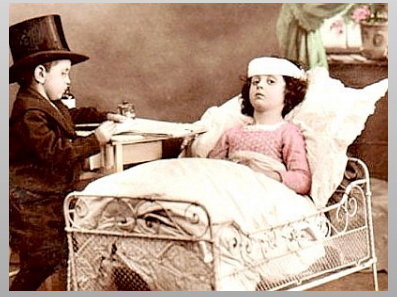
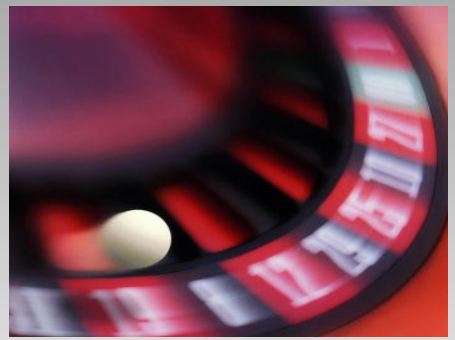
Sir William Osler

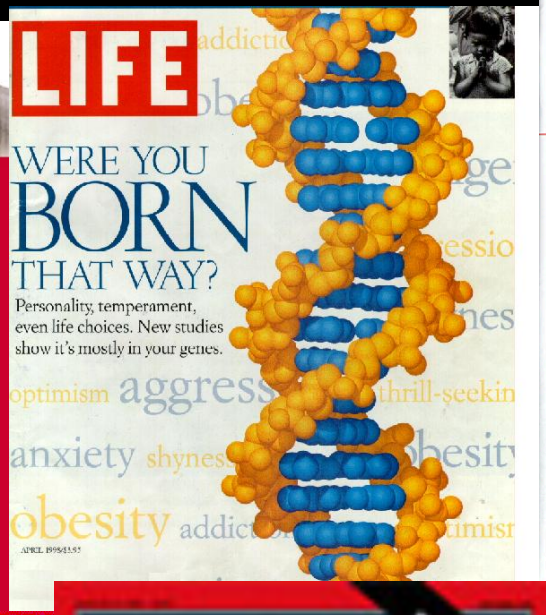
(1849-1919)

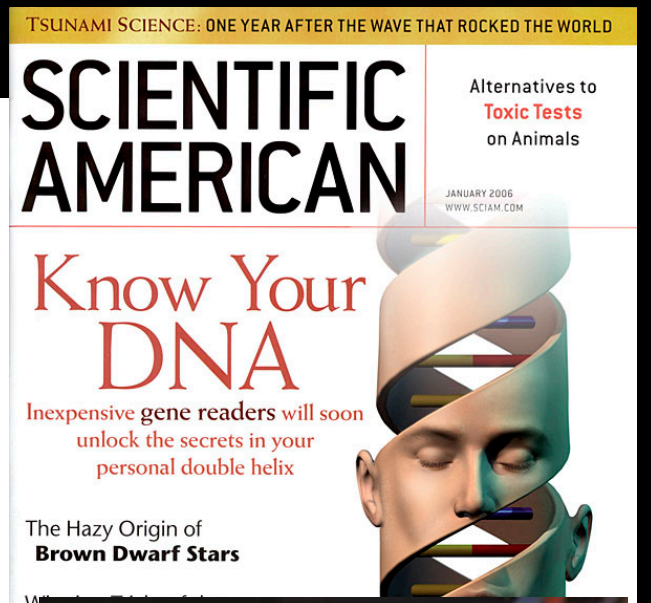
“Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike, and behave alike under the abnormal conditions which we know as disease.”






TIME
THE FUNNIEST MAN IN AMERICA
What scientists have uncovered about HOW MEMORY WORKS and how to improve it
THE I.Q. GENE?

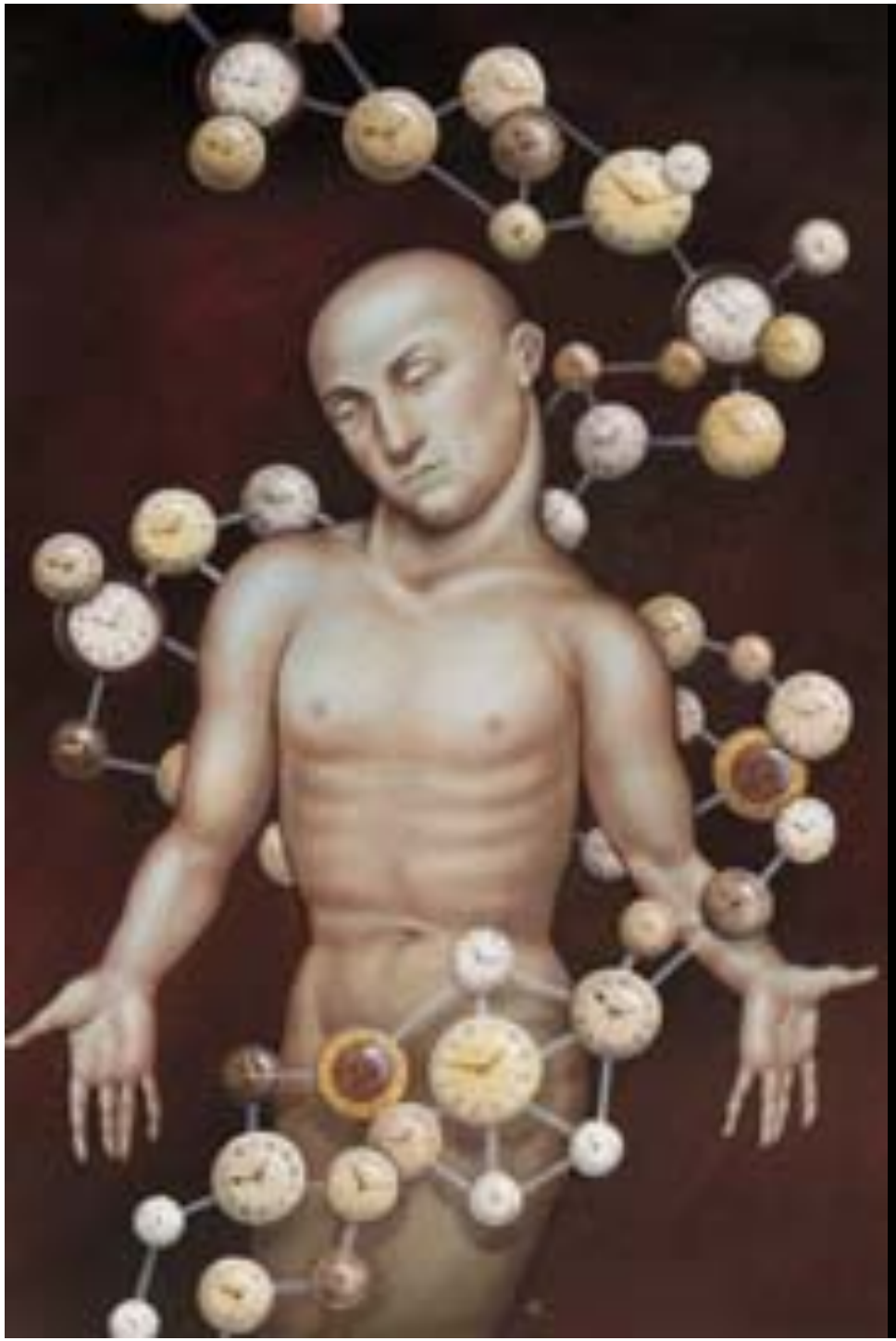

LIFE
WERE YOU BORN THAT WAY?
Personality, temperament, even life choices. New studies show it's mostly in your genes.
optimism
aggress
anxiety
shynes
obesity
addict


TSUNAMI SCIENCE: ONE YEAR AFTER THE WAVE THAT ROCKED THE WORLD
SCIENTIFIC AMERICAN
Alternatives to Toxic Tests on Animals
JANUARY 2006
WWW.SCIAM.COM
Know Your DNA
Inexpensive gene readers will soon unlock the secrets in your personal double helix
The Hazy Origin of Brown Dwarf Stars


TIME
SPECIAL REPORT
COUNTDOWN TO
SOLVING THE MYSTERIES OF DNA
The 50th Anniversary: Reliving Watson and Crick's historic discovery
How gene science has changed our lives
Visions of the future


TIME
SPECIAL ISSUE
THE FUTURE OF MEDICINE

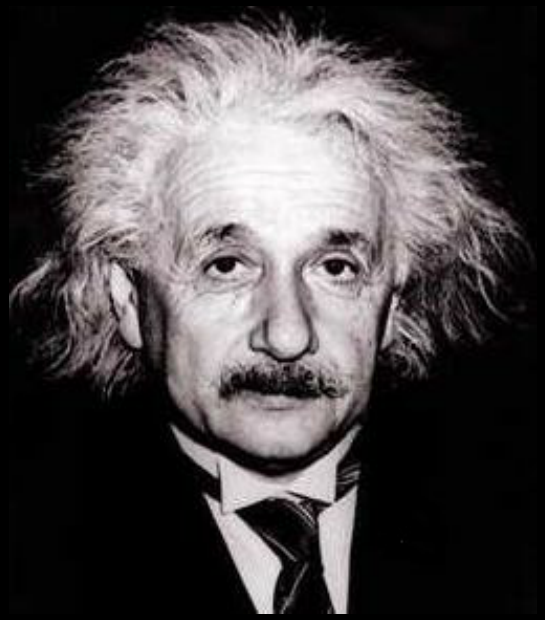

LIFE
JACKIE ROBINSON SCOUTS THE SERIES
Scientists close in on
The Secret of Life
2NeatBooks.com



“svelato il linguaggio con cui Dio ha creato la vita”.

[11 Febbraio 2001-Bill Clinton]

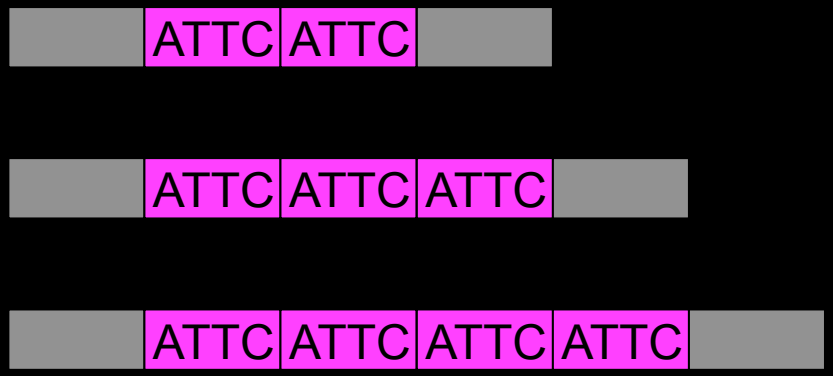
Paradosso del valore N: la complessità non correla con il numero dei geni.



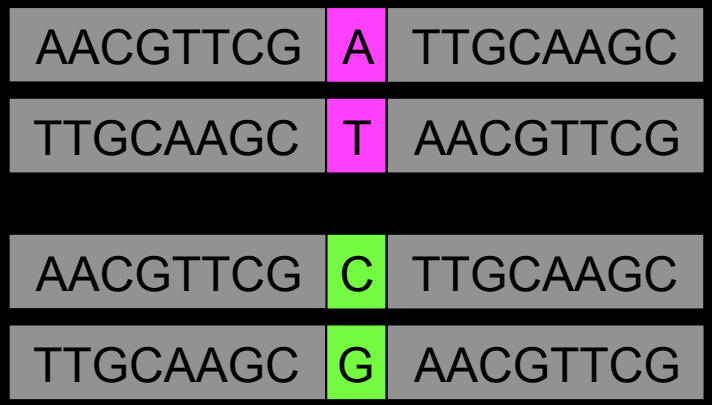
~21,000 genes

~50,000 genes

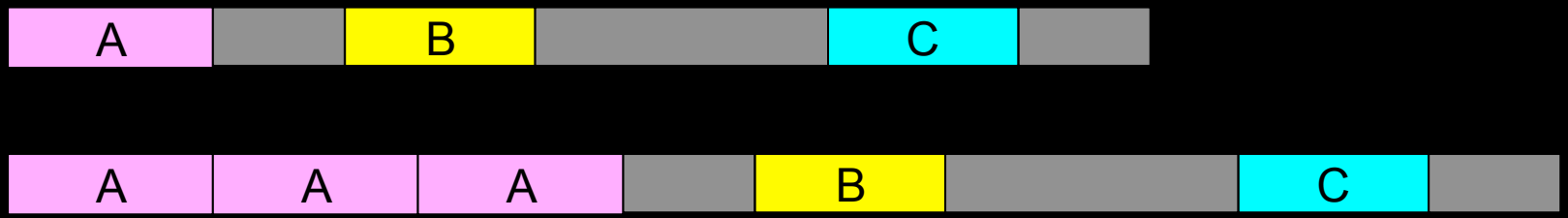
Polimorfismi di lunghezza



Polimorfismi di sequenza



Copy Number Variation



Personalized Medicine

"Personalized medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not." —

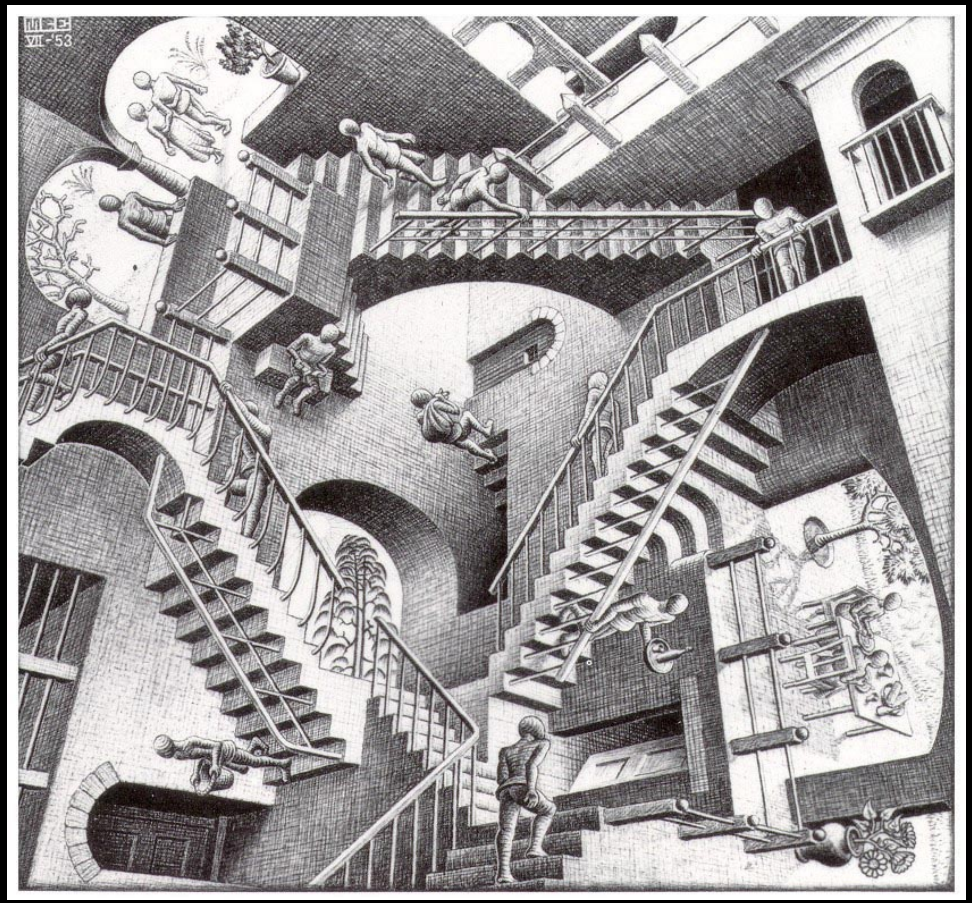
The DNA paradox

✓Your DNA identical for 99.1 percent like that of the person next to you

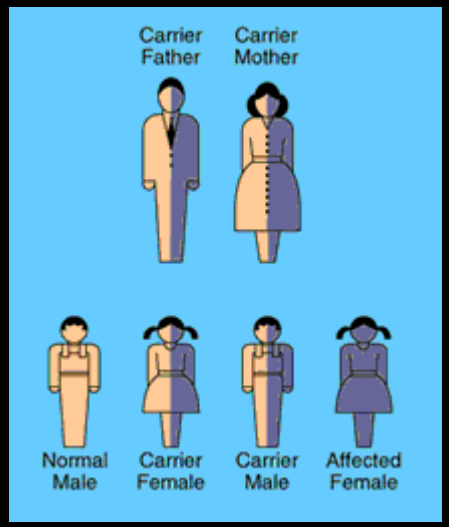
✓The 0.9 percent difference is immensely important

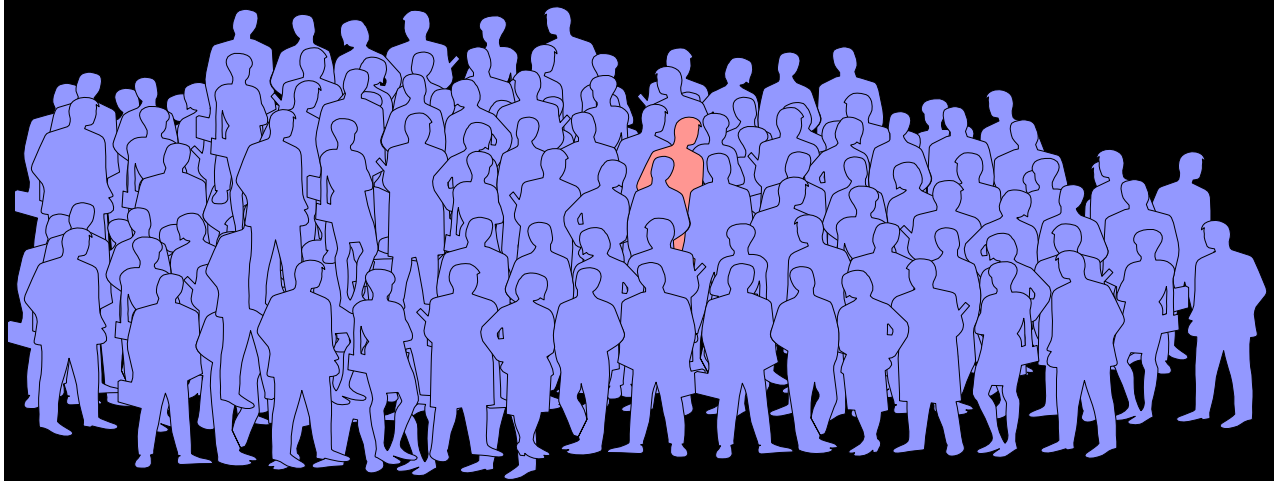
✓It means we differ at some millions letters

