

**CORSO DI FORMAZIONE IN BIOETICA NELLA RICERCA E NEL PERCORSO
CLINICO ASSISTENZIALE**

Fatebenefratelli -Isola Tiberina

Bioetica generale: la ricerca sulle malattie genetiche



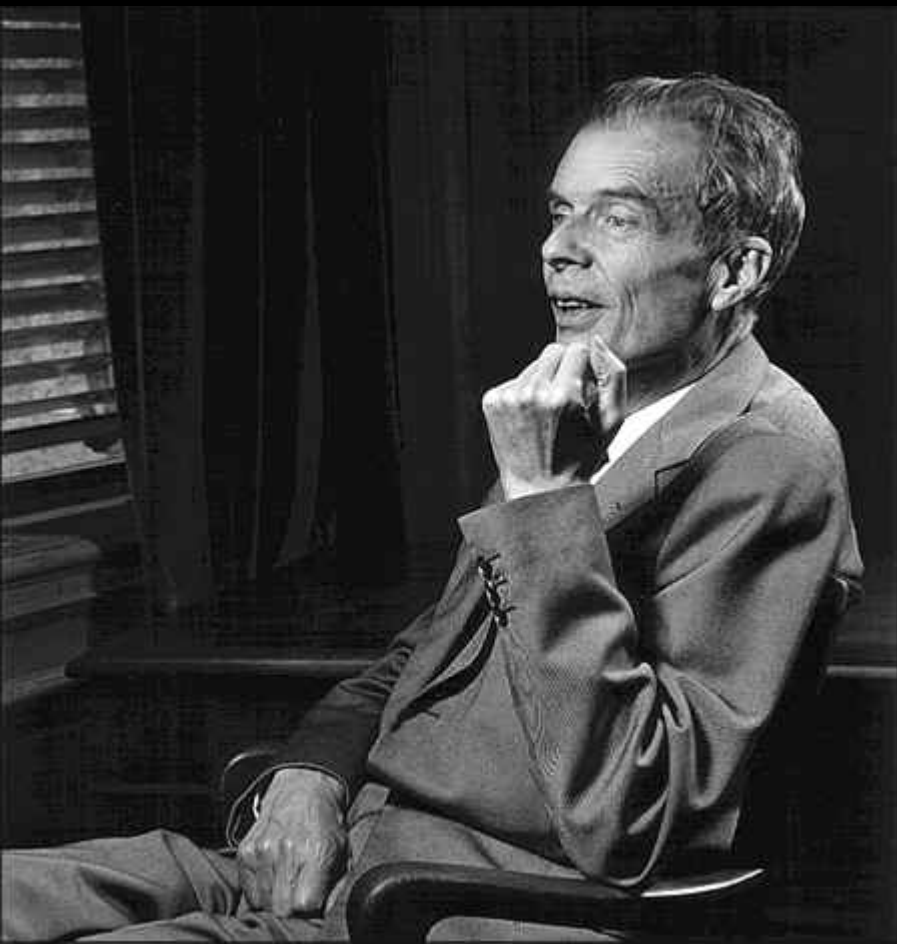
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Roma, 14/02/2008

**L'esistere del mondo è uno stupore infinito, ma
nulla è più stupendo dell'uomo.**

**Egli viaggia verso l'altra sponda del mare spumoso
con l'aiuto del tempestoso vento del sud, avanzando
sotto le ruggenti onde, e alla più potente delle dee,
l'imperitura e infaticabile Terra, lavora senza posa,
facendo girare gli aratri anno dopo anno [...].
Grazie alla sua capacità, si impossessa degli animali
della campagna...e sottomette al gioco il cavallo dal
crino fluente [...]. Niente del futuro lo coglie
sprovvisto di risorse. Solo dalla morte non potrà
fuggire. Di malattie che non avevano rimedio già
respinge l' assalto. Possedendo oltre misura la
capacità di inventare risorse questa lo volge talvolta
al male e talvolta al bene.**

[Sofocle, Antigone]



