA risk ratio (λHLA) is calculated by dividing the frequency of the HLA allele in the patient population by the frequency in the general population

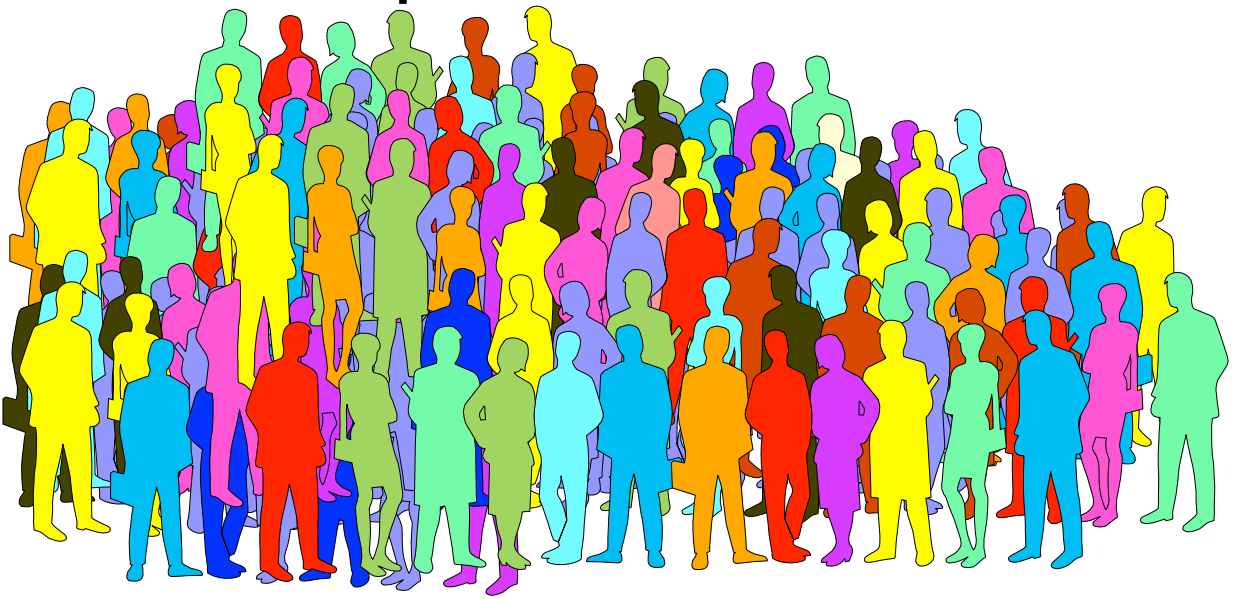
$$\lambda\text{HLA} = \frac{\text{(Ag+/Ag-) disease}}{\text{(Ag+/Ag-) control}} \quad \frac{\text{(90/10)}}{\text{(5/95)}} = 171$$

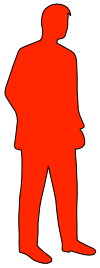


90/100

Popolazione malata

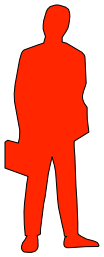
Popolazione sana



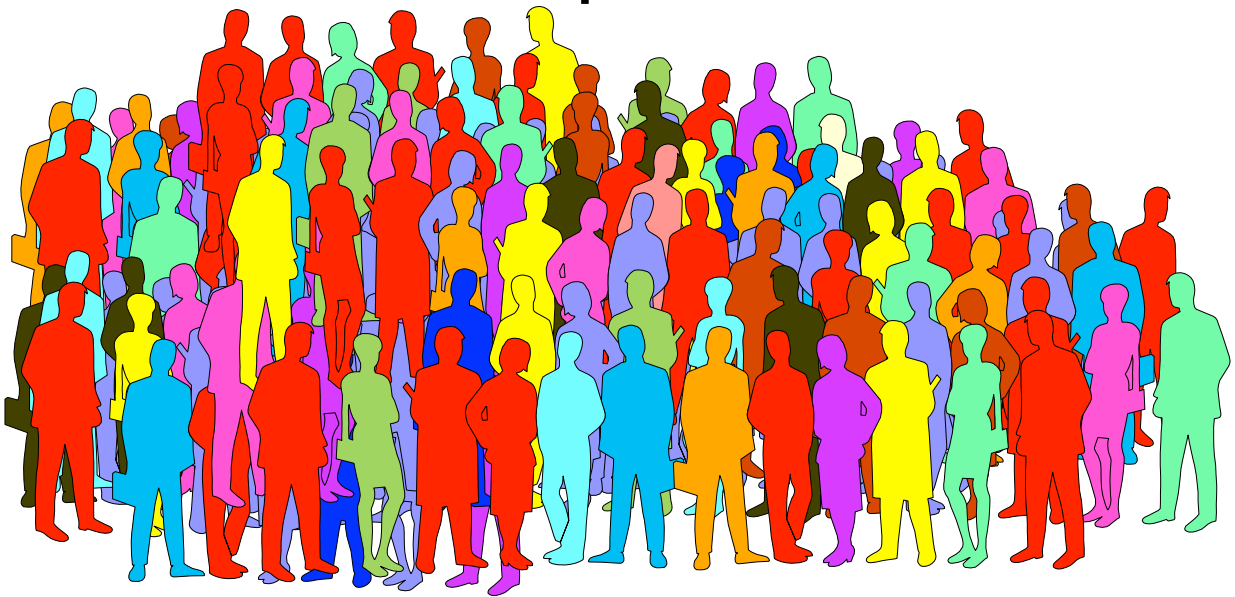


5/100

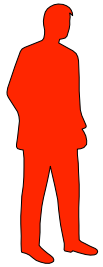
Popolazione malata



15/100

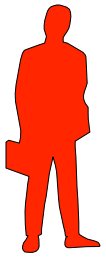


Popolazione sana



5/100

$$\lambda HLA = \frac{(Ag+/Ag-)\ disease}{(Ag+/Ag-)\ control} \quad \frac{(15/85)}{(5/95)} = 3{,}35$$



15/100

Popolazione malata

Per la celiachia, λHLA = 4

Il rischio è quindi determinato in maniera preponderante da fattori genetici non-HLA

Risk Ratios for Relatives of Probands with Diseases Showing Familial Aggregation

Disease	*Relationship*	λ_r
Schizophrenia	MZ twins	48
	Siblings	12
Autism	MZ twins	2000
	Siblings	150
Manic-depressive (bipolar) disorder	MZ twins	60
	Siblings	7
Type I diabetes mellitus	MZ twins	80
	Siblings	12
Crohn's disease	MZ twins	840
	Siblings	25
Multiple sclerosis	MZ twins	800
	Siblings	24

Heritability

- Heritability (h^2) - developed to quantify the role of genetic differences in determining variability of quantitative traits
- Defined as the fraction of the total phenotypic variance of a quantitative trait that is caused by genes and is, therefore, a measure of the extent of to which different alleles at various loci are responsible for the variability in a given trait across a population.
- The higher the heritability, the greater is the contribution of genetic differences among people in causing variability of the trait.

Ereditabilità

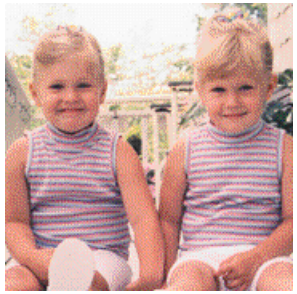
- misura dei fattori genetici: l'ereditabilità (h^2):

$$5\frac{\text{Conc. monozigotici - Conc. dizigotici}}{1 - \text{concordanza dizigotici}}$$

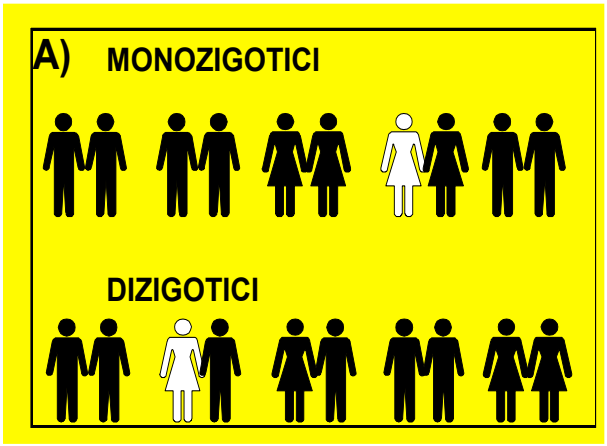
5



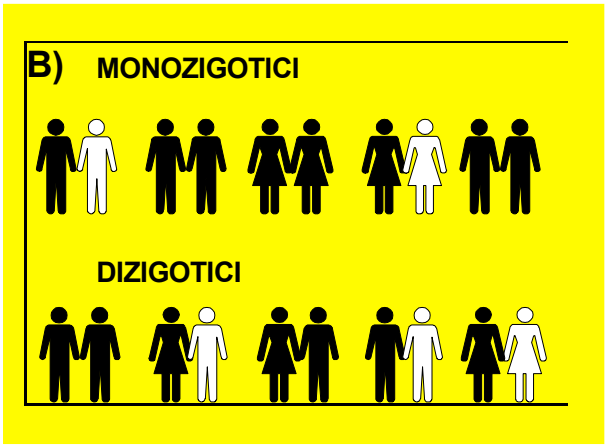


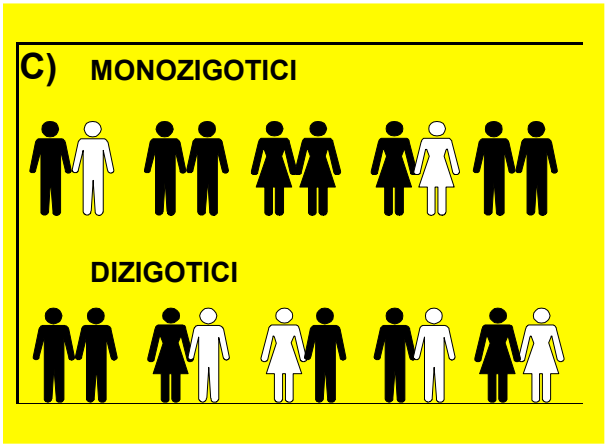


Nessuna differenza
nessuna ereditabilità



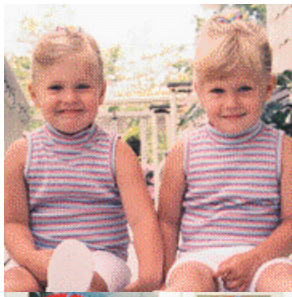
Poca differenza
poca ereditabilità



Maggiore differenza
maggiore ereditabilità

Trait	Concordance Identical Twins (%)	Concordance Full Siblings (%)
labbro leporino	40	5
stenosi del piloro	22	4
piede equino	32	3
dislocazione dell'anca congenita	33	4

Concordance rates for CD among twins

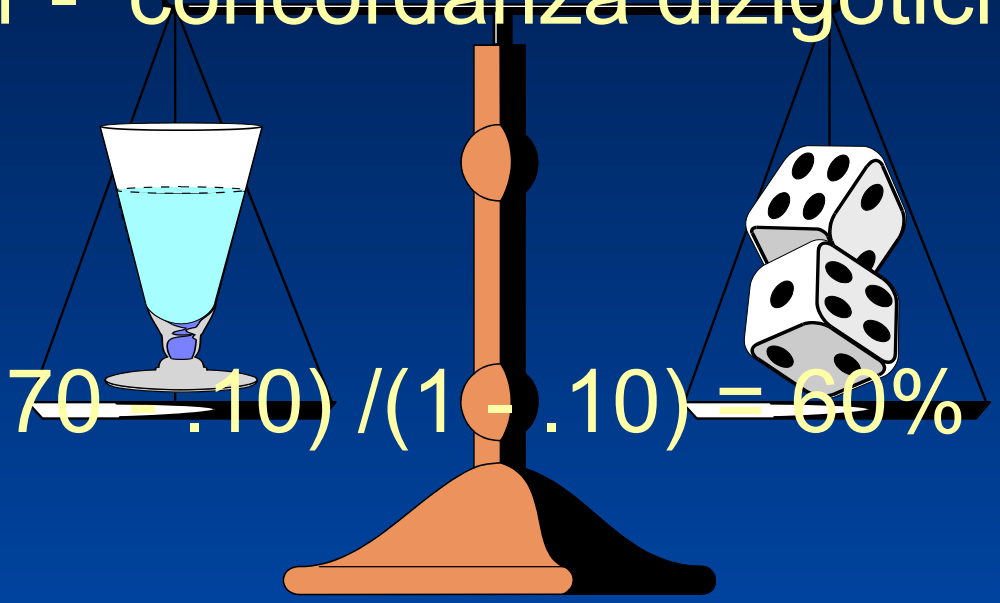


	concordant	*discordant*
Monozygotic	**70%**	**30%**
Dizygotic	**10%**	**90%**

Ereditabilità della celiachia

- misura dei fattori genetici: l'ereditabilità (h_2):

$$\frac{\text{Conc. monozigotici - Conc. dizigotici}}{1 - \text{concordanza dizigotici}}$$



(.70 – .10) /(1 - .10) = 60%

Complex diseases

- definition
- How you recognize them
- How you measure genetic susceptibility
- Genetic polymorphisms
- How you study them

COMPLEX TRAITS INVOLVE MANY GENES, & EACH MAY HAVE MANY VARIATIONS

Polymorphism or genetic marker

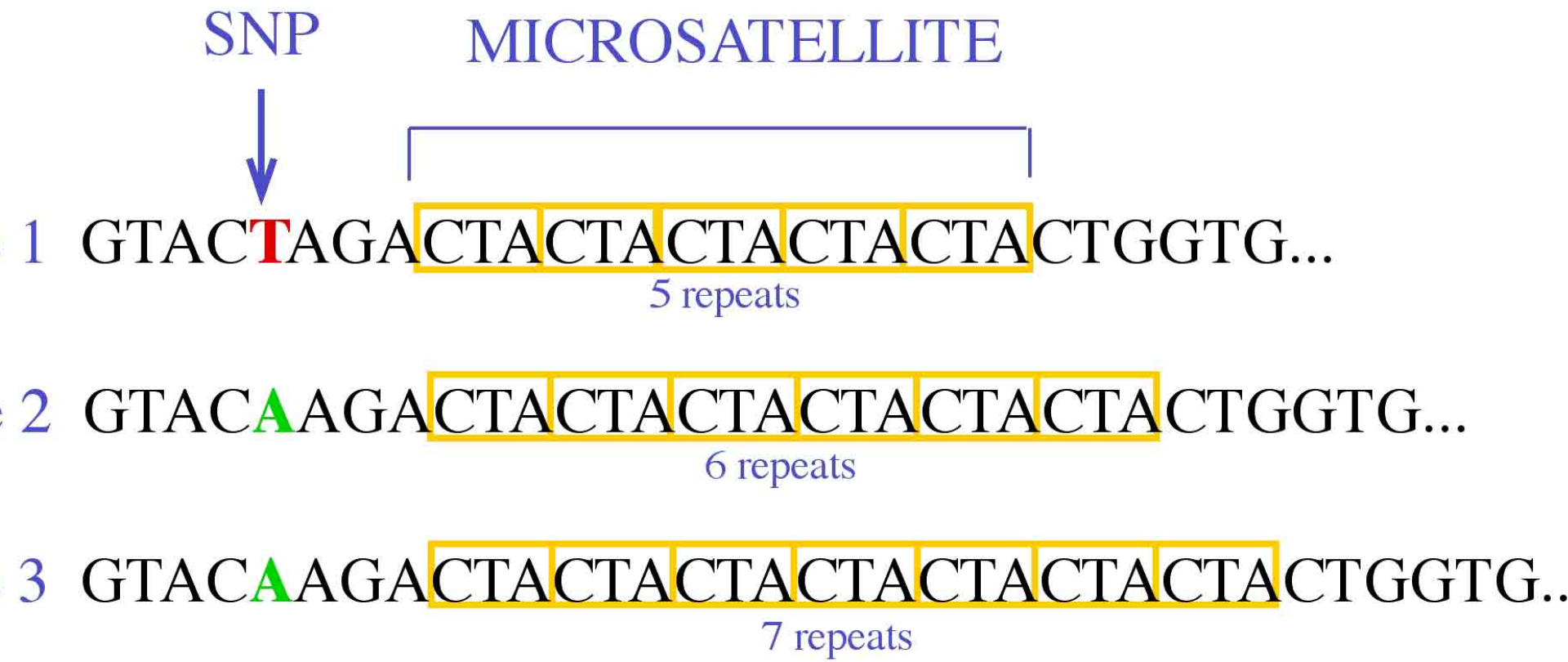
is any stretch of DNA that have the following characteristics:

-is polymorphic, the marker must have at least two alternate alleles of which the rarest allele must be represented at least 1% in the general population

-it is easy to identify and stable from generation to generation

-segregates in Mendelian way

GENETIC MARKERS



SNP = Single Nucleotide Polymorphism

GENETIC MARKERS

- SNPs

7 milions estimated with MAF > 5%
10 milions with MAF > 1%

  - Two genomes differ in approximately 0.1% = 3 million difference
  - Currently 4 mio SNPs in public databases (dbSNP and HapMap)

http://www.ncbi.nlm.nih.gov/SNP/

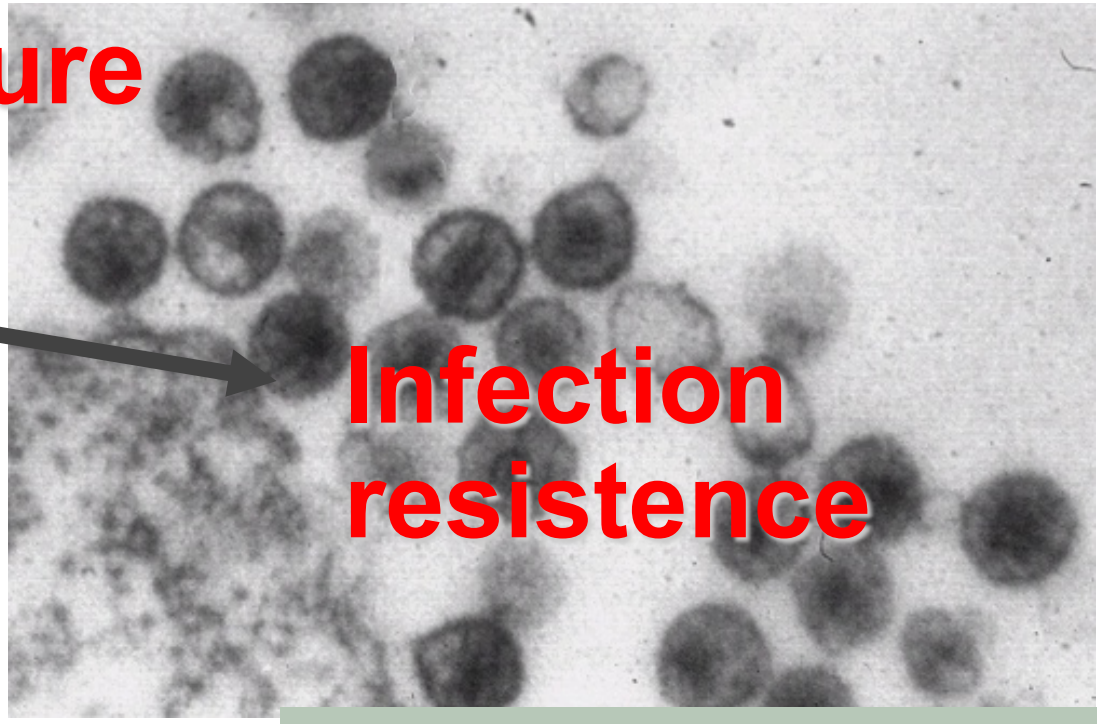
- Microsattelites
  - AAAAAAAAAAA : $(A)_{11}$
  - GTGTGTGTGTGT : $(GT)_6$
  - CTGCTGCTGCTG : $(CTG)_4$
  - ACTCACTCACTCACTC : $(ACTC)_4$
  - Alleles at a specific location (locus) can differ in the number of repeats.
  - 5264 loci on map (deCODE) (Kong et al (2002), http://www.decode.com)
  - Potential # loci: 100.000 (Strachan & Read, 2003)

http://www.hapmap.org/

CNV

Copy Number Variation
Anomalie quantitative dell'intero genoma umano
Scoperte grazie all'approccio CGH array