✓We are both very alike and very different

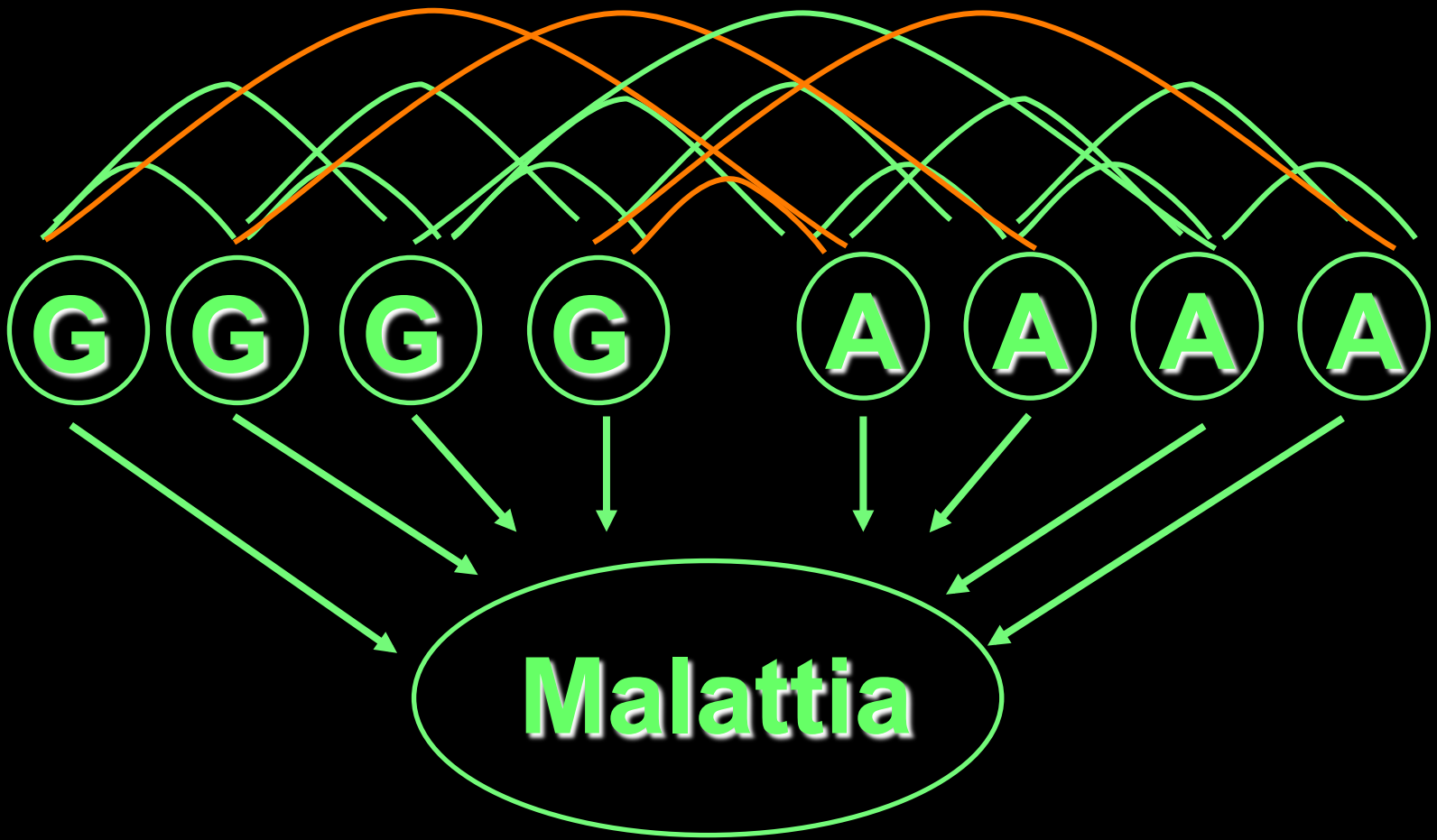


Evoluzione del concetto di rischio





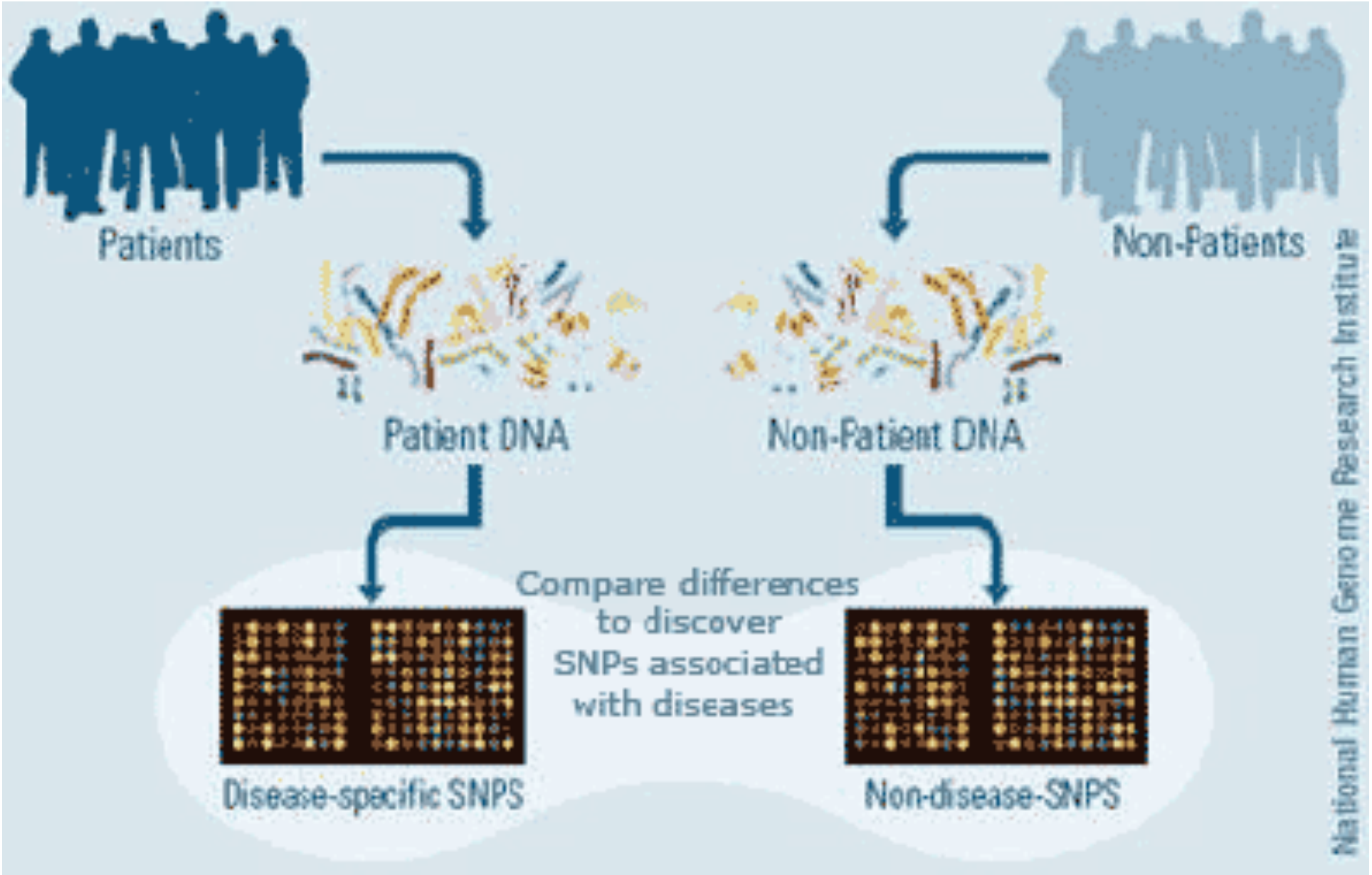
Malattie Complesse

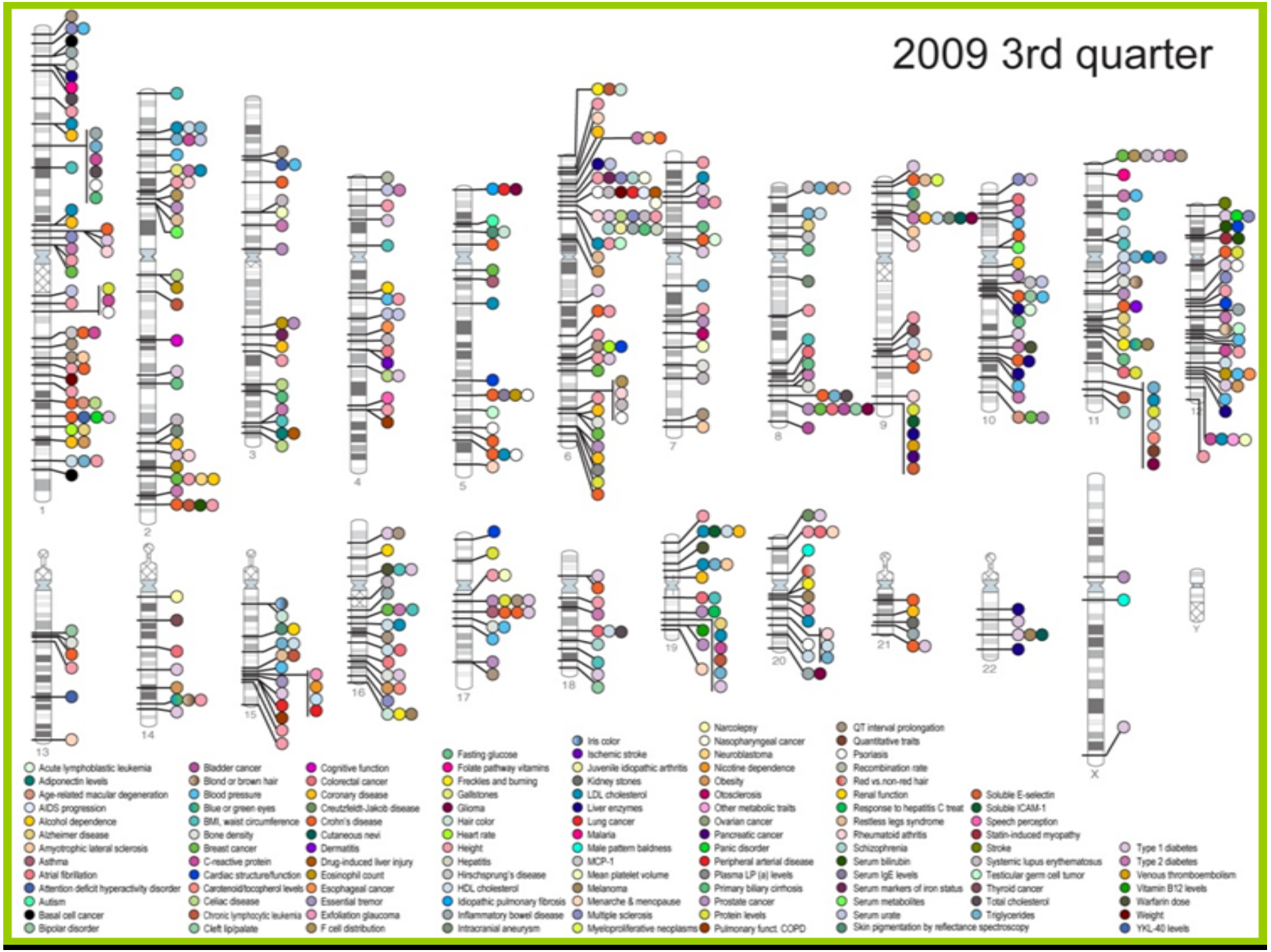


Recent advances of human genetics are driven by Accelerating Technology

- In 1997 it took about a day to genotype a one Single Nucleotide Polymorphism
  - Cost was ~$100
- Now in a matter of days one can genotype an individual at >2,000,000 sites
  - At a cost of < $500
    - Reduction in cost of >400,000 fold

$795 in 1977 (=$2,800 in current $


Patients
Non-Patients
Patient DNA
Non-Patient DNA
Compare differences
to discover
SNPs associated
with diseases
Disease-specific SNPS
Non-disease-SNPS
National Human Genome Research Institute


2009 3rd quarter
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Acute lymphoblastic leukemia
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alzheimer disease
Amyotrophic lateral sclerosis
Asthma
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Bipolar disorder
Bladder cancer
Blond or brown hair
Blood pressure
Blue or green eyes
BMI, waist circumference
Bone density
Breast cancer
C-reactive protein
Cardiac structure/function
Carotenoid/tocopherol levels
Celiac disease
Chronic lymphocytic leukemia
Cleft lip/palate
Cognitive function
Colorectal cancer
Coronary disease
Creutzfeldt-Jakob disease
Crohn's disease
Cutaneous nevi
Dermatitis
Drug-induced liver injury
Eosinophil count
Esophageal cancer
Essential tremor
Exfoliation glaucoma
F cell distribution
Fasting glucose
Folate pathway vitamins
Freckles and burning
Gallstones
Glioma
Hair color
Heart rate
Height
Hepatitis
Hirschsprung's disease
HDL cholesterol
Idiopathic pulmonary fibrosis
Inflammatory bowel disease
Intracranial aneurysm
Iris color
Ischemic stroke
Juvenile idiopathic arthritis
Kidney stones
LDL cholesterol
Liver enzymes
Lung cancer
Malaria
Male pattern baldness
MCP-1
Mean platelet volume
Melanoma
Menarche & menopause
Multiple sclerosis
Myeloproliferative neoplasms
Narcolepsy
Nasopharyngeal cancer
Neuroblastoma
Nicotine dependence
Obesity
Otosclerosis
Other metabolic traits
Ovarian cancer
Pancreatic cancer
Panic disorder
Peripheral arterial disease
Plasma LP (a) levels
Primary biliary cirrhosis
Prostate cancer
Protein levels
Pulmonary funct. COPD
QT interval prolongation
Quantitative traits
Psoriasis
Recombination rate
Red vs.non-red hair
Renal function
Response to hepatitis C treat
Restless legs syndrome
Rheumatoid arthritis
Schizophrenia
Serum bilirubin
Serum IgE levels
Serum markers of iron status
Serum metabolites
Serum urate
Skin pigmentation by reflectance spectroscopy
Soluble E-selectin
Soluble ICAM-1
Speech perception
Statin-induced myopathy
Stroke
Systemic lupus erythematosus
Testicular germ cell tumor
Thyroid cancer
Total cholesterol
Triglycerides
Type 1 diabetes
Type 2 diabetes
Venous thromboembolism
Vitamin B12 levels
Warfarin dose
Weight
YKL-40 levels


68
DNA
DOCTOR
Genome Medical Futures

Present difficulties of the Medicine of tomorrow

1. Effect-sizes are modest for common variants
   (mostly increases by 1.1-1.5)

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6. There is great variation between studies and ethnic groups

Pathophysiological processes	Susceptibility genes
Lipid and cholesterol metabolism:	
LDL metabolism	LDLR, LDLRAP1, LRP,LRP6, APOB, APOE, PCSK9, CYP7A1, SREBP-2/SCAP, USF1, PSRC1 and CELSR2
HDL metabolism	**LCAT, apoA-1, ABCA1, SR-B1, PON, LIPC, CETP**
Triglyceride metabolism	LPL, apoA5, apoC-III
Lipoprotein(a)	Apo(a)
Endothelial dysfunction	NOS3, MnSOD, KDR
Oxidative stress	CYBA, MPO, EC-SOD, GPX1, GST, UCP2, HO-1
Inflammation	Interleukins: IL-1, IL-1Ra, IL-6, IL-10
	Cytokines and cytokines receptors: TNF-, TNF-receptor, LTA
	Adhesion molecules: selectins, ICAM-I, VCAM-I, PECAM
	Chemokines and chemokine receptors: CX3CR1, CCR5, CCR2, CXCL12, RANTES, MCP-1
	Eicosanoids: ALOX5, ALOX5AP, LTA4H, LTC4S, PTGS1, PTGS2, L-PGDS
	Others: Connexin 37, MEF2A, TLR-4, CRP, TNFS4, MHC2TA
Vascular remodeling	TGF-1, MMP-1, MMP-3,MMP-7, MMP-9, MMP-12
Arterial thrombosis	Hemostatic system: Wbrinogen, prothrombin, factor V, factor VII, Factor XIII, thrombomodulin
	Fibrinolytic system: PAI-1, TAFI, t-PA
	Platelet surface receptors: glycoprotein IIb/IIIa, Ia/IIa and Ib
Cell cycle regulators	CDKN2A, CDKN2B
Vascular progenitor cell regulators	CXCL12, GATA2

Band	SNP	Gene(s) in region	Risk allele frequency (risk allele)	Odds ratio
1p13.3	rs599839	SORT1	0.78 (A)	**1.11 (1.08–1.15)**
1q41	rs17465637	MIA3	0.74 (C)	**1.14 (1.09–1.20)**
2q33.1	rs6725887	WDR12	0.15 (C)	**1.14 (1.09–1.19)**
3q22.3	rs2306374	MRAS	0.18 (C)	**1.12 (1.07–1.16)**
6p24.1	rs12526453	PHACTR1	0.67 (C)	**1.10 (1.06–1.13)**
9p21.3	rs1333049	CDKN2,CDKN2B	-	**1.29 (1.23–1.36)**
10q11.21	rs1746048	CXCL12	0.87 (C)	**1.09 (1.07–1.13)**
10q24.32	rs12413409	CYP17A1CNNM2, NT5C2	0.89 (G)	**1.12 (1.08–1.16)**
12p13.2	rs3736235	OLR1	0.52 (C)	**p<0.05**
19p13.2	rs1122608	LDLR	0.77 (G)	**1.14 (1.09–1.18)**
21q22.11	**rs9982601**	**MRPS6**	**0.15 (T)**	**1.18 (1.12–1.24)**

nature genetics

Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque

VOLUME 43 | NUMBER 10 | OCTOBER 2011 NATURE GENETICS

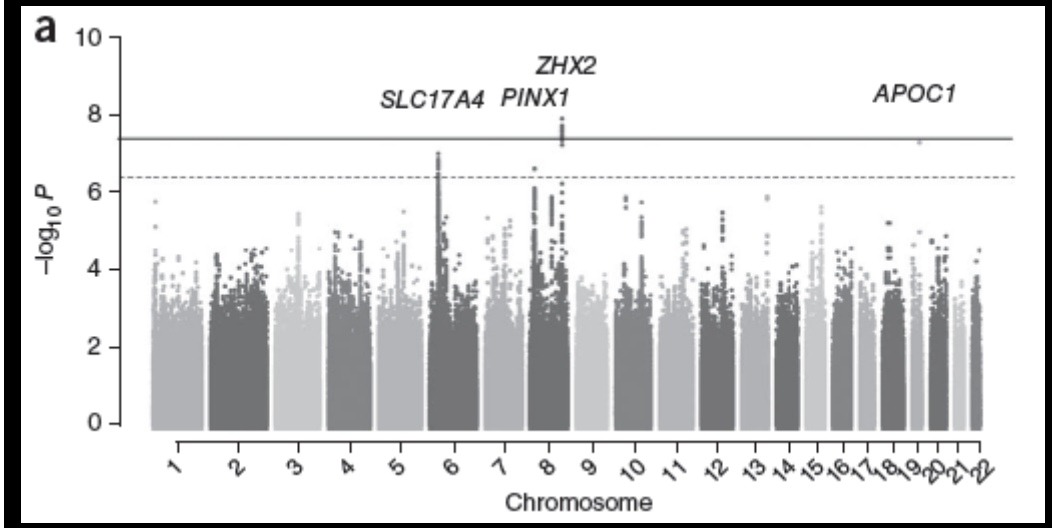
Table 1 Discovery, second stage and combined meta-analysis for common cIMT and plaque

					Discovery GWAS					Second stage meta-analysis					Combined meta-analysis		
	SNP	Chr.	Nearest gene	Alleles	AF	β	s.e.m.	*N*	*P*	AF	β	s.e.m.	*N*	*P*	β	s.e.m.	*P*
cIMT	rs11781551	8	*ZHX2*	A/G	0.48	−0.0081	0.0014	30,894	1.3×10^{-8}	0.47	−0.0072	0.0020	10,401	0.0004	−0.0078	0.0012	2.4×10^{-11}
	rs445925	19	*APOC1*	A/G	0.11	−0.0179	0.0033	12,395	5.2×10^{-8}	0.10	−0.0116	0.0047	4,790	0.01	−0.0156	0.0028	1.7×10^{-8}
	rs6601530	8	*PINX1*	G/A	0.45	0.0078	0.0015	28,124	2.5×10^{-7}	0.46	0.0073	0.0029	4,507	0.01	0.0078	0.0014	1.7×10^{-8}
	SNP	Chr.	Nearest gene	Alleles	AF	OR (95% CI)		*N*	*P*	AF	OR (95% CI)		*N*	*P*	OR (95% CI)		*P*
Plaque	rs17398575	7	*PIK3CG*	A/G	0.25	1.17 (1.12–1.23)		23,520	2.8×10^{-10}	0.25	1.20 (1.07–1.35)		5,735	0.002	1.18 (1.12–1.23)		2.3×10^{-12}
	rs1878406	4	*EDNRA*	T/C	0.13	1.21 (1.13–1.28)		24,089	3.1×10^{-9}	0.13	1.31 (1.13–1.52)		5,738	0.0003	1.22 (1.15–1.29)		6.9×10^{-12}

DISCOVERY COHORT
31211 partecipants
9 GWAS
2.5 millions SNPs

REPLICATION COHORT
11273 partecipants
7 GWAS
2.5 millions SNPs

COMMON cIMT

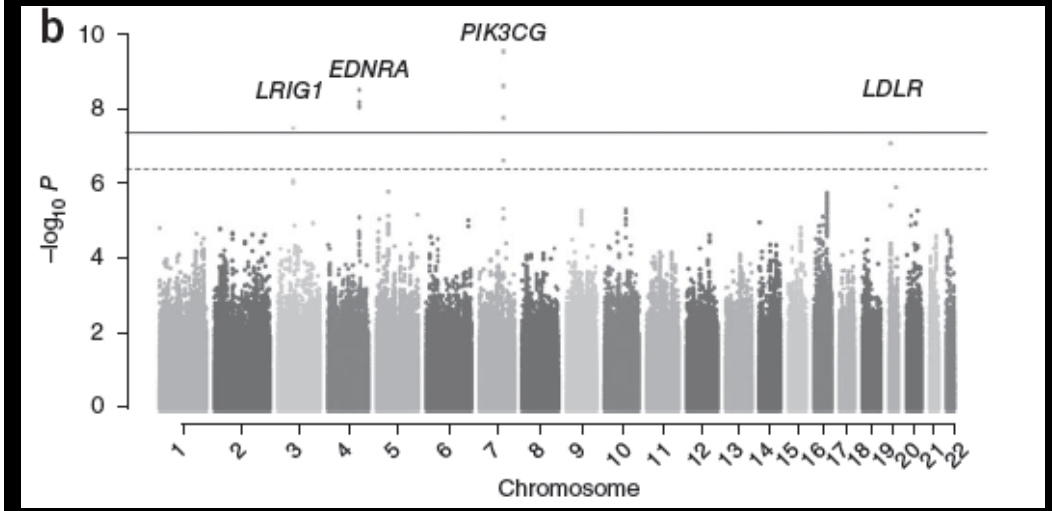


ZHX2: transcriptional repressor

APOC1: low-density lipoprotein metabolism. modulate the interaction of APOE with beta-migrating VLDL and inhibit binding of beta-VLDL to the LDL receptor-related protein.

PINX1: telomere maintenance. telomerase inhibitor

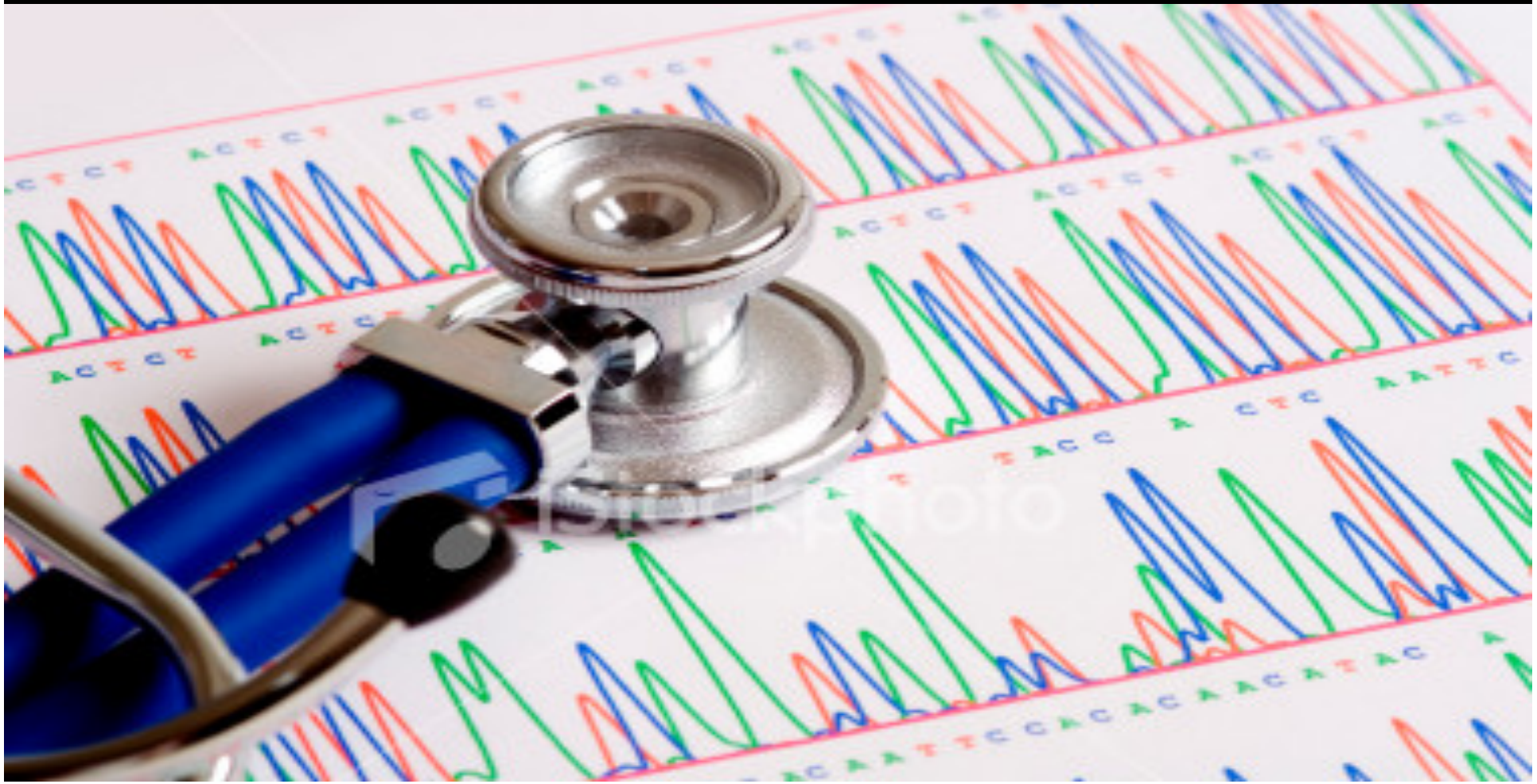
PLAQUE



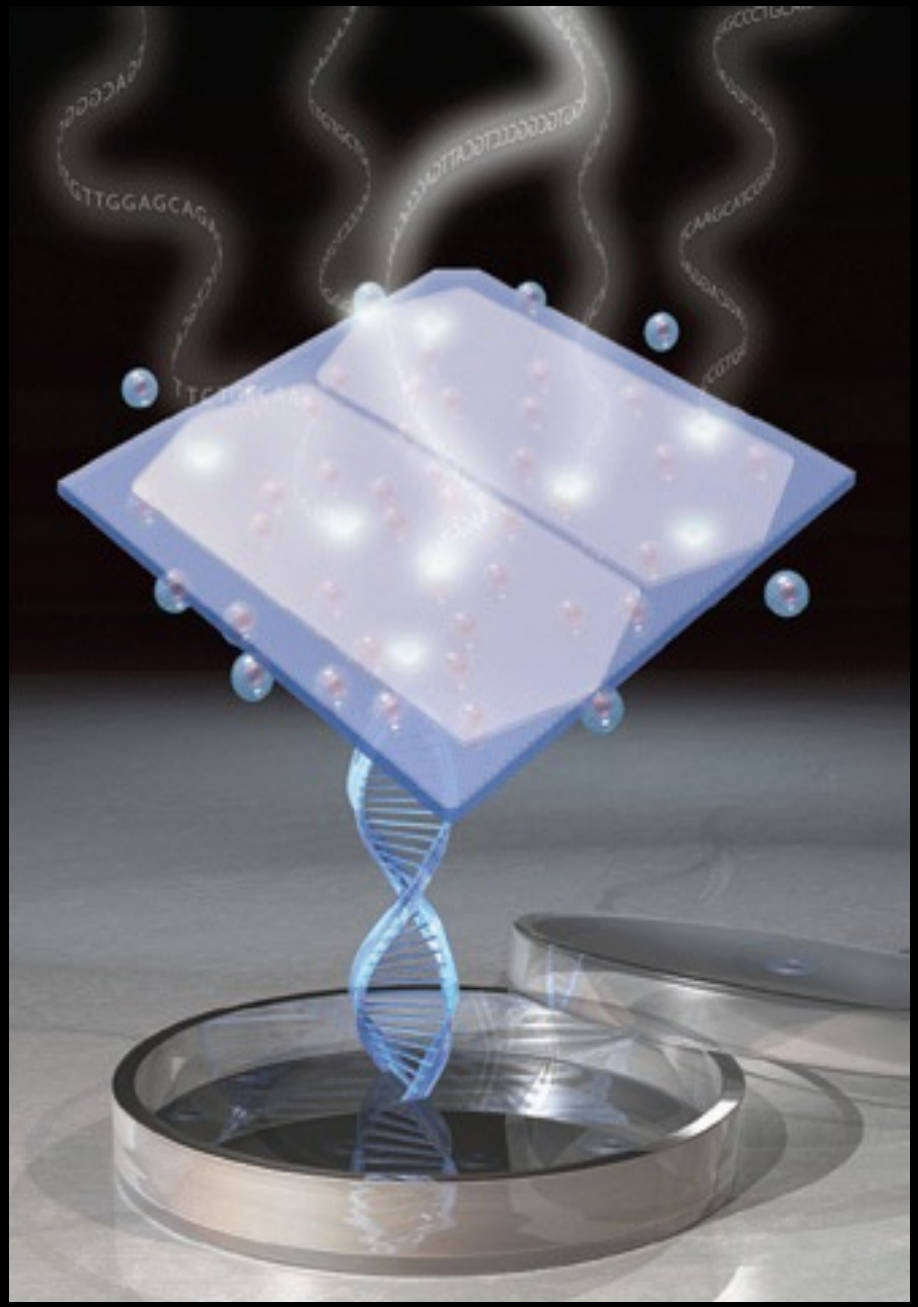
PIK3CG: platelet biology, maintanance of functional integrety of epithelia

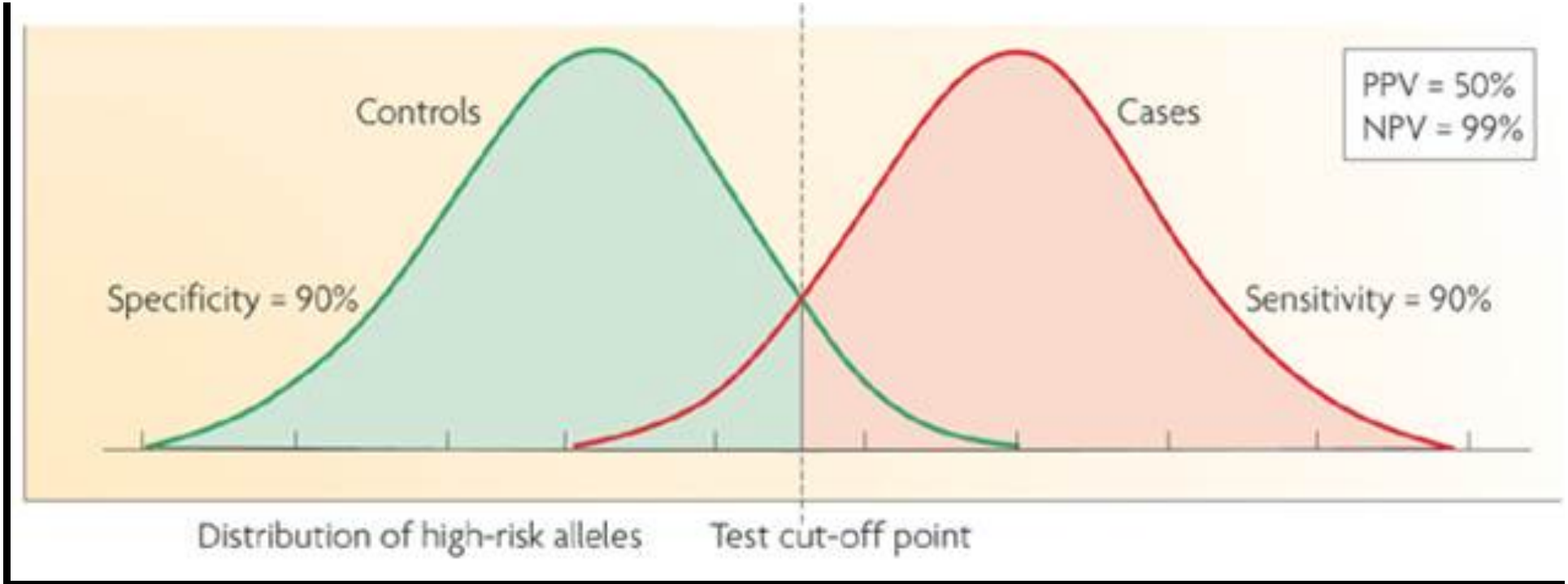
EDNRA: endothelian disfunction. endothelin receptor A associated with blood pressure, atherosclerosis and CVD.

SCIENTIFIC EVIDENCE
≠
CLINICAL UTILITY



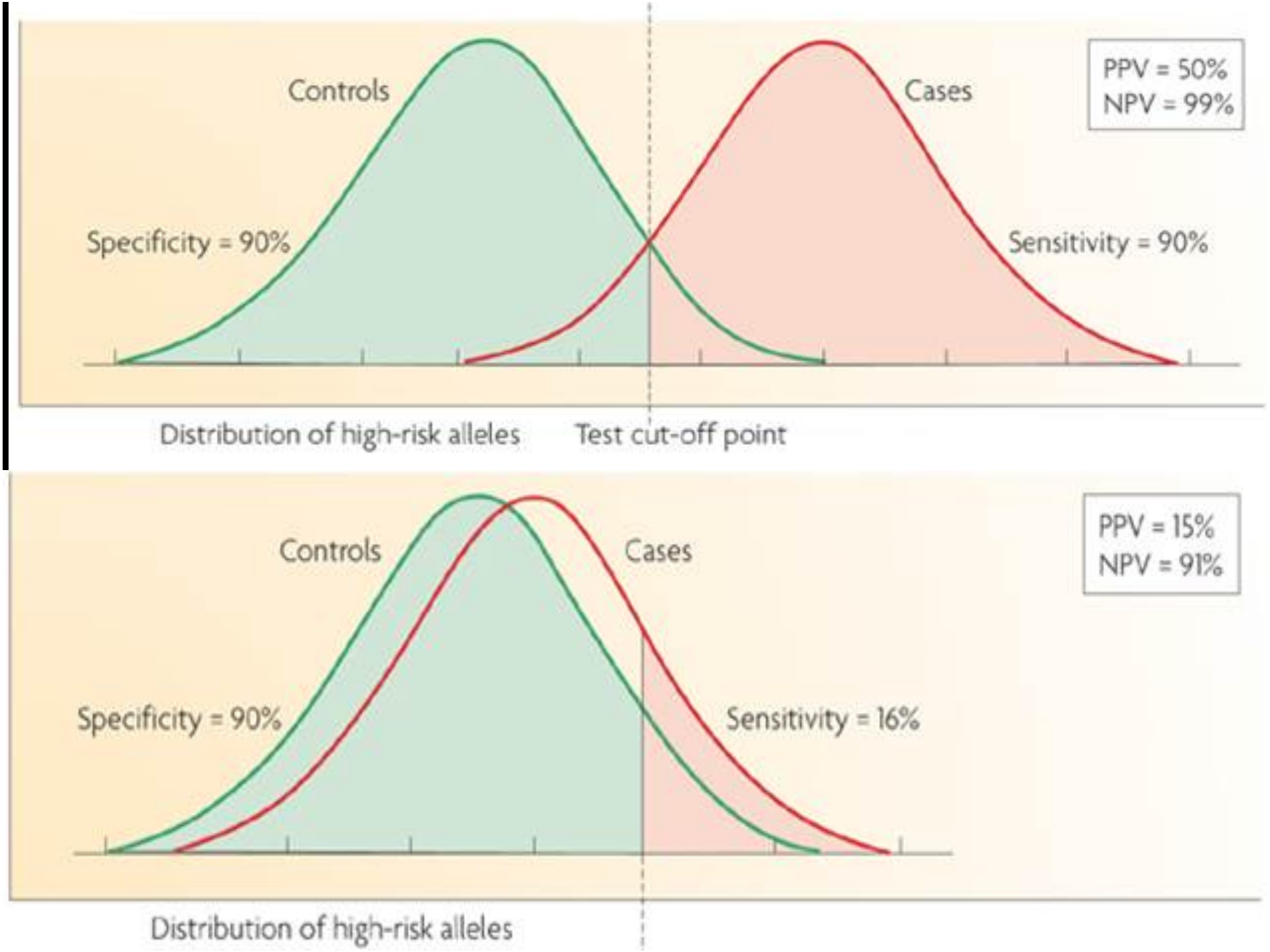
The main goal of these studies is not prediction of individual risk but rather discovery of biologic pathways underlying polygenic diseases and traits.

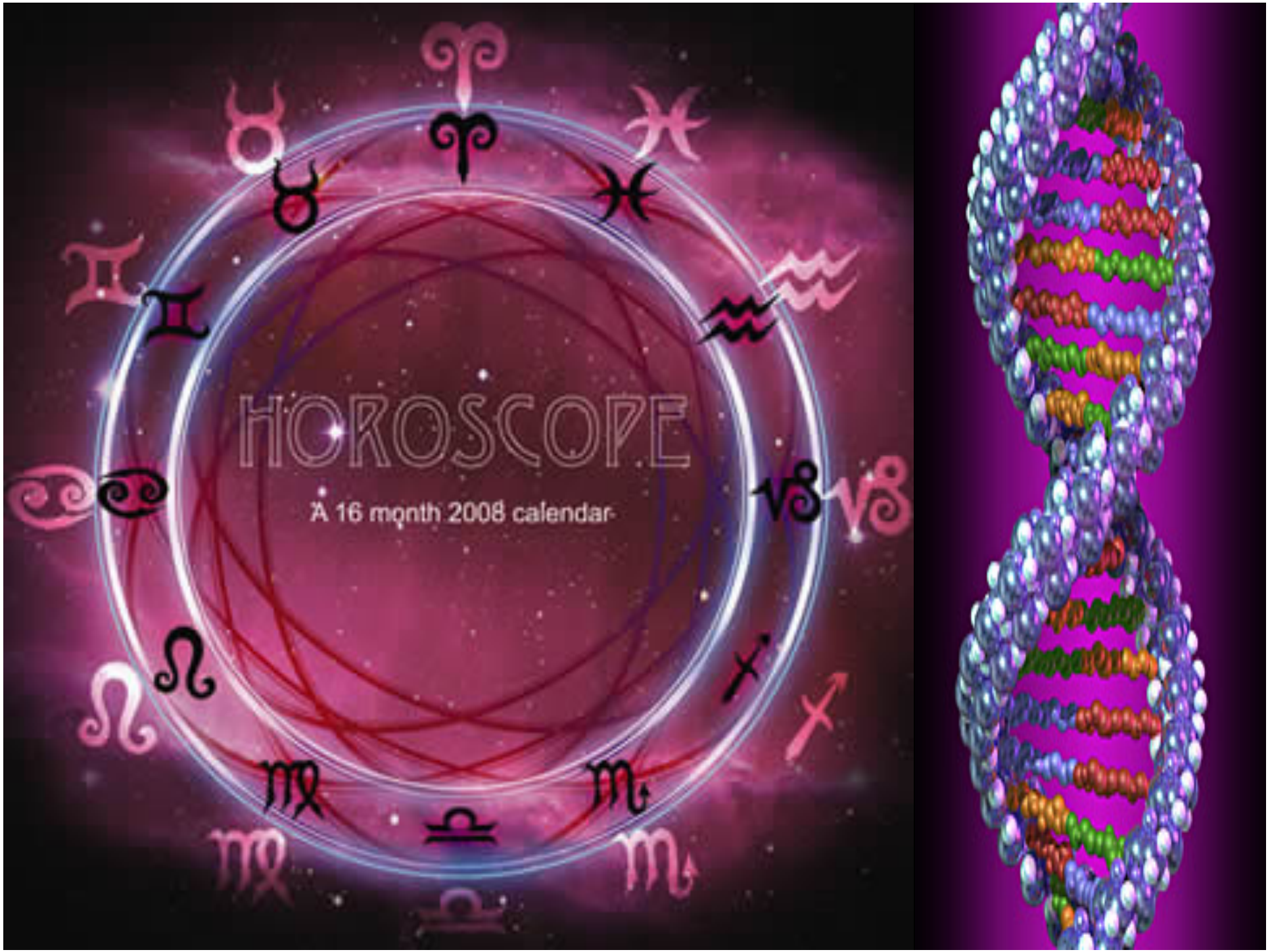




Genetic profiles different between cases and controls

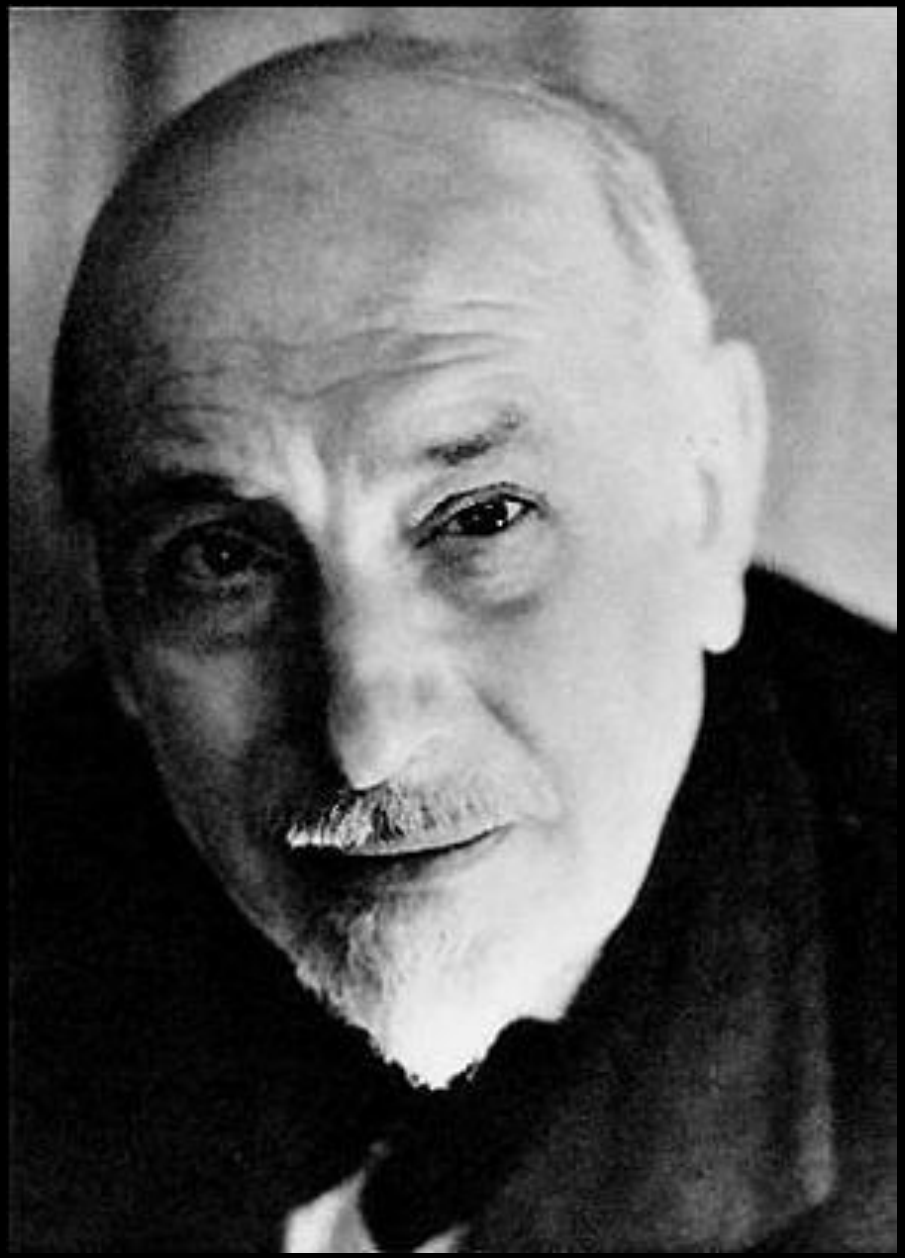
Discrimination between at risk and protective individuals


Controls
Cases
PPV = 50%
NPV = 99%
Specificity = 90%
Sensitivity = 90%
Distribution of high-risk alleles
Test cut-off point
Controls
Cases
PPV = 15%
NPV = 91%
Specificity = 90%
Sensitivity = 16%
Distribution of high-risk alleles

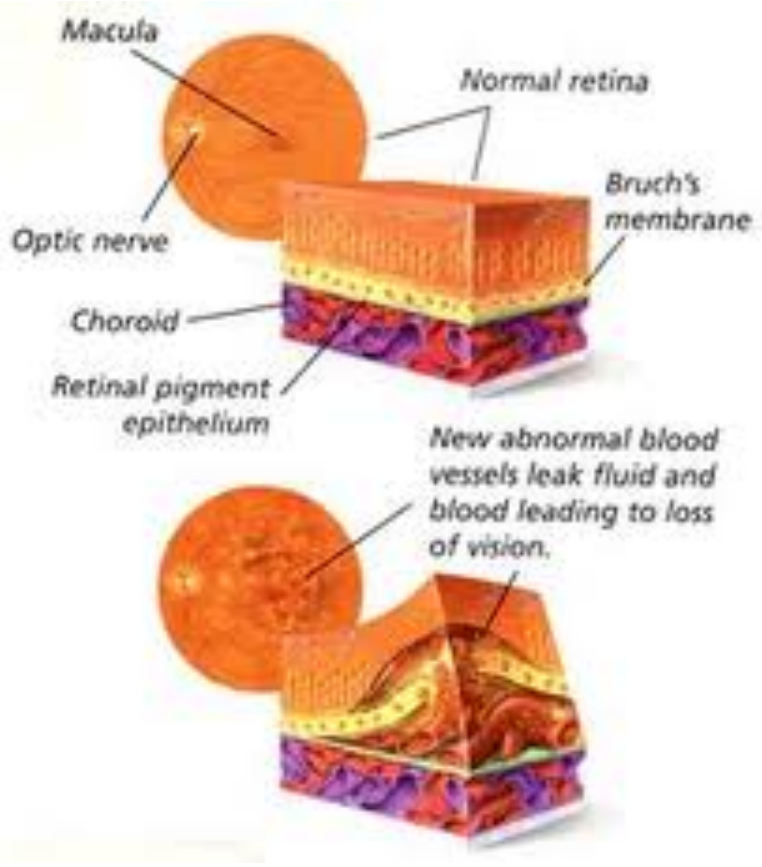

HOROSCOPE
A 16 month 2008 calendar

Risk Estimates Differ for the sampe individual between different commercially available tests

Condition	23andMe Risk Susannah Wedgewood	DeCODE Risk Susannah Wedgewood
Age-Related Macular Degeneration	0.623	0.25
Breast Cancer	1.13	1.16
Celiac Disease	0.471	0.38
Colorectal Cancer	**0.99**	**1.149**
Crohn's Disease	**0.907**	**2.29**
Heart Attack	0.989	0.87
Multiple Sclerosis	1.365	1.52
Obesity	1.018	1.05
Prostate Cancer	**1.03**	**0.85**
Restless Leg Syndrome	**0.75**	**1.6**
Rhematoid Arthritis	1.381	2.32
Type 1 Diabetes	0.56	0.46
Type 2 Diabetes	0.808	0.76
Venous Thromboembolism	0.976	0.88



DEGENERAZIONE MACULARE LEGATA ALL'ETA'

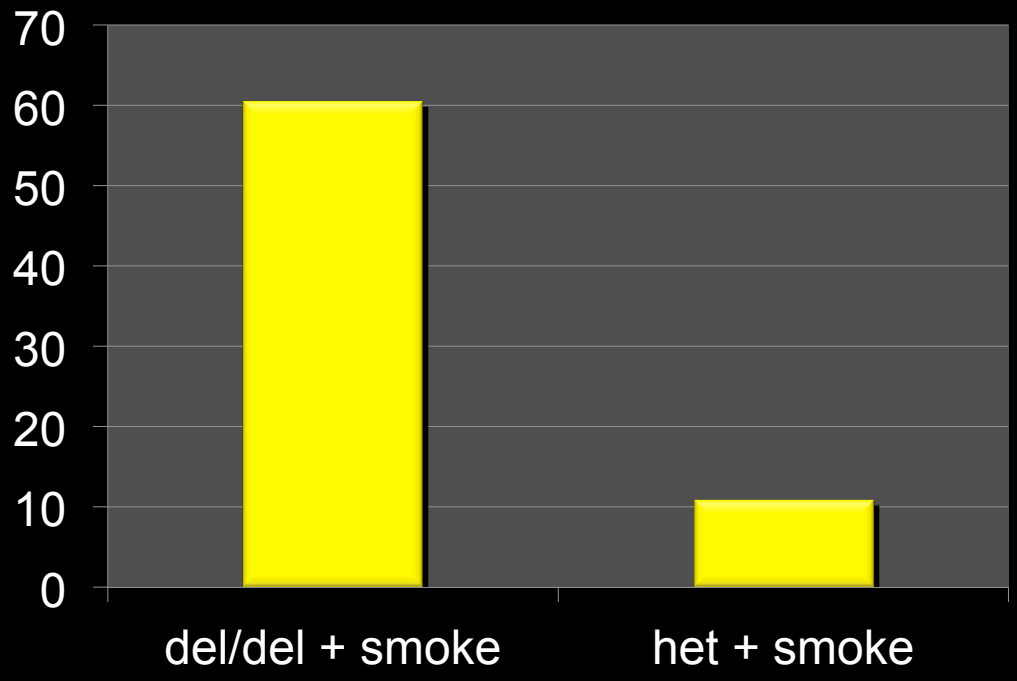


La DMLE è dovuta all'accentuazione ed accelerazione dei fisiologici processi di invecchiamento della retina, in particolare a carico dell'epitelio pigmentato retinico e della membrana di Bruch.