HIV exposure

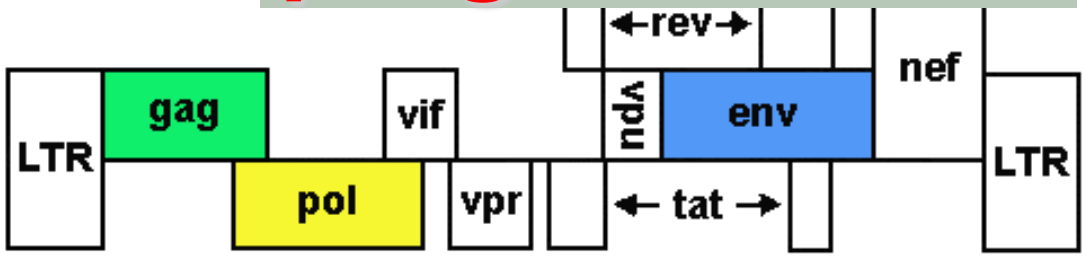


Infection resistence

infection

Long term non progressors

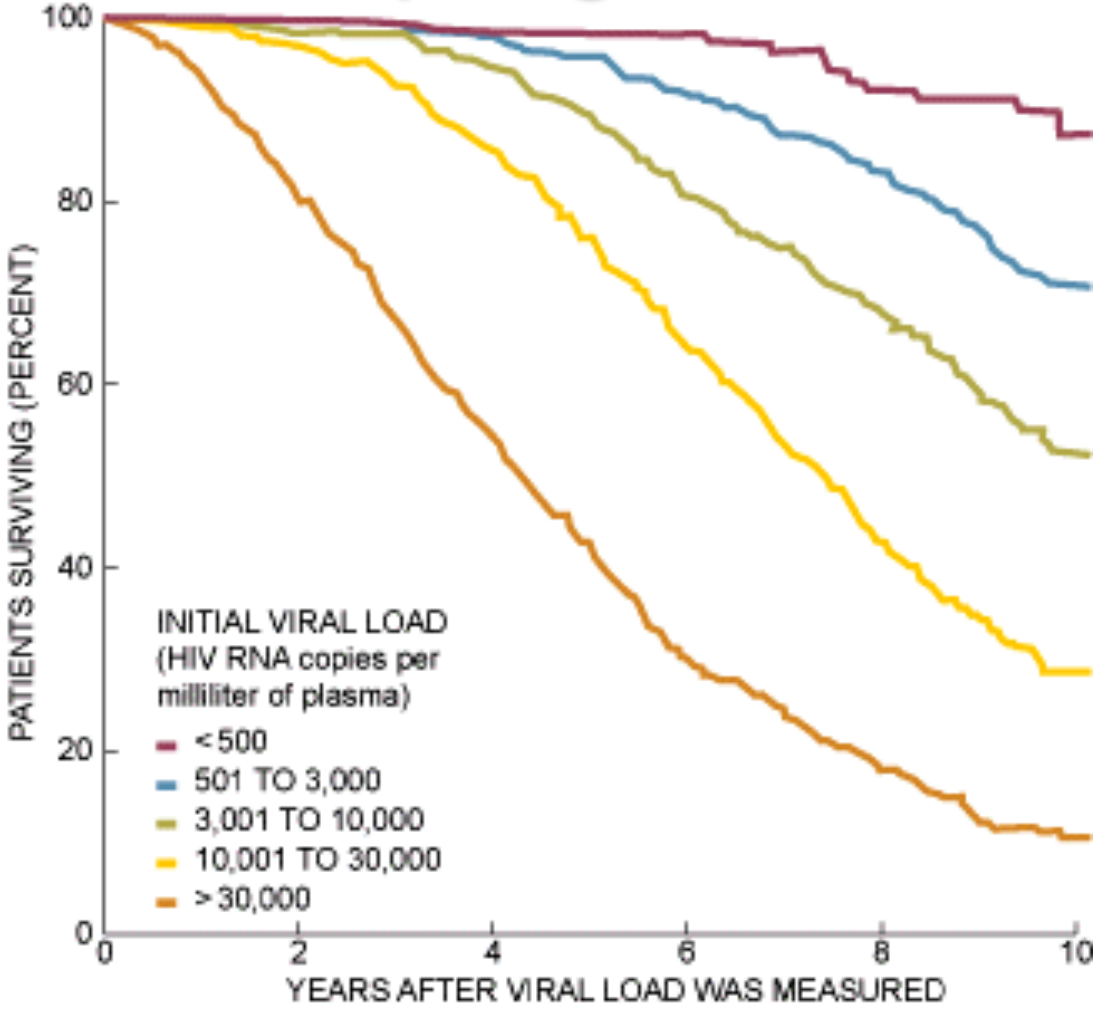
AIDS rapid progressors



HIV-1

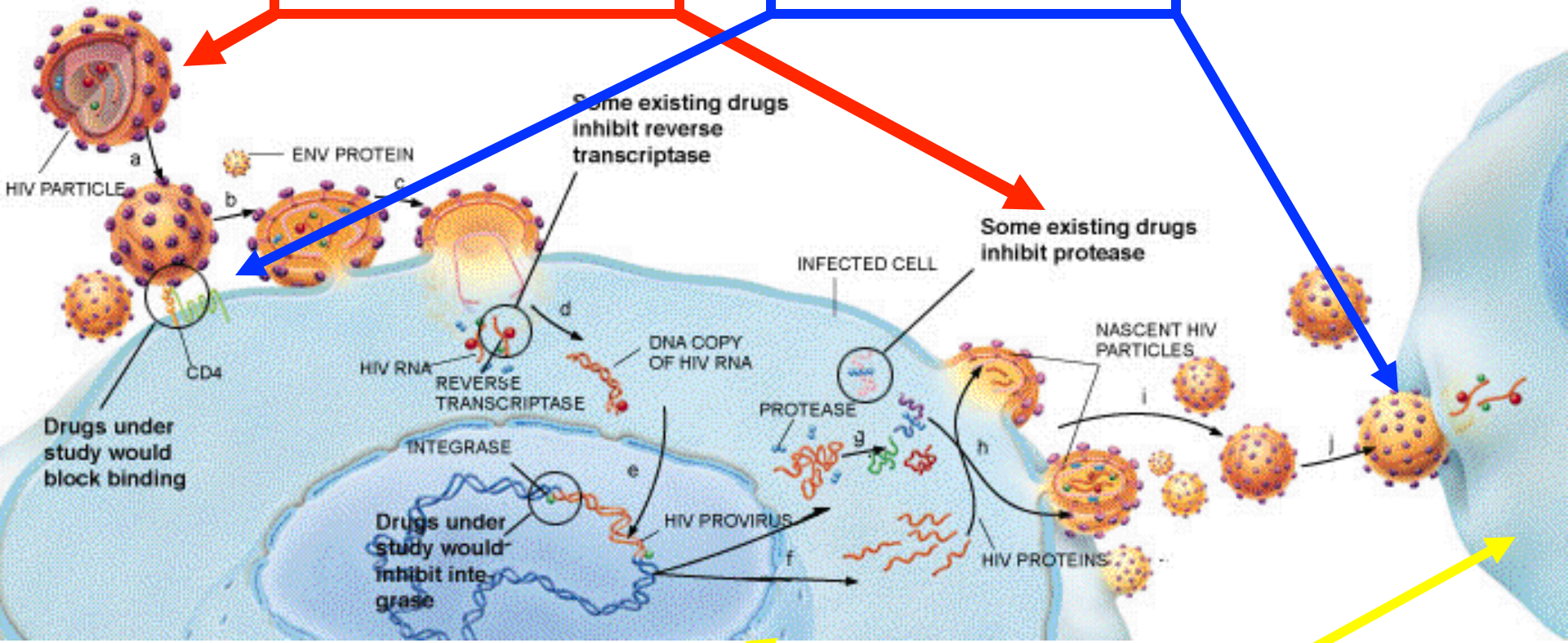
What are the factors implicated in the susceptibility of HIV infection and AIDS progression?

- What are the genes possibly involved?

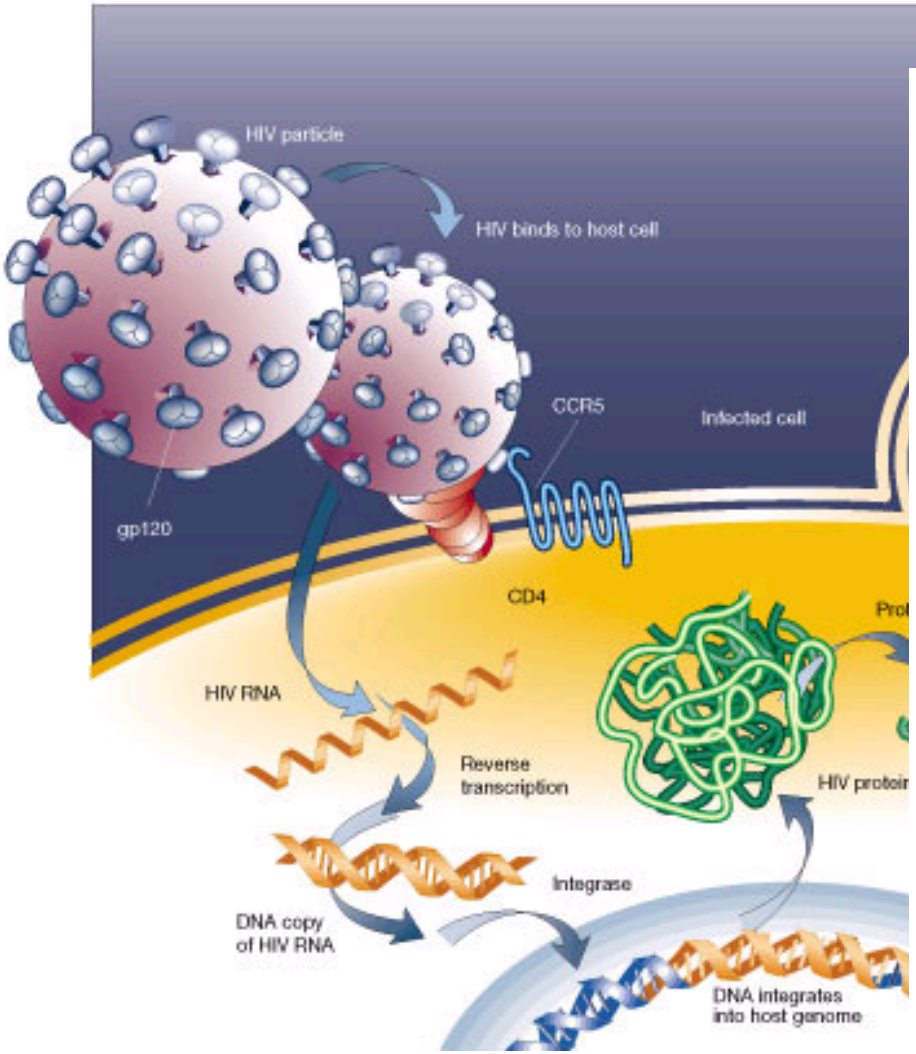


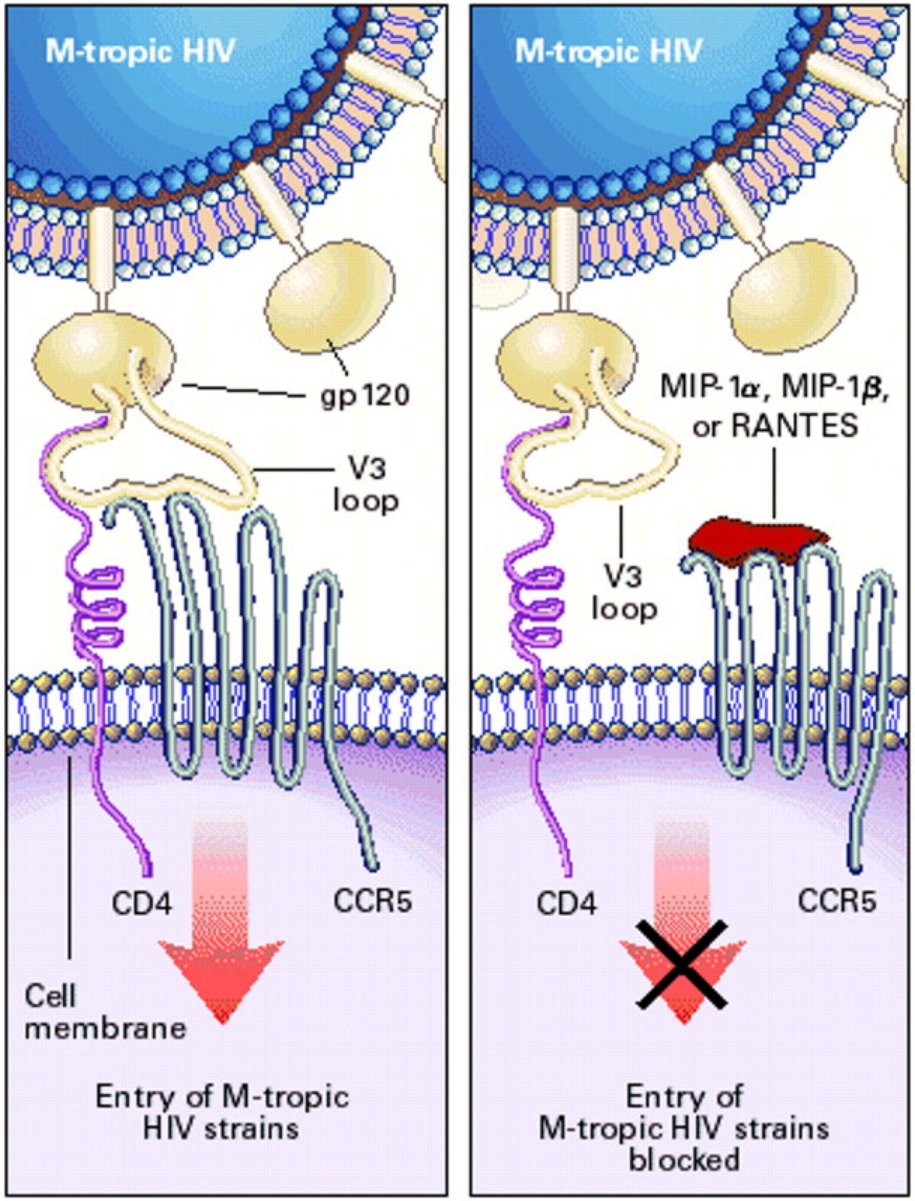
natural immunity

HIV entry



specific immunity


HIV particle
HIV binds to host cell
CCR5
Infected cell
gp120
CD4
HIV RNA
Reverse transcription
Integrase
DNA copy of HIV RNA
DNA integrates into host genome

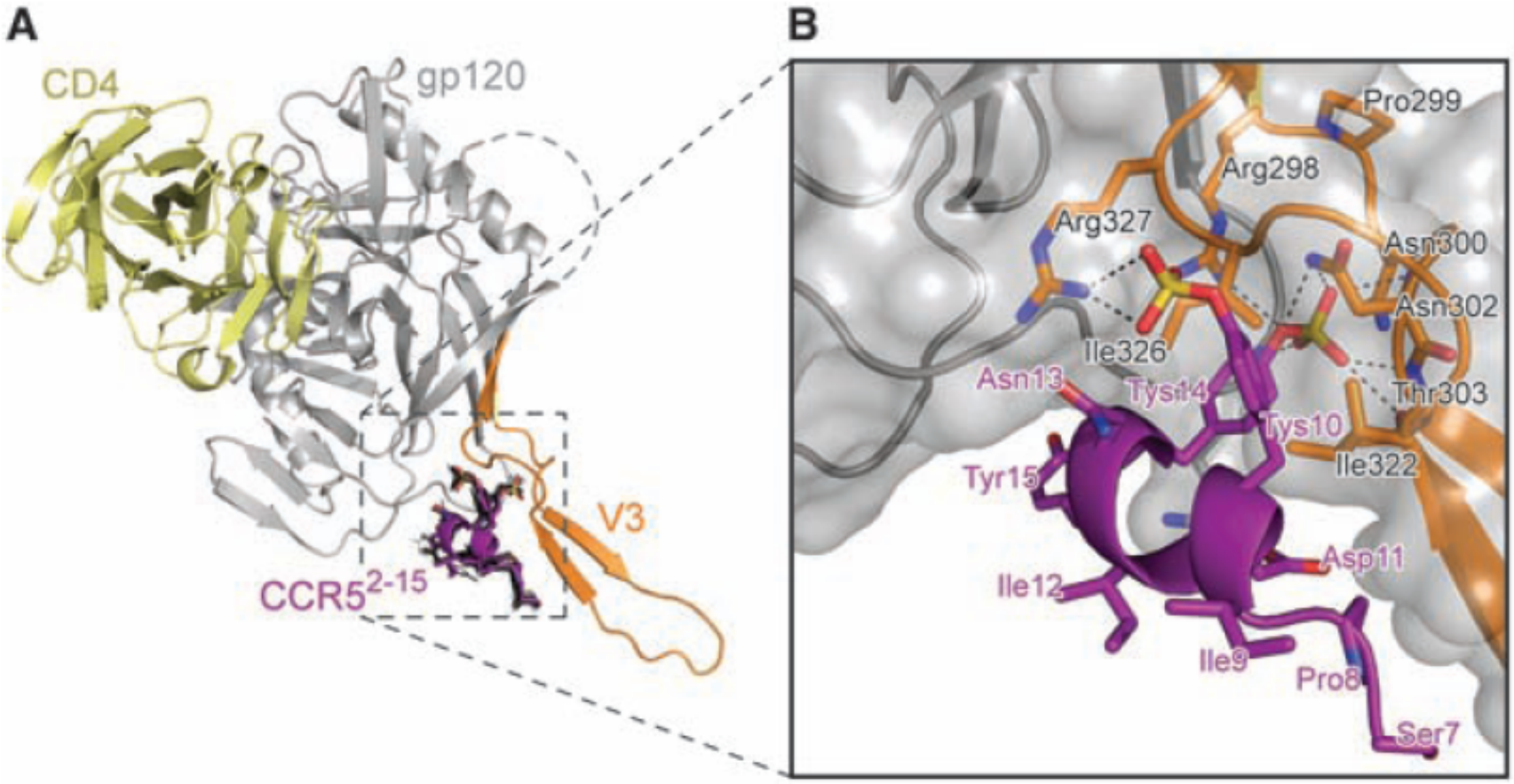

M-tropic HIV
gp 120
V3 loop
CD4
CCR5
Cell membrane
Entry of M-tropic HIV strains
M-tropic HIV
MIP-1α, MIP-1β, or RANTES
V3 loop
CD4
CCR5
Entry of M-tropic HIV strains blocked

28 SEPTEMBER 2007 VOL 317 SCIENCE www.sciencemag.org

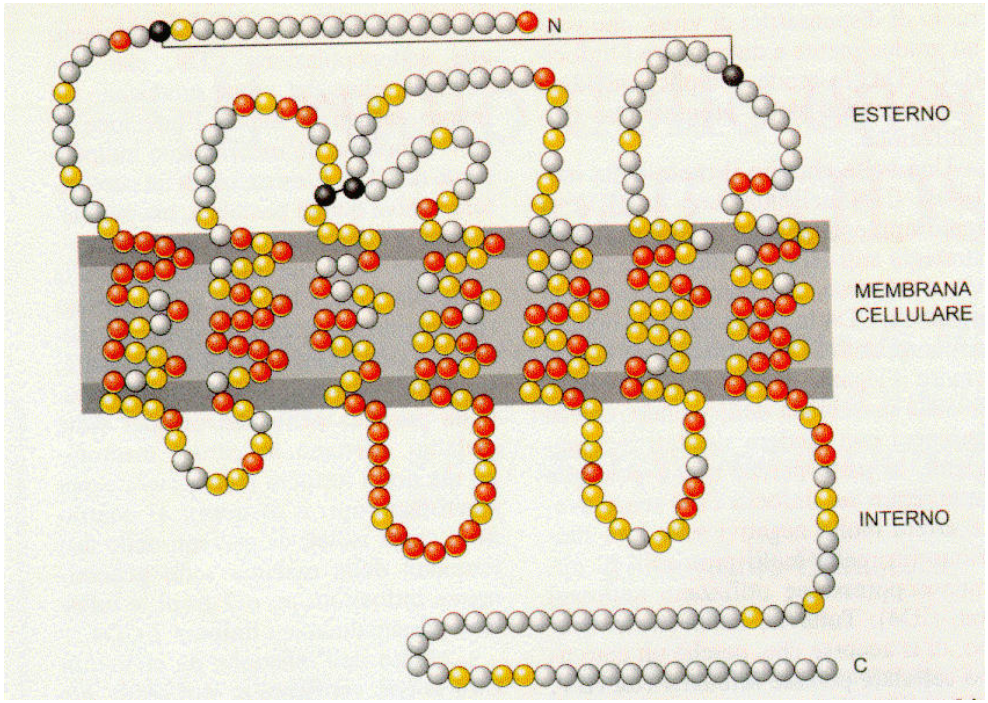
Structures of the CCR5 N Terminus and of a Tyrosine-Sulfated Antibody with HIV-1 gp120 and CD4