INCIDENZA

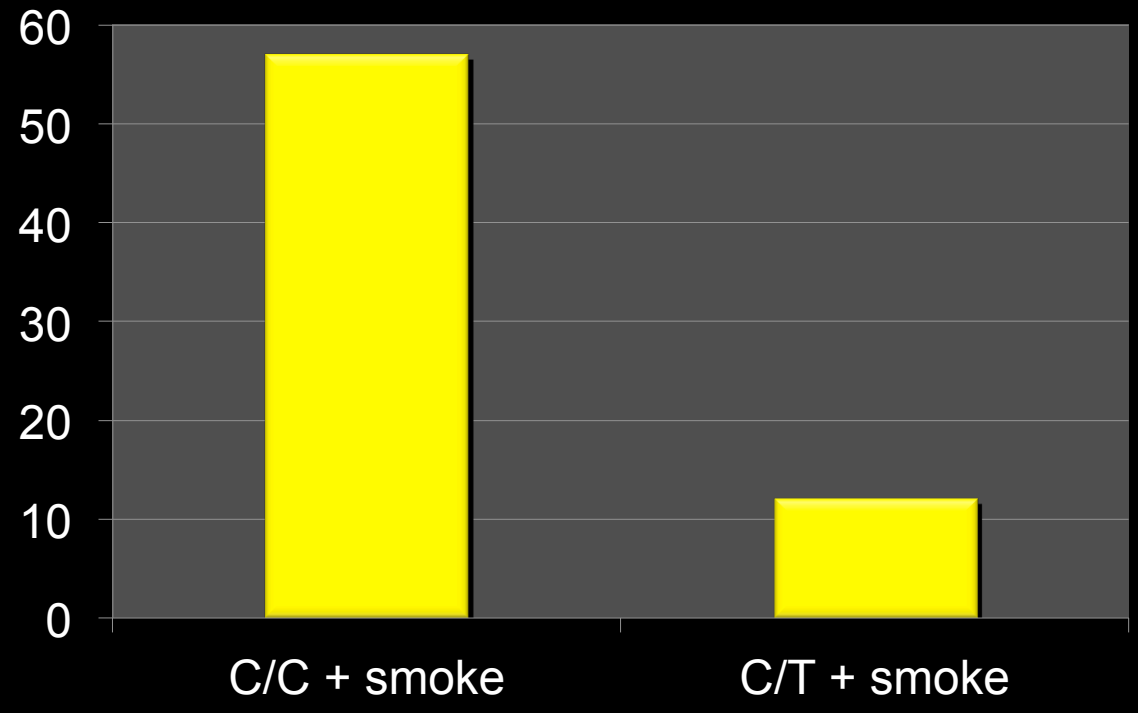
- E’ la principale causa di perdita irreversibile della funzione visiva centrale nei soggetti di età superiore a 65 anni che vivono nei paesi industrializzati.
- Incidenza annua: 600mila-1milione e 100 mila in USA. 150.000 –275.000 in Italia.
- Fattori esogeni (alimentazione,radiazioni UV,fumo, ecc.)

ARMS2

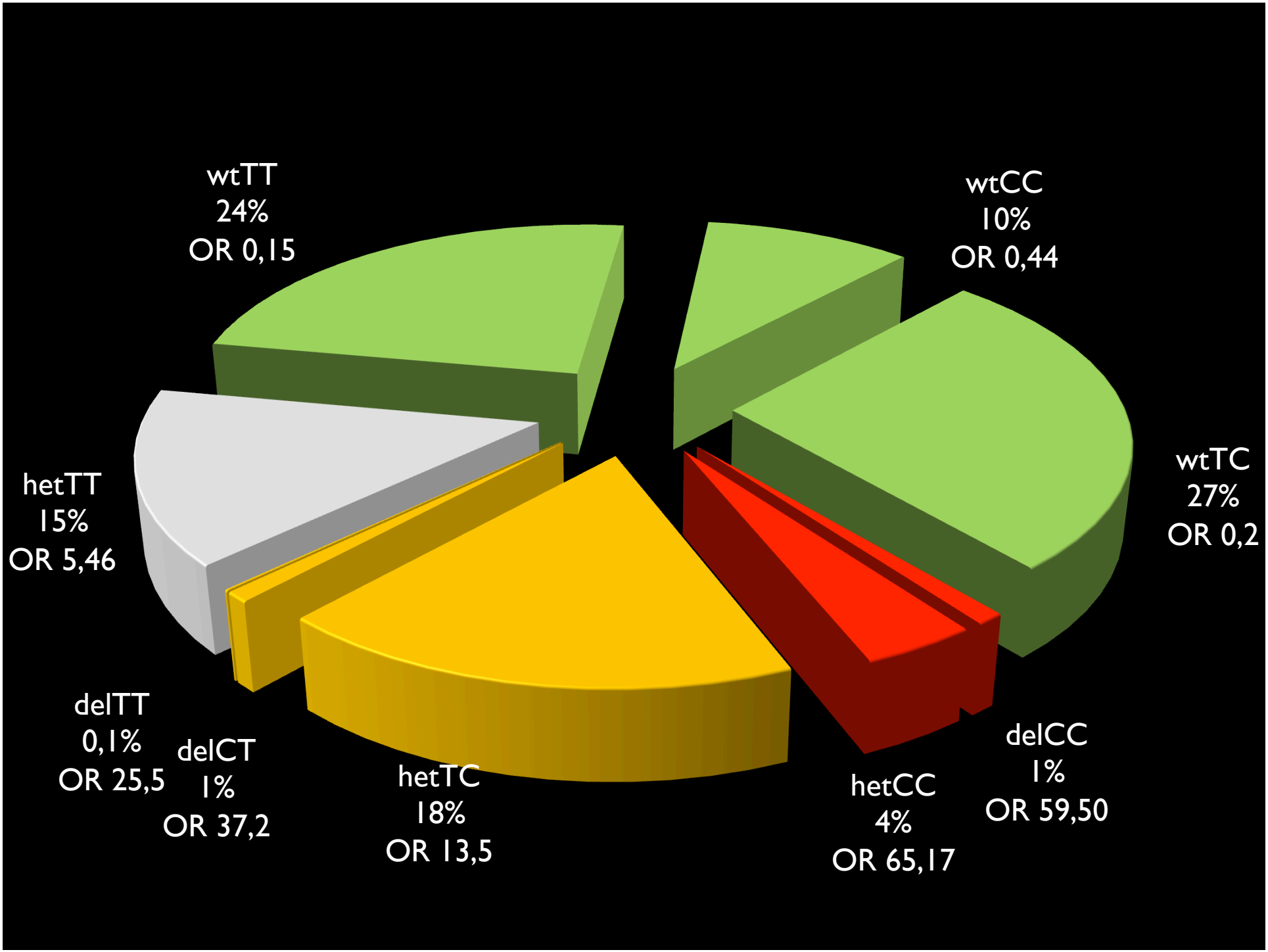


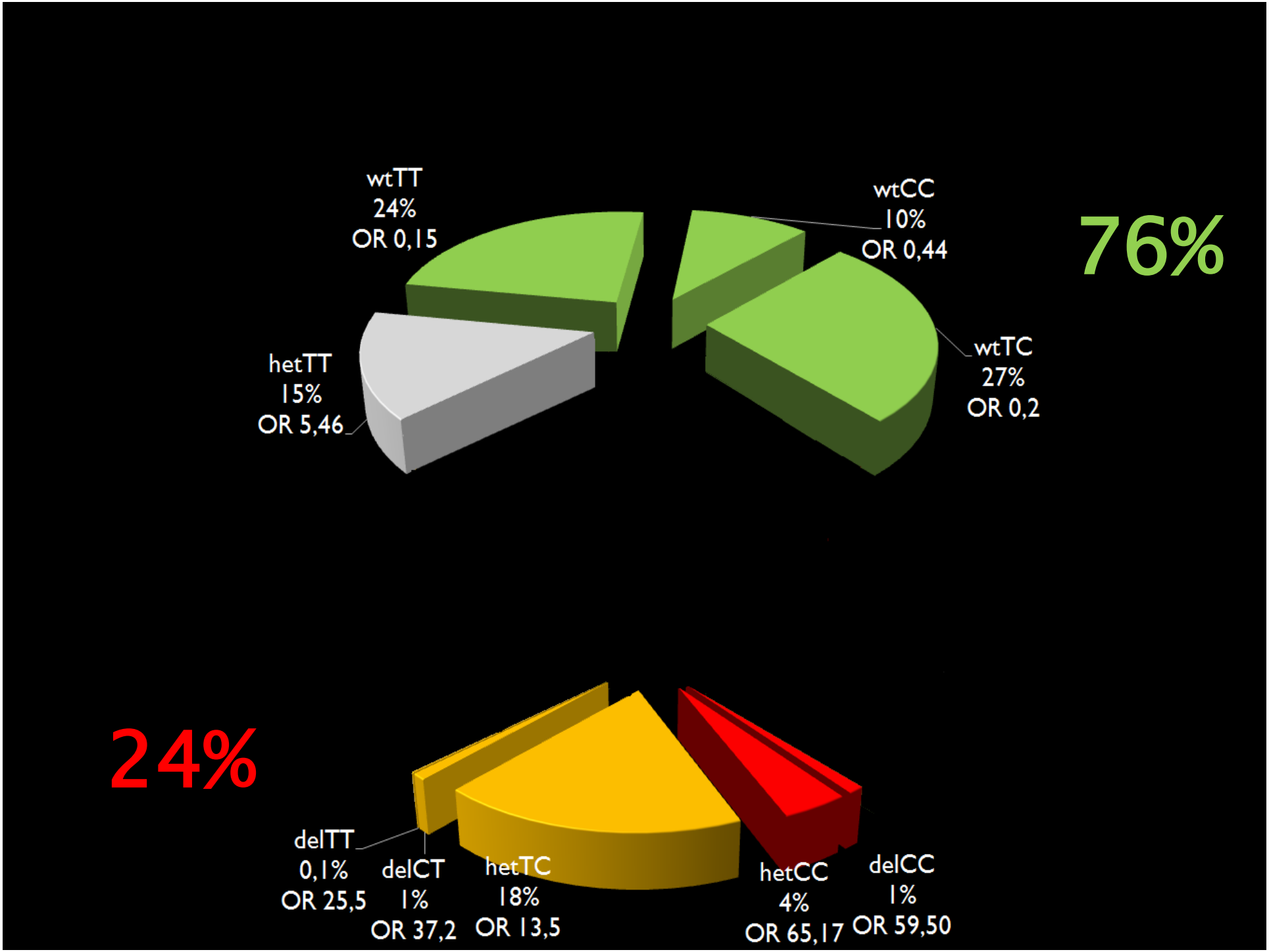
Genotype	OR (cases vs controls)
del/del	20.61 (8.83-48.11)
del/del + smoke	60.5 (13.69-267.40)
het	3.18 (2.01-5.03)
het + smoke	10.95 (6.07-19.74)

CFH Y402H

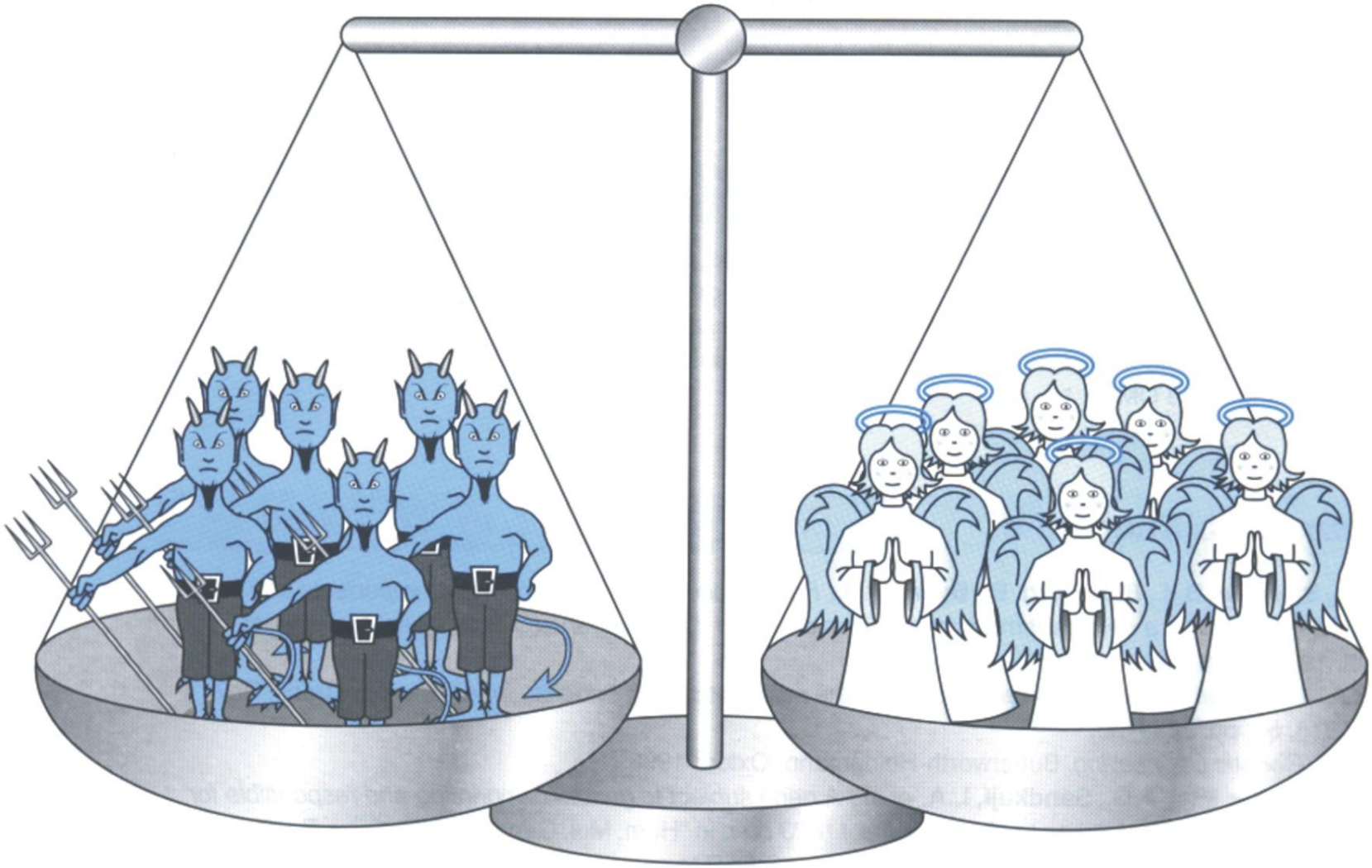


Genotype	OR (cases vs controls)
C/C	13.06 (6.27-27.19)
C/C + smoke	57 (16.12-201.54)
C/T	2.88 (1.76-4.72)
C/T + smoke	12.15 (6.51-22.67)


wtTT
24%
OR 0,15
wtCC
10%
OR 0,44
wtTC
27%
OR 0,2
hetTT
15%
OR 5,46
delTT
0,1%
OR 25,5
delCT
1%
OR 37,2
hetTC
18%
OR 13,5
hetCC
4%
OR 65,17
delCC
1%
OR 59,50


wtTT
24%
OR 0,15
wtCC
10%
OR 0,44
76%
hetTT
15%
OR 5,46
wtTC
27%
OR 0,2
24%
delTT
0,1%
OR 25,5
delCT
1%
OR 37,2
hetTC
18%
OR 13,5
hetCC
4%
OR 65,17
delCC
1%
OR 59,50


GOOD
GENES
TREATMENT
GOOD
GENES
SUNDAY RILEY




GOOD OR EVIL
Who Decides?

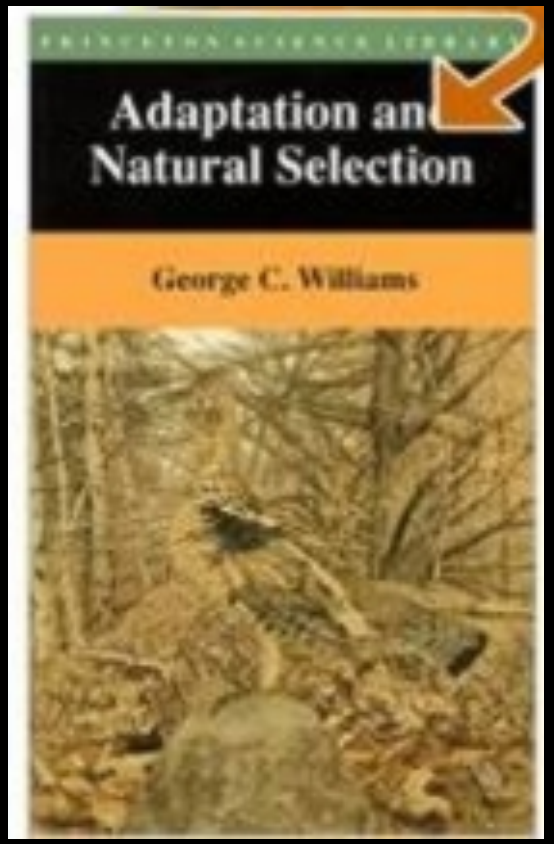
Gli yanomamo sono perfettamente adattati al loro ambiente e alla loro dieta.

L’esempio dell’ipertensione

Yanomamo indians
(Brasile)

10mg di sodio/die (1/1000 della media)

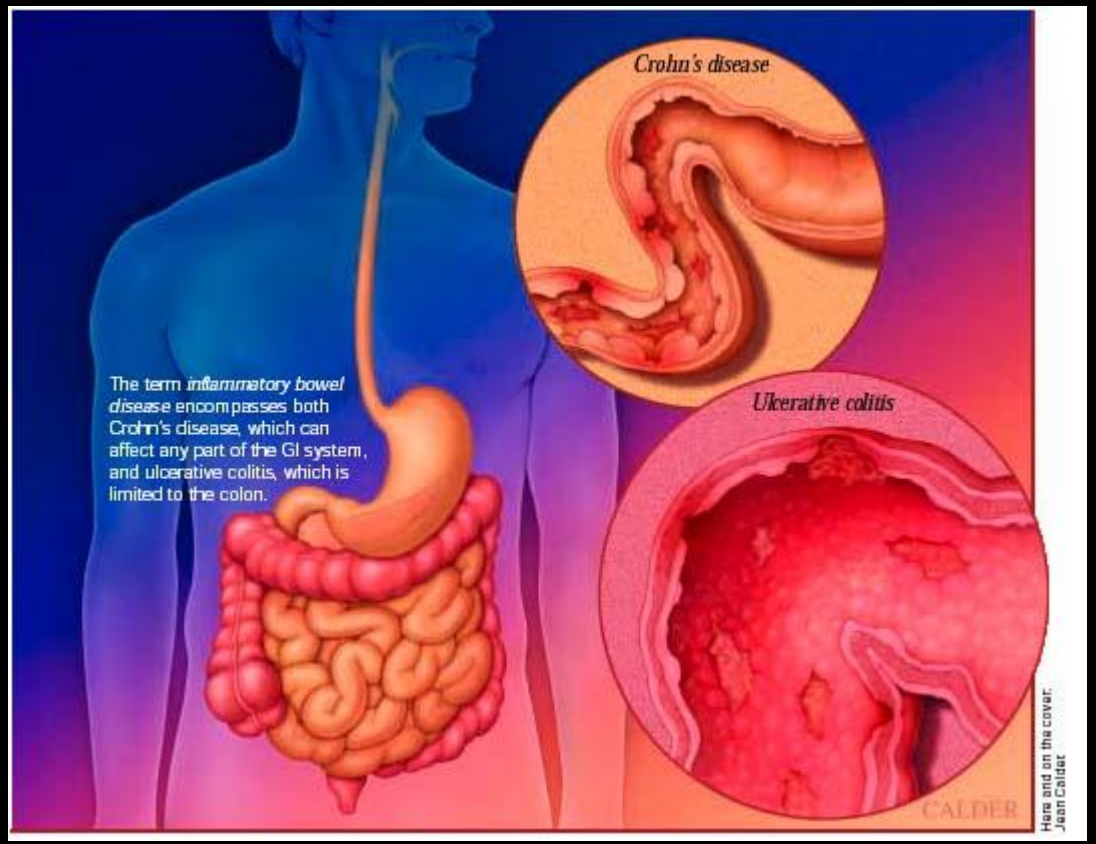
George C. Williams



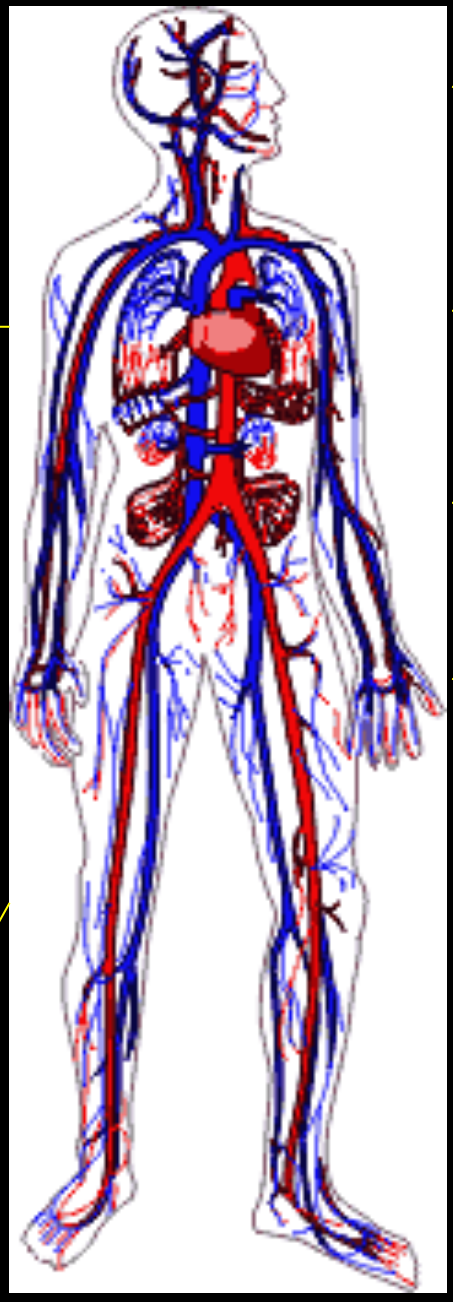
“Pleiotropy is the ultimate reason for all these things.”

L’esempio degli ebrei Ashkenazi

Gli ebrei Ashkenazi (mid-east Europe) hanno alte frequenze di IBD, per reazione alla costrizione nei ghetti dove le condizioni sanitarie erano mediocri e la popolosità elevata.



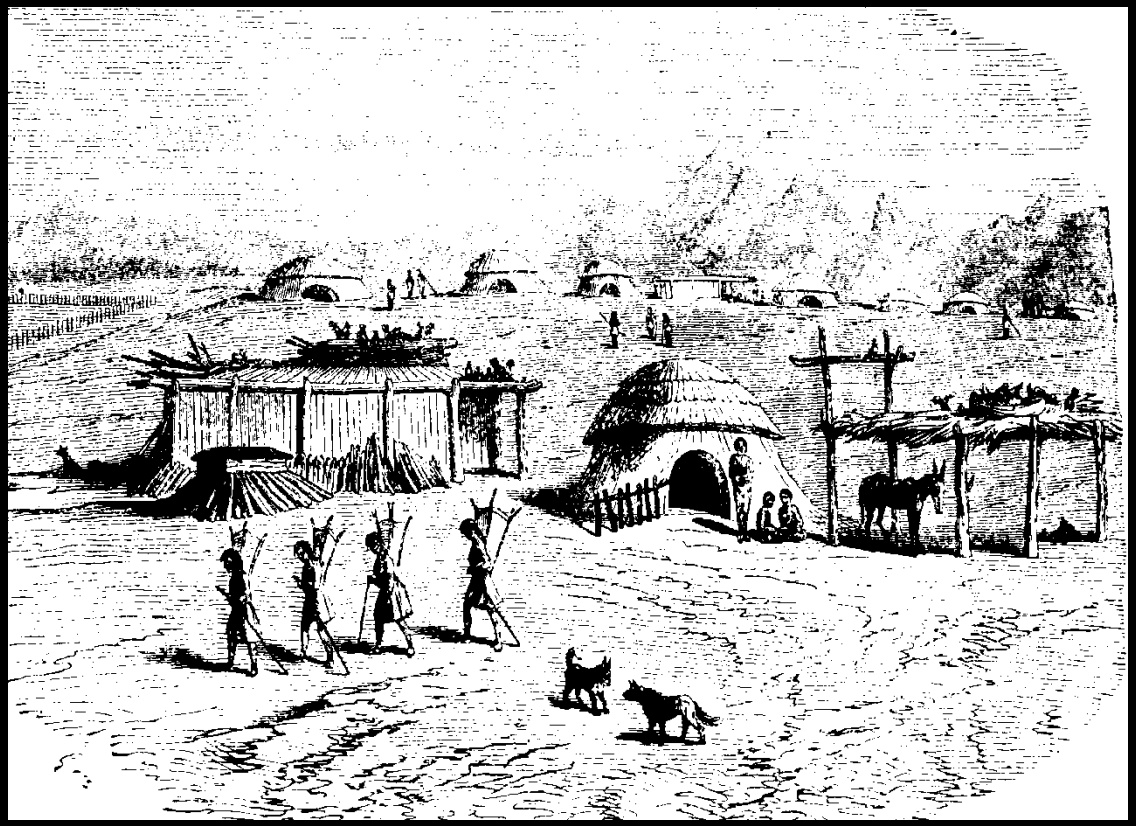
Le malattie della “Coca-colonizzazione”



- ictus
- Cancro mammella
- Diabete
- Obesità
- Patologie dell’intestino
- Depressioni-manie
- Infarto del miocardio
- Ipertensione
- ipercolesterolemia
- Schizofrenia

La coca-colonizzazione anche negli zoo…

L’esempio degli Indiani Pima



- Popolazioni caratterizzate da ridotto consumo energetico basale, insulinoresistenza muscolare ed epatica (con minor consumo e maggior produzione di glucosio nei periodi di carenza per preservare la funzione vitale cerebrale glucosiodipendente), ed ultimamente anche implicazioni della insulinoresistenza su una riduzione della funzione ovarica che avrebbe così rappresentato un controllo automatico della fertilità vantaggioso dal punto di vista evoluzionistico (minore fertilità in carenza di cibo).

"i geni vecchi in un ambiente nuovo"

1888

2000

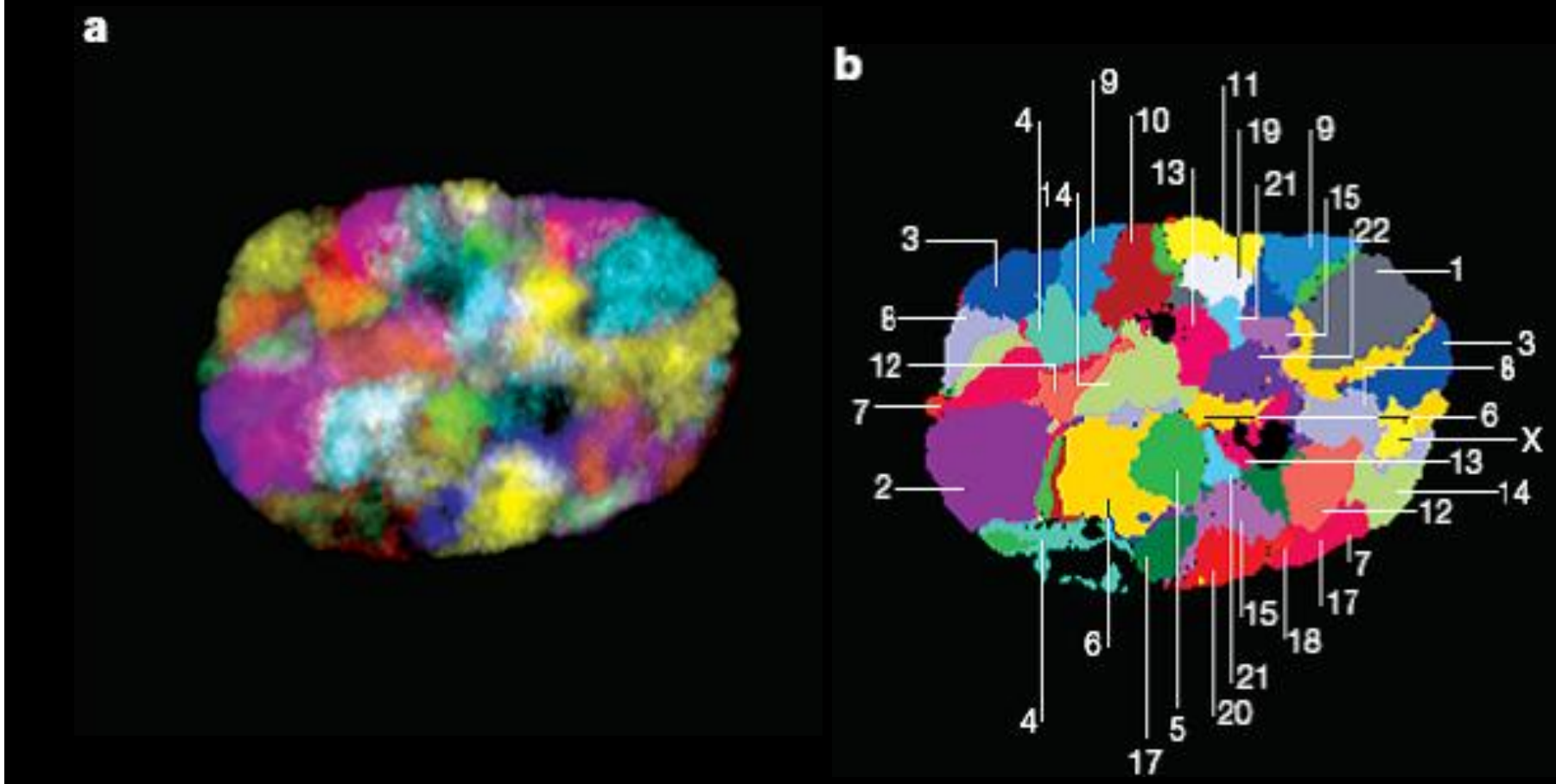
L’esempio di Apo E

- *ApoE* (19q13) codifica per una lipoproteina deputata al trasporto del colesterolo e dei fosfolipidi.
- Lipidi e lipoproteine sembrano svolgere un ruolo protettivo nei confronti degli agenti virali.
- Nel cervello, in età adulta, questo gene da protettivo diventa di suscettibilità per la malattia di Alzheimer

L’esempio delle IBDs

- I geni che predispongono alle IBD hanno un ruolo protettivo nei confronti delle infezioni mucosali nei paesi non industrializzati.

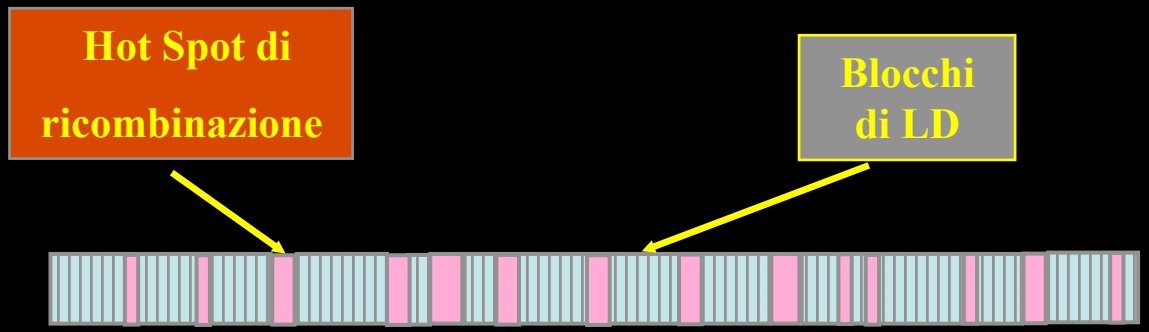
- Nei paesi industrializzati, non essendoci più la continua esposizione agli agenti patogeni, si sviluppa una reazione autoimmune che causa, ad esempio, il morbo di Crohn.


a
b
9
11
4
10
19
9
13
21
15
14
22
3
1
8
3
12
8
7
6
X
13
2
14
12
7
17
15
18
6
21
4
20
5
17


NIKE

Ridotta variabilità (LD), maggiore facilità di mappare geni di suscettibilità

Il numero di SNPs da caratterizzare diminuisce, poiché non sono indipendenti tra loro



(515-450 circa aC).

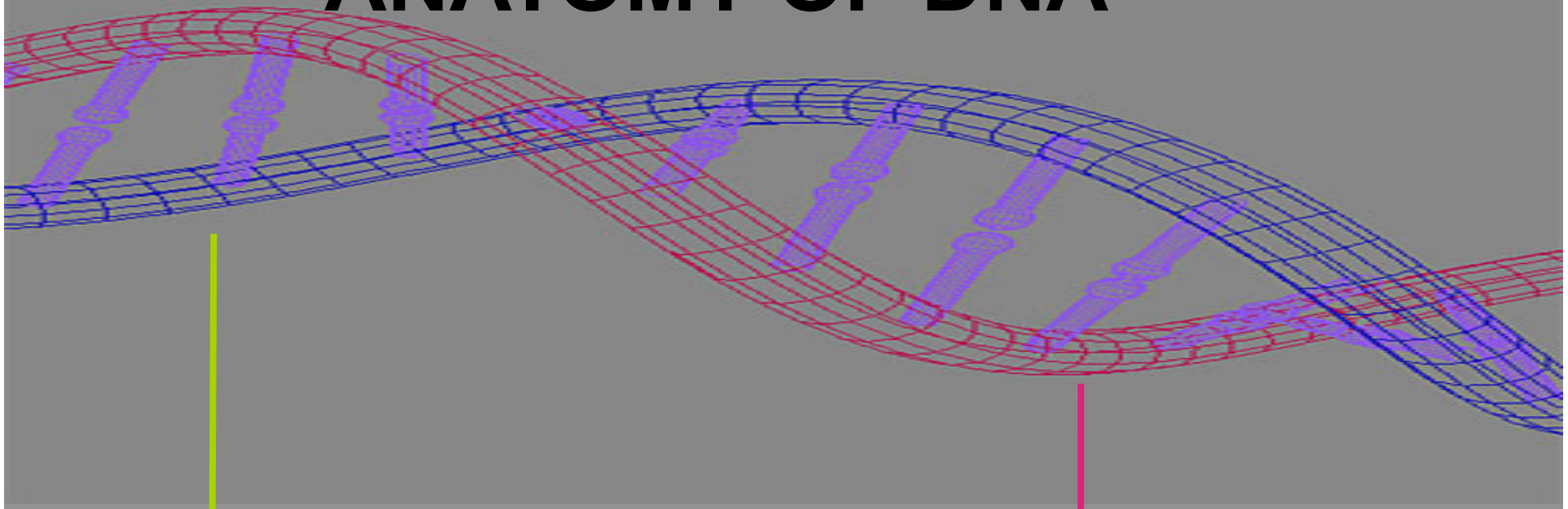
[...] Essendo ingenerato è anche imperituro,
tutt’intero, unico, immobile e senza fine.
Non mai era né sarà, perché è ora tutt’insieme,
uno, continuo. Difatti quale origine gli vuoi cercare?
Come e donde il suo nascere? Dal non essere non ti permetterò né
di dirlo né di pensarlo. Infatti non si può né dire né pensare
ciò che non è.

(Parmenide, *I presocratici. Testimonianze e frammenti*,)

…tutto scorre…niente permane

(Efeso ca. 520- 460 a. C.)

ANATOMY OF DNA



ENVIRONMENTAL/INTERACTION GENES
NEED FOR GREAT VARIABILITY
POLYMORPHIC REGIONS

CORE BIOLOGY FUNCTION GENES
NO NEED FOR GREAT VARIABILITY
BLOCKED REGIONS

nature genetics

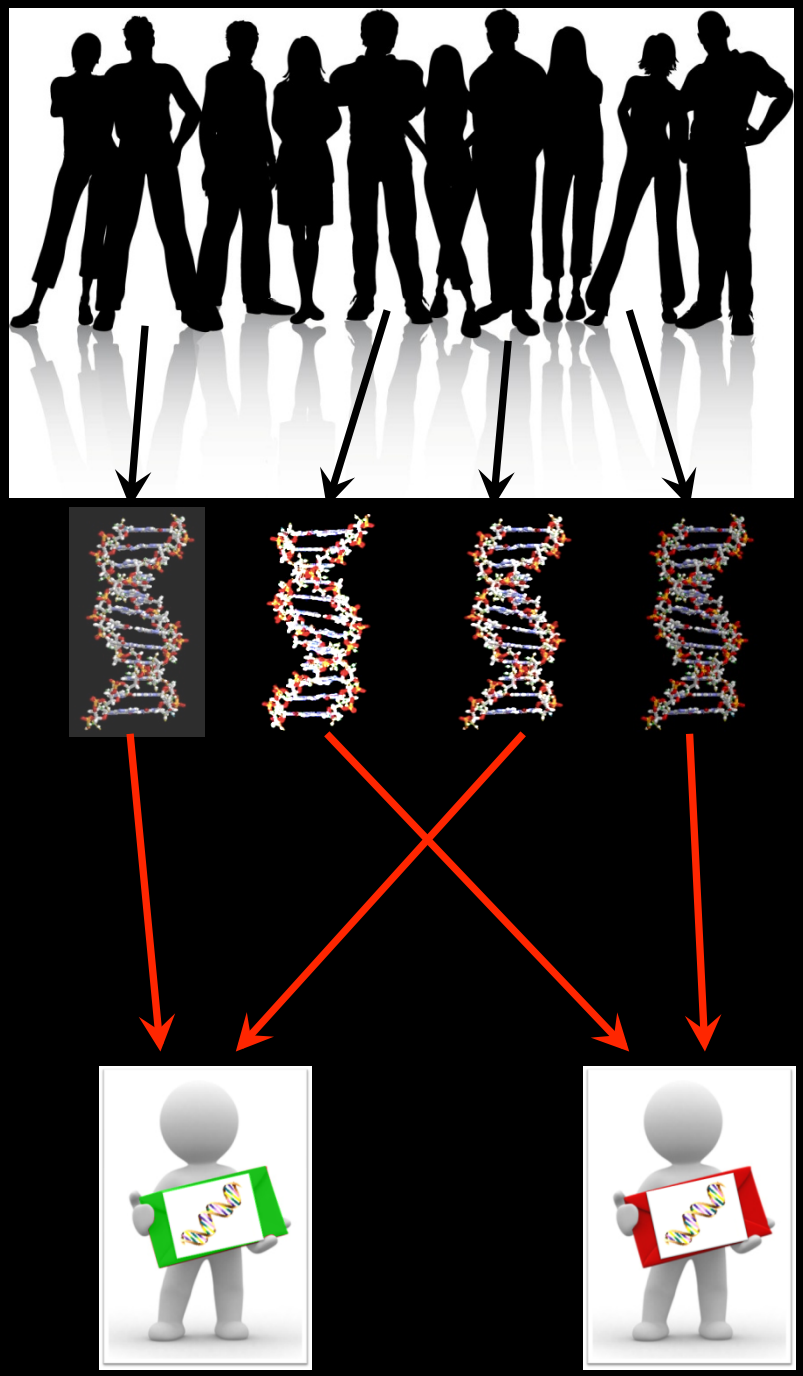
October, 2006

Mammalian ultraconserved elements are strongly depleted among segmental duplications and copy number variants

Adnan Derti[1–4], Frederick P Roth[1,5], George M Church[2,3] & C-ting Wu[6]

ture.com/naturegenetics

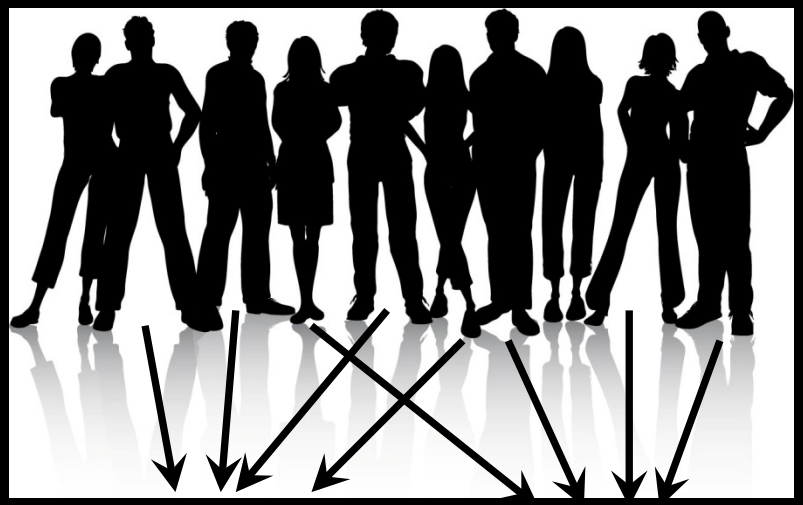
…ultraconserved elements (UCEs) are believed to be important for functions involving DNA binding, RNA processing and the regulation of transcription and development.