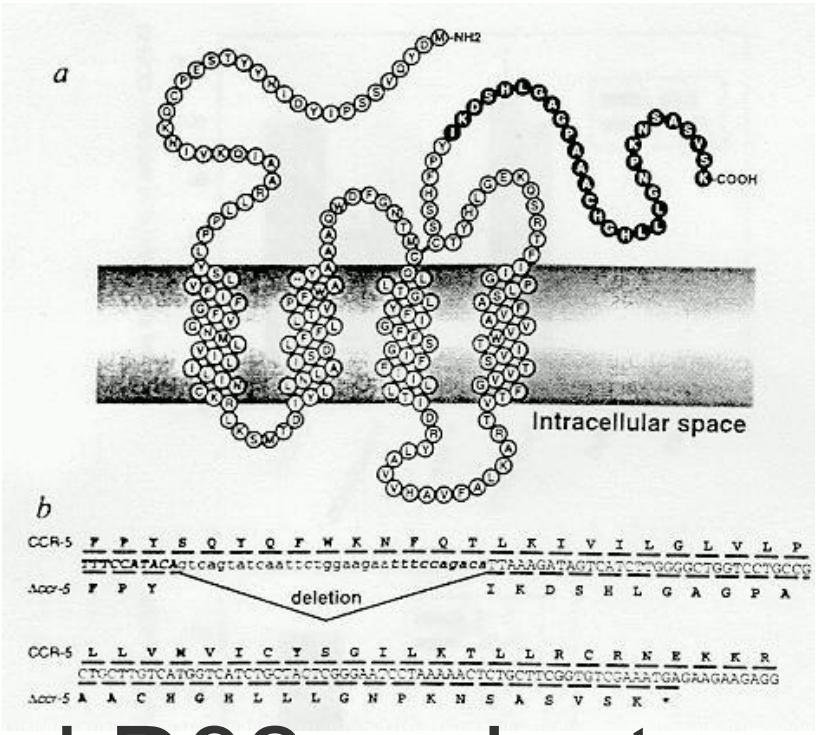
Chih-chin Huang,[1*] Son N. Lam,[2*] Priyamvada Acharya,[1] Min Tang,[1] Shi-Hua Xiang,[3] Syed Shahzad-ul Hussan,[2] Robyn L. Stanfield,[4] James Robinson,[5] Joseph Sodroski,[3] Ian A. Wilson,[4] Richard Wyatt,[1] Carole A. Bewley,[2]† Peter D. Kwong[1]†

The CCR5 co-receptor binds to the HIV-1 gp120 envelope glycoprotein and facilitates HIV-1 entry into cells. Its N terminus is tyrosine-sulfated, as are many antibodies that react with the co-receptor binding site on gp120. We applied nuclear magnetic resonance and crystallographic techniques to analyze the structure of the CCR5 N terminus and that of the tyrosine-sulfated antibody 412d in complex with gp120 and CD4. The conformations of tyrosine-sulfated regions of CCR5 (α-helix) and 412d (extended-loop) are surprisingly different. Nonetheless, a critical sulfotyrosine on CCR5 and on 412d induces similar structural rearrangements in gp120. These results now provide a framework for understanding HIV-1 interactions with the CCR5 N terminus during viral entry and define a conserved site on gp120, whose recognition of sulfotyrosine engenders posttranslational mimicry by the immune system.

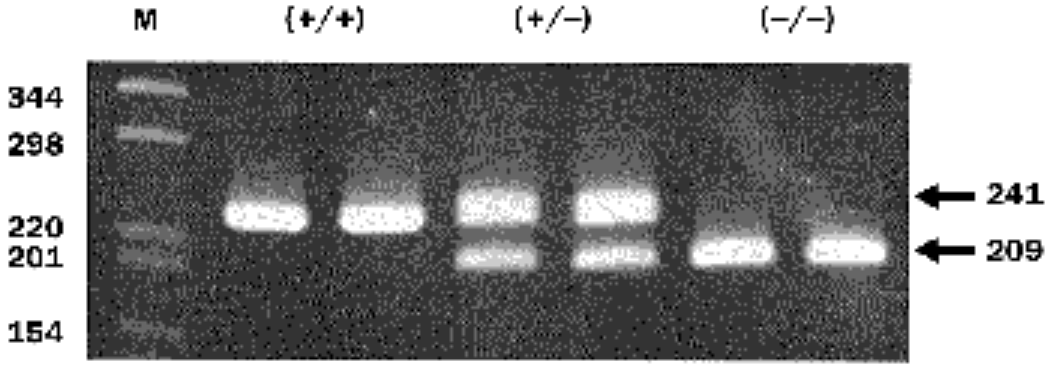


CCR5 molecule

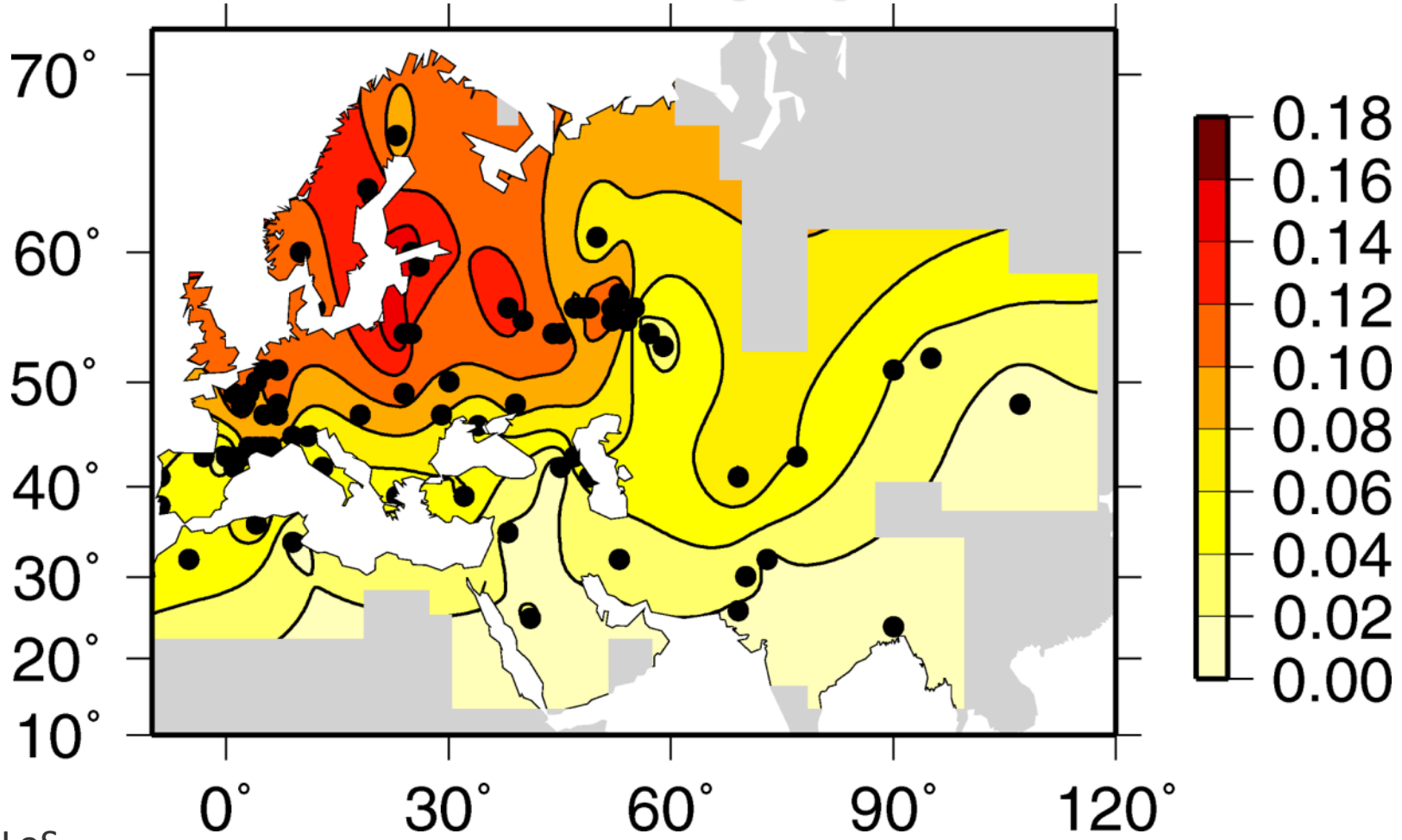




Wild type protein and D32 variant



Distribution of the CCR5Δ32 mutation in human populations



from PLoS Biology, Nov 2005

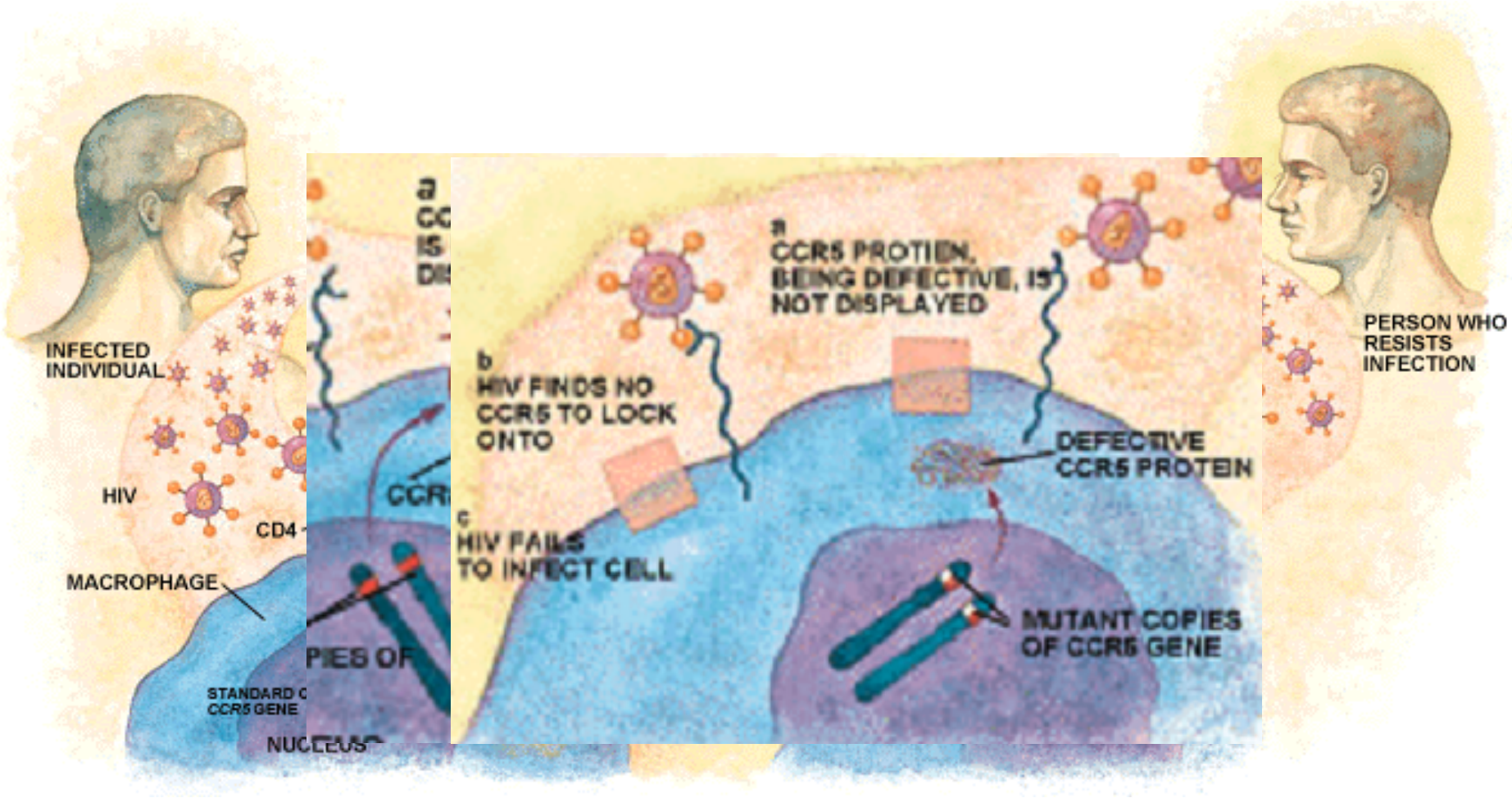
Galvani, AP and Slatkin, M. 2003. Evaluating plague and smallpox as historical selective pressures for the CCR5-D32 HIV resistance allele. PNAS 25:15276-15279.

Macrophage tropic HIV, the predominant form early in infection uses CCR5 as a coreceptor. Individuals homozygous for a mutation that removes CCR5 are resistant to HIV while people who are heterozygous are partially protected and AIDS takes longer to develop. Loss of CCR5 does not appear to have deleterious effects and other chemokine receptors probably compensate for its loss. Frequency of allele in Northern populations is 10% suggesting strong selective pressure. The allele is almost non-existent in Asian, African, middle eastern or N. American Indian populations. High frequency in northern people suggests events about 700 years ago that selected for mutation. Since HIV is a relatively recent disease there must have been some other disease. There are two main candidates - the plague (peste) and smallpox (vaiolo)(1336-1352, intermittent outbreaks, 1665-1666). Galvani and Slatkin use modeling to show that plague could not have accounted for high frequency of allele and that smallpox was the more likely cause. Based on three points - population genetics model, geographical distribution of allele and clinical effects of mutation.

While the plague caused extensive deaths the disease was only present in Europe intermittently and during a relatively small window of 400 years. The selective pressure of plague would also be removed after it died out in 1700s. Smallpox, on the other hand, was continuously present for over 2,000 years and was only recently eradicated in 1978, coincident with the appearance of HIV. Plague affected people of all ages while smallpox was largely a disease of the very young who would not have immunity against a disease that was continually present. The model predicts that the plague could only have accounted for a frequency of at most 1% while smallpox could account for the 10% frequency of CCR5-D32. Plague affected all of Europe and Asia while there is evidence that the northern European countries were more severely affected by smallpox. This might account for the 14% - 0% gradient seen from north to south in Europe. Poxviruses also use CCR5 as a receptor (Lalani et al. 1999, Science 286:1968-1971).

Pfizer drug that blocks CCR5 - UK-427,857 - Shows promise in clinical trials http://www.aidsmeds.com/news/20040713drgd004.html.

Resistence to HIV infection



Don’t trust your genes, hoping to have inherited a composition conducing to HIV resistance...

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

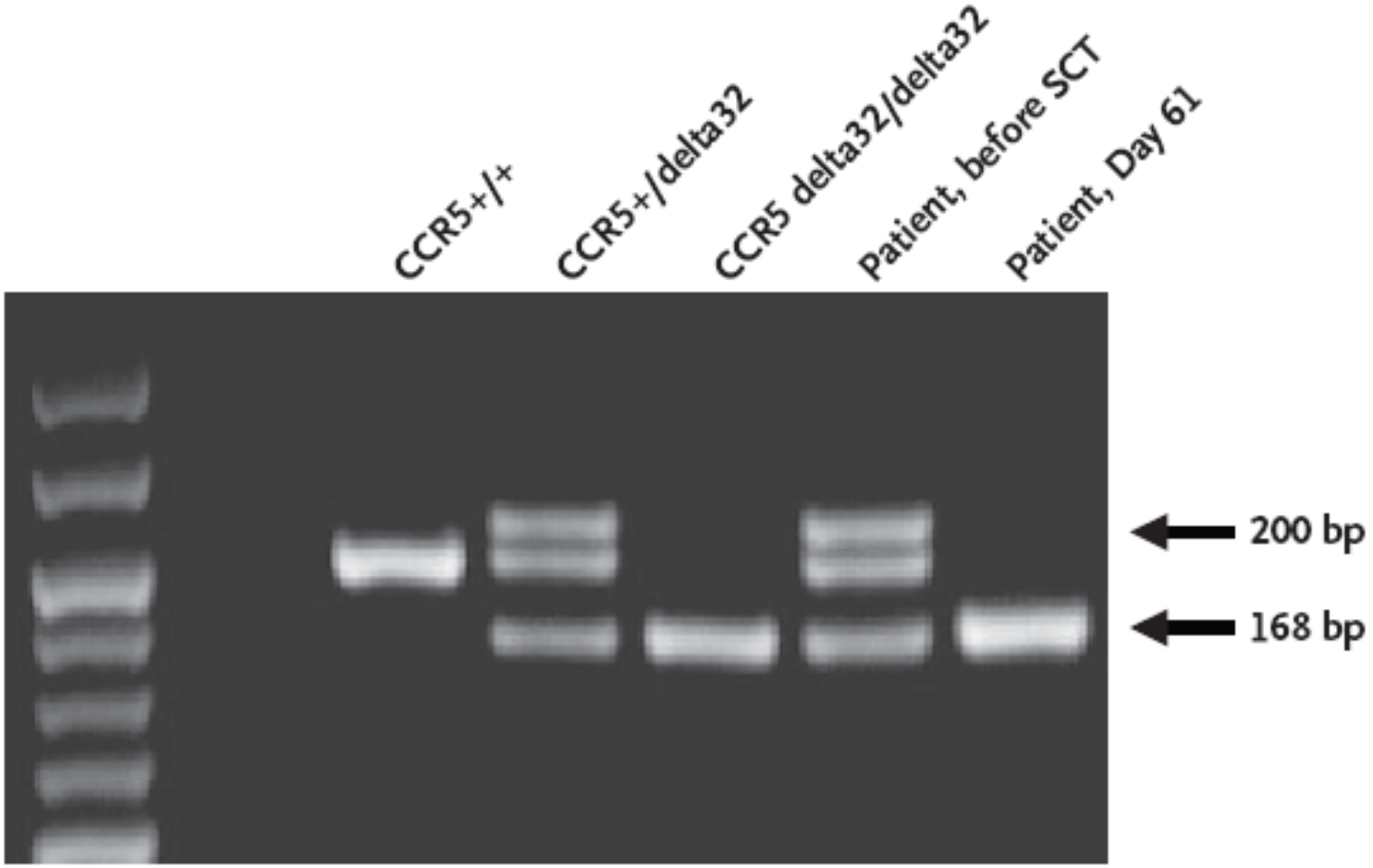
Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

SUMMARY

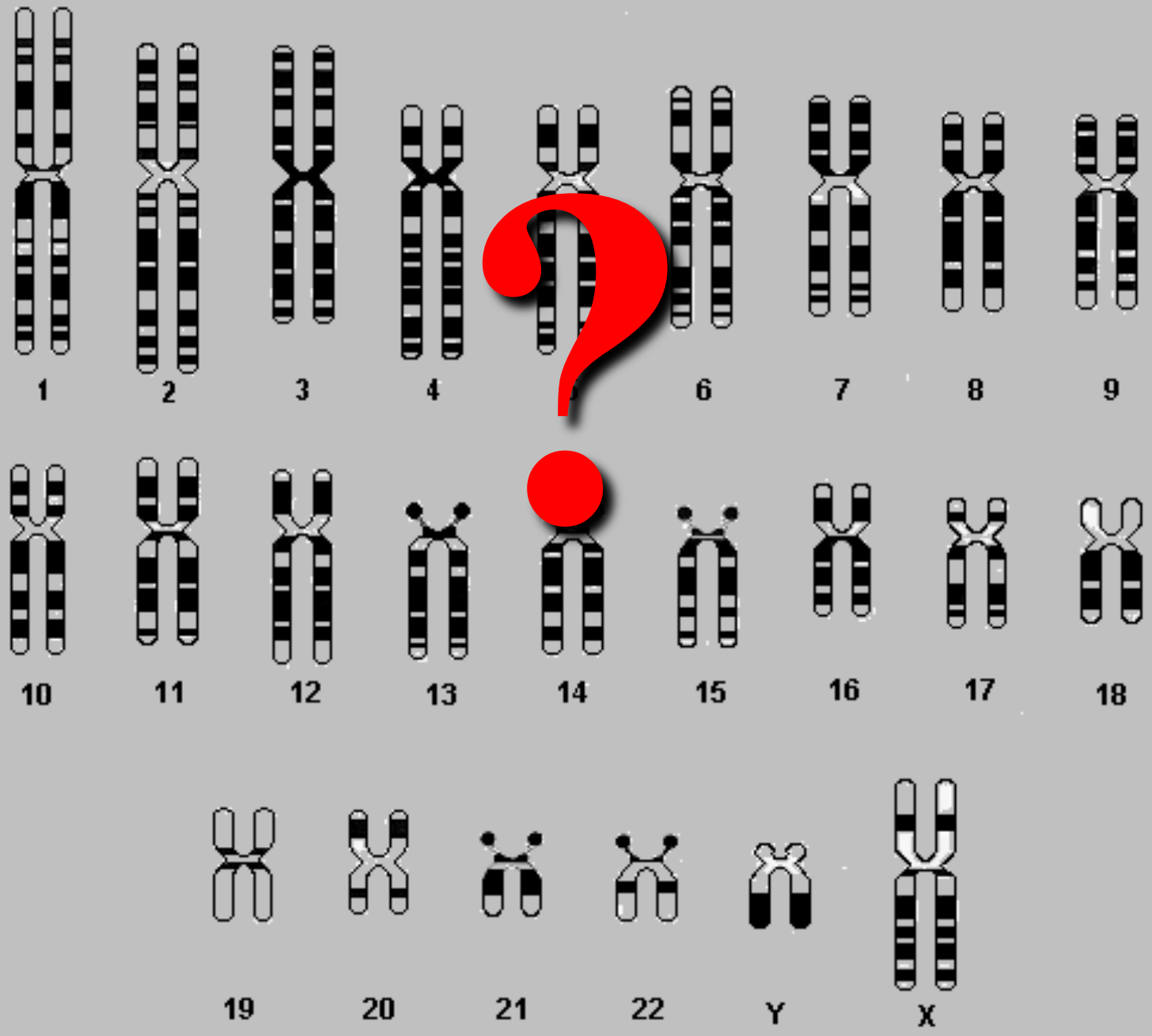
Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the *CCR5* allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for *CCR5* delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role *CCR5* plays in maintaining HIV-1 infection.