Different individuals

Different genomes

Different outcomes

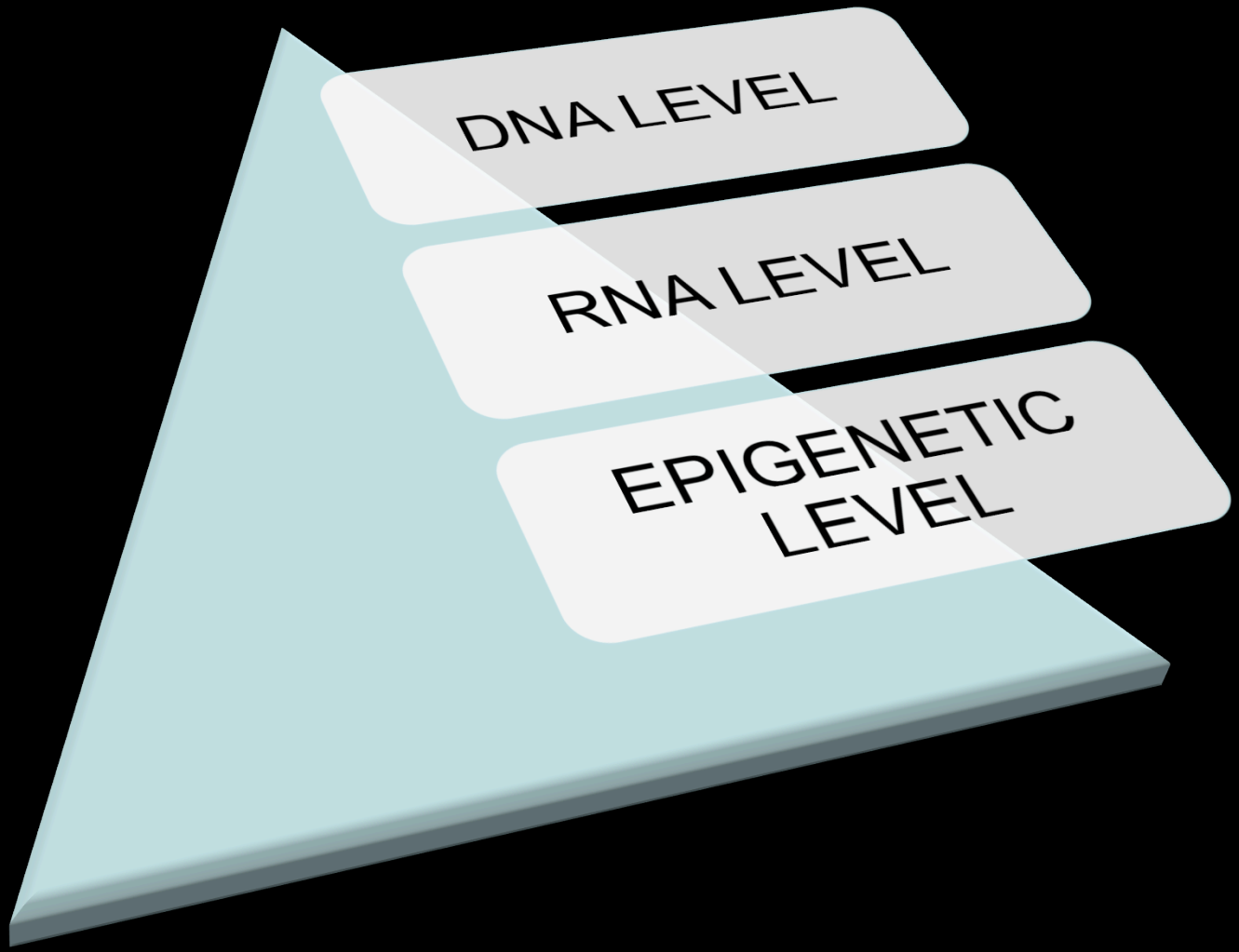


Different individuals

Similar genetic risk profiles

Different outcomes

DNA IS NOT THE ONLY SOURCE OF PHENOTYPIC VARIATION



The epigenome includes DNA methylation, nucleosome occupancy, histone deacetylation and other histone modifications, and corresponding coding and non-coding RNA.

From a static to a dynamic view of genetic risk

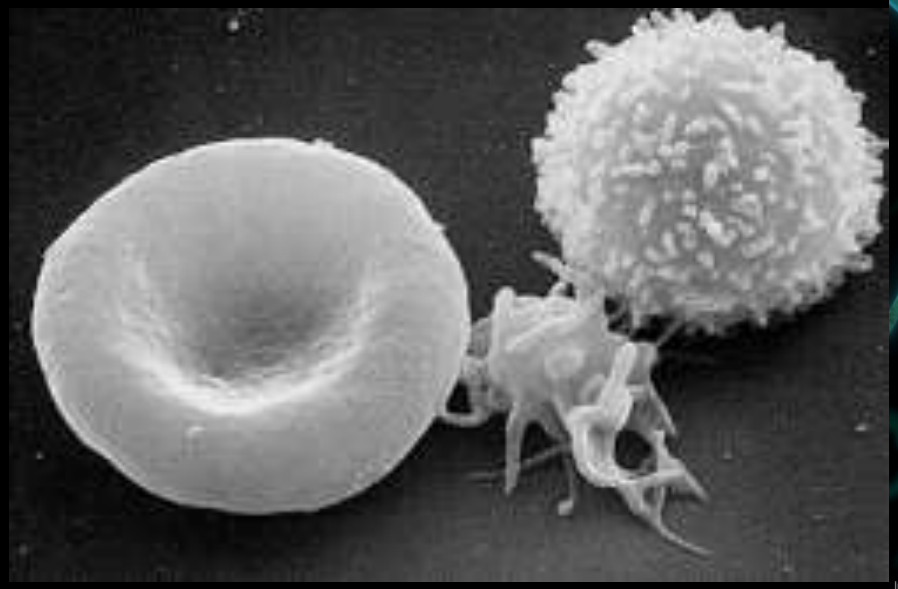
✓ variation in chromatin states is common in humans and could therefore provide an additional source of phenotypic variation

✓ chromatin differences between individuals can exist independently of DNA sequence polymorphisms

✓ the dynamic quality of epigenetic modification, which stands in contrast to static nucleotide sequence information, provide the basis for an individual's response to a constantly changing environment

✓ Epigenetic factors affect the expression of drug-metabolizing enzymes, drug transporters, and nuclear receptors that regulate the expression of variuos genes and ultimately affect the response to drug

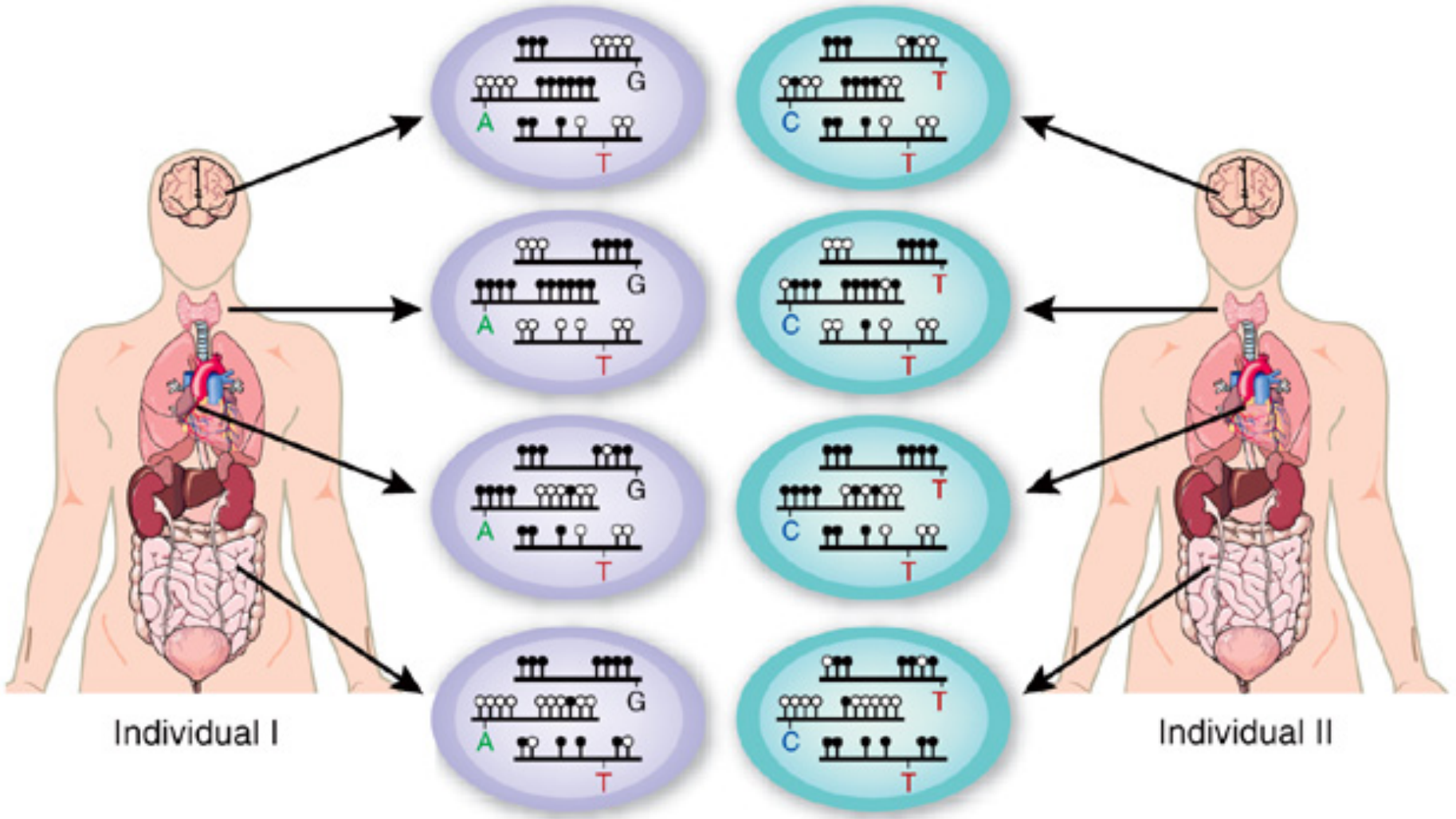
- A SINGLE MAMMALIAN GENOME RESULTS IN DIFFERENT GENE PATTERNS IN ABOUT 200 DIFFERENT CELL TYPES AT DIFFERENT STAGES OF DEVELOPMENT.



Most of these changes occur in early development, but cells collect further changes throughout their life. This means that the epigenome varies from individual to individual, and even from cell to cell, and studying the epigenome could help clarify the links between genes, environment and health or disease.

Heritability components

- a component originating from DNA sequence variation,
- a component originating from epigenetic variation,
- a component of non-heritable chromatin variation
- a component of heritable chromatin variation
- a component of unexplained (residual) variation

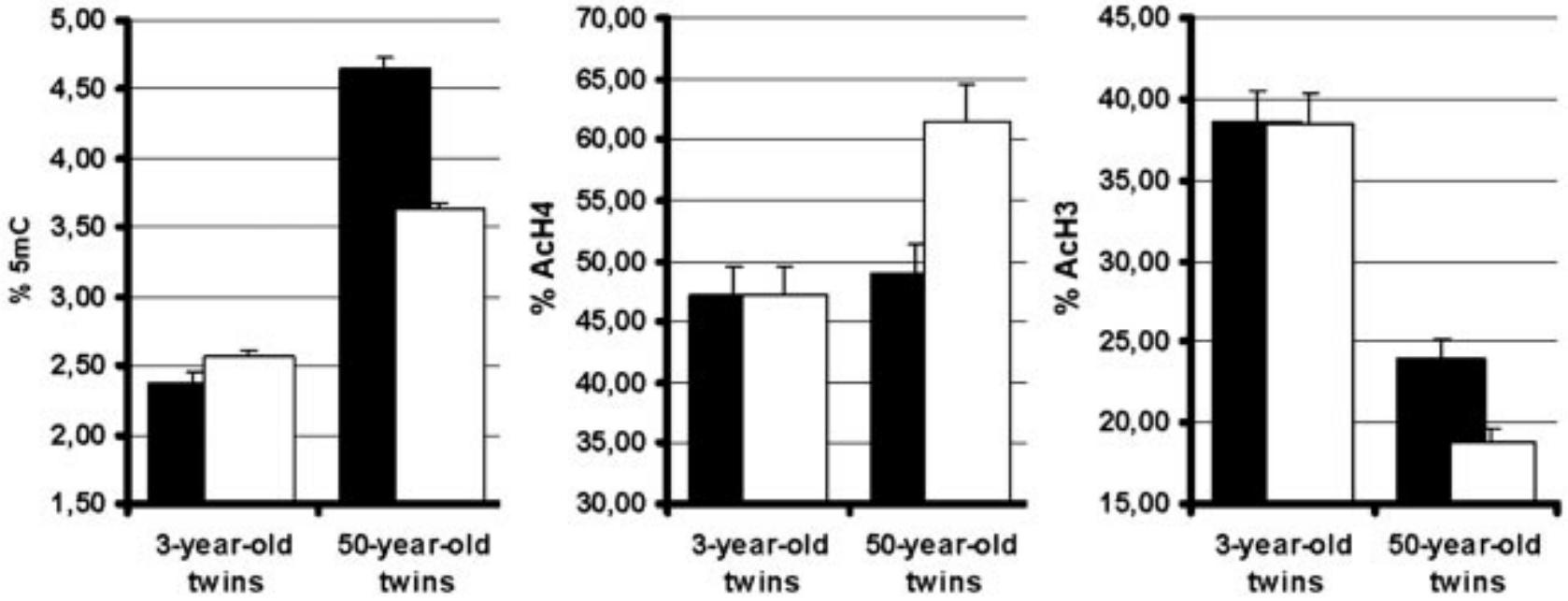

G
A
T
C
T
Individual I
Individual II
Kim Caesar

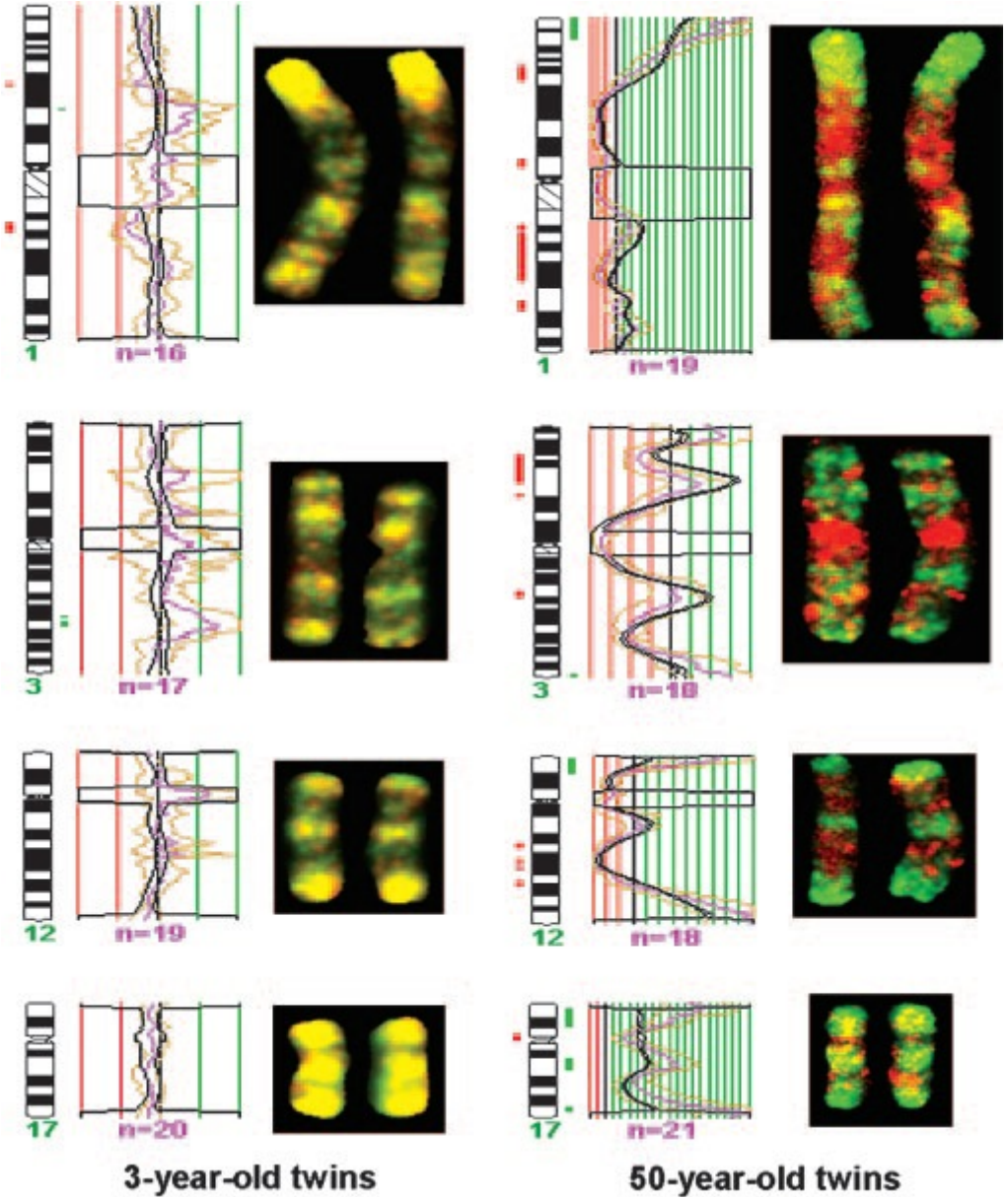
The regulation of genes changes over the time

Epigenetic differences arise during the lifetime of monozygotic twins

PNAS | July 26, 2005 | vol. 102 | no. 30

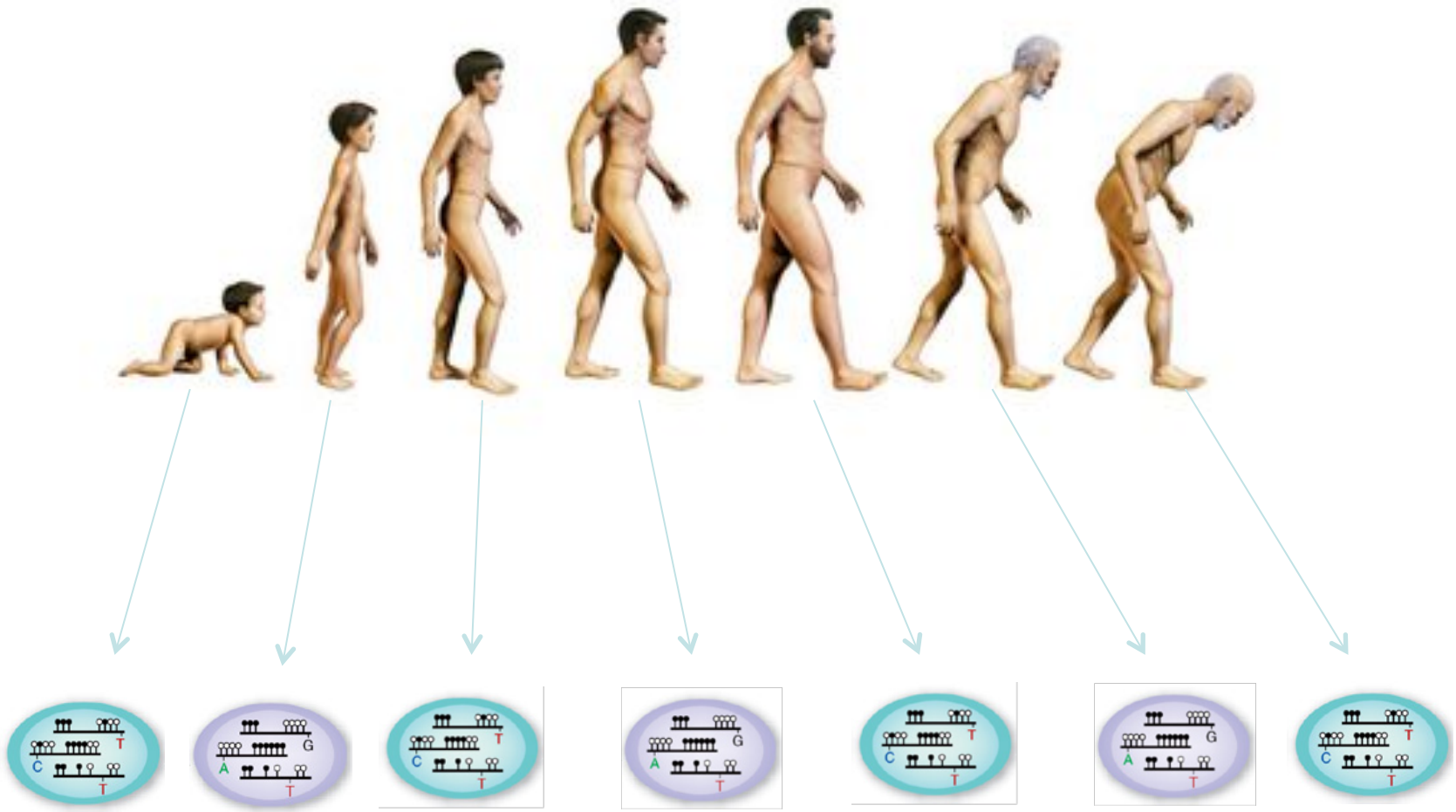
Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling‖, Emma Carlsson‖, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§