FEBRUARY 12, 2009


CCR5+/+
CCR5+/delta32
CCR5 delta32/delta32
Patient, before SCT
Patient, Day 61
200 bp
168 bp

Complex diseases

- definition
- How you recognize them
- How you measure genetic susceptibility
- Genetic polymorphisms
- How you study them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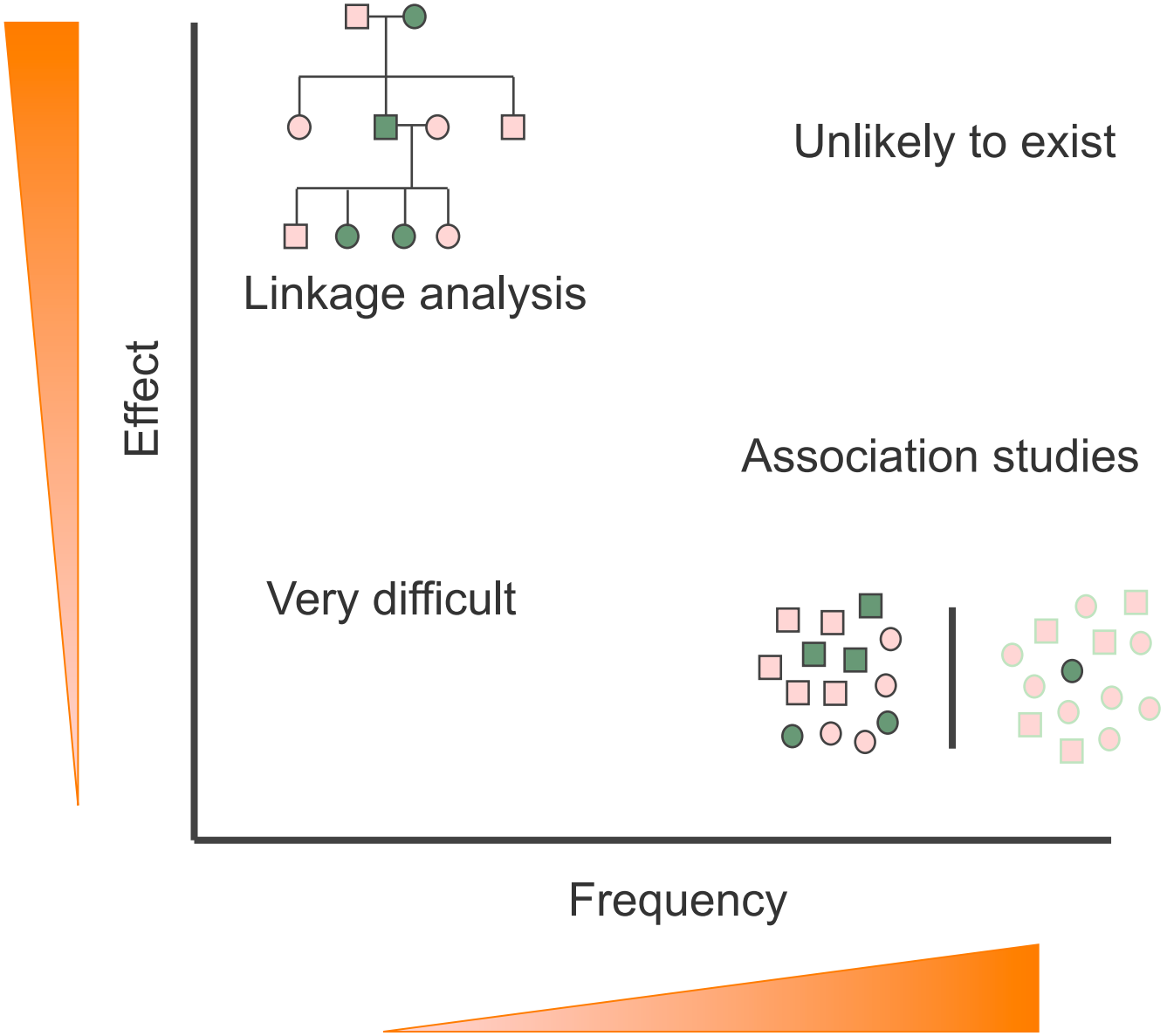
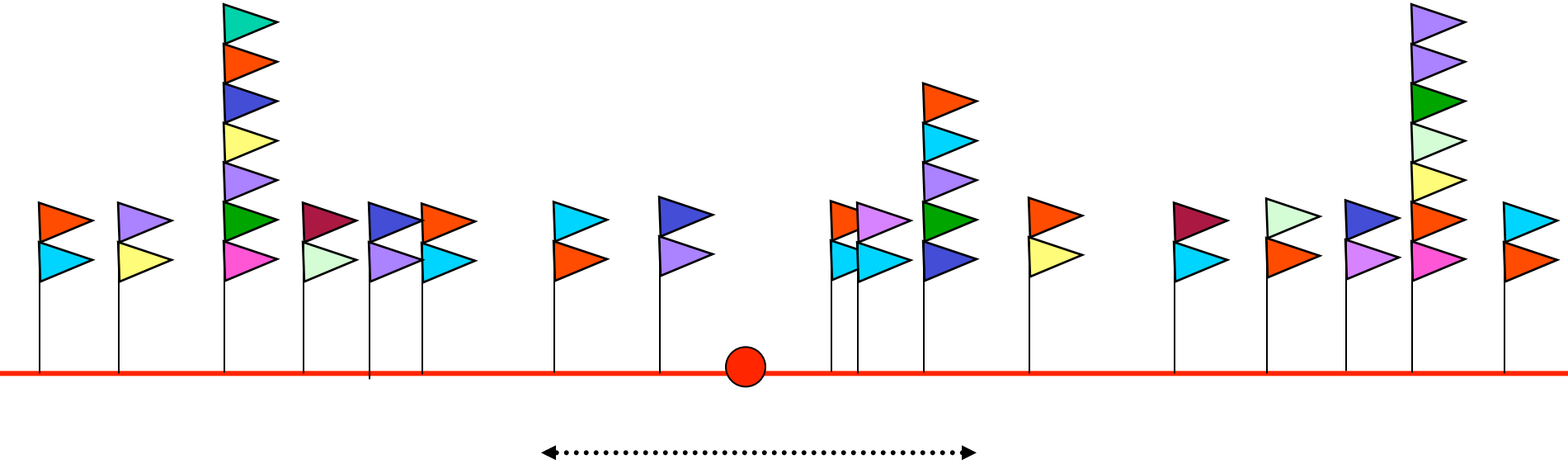
Y
X

Statistical genetic methods for disease gene identification





CO-TRANSMISSION

LINKAGE analysis follows the co-transmission from generation to generation

ASSOCIATION study follows the co-transmission from a common ancestor after many generations

LINKAGE ANALYSIS

It is based on the study of polymorphic genetic markers segregation within families in which the character under study is present.

PARAMETRIC ANALYSIS: phenotypically homogeneous families must be analyzed, it is needed to know the type of inheritance (very complex when considering multifactorial characters)

NON-PARAMETRIC ANALYSIS: Although based on the study of families do not consider non-affected and the analysis is focused on looking for common alleles among affected individuals

NON-PARAMETRIC ANALYSIS

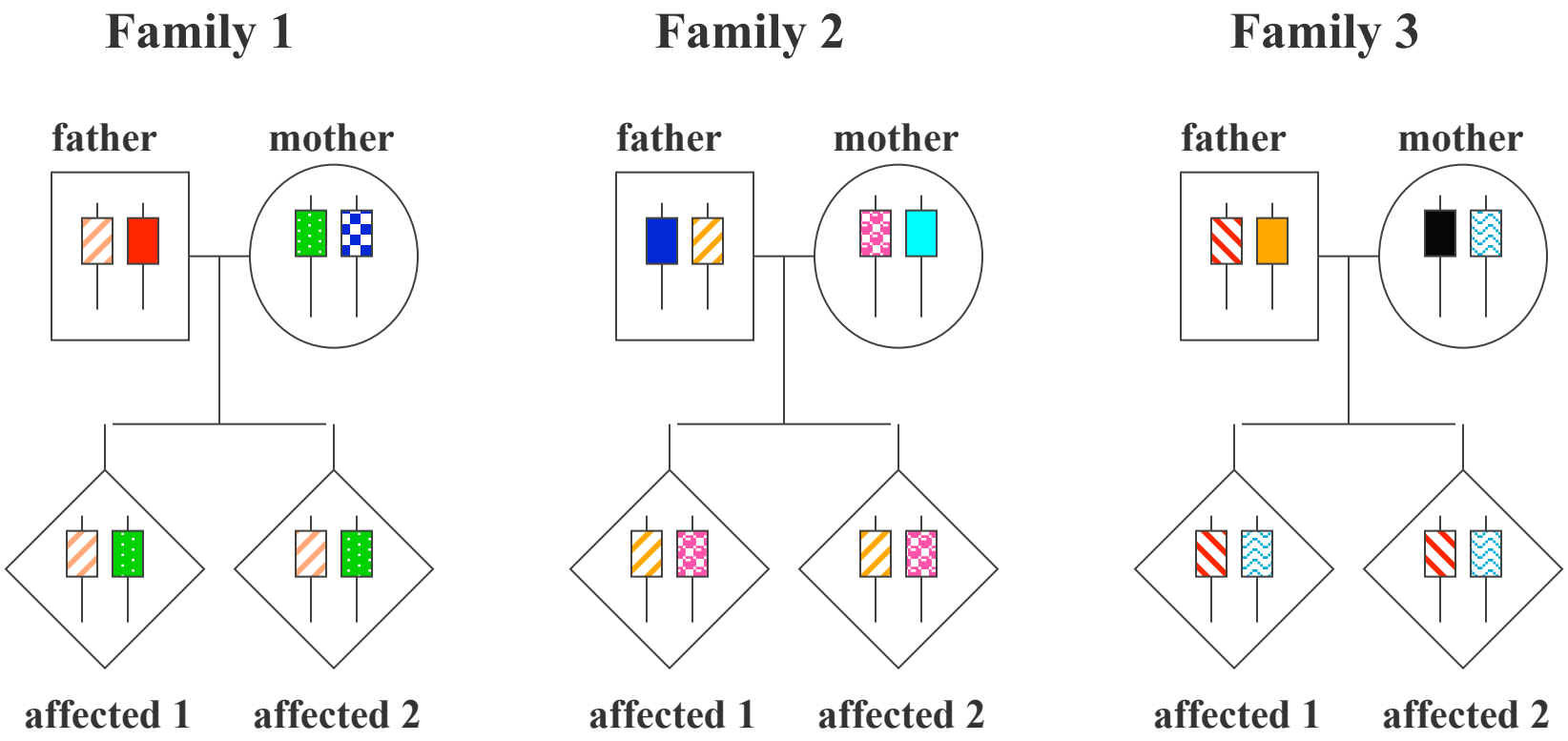
One of the most commonly used methods is the analysis of shared alleles in siblings (ASP, Affected Sib Pairs)

This methodology is based on the assumption that two individuals with the same family should have in common susceptibility alleles that predispose to disease

Assuming that an average of 50% of the brothers should inherit equal paternal or maternal alleles, if between pairs of siblings sharing rate of a marker is significantly greater than expected by chance, you will tend to conclude that there is a relationship between the complex character and a gene located in the chromosomal region disorder where the marker is mapped

The need to study a very large number of pairs of brothers to reach a good statistical significance is a limit to the application of this analysis

Linkage analysis



CASE-CONTROL ASSOCIATION STUDIES

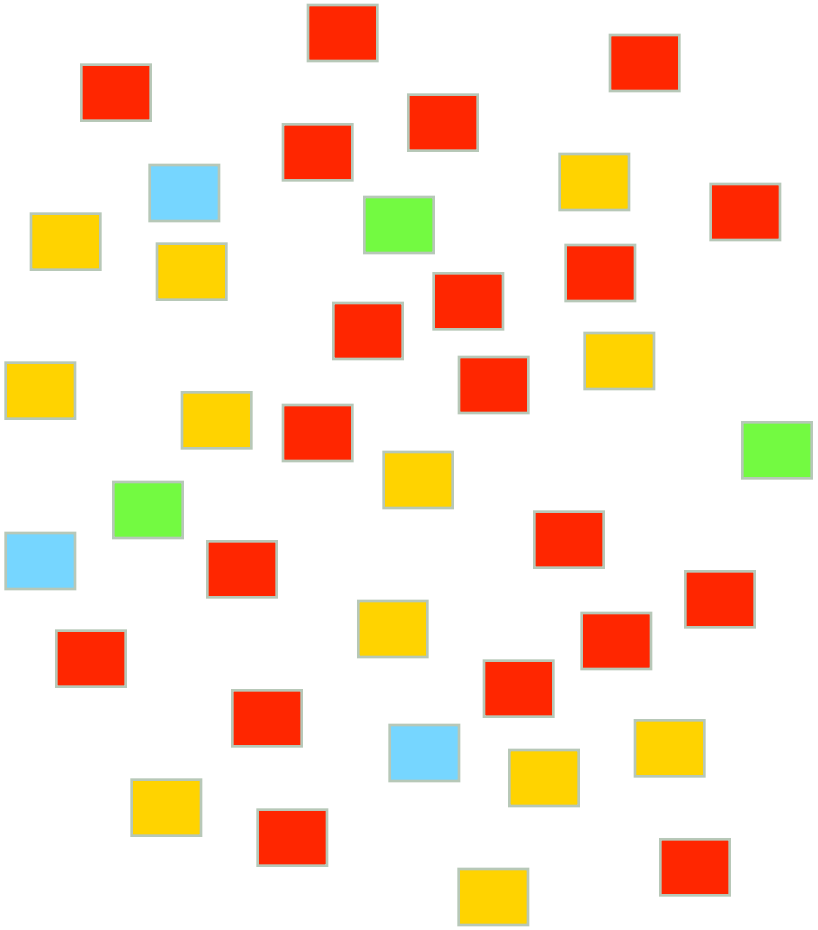
It is the most used method to identify the genes involved in multifactorial characters.

It consists in the comparison of the frequency of a particular polymorphism, SNP and more recently CNV in two groups of subjects divided depending on presence (cases) or absence (controls) of the character.

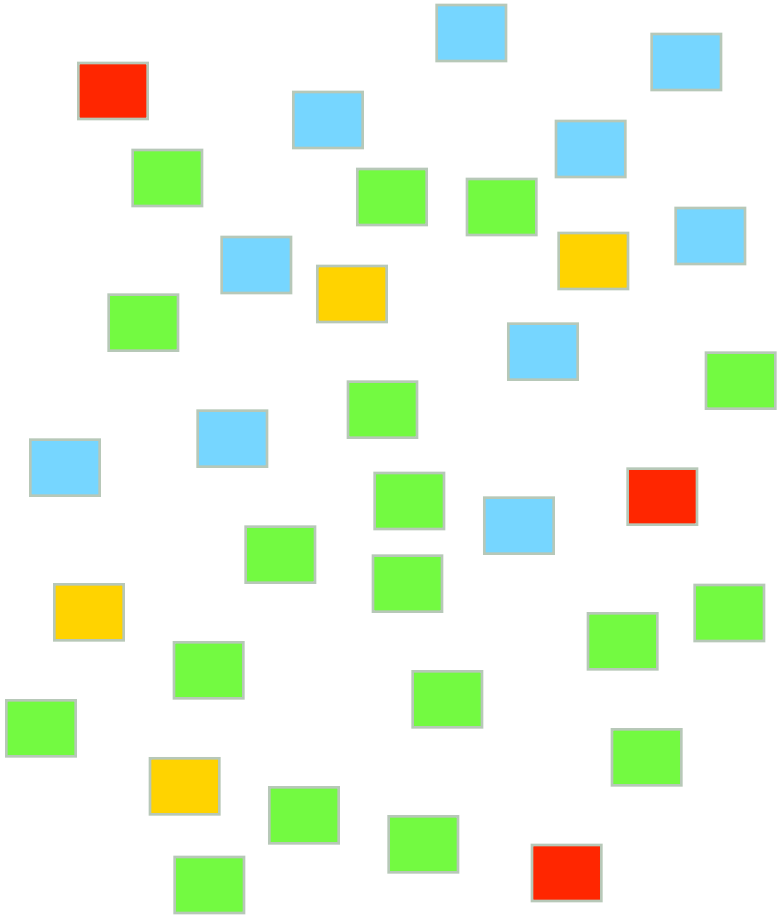
One of the main advantages is the ability to analyze sporadic cases, more easily recruited compared to households required for linkage analysis.

These studies were originally used to consider the hypothesis of a candidate gene involved in susceptibility to the character/ disease.