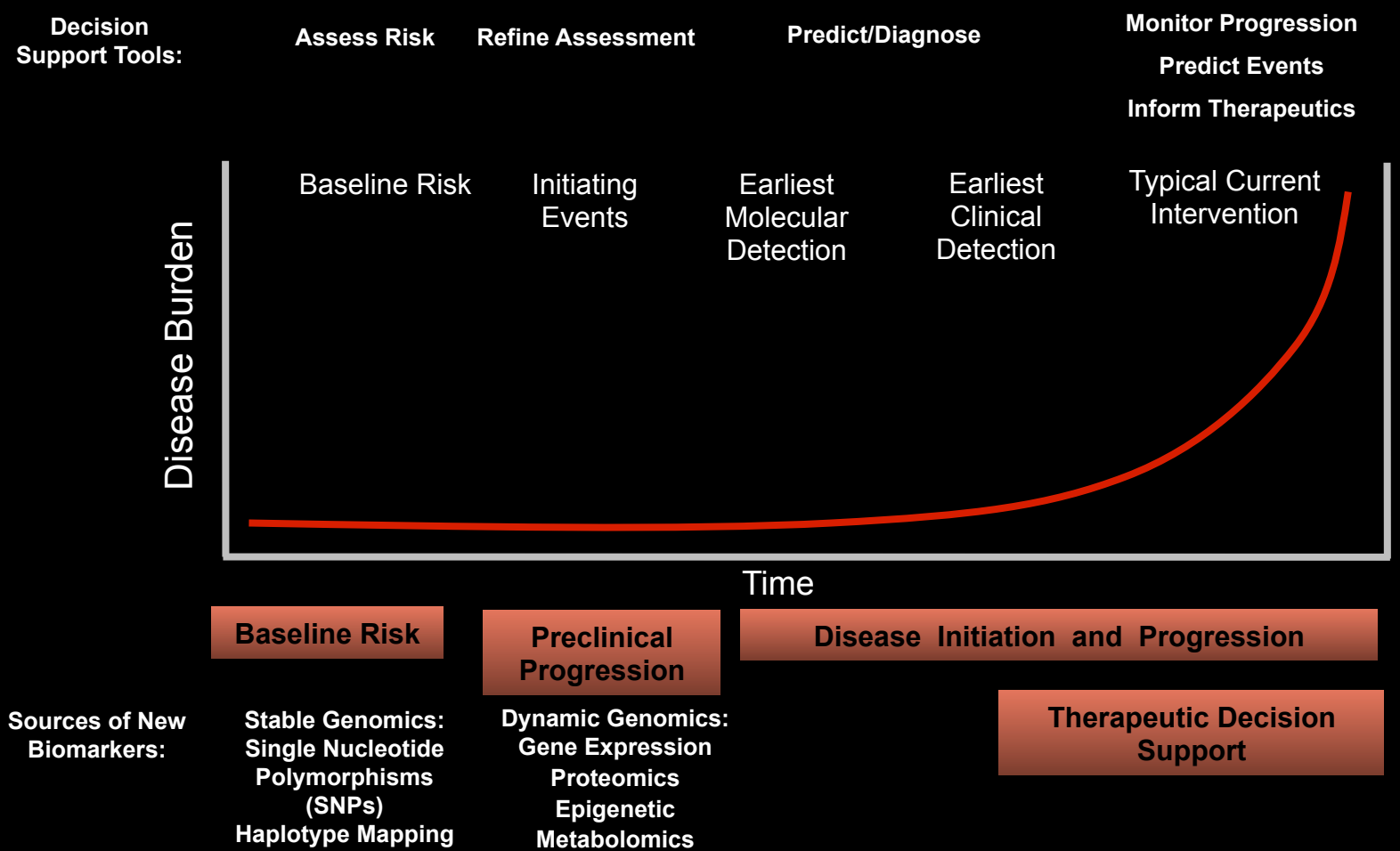
3-year-old twins

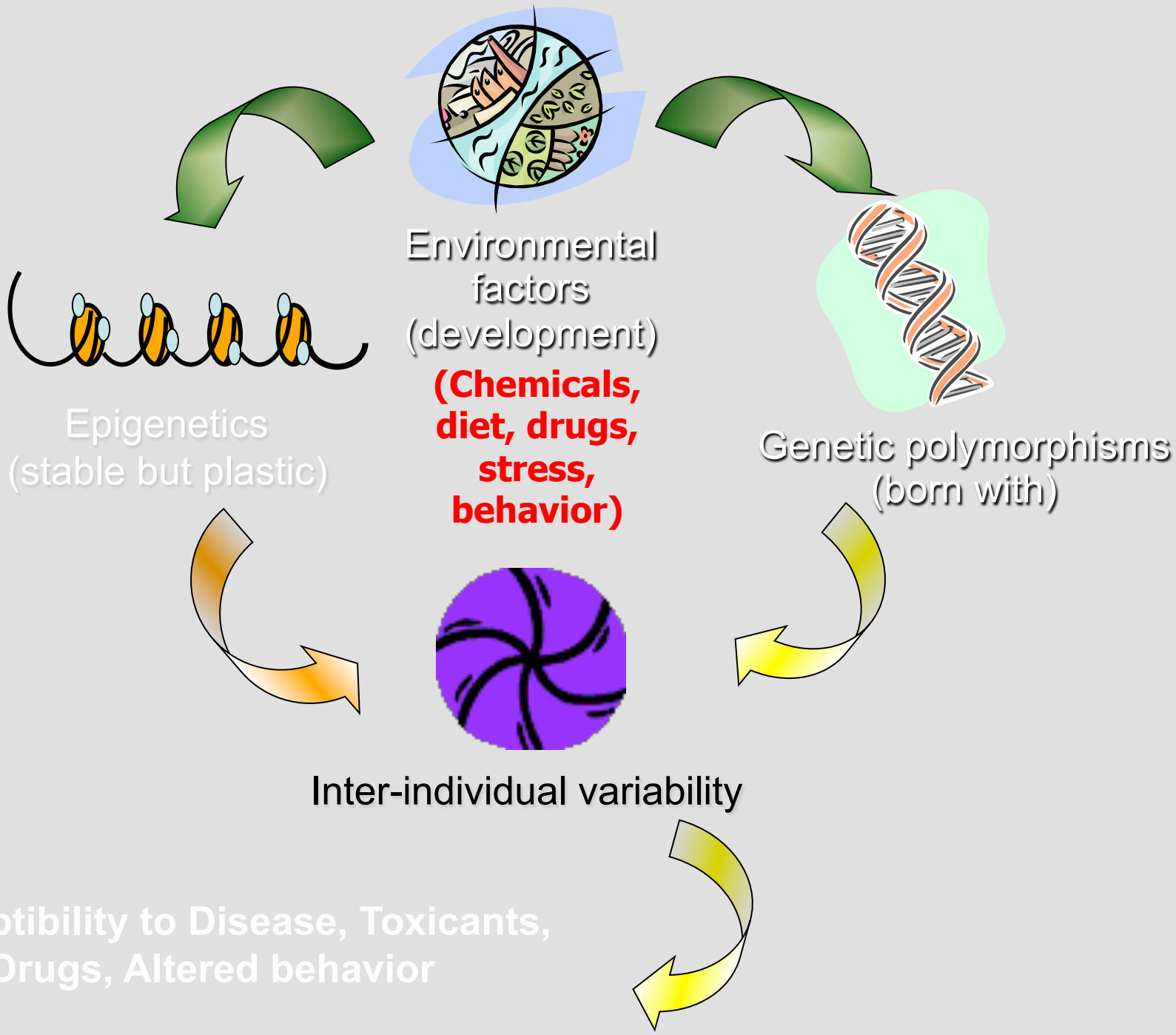
50-year-old twins



Methylation patterns and their control of gene silencing influence gene expression and cellular function. These variation both environmental and inherited accumulated during the life modify the risk for complex diseases later in life.

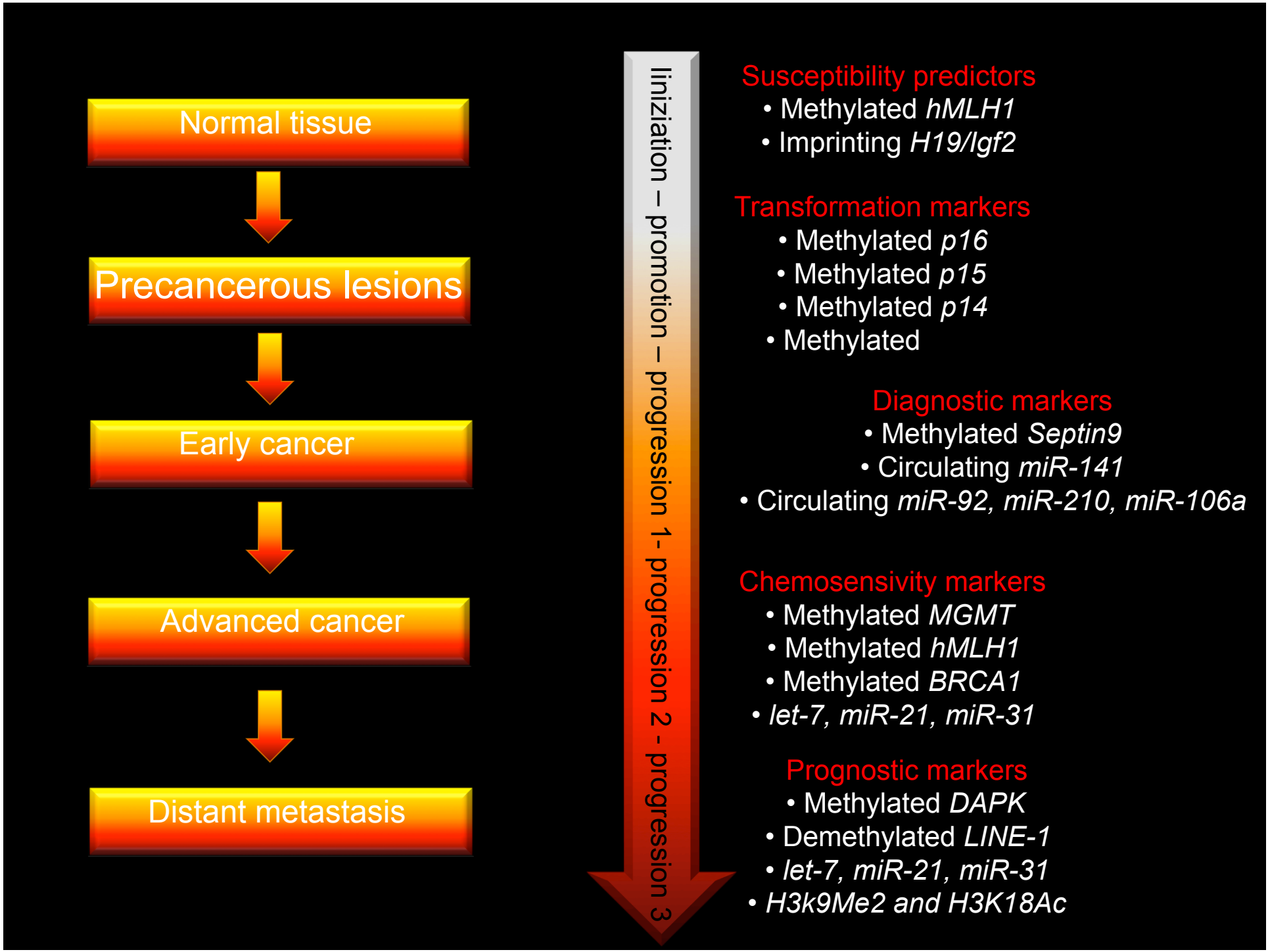
The genetic risk is dependent on the time and it is not stable across the lifespan




Environmental factors (development)
(Chemicals, diet, drugs, stress, behavior)
Epigenetics (stable but plastic)
Genetic polymorphisms (born with)
Inter-individual variability
Susceptibility to Disease, Toxicants, Drugs, Altered behavior

from interindividual variability…

to intra-individual variability


Normal tissue
Precancerous lesions
Early cancer
Advanced cancer
Distant metastasis
Iniziation – promotion – progression 1- progression 2 - progression 3
Susceptibility predictors
• Methylated hMLH1
• Imprinting H19/Igf2
Transformation markers
• Methylated p16
• Methylated p15
• Methylated p14
• Methylated
Diagnostic markers
• Methylated Septin9
• Circulating miR-141
• Circulating miR-92, miR-210, miR-106a
Chemosensivity markers
• Methylated MGMT
• Methylated hMLH1
• Methylated BRCA1
• let-7, miR-21, miR-31
Prognostic markers
• Methylated DAPK
• Demethylated LINE-1
• let-7, miR-21, miR-31
• H3k9Me2 and H3K18Ac

Classificazione dei biomarker genomici

- *Validi*
  - **Accettati dalla comunità scientifica per predire fenotipi clinici o pre-clinici.**
- *Probabilmente validi*
  - **Sembrano avere un valore predittivo ma non sono stati replicati o universalmente accettati.**

Esempi di biomarker validi:

- ***Sicurezza***
  - **TPMT (6-MP, azathioprine)**
  - **UGT1A1 (irinotecano)**
  - **CYP2C9/VKORC1 (warfarina)**
  - **CYP2D6 (Strattera)**
- ***Efficacia***
  - **EGFR status (Erbitux, Tarceva)**
  - **Her2/neu status (Herceptin)**
  - **Philadelphia chromosome ~ Bcr-abl (Gleevec)**
  - **C-kit (Gleevec)**

Probabilmente Validi :

- ***Sicurezza***
  - **Kim1 ~ preclinical (nephrotoxicity)**
  - **Gene panels used for preclinical safety evaluation**
- ***Efficacia***
  - **EGFR mutations (Iressa)**
  - **CYP2D6 (Tamoxifen)**
  - **OncotypeDx gene panel (radiation therapy)**

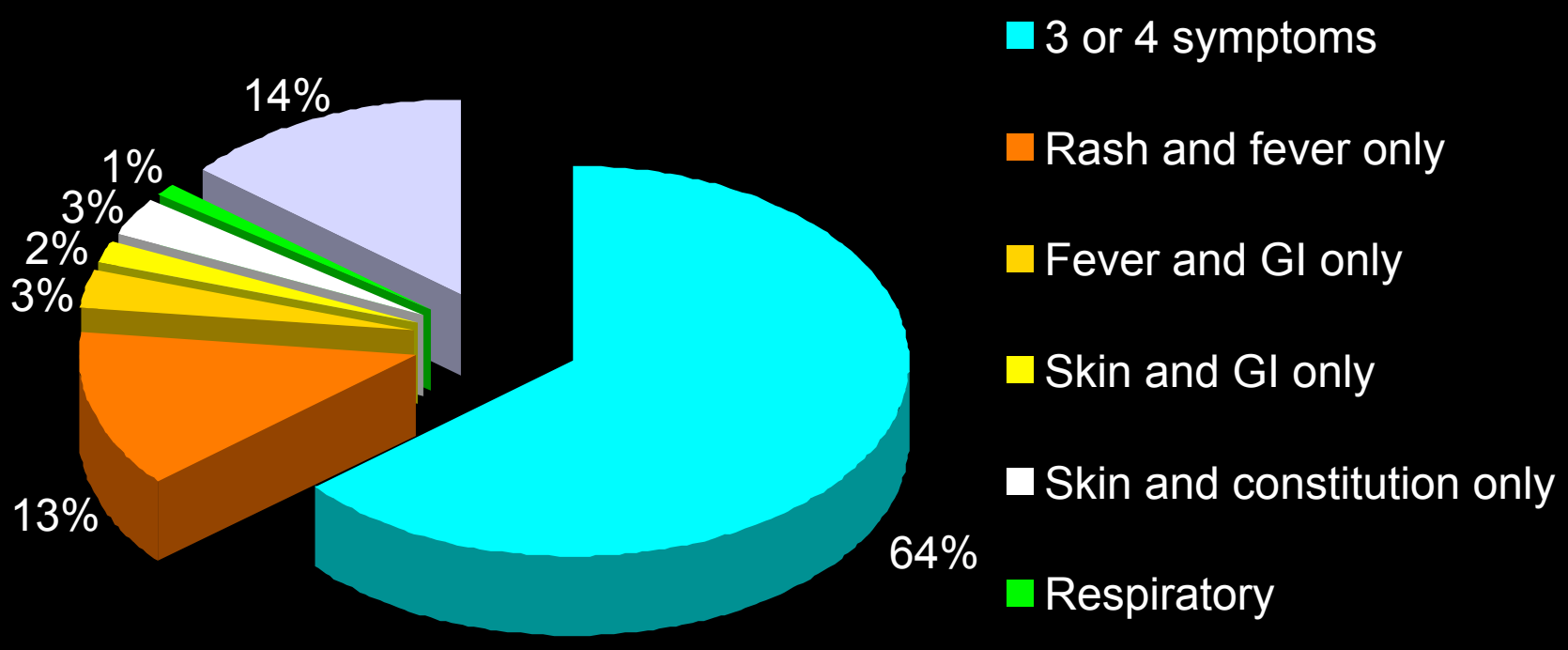
ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	P Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

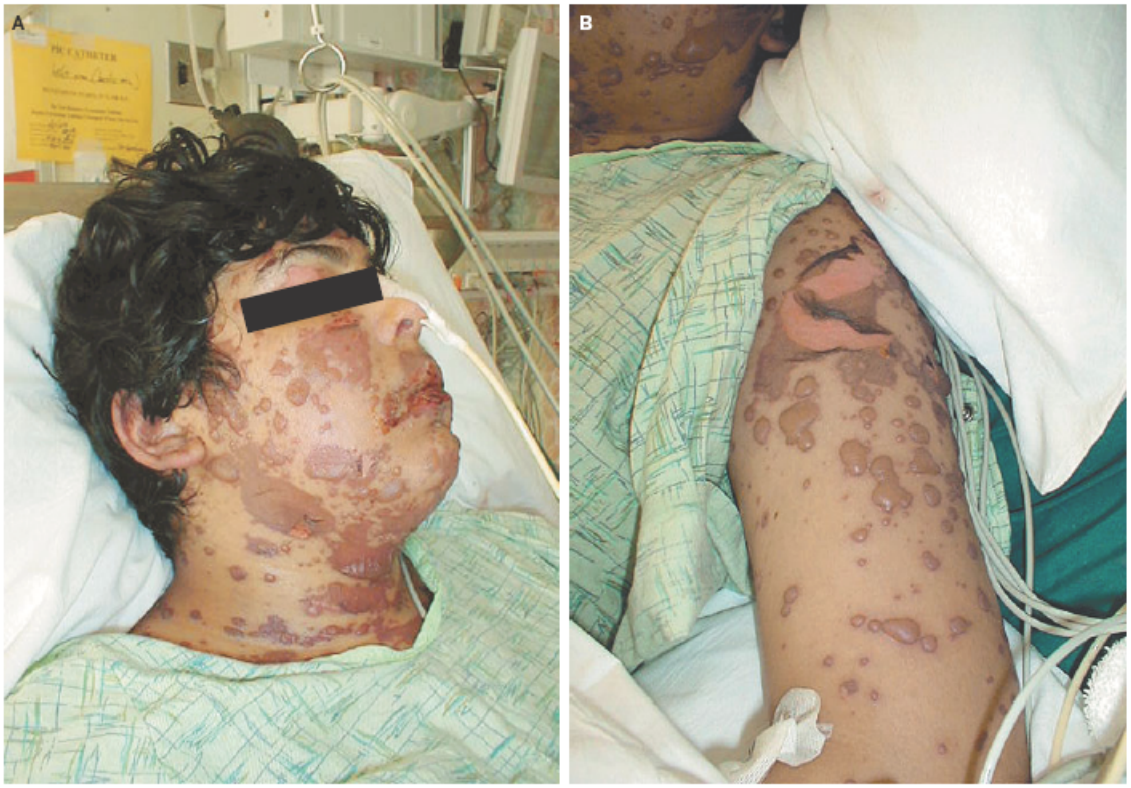
Combinazione di sintomi comunemente riportati con ipersensibilità (n=1,306)



Sintomi multipli sono tipicamente presenti nella maggioranza dei casi di ipersensibilità

Hetherington SV. 2nd International Symposium on Mechanisms, Models and Predictions of Idiosyncratic Drug Toxicity. 11–13 June 2001.

Stevens–Johnson Syndrome

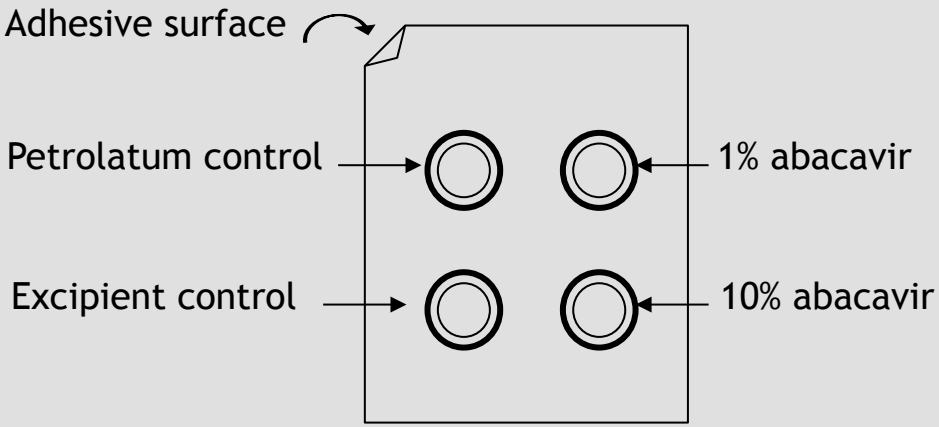


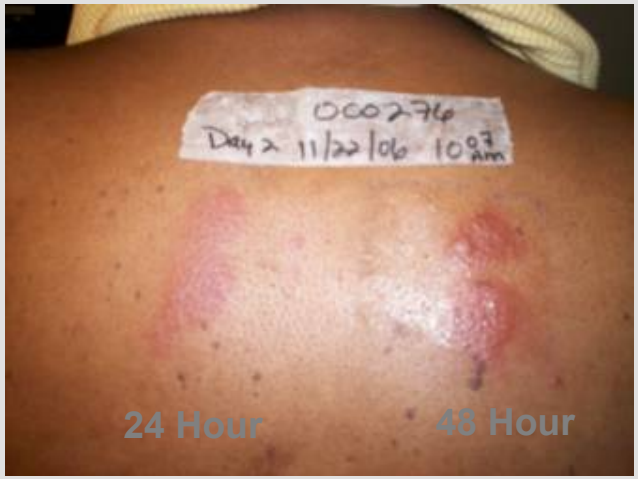
carbamazepine (CBZ), lamotrigine (LTG), phenobarbital (PHB), phenytoin (PHT), or valproic acid (VPA)

Abacavir Skin Patch Testing

- Immune cell-mediated reaction
- Research tool used to identify patients with immune-mediated abacavir HSR