Association studies



Patients

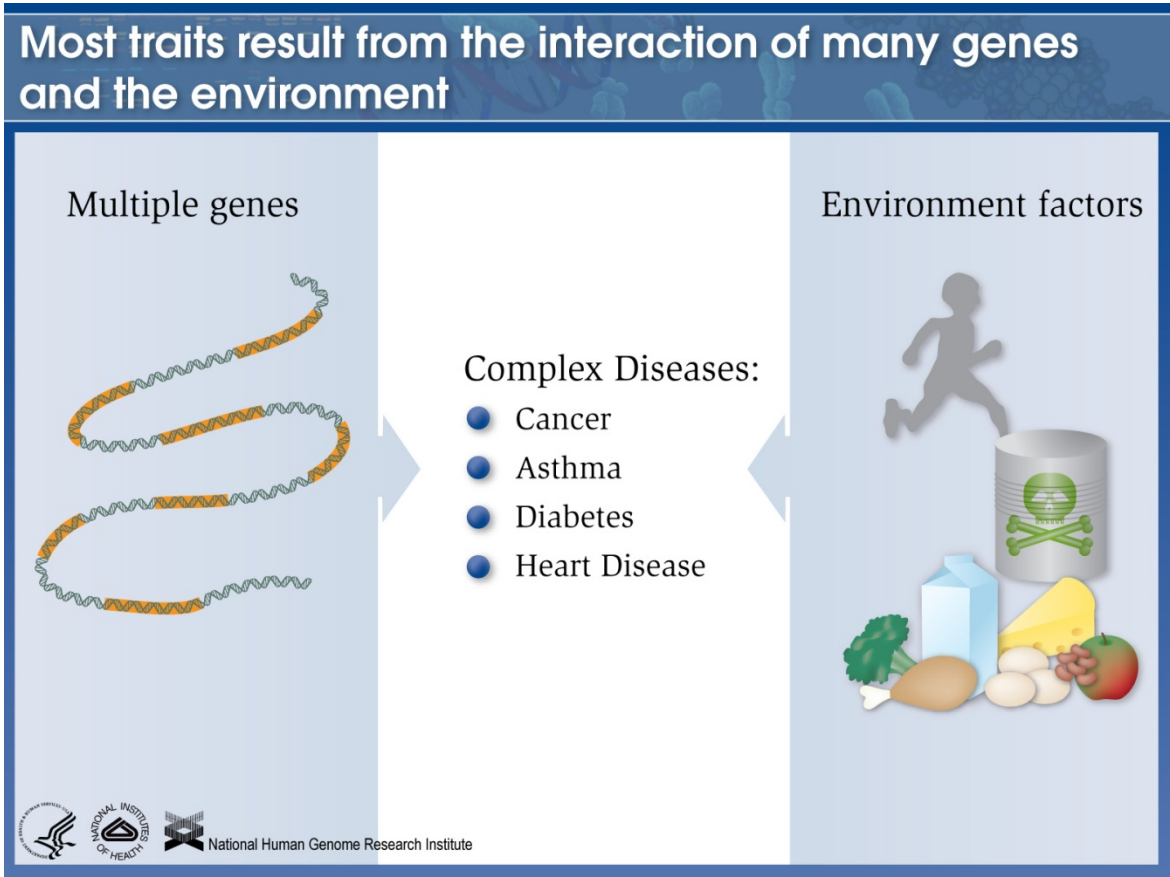


Controls

In any case remember that:

- These are complex diseases, due to the interaction of environmental factors and genetic factors
- We are considering only the genetic component

- In addition often limited to one single gene
- Much better would be to evaluate susceptibility contribution of all involved genes to the disease



The future….

Science

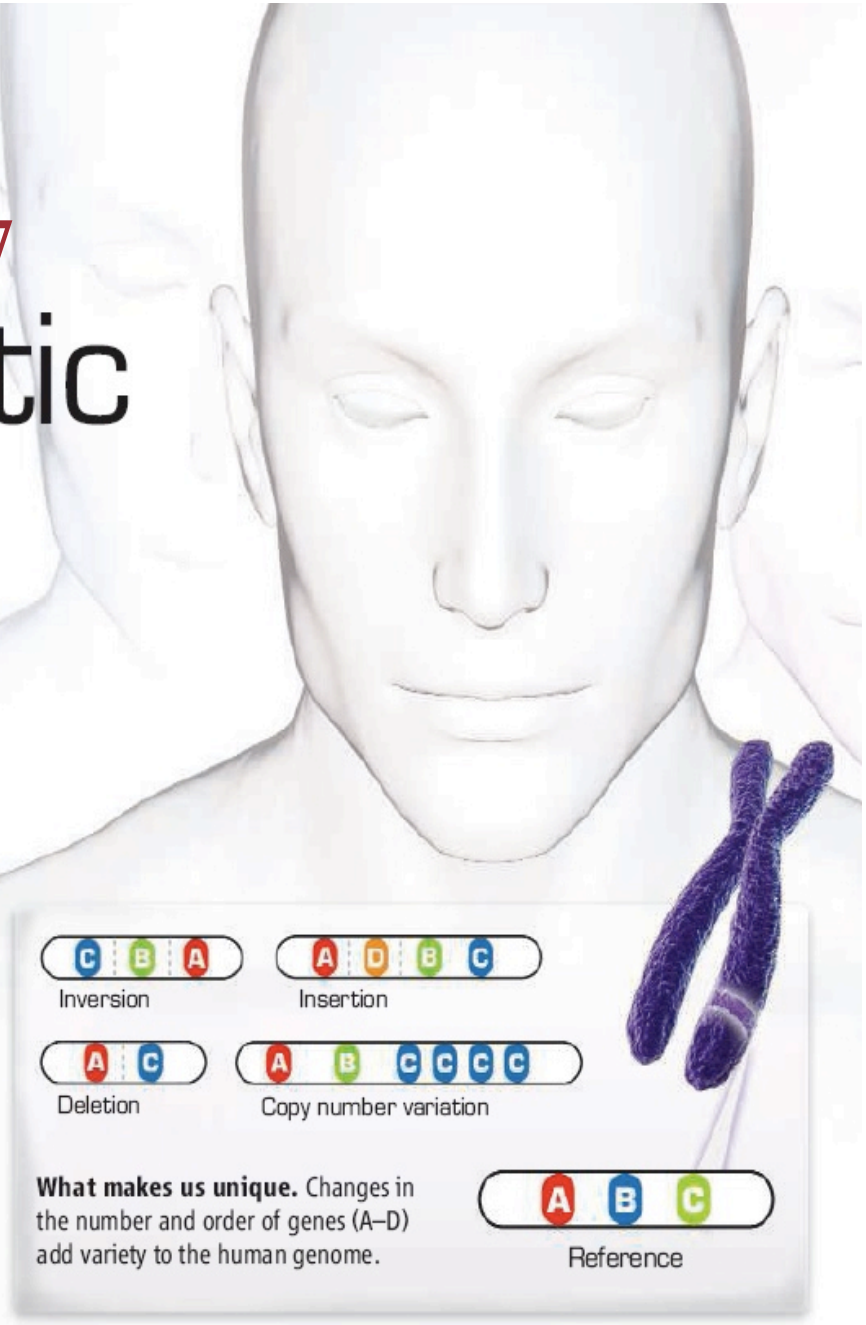
BREAKTHROUGH OF THE YEAR 2007

Human Genetic Variation

Equipped with faster, cheaper technologies for sequencing DNA and assessing variation in genomes on scales ranging from one to millions of bases, researchers are finding out how truly different we are from one another

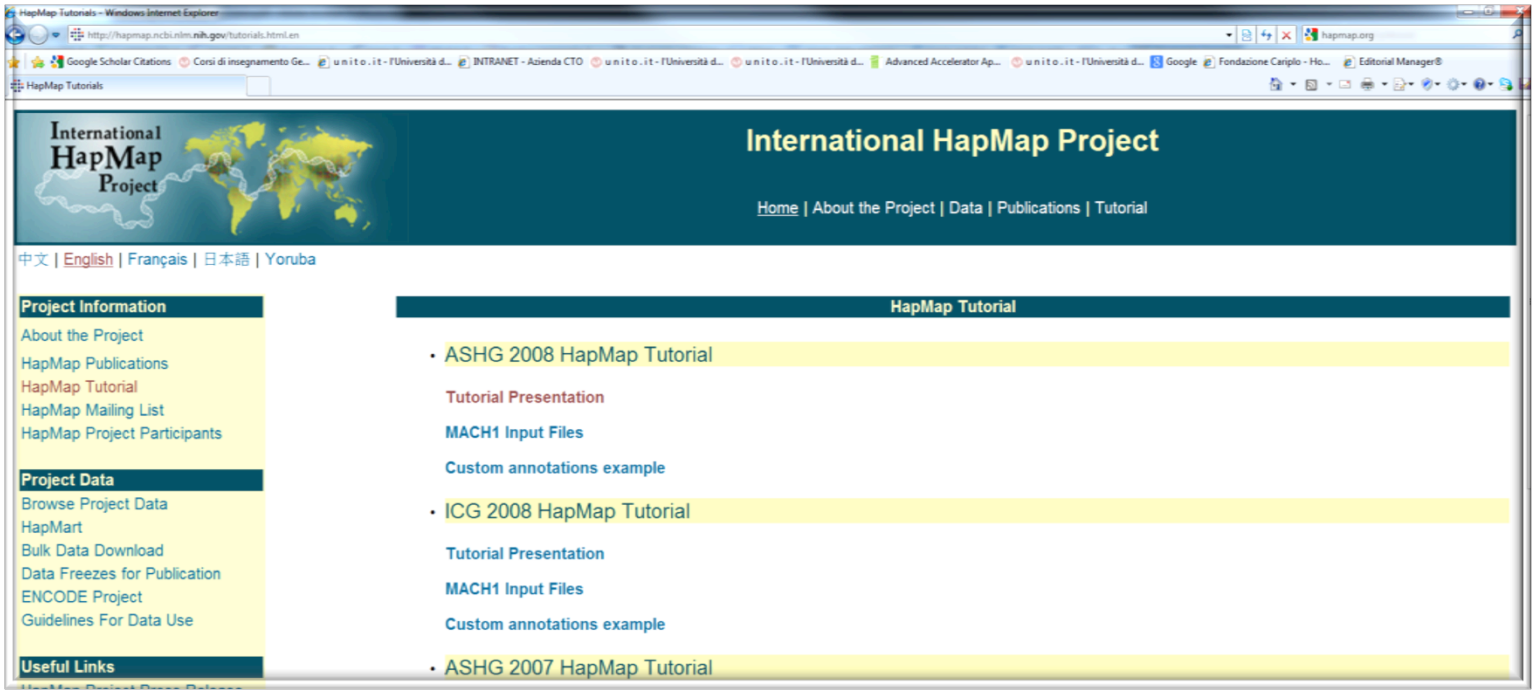
THE UNVEILING OF THE HUMAN GENOME ALMOST 7 YEARS AGO cast the first faint light on our complete genetic makeup. Since then, each new genome sequenced and each new individual studied has illuminated our genomic landscape in ever more detail. In 2007, researchers came to appreciate the extent to which our genomes differ from person to person and the implications of this variation for deciphering the genetics of complex diseases and personal traits.

Less than a year ago, the big news was triangulating variation between us and our primate cousins to get a better handle on genetic changes along the evolutionary tree that led to humans. Now, we have moved from asking what in our DNA makes us human to striving to know what in my DNA makes me me.



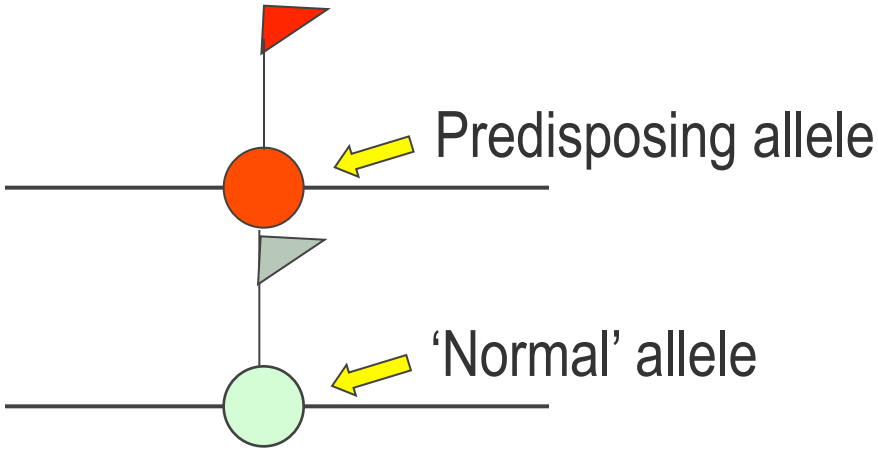
What makes us unique. Changes in the number and order of genes (A–D) add variety to the human genome.

THE GENOME IS STRUCTURED IN "BLOCKS" OF LINKAGE DISEQUILIBRIUM FLANKED BY RECOMBINATION HOTSPOTS

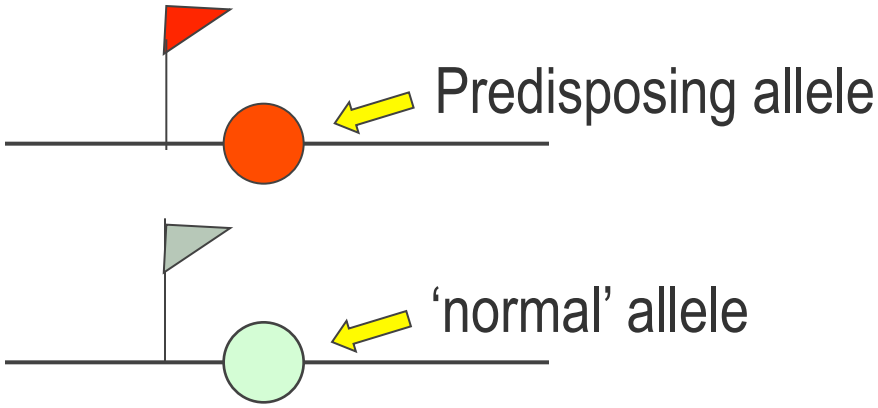


Hap-Map project
http://www.hapmap.org/

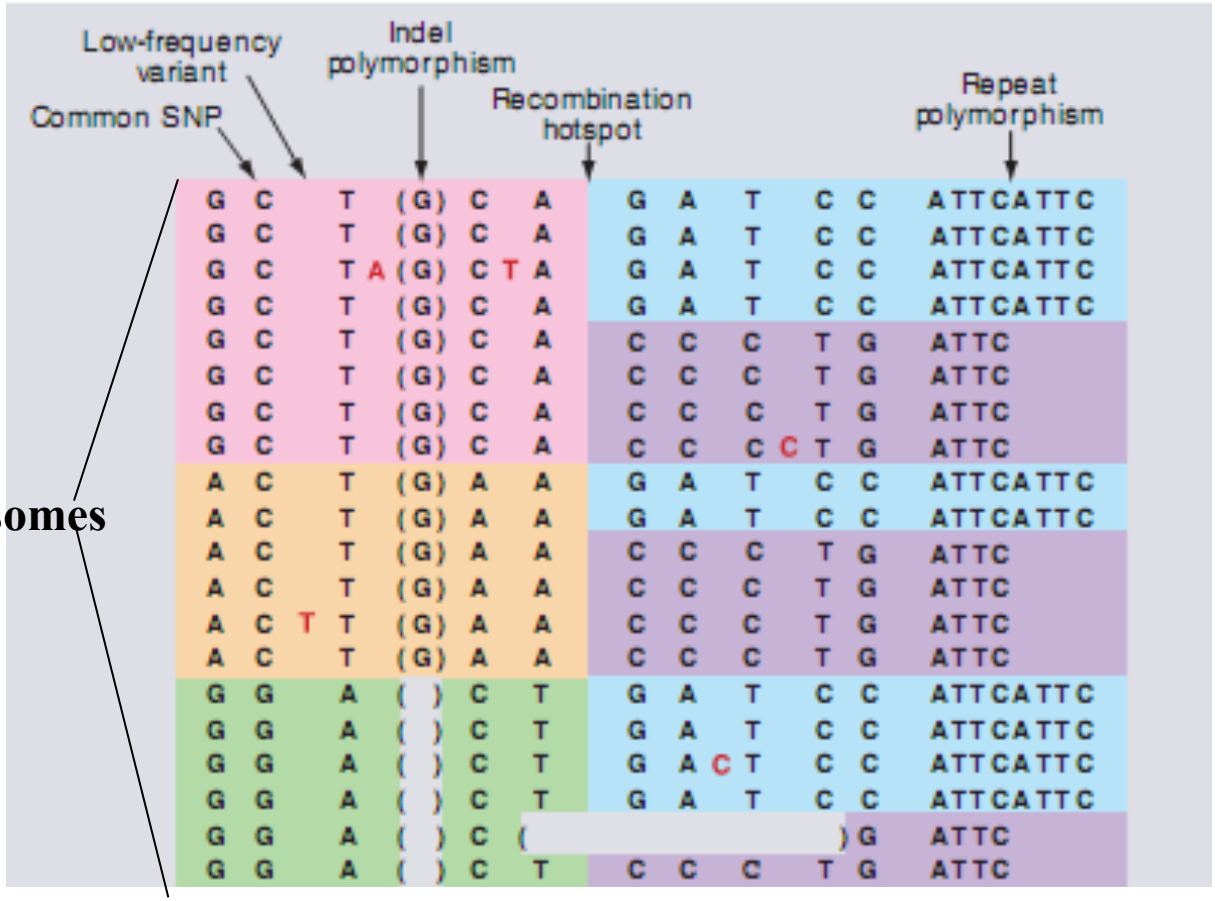
1) Marker allele is directly involved in the disease



2) Marker allele is very close to the predisposing allele thanks to the linkage disequilibrium



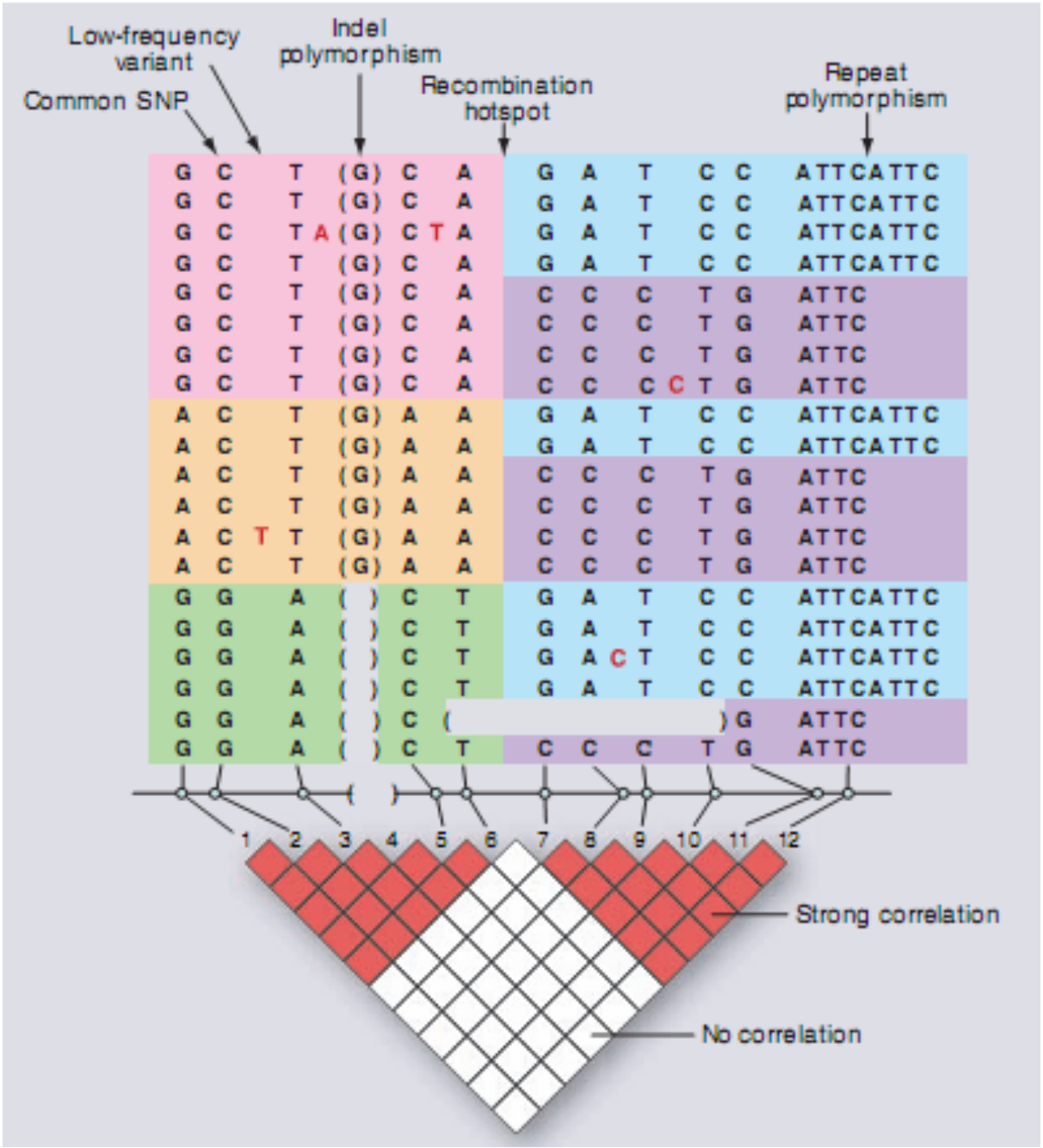
DNA SEQUENCE VARIATIONS IN HUMAN GENOME…



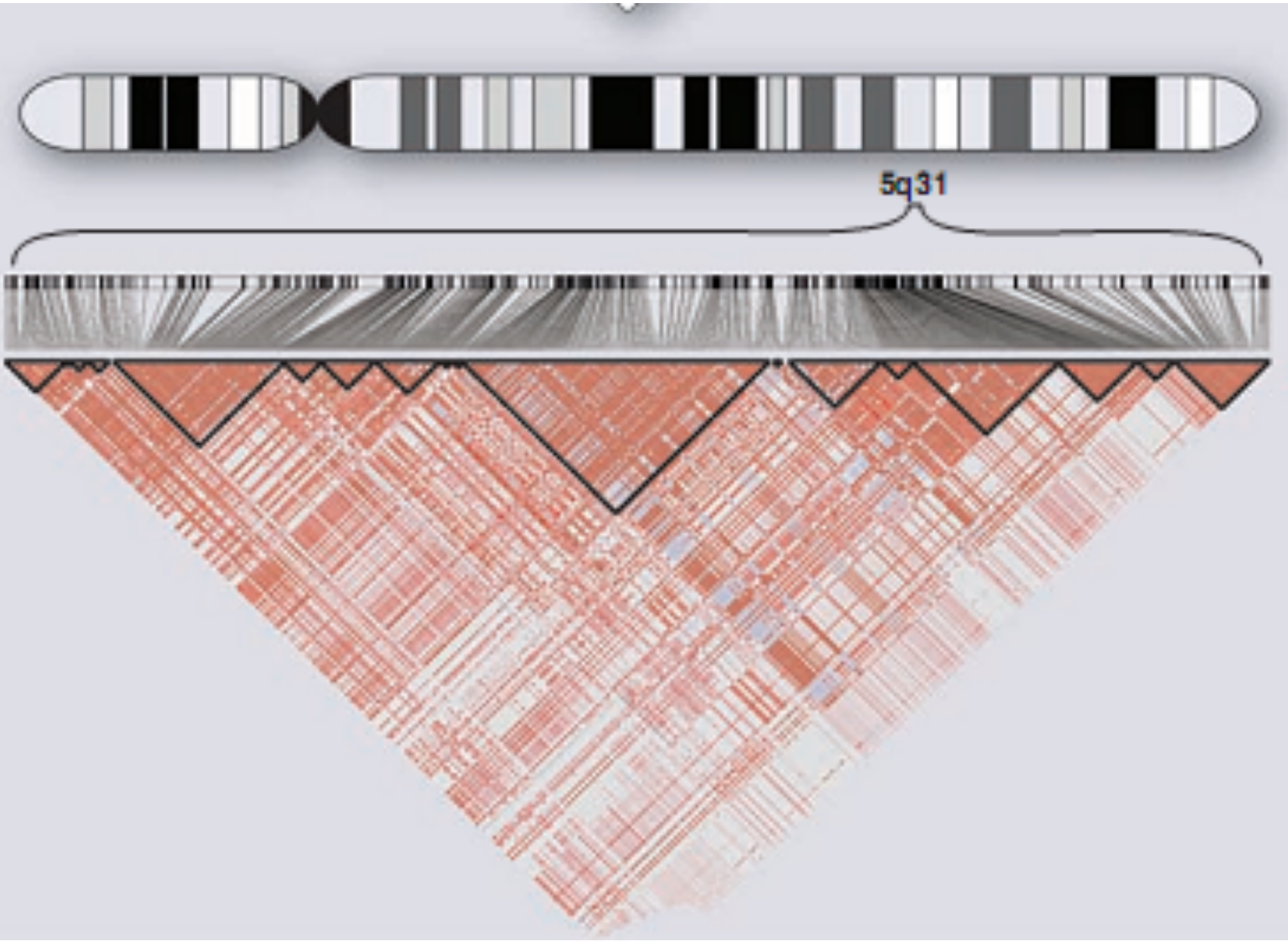
…AND THEIR HAPLOTYPE COMBINATION IN THE POPULATION

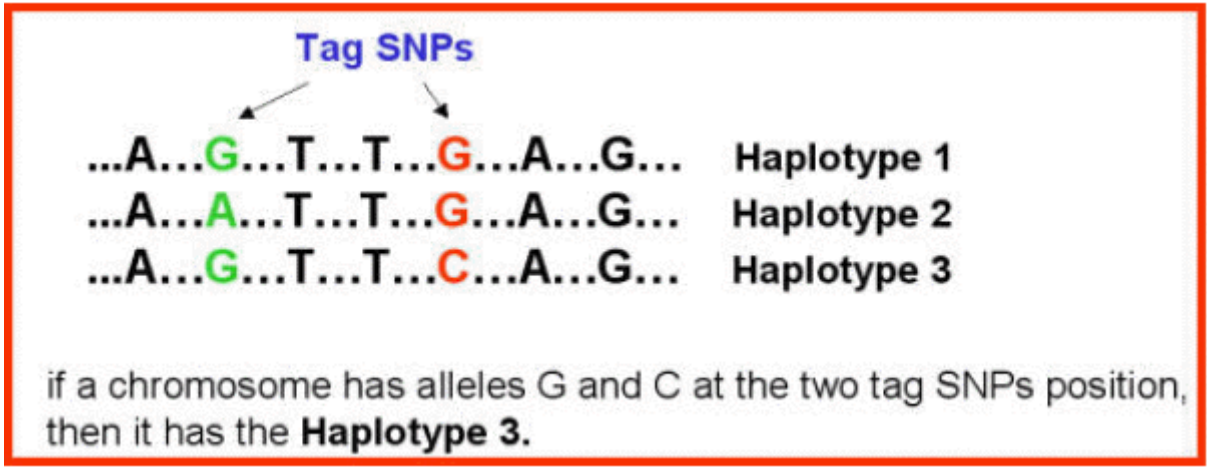
HAPLOTIPE: combination of allelic variants to close loci along a chromosome or in a chromosomal segment

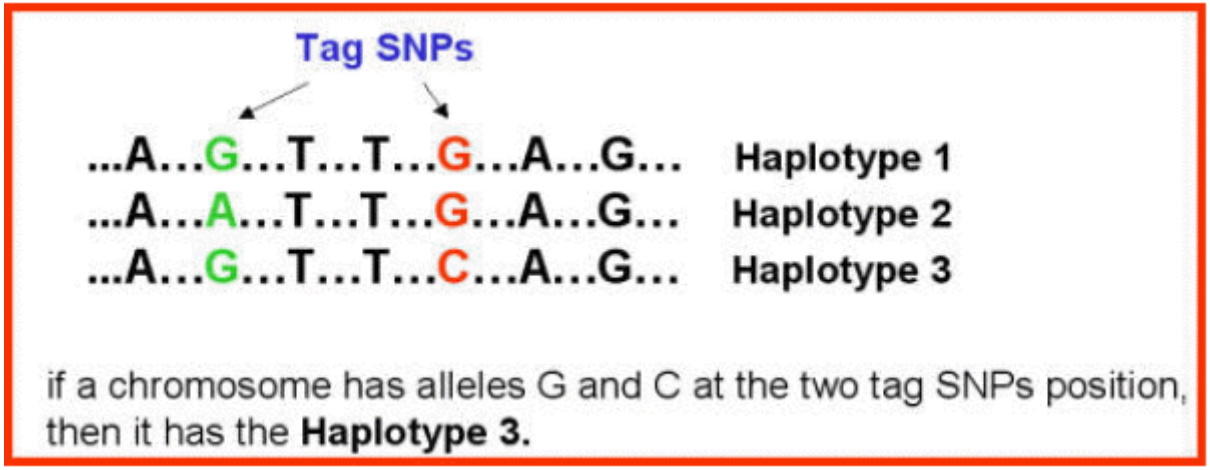
DNA SEQUENCE VARIATIONS IN HUMAN GENOME



BLOCKS




Tag SNPs
...A...G...T...T...G...A...G... Haplotype 1
...A...A...T...T...G...A...G... Haplotype 2
...A...G...T...T...C...A...G... Haplotype 3
if a chromosome has alleles G and C at the two tag SNPs position, then it has the **Haplotype 3.**



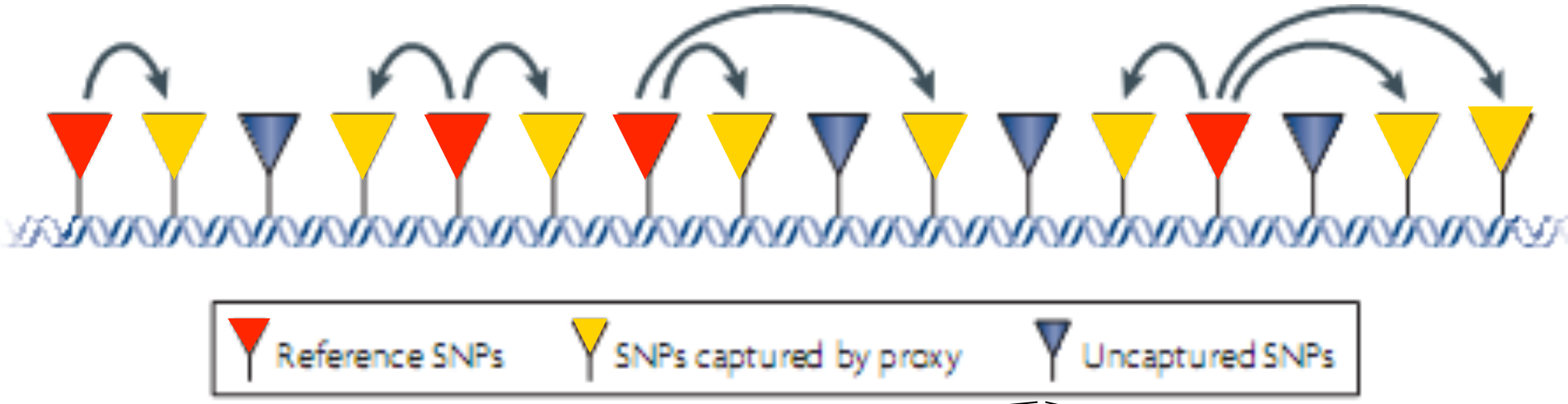
It is possible to study a limited number of SNPs in a genomic region

~20.000 nt / block → 150.000 blocks tot. → 2-3 SNPs / block

Total = ~ **500.000 SNPs** (and not 7-10 millions)

Possibility of genomic screening with SNPs

Selection of markers for association studies on whole genomes



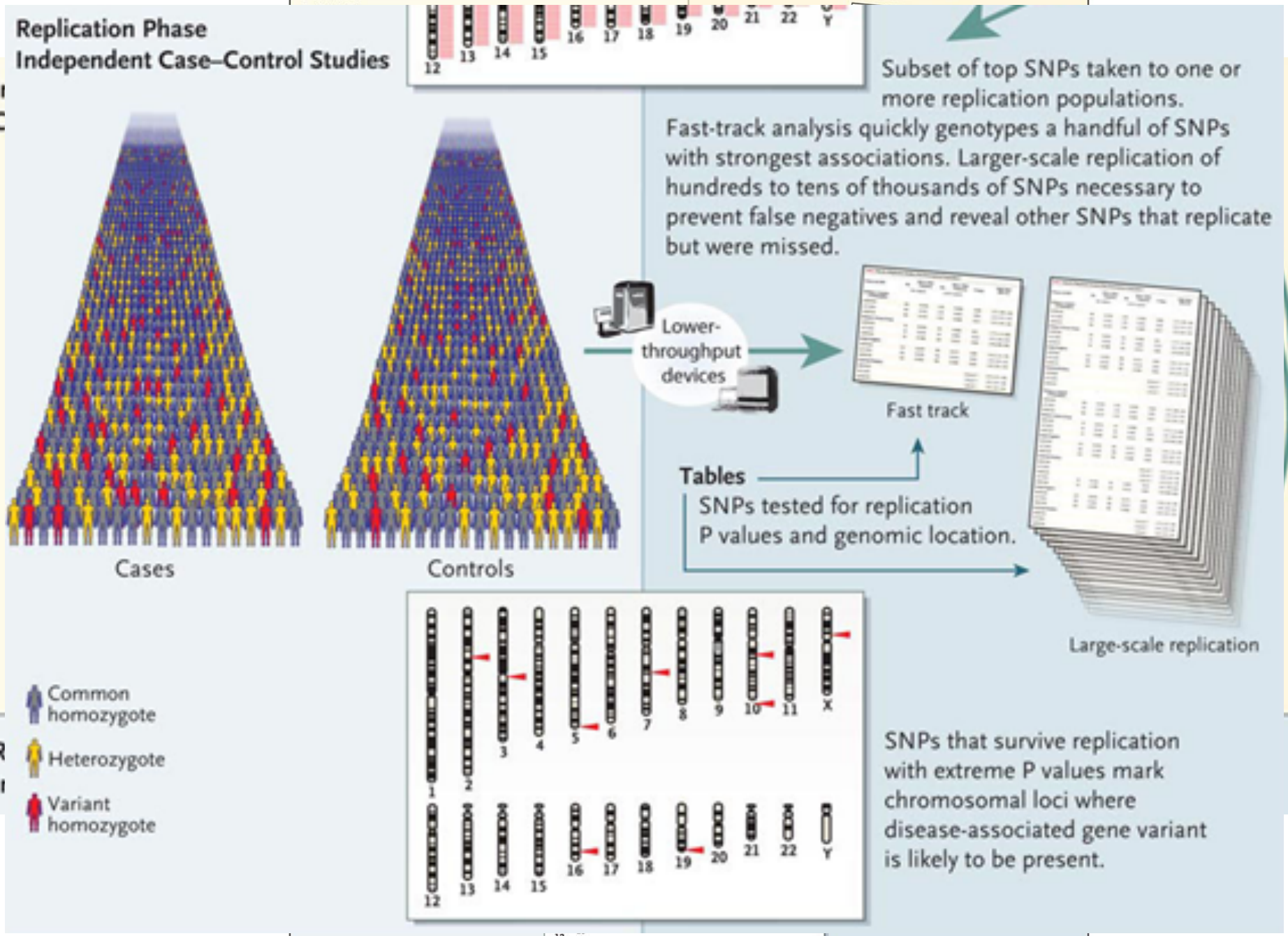
With this approach, rare variations and variations non-correlated with reference markers (linkage disequilibrium) are <u>not</u> analysed

(GWAS based of the hypothesis: "common disease, common variant")

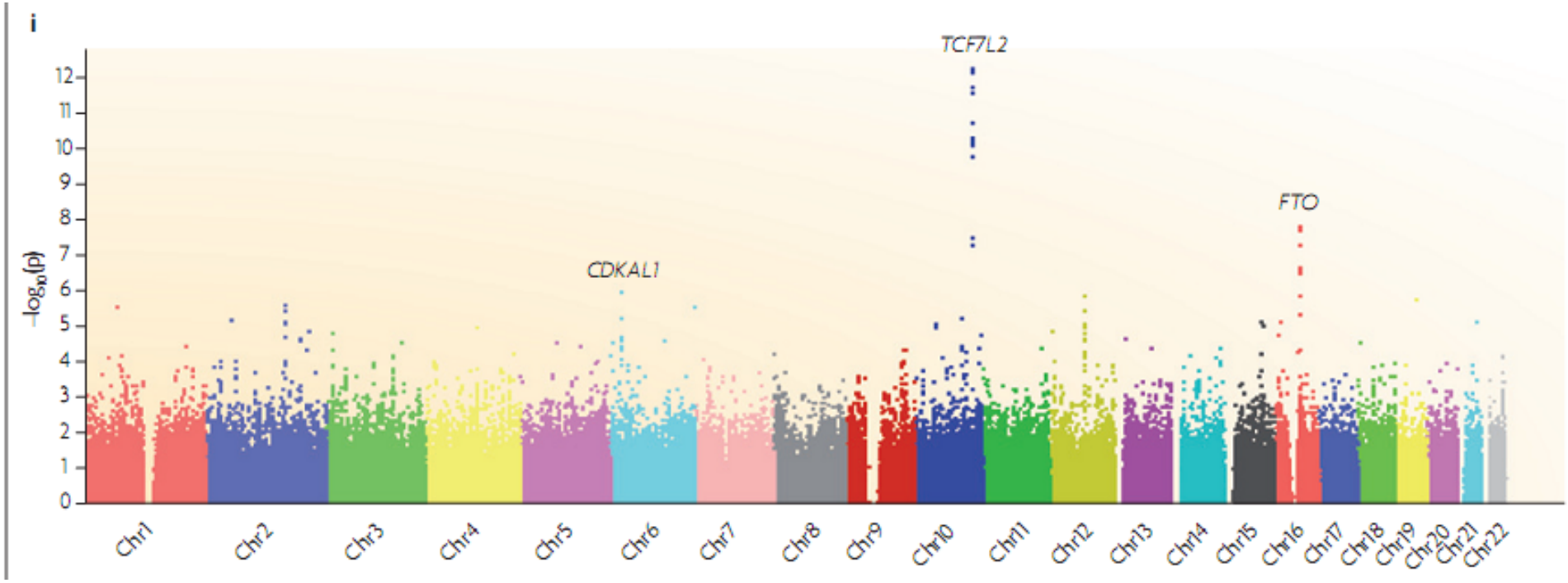
OLIGONUCLEOTIDE MICROARRAY

- **Oligonucleotides (20-25 bases) are synthesized directly on a ultrafine solid slide**
- **Microchip containing over 500.000 different oligonucleotides in an array of 1,28x1,28 cm**

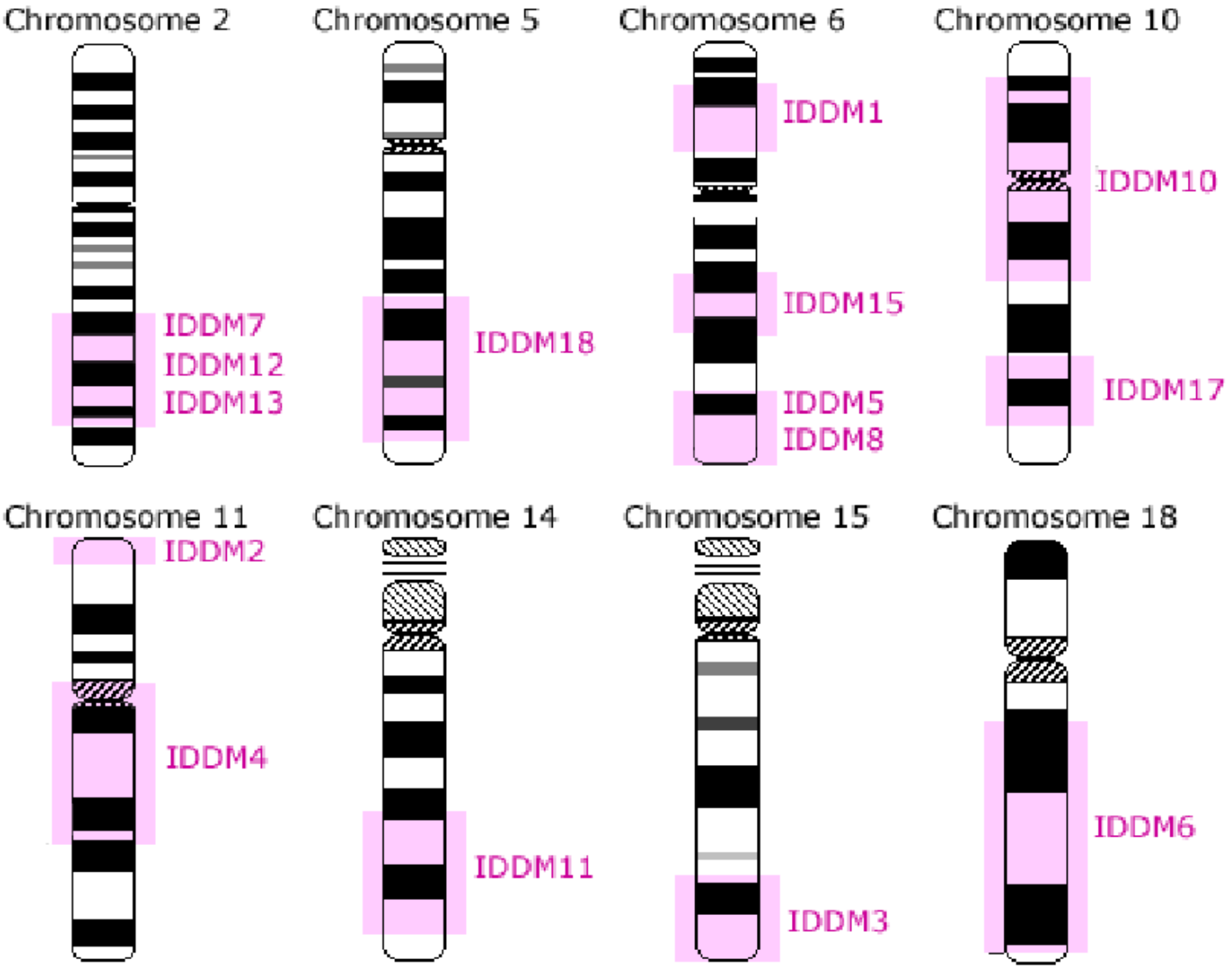
OLIGONUCLEOTIDE MICROARRAYS


Replication Phase
Independent Case–Control Studies
Subset of top SNPs taken to one or more replication populations.
Fast-track analysis quickly genotypes a handful of SNPs with strongest associations. Larger-scale replication of hundreds to tens of thousands of SNPs necessary to prevent false negatives and reveal other SNPs that replicate but were missed.
Cases
Controls
Lower-throughput devices
Fast track
Tables
SNPs tested for replication
P values and genomic location.
Large-scale replication
Common homozygote
Heterozygote
Variant homozygote
SNPs that survive replication with extreme P values mark chromosomal loci where disease-associated gene variant is likely to be present.