Schematic top view of skin patch

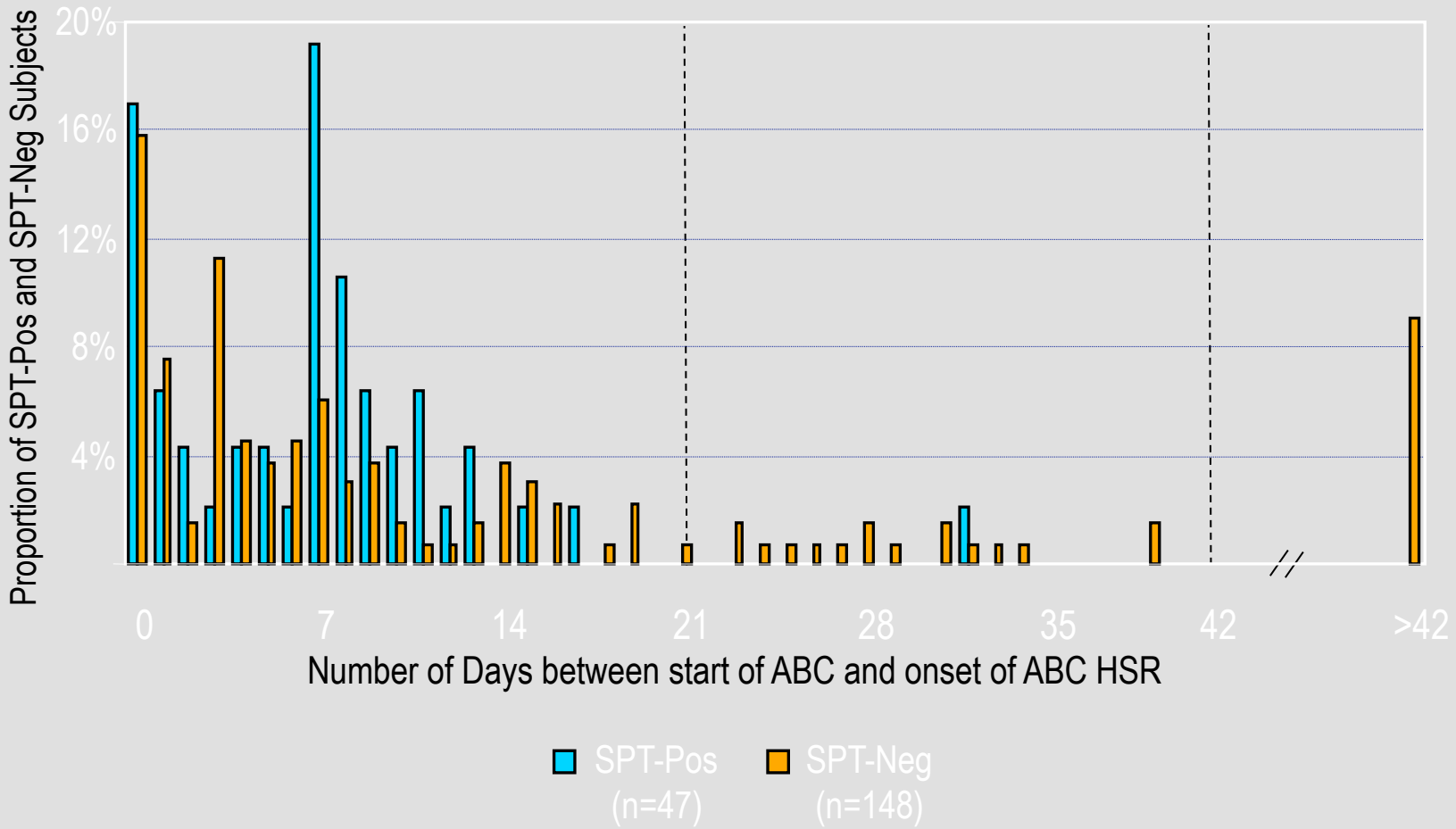




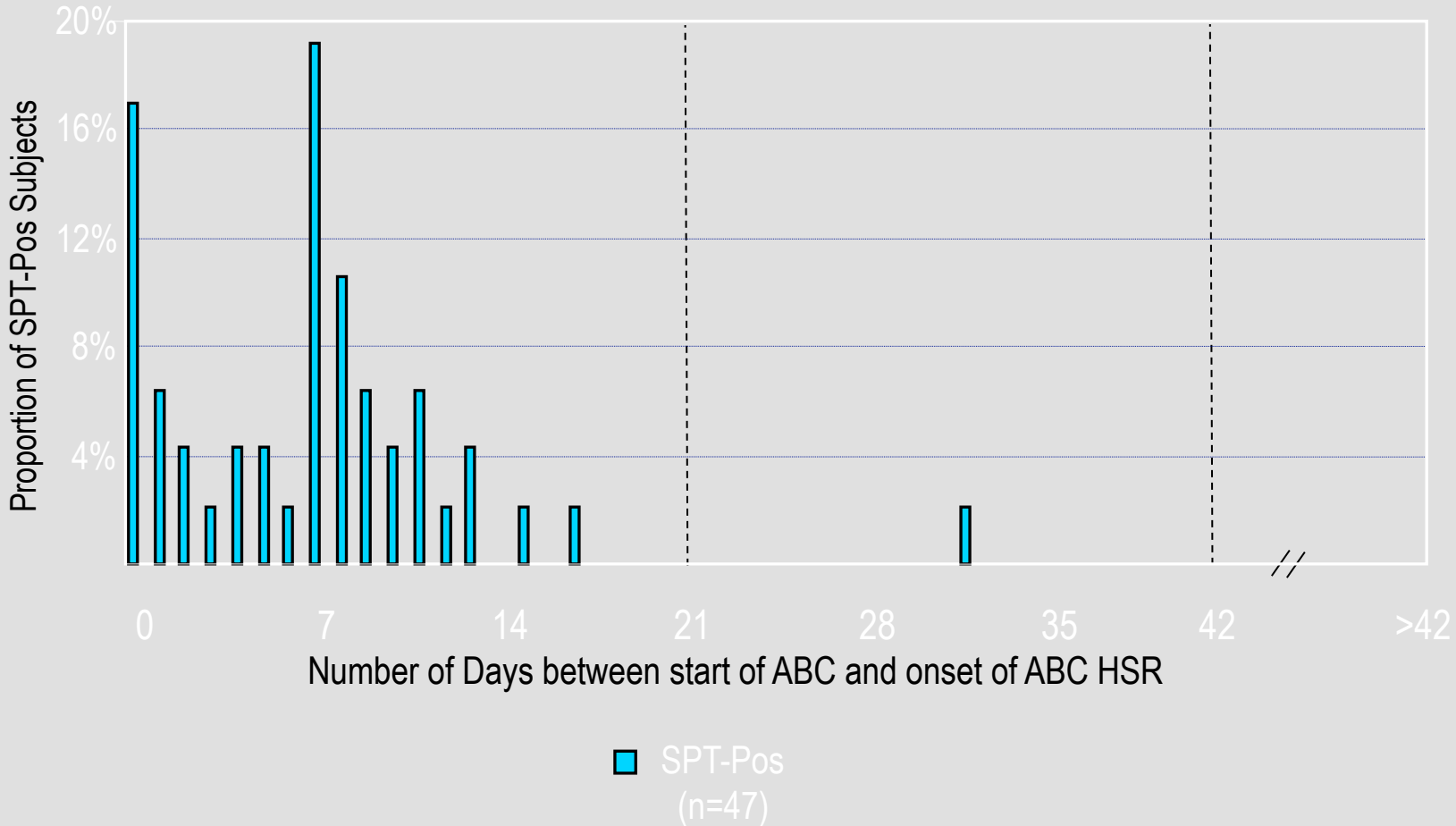
Phillips et al. AIDS 2002 and 2005

Phillips et al. IAS 2007 Abstract MOPEB001

Days to Onset of ABC HSR



Days to Onset of ABC HSR



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Leading causes of Death

	1900	2000
1)	Pneumonia	Heart disease
2)	Tuberculosis	Cancer
3)	Diarrhea/enteritis	Stroke
4)	Heart disease	Emphysema
5)	Liver disease	Injuries/accidents
6)	Stroke	Pneumonia/ flu
7)	CA, Senility, Diphtheria	AD, Kd Dz, Septicemia

1900, U.S. Department of Health and Human Services 2000, 22. For 2000, National Center for Health Statistics 2001

Alarming change over 51 years.

27 Vegetables

- Loss of 16% of their Potassium content
- Loss of 24% of their Magnesium content
- Loss of 46% of their Calcium content
- Loss of 27% of their Iron content
- Loss of 76% of their Copper content
- Loss of 59% of their Zinc content

17 Fruits

- **Loss of 19% of their Potassium**
- **Loss of 16% of their Magnesium**
- **Loss of 16% of their Calcium**
- **Loss of 24% of their Iron**
- **Loss of 20% of their Copper**
- **Loss of 27% of their Zinc**

- Unlike a vegetable, when a fruit is harvested the whole plant is not taken.

10 Types of Meats

- **Loss** of 16% of their Potassium
- **Loss** of 28% of their Phosphorous
- **Loss** of 10% of their Magnesium
- **Loss** of 41% of their Calcium
- **Loss** of 54% of their Iron
- **Loss** of 24% of their Copper

Caloric Restriction and Longevity

Calorie-Counting Monkeys Live Longer

Science News 9 July 2009

Canto, left, a 27-year-old rhesus monkey, is on a restricted diet, while Owen, 29, is not.

Caloric Restriction and Longevity

- Previous caloric restriction studies successful in mice, rats, worms and yeast
- 30% fewer calories than usual vs. free-feeding
- Vitamin and mineral supplements to prevent malnutrition
- Diet was stared in monkeys as they reached young adulthood (7-14 years old)
- Average normal lifespan 27 years; max 40
- **Leaner diets reduced deterioration of muscle and brain gray matter, two conditions associated with aging.**
- **63% of the calorie-restricted animals are still alive compared to only 45% of their free-feeding counterparts**

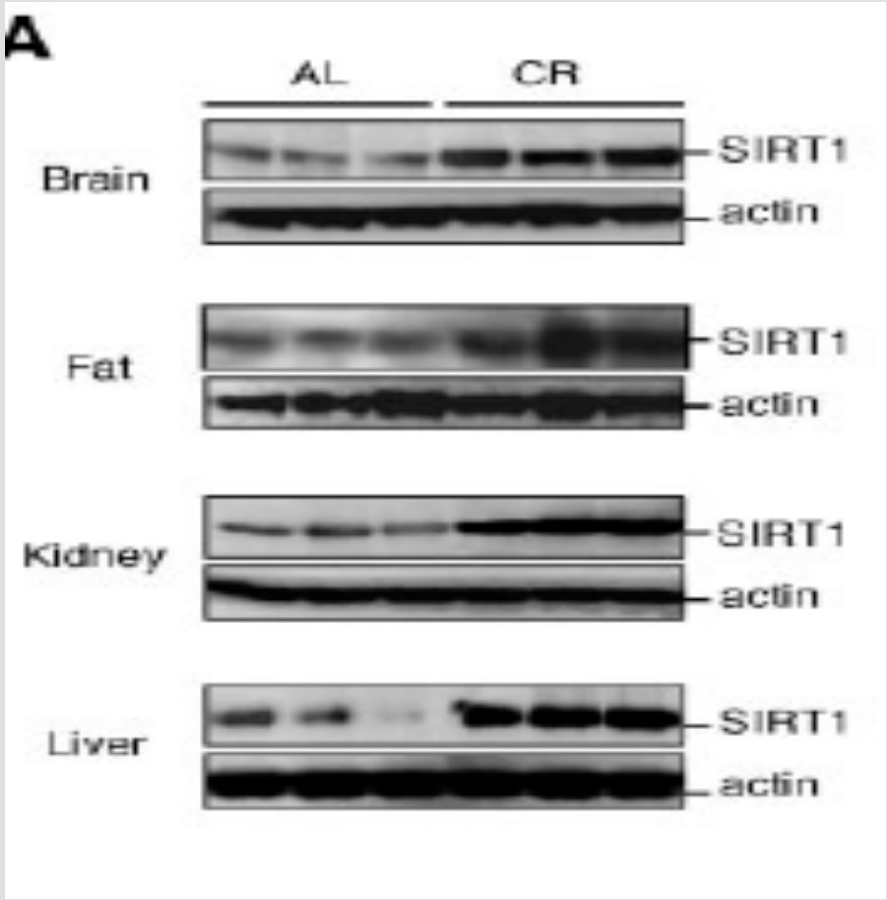
Science. 2009 Jul 10;325(5937):201-4

Sirtuin 1 (SIRT1): a protein deacetylase

- Mammalian orthologue of the yeast SIR2
- Expression associated with longevity, cell survival
- NAD+-dependent histone deacetylase
- SIRT1 deacetylates histone polypeptides with a preference for histone H4 lysine 16 and H3 lysine 9 in vitro.
- RNAi-mediated decreased expression of SIRT1 in human cells resulted in hyperacetylation of H4-K16 and H3-K9 in vivo.
- SIRT1 protein deacetylates non-histone substrates (p53, MyoD), as well as histone substrates

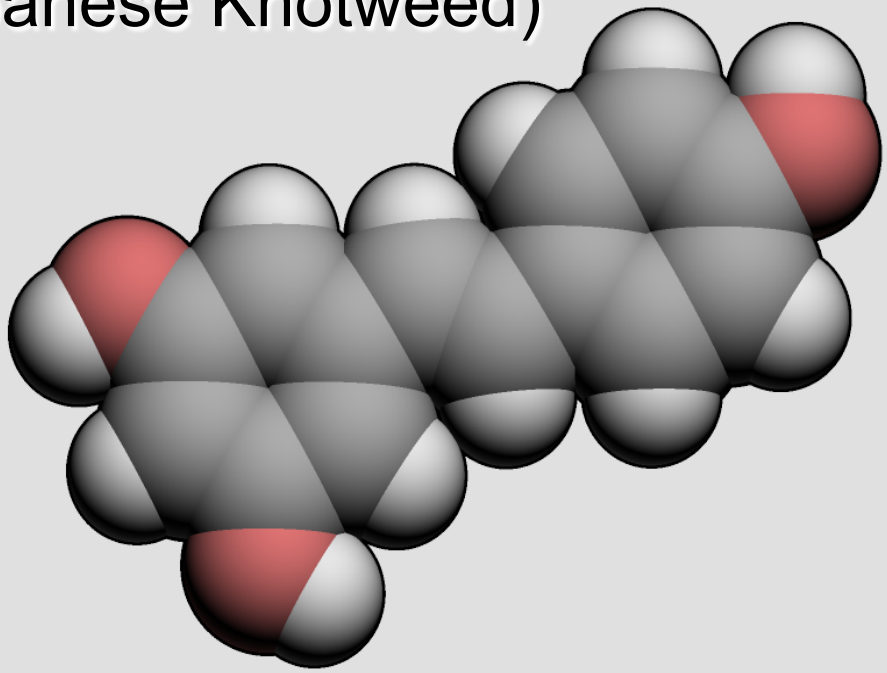
Vaquero A, et al. Mol Cell. 16:93-105, 2004.

Caloric restriction increases SIRT1 expression in a variety of rat tissues



Cohen HY, et al. Science 305:390-392, 2004.

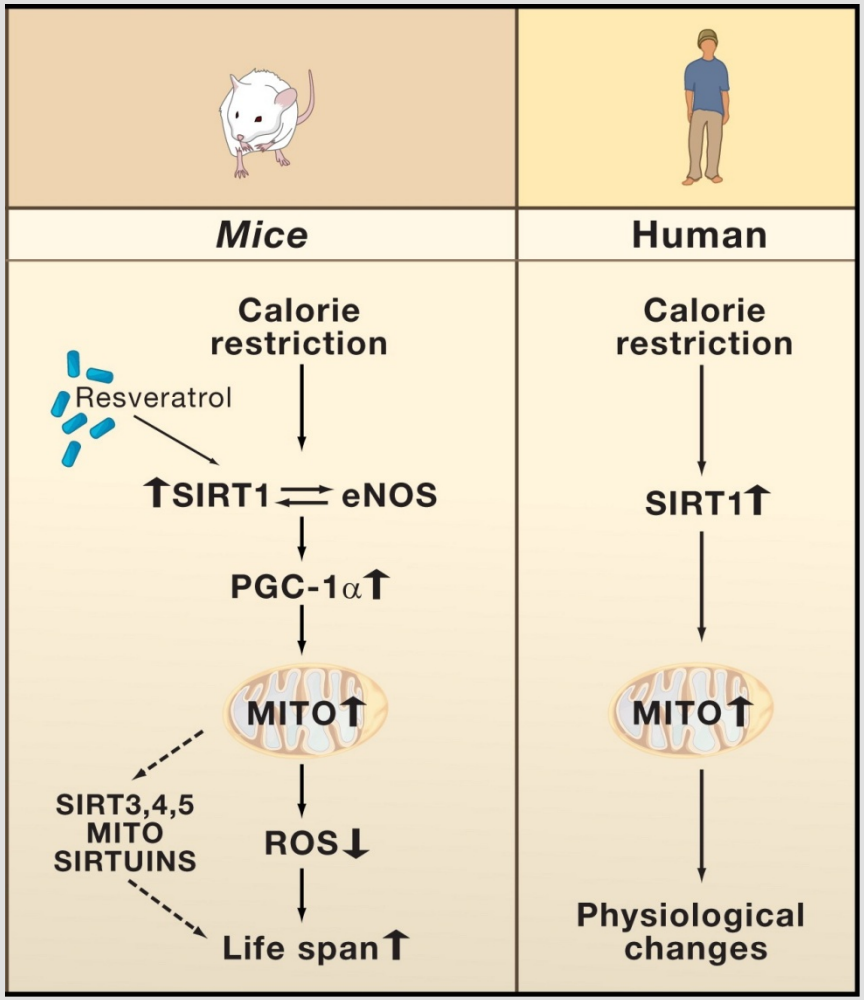
- **Resveratrol** is the most potent ***natural*** compound able to activate SIRT1, **mimicking the positive effect of calorie restriction.**
- Resveratrol might help in the treatment or prevention of obesity and in preventing the aging-related decline in heart function and neuronal loss.
- **Resveratrol** is found in grape skins (red wine > white), red peanut skins, some berries & the root of *Polygonum cuspidatum (*Japanese Knotweed)



Potential Benefits of Resveratrol

- Inhibits the proliferation of a variety of human cancer cell lines, including those from breast, prostate, stomach, colon, pancreatic, and thyroid cancers. It is not known whether high intakes of resveratrol can prevent cancer in humans.
- Increases the lifespan of yeast, worms, fruit flies, fish, and mice fed a high-calorie diet, but it is not known whether resveratrol will have similar effects in humans.

Anti- Aging Therapies: Calorie Restriction (CR)



- Restriction in calorie intake extends the lifespan of yeast, nematode and mice
- Sirtuins: family of antiaging proteins
- NAD-dependent protein deAc
- SIRT1 increases mitochondrial biogenesis
- Resveratrol is a SIRT1 activator
- improve physical activity
- longer average life span

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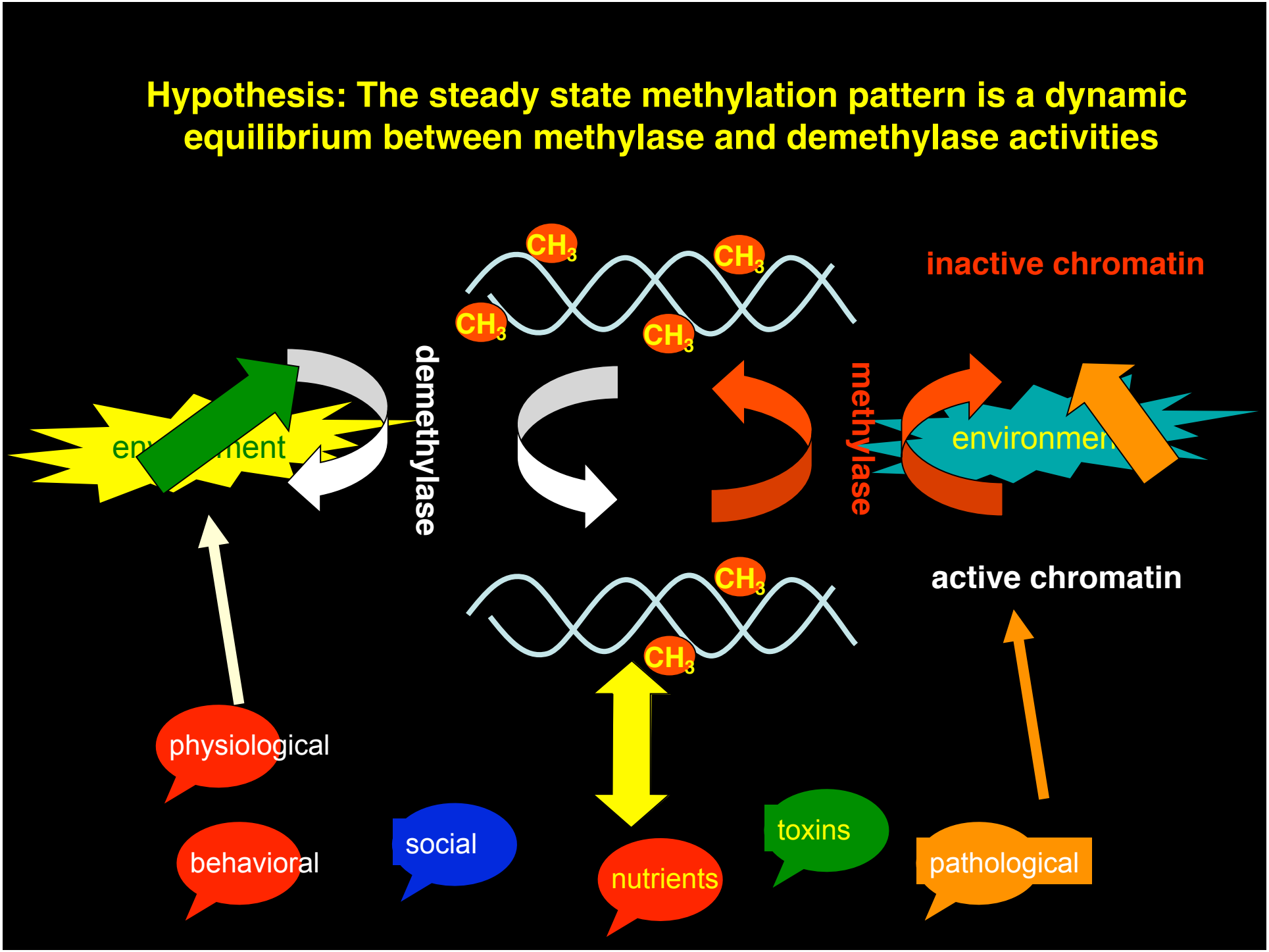
Hypothesis: The steady state methylation pattern is a dynamic equilibrium between methylase and demethylase activities
CH3
CH3
CH3
CH3
inactive chromatin
demethylase
methylase
environment
environmen
CH3
CH3
active chromatin
physiological
behavioral
social
nutrients
toxins
pathological