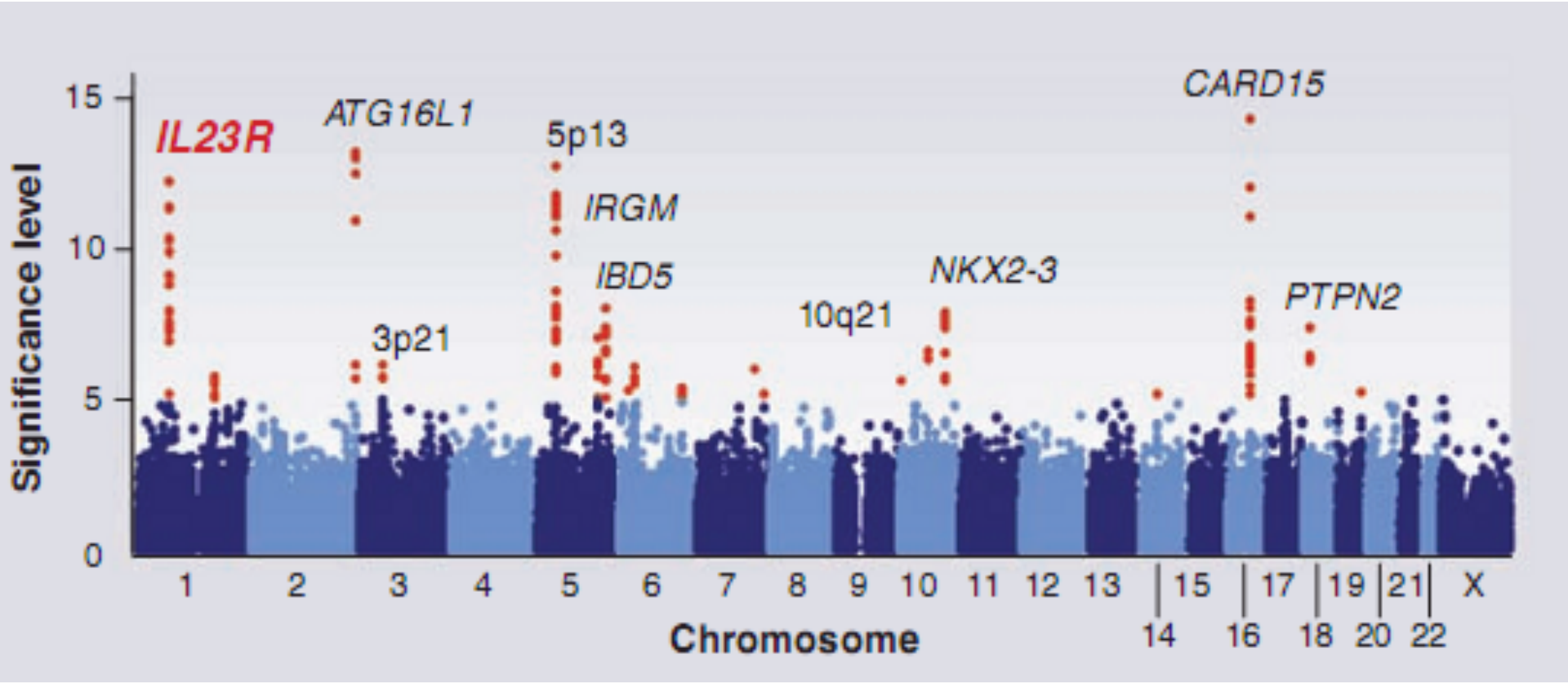
Type 2 Diabetes



Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678 (2007).

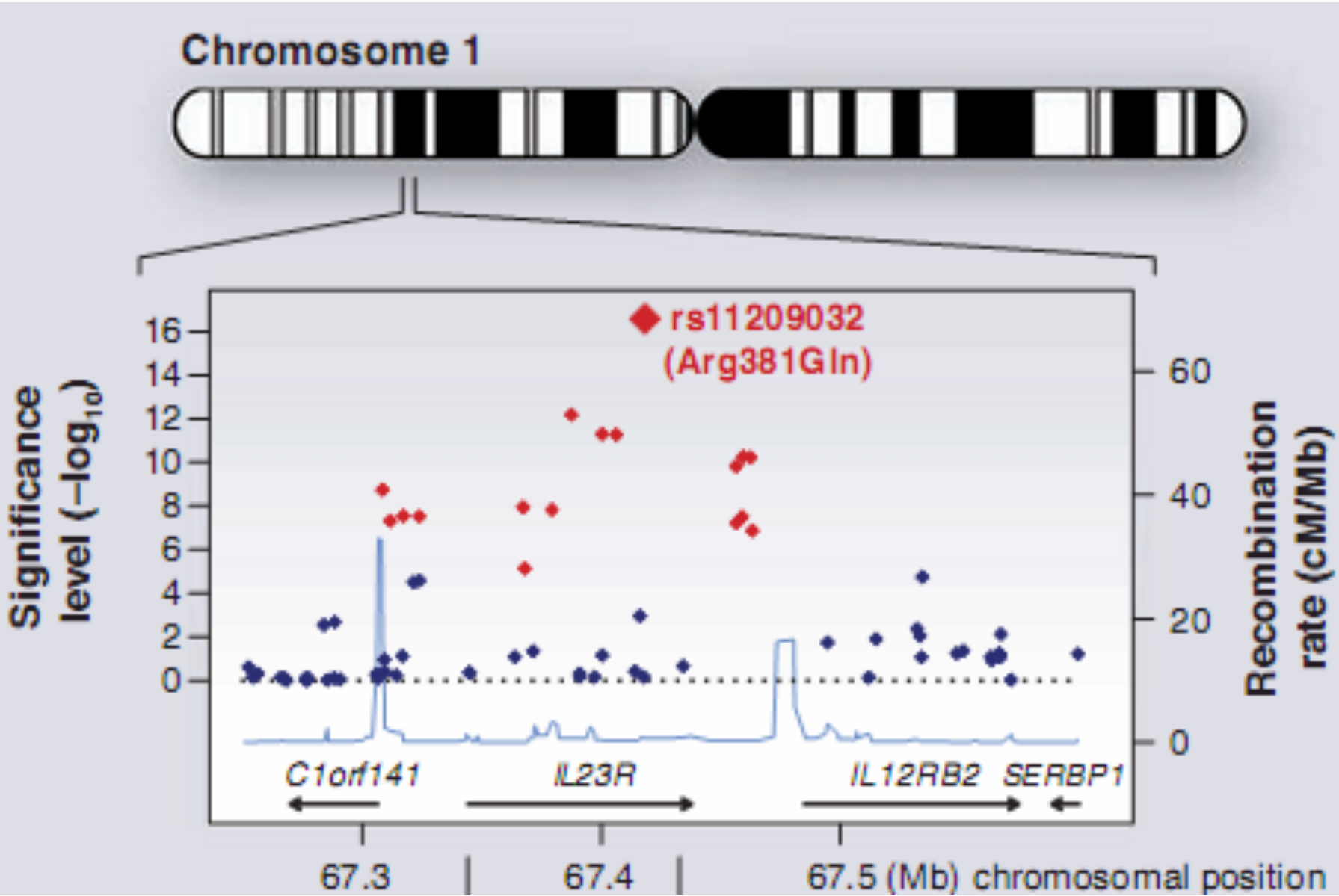

Chromosome 2
IDDM7
IDDM12
IDDM13
Chromosome 5
IDDM18
Chromosome 6
IDDM1
IDDM15
IDDM5
IDDM8
Chromosome 10
IDDM10
IDDM17
Chromosome 11
IDDM2
IDDM4
Chromosome 14
IDDM11
Chromosome 15
IDDM3
Chromosome 18
IDDM6

500.000 SNPs analysed in Crohn disease

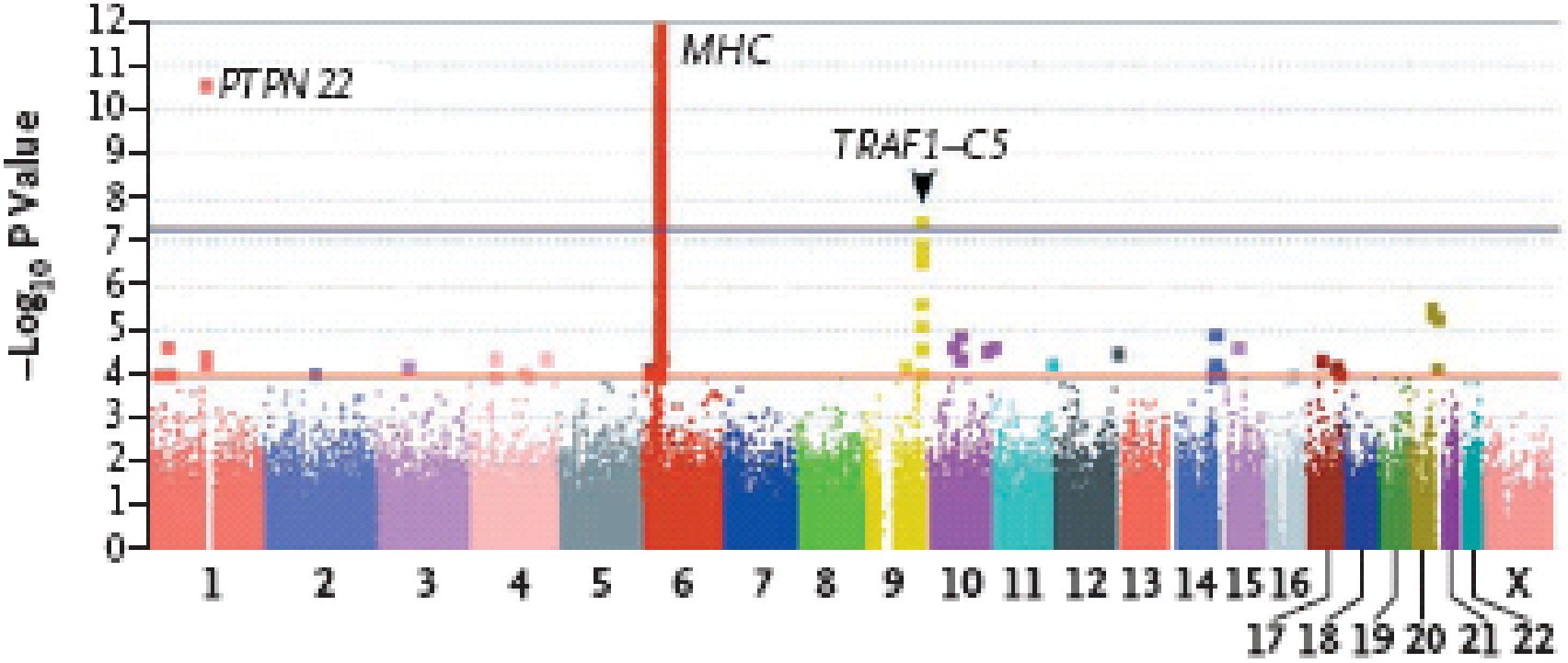


Results are replicated in different studies

FINE MAPPING

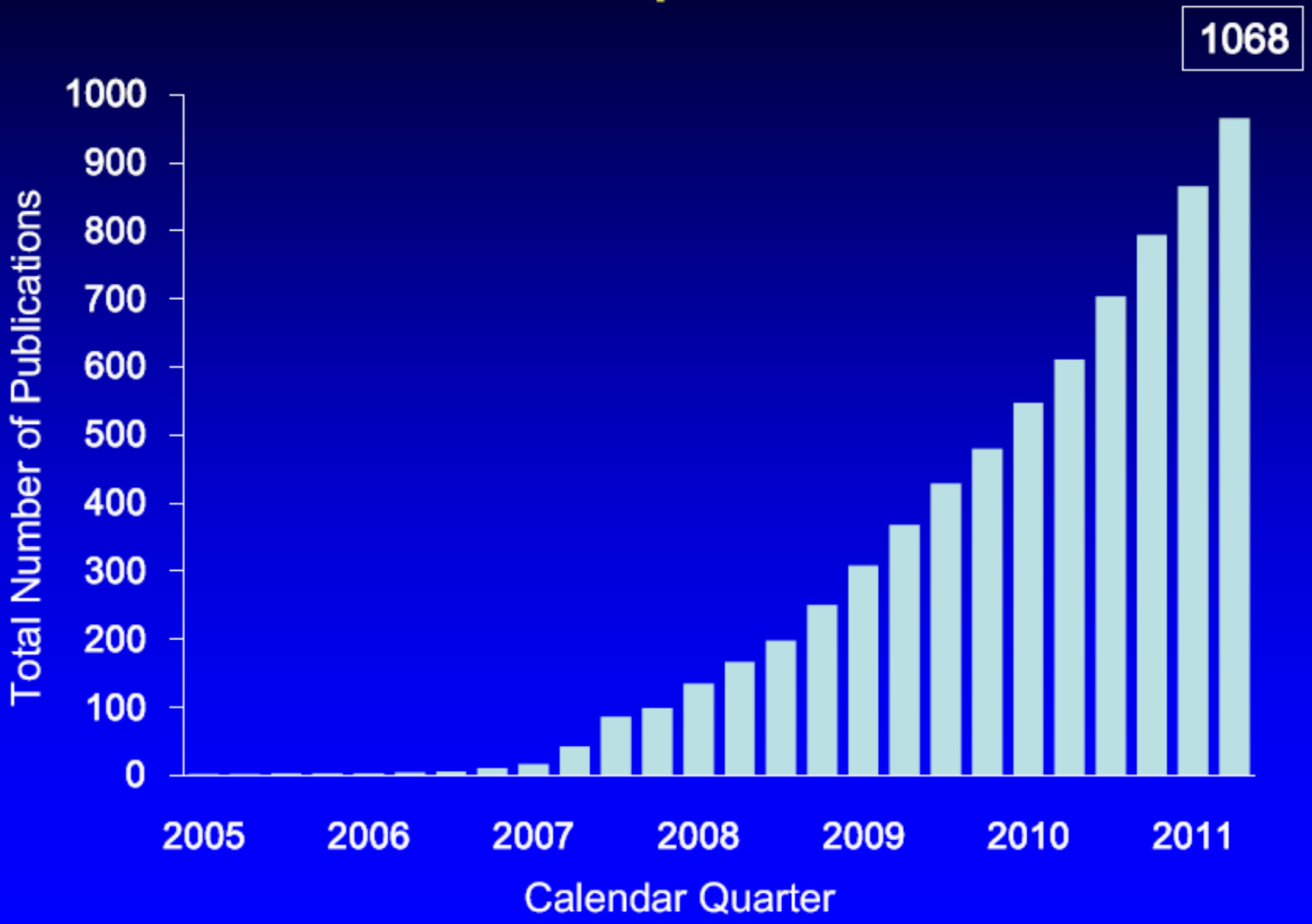


REUMATOID ARTHRITIS



N Engl J Med 2007;357.

Published GWA Reports, 2005 – 9/2011



Through 9/30/10 postings

Research for the future: Identifying genetic susceptibility to disease

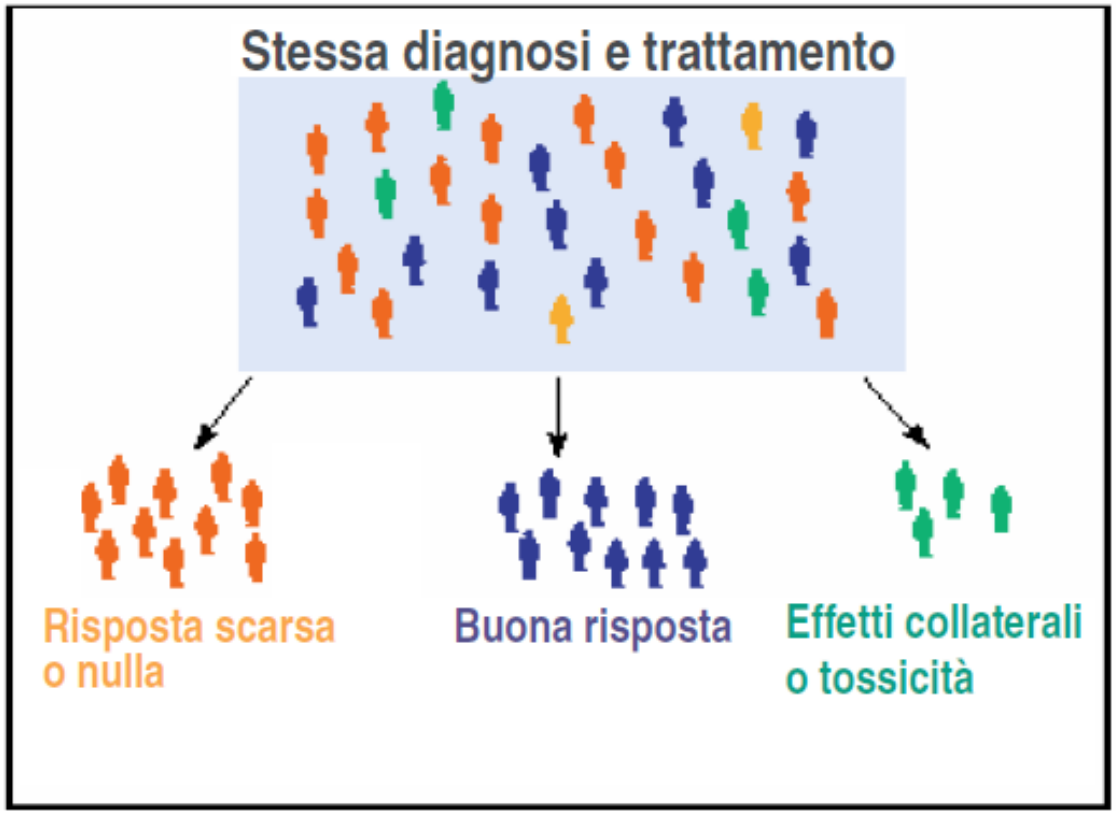
- Identify genetic differences between people that predict susceptibility to disease
- Develop genetic tests that predict whether an individual will develop a particular disease
- Offer treatments to prevent or delay onset of disease

A similar area of research is understanding how people differ in their susceptibility to certain diseases.

Researchers are developing genetic tests that can predict a person's risk of developing some common diseases such as heart disease or asthma for example.

In the future, a doctor might prescribe a drug developed to prevent the onset of a disease and recommend lifestyle changes the at-risk individual should make.

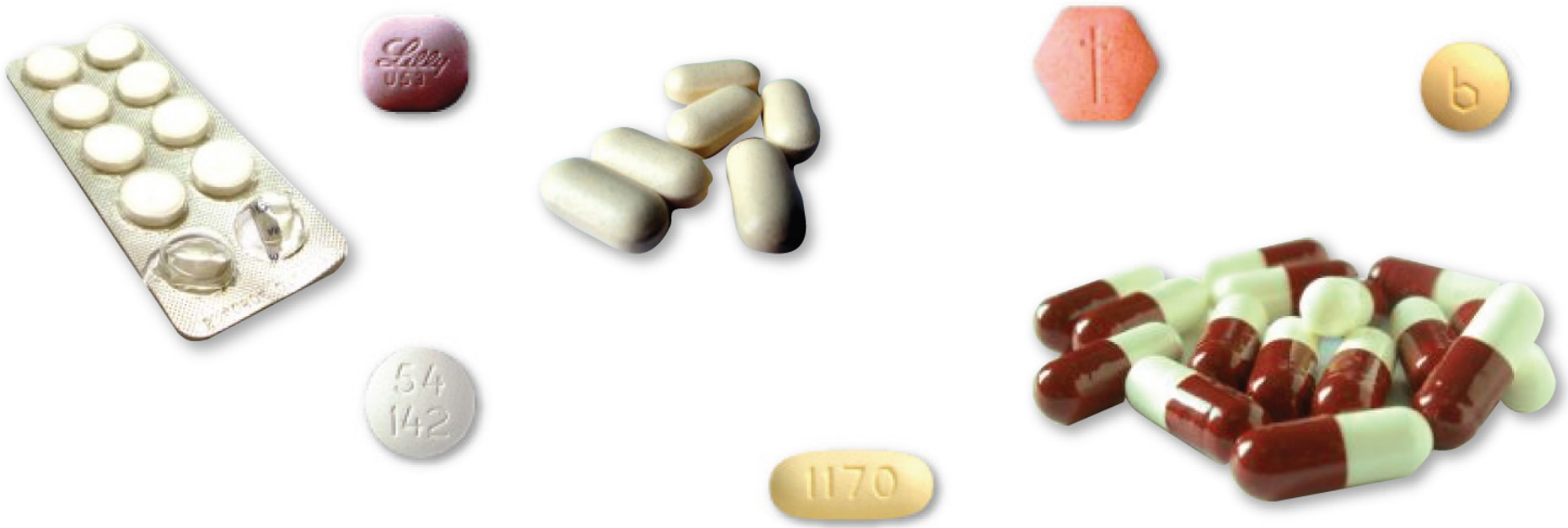
RESPONSE TO DRUGS



People vary in their response to a prescribed medication, both with respect to how well it works and to adverse side effects.

Research for the future: Personalized medicine

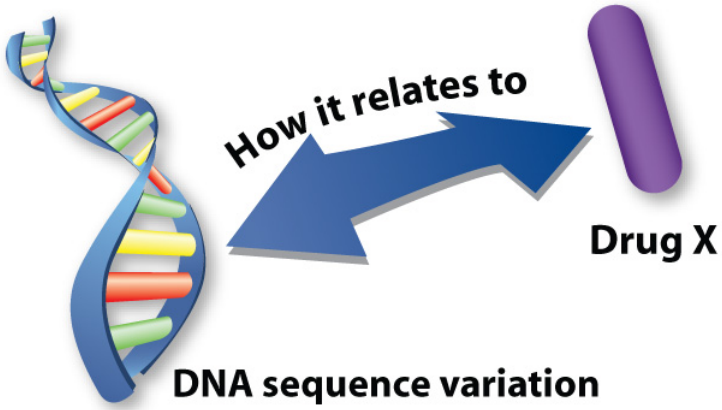
- Every year, over 106,000 people in the United States die from adverse reactions to correctly prescribed doses of drugs
- Another 2.2 million suffer serious, but not deadly, side effects



Research for the future: Personalized medicine

Goals for personalized medicine:

- Identify genetic differences between people that affect drug response
- Develop genetic tests that predict an individual's response to a drug
- Tailor medical treatments to the individual
  - Increase effectiveness
  - Minimize adverse side effects



Pharmacogenetics

Evaluates how an individual's genetic makeup corresponds to their response to a particular medication.

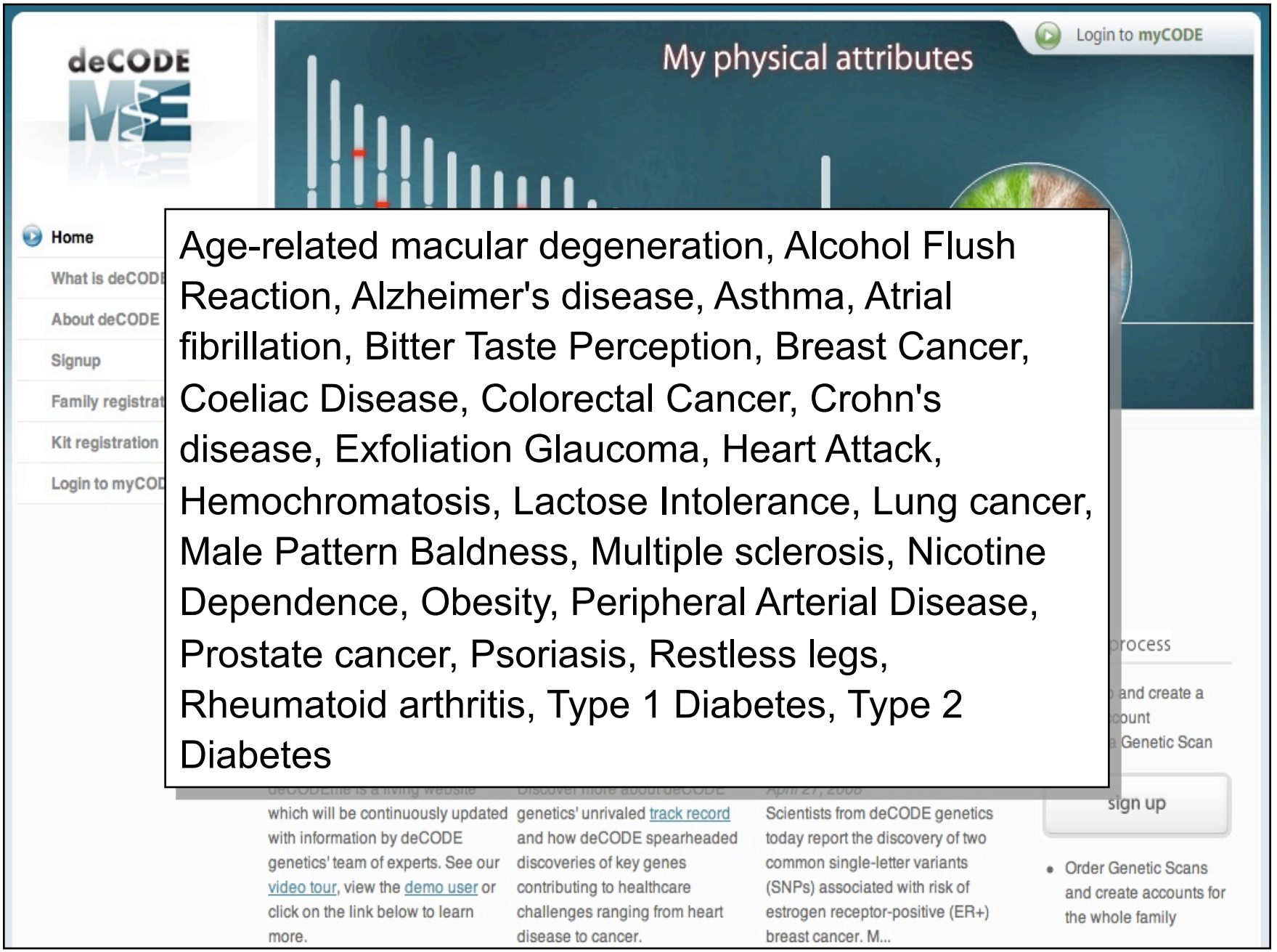
Pharmacogenomics

Combines pharmacogenetics with genomic studies. Uses large groups of patients to evaluate how candidate drugs interact with a range of genes and their protein products.

National Human Genome Research Institute

Per$onal Genomic$

Con$umer Genomic$


deCODE
Login to myCODE
My physical attributes
Home
What is deCOD
About deCODE
Signup
Family registrat
Kit registration
Login to myCOD
Age-related macular degeneration, Alcohol Flush Reaction, Alzheimer's disease, Asthma, Atrial fibrillation, Bitter Taste Perception, Breast Cancer, Coeliac Disease, Colorectal Cancer, Crohn's disease, Exfoliation Glaucoma, Heart Attack, Hemochromatosis, Lactose Intolerance, Lung cancer, Male Pattern Baldness, Multiple sclerosis, Nicotine Dependence, Obesity, Peripheral Arterial Disease, Prostate cancer, Psoriasis, Restless legs, Rheumatoid arthritis, Type 1 Diabetes, Type 2 Diabetes
which will be continuously updated with information by deCODE genetics' team of experts. See our video tour, view the demo user or click on the link below to learn more.
genetics' unrivaled track record and how deCODE spearheaded discoveries of key genes contributing to healthcare challenges ranging from heart disease to cancer.
Scientists from deCODE genetics today report the discovery of two common single-letter variants (SNPs) associated with risk of estrogen receptor-positive (ER+) breast cancer. M...
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sign up
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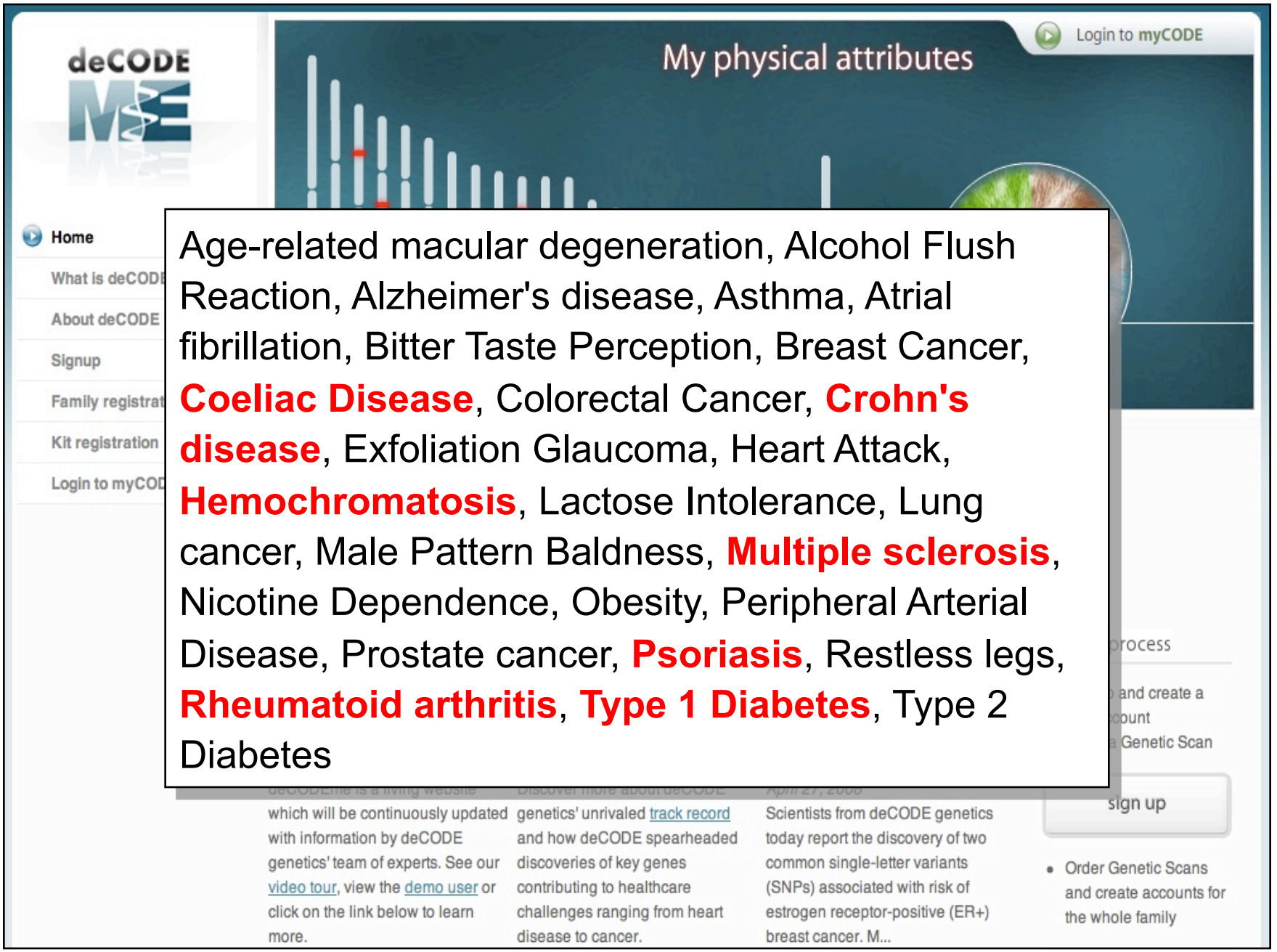
deCODE
My physical attributes
Login to myCODE
Home
What is deCOD
About deCODE
Signup
Family registrat
Kit registration
Login to myCOD
Age-related macular degeneration, Alcohol Flush Reaction, Alzheimer's disease, Asthma, Atrial fibrillation, Bitter Taste Perception, Breast Cancer, Coeliac Disease, Colorectal Cancer, Crohn's disease, Exfoliation Glaucoma, Heart Attack, Hemochromatosis, Lactose Intolerance, Lung cancer, Male Pattern Baldness, Multiple sclerosis, Nicotine Dependence, Obesity, Peripheral Arterial Disease, Prostate cancer, Psoriasis, Restless legs, Rheumatoid arthritis, Type 1 Diabetes, Type 2 Diabetes
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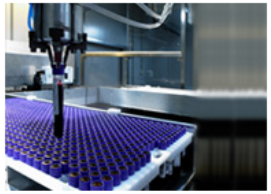
1 **Visit our store**

Complete Scan

2 **Collect your sample**
You collect your own sample from your cheek, using our easy-to-use DNA collector.

USING THE COLLECTOR



3 **Your DNA is analyzed**
Our CLIA certified labs scan up to one million variants using state of the art equipment.

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See how your DNA affects your health and what it reveals about your ancestry.

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deCODEme is a genetic health scan

Getting to know your personal genome will empower you and provide you with a road map to improve your health. In many cases, early detection of risk allows you to prevent a disease from ever taking hold.

Your genes, your health, your data

deCODEme gives you direct access to your genetic data and the tools to translate them into valuable information to which you have exclusive and secure access.

This content was last reviewed on May 26, 2011.

Making personal genetics meaningful for you

We help you to interpret your results and show you how they relate to your health. View them online, contact one of our experts or share your results with your physician.

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deCODEme

Celiac Disease

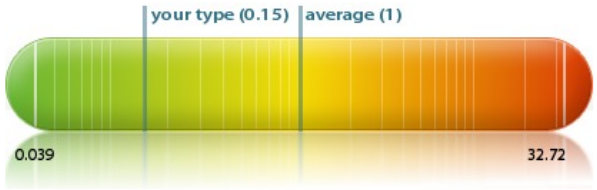
Celiac disease (also known as coeliac disease, celiac sprue, nontropical sprue, and gluten-sensitive enteropathy) is caused by an abnormal immune response to wheat gluten and similar proteins in barley and rye.

Results can vary according to population and/or gender. Results currently based on:

European ancestry

Male

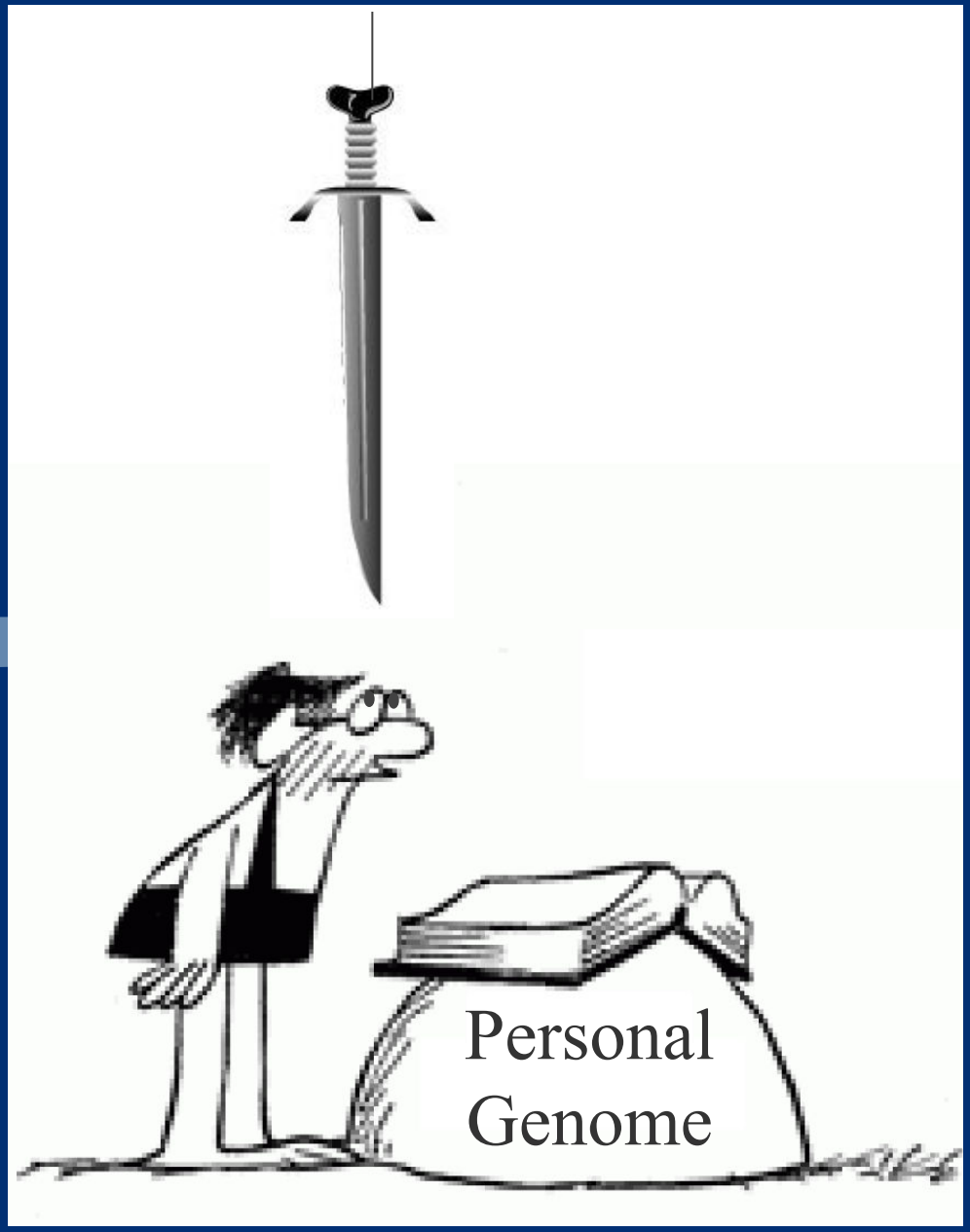
CHANGE



According to the selected literature, the relative genetic risk calculated from your genotype for males of European ancestry is **0.15**. This corresponds to a **0.15% lifetime risk** of developing celiac disease, which is **85% less than** for males of European ancestry in general (source) . Note that these calculations may not include all risk factors.

Consult with our experts

Do we really want to know the sequence of our genome….?



How to ruin your life for $1000

"Last year two online services, deCODEme and 23andMe, started offering DNA analysis and calculating your risk of developing 20 diseases, including Alzheimer's"

"If you find out you've an increased risk of diabetes and heart diseases, the advice you'd be given is exactly the same as if you didn't have an increased risk: eat well, exercise, don't smoke, don't get too fat, have a test if you get symptoms"

Dr Ann Robinson

claudia.giachino@unito.it

"[illegible]" Davies