Aldous (Leonard) Huxley
1894-1963

*Una volta gli esseri umani
erano vivipari, e i genitori
erano il padre e la madre.
Sono fatti sgradevoli, lo so.*

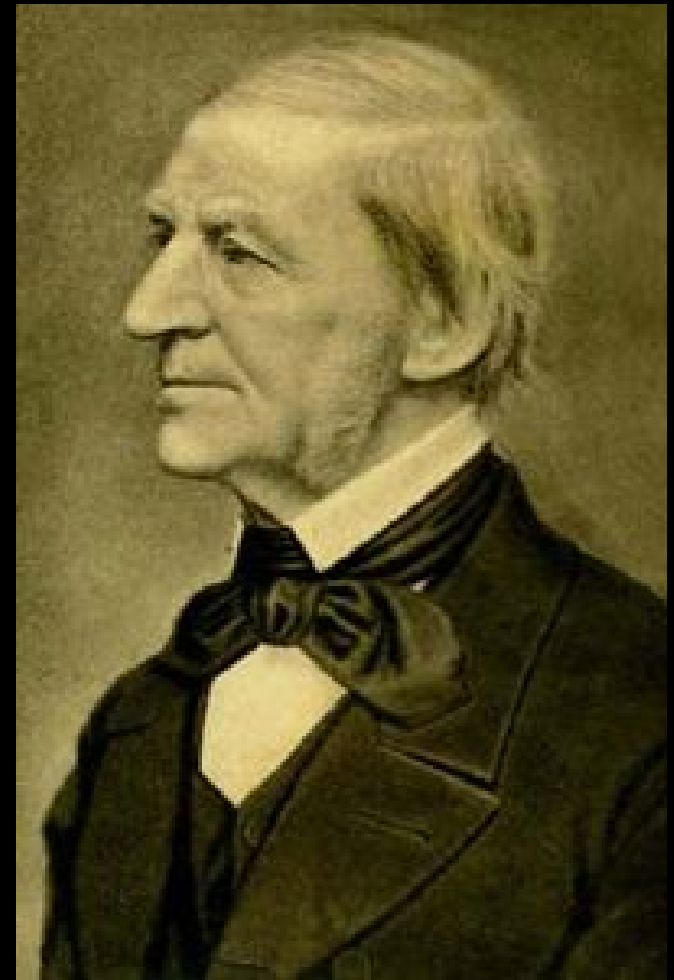
*Noi inoltre li predestiniamo e li
condizioniamo. Travasiamo i
nostri bambini sotto forma di
esseri viventi socializzati,
come tipi alfa o epsilon, come
vuotatori di fogne o direttori.*

La riduzione dell'identità alla mera corporeità biologica



*“[...] l'idea che la forma uomo sia solo aggregato di fattori accidentali, composti in un insieme in costante trasformazione e suscettibile, anzi bisognoso, di una continua implementazione. **Liberatosi dell'ingombrante immagine di un sé ontologicamente consistente, l'individuo viene sollecitato a pensarsi come organismo non solo costruito ma ri-costruibile all'infinito, come macchina liberamente riformabile** in vista di un suo funzionamento sempre più efficiente e di un'esistenza sempre più gradevole” . [A. Punzi]*

"La conoscenza è l'antidoto della paura; Conoscenza, Uso e Ragione, coi loro ausili più elevati. Il bambino su una scala, o un graticolato, o in una vasca da bagno, o con un gatto, è in pericolo quanto il soldato davanti al cannone o a un'imboscata. Ciascuno sormonta le paure non appena comprende precisamente il pericolo e impara i mezzi di resistenza. Ciascuno è soggetto al panico, che è, esattamente, il terrore dell'ignoranza arresa all'immaginazione."



Ralph Waldo Emerson
(Boston 1803-1882)

Solo la conoscenza rende liberi

La scienza come recupero dell'autonomia



PROMETEO: “Ascoltate...la misera storia dei mortali, come io li resi acuti - da stolti che erano - e padroni della propria mente...Dapprima essi vedevano, ed era un vano guardare; ascoltavano ma senza udire; simili alle forme dei sogni trascorrevano la loro lunga esistenza confusi e senza meta...”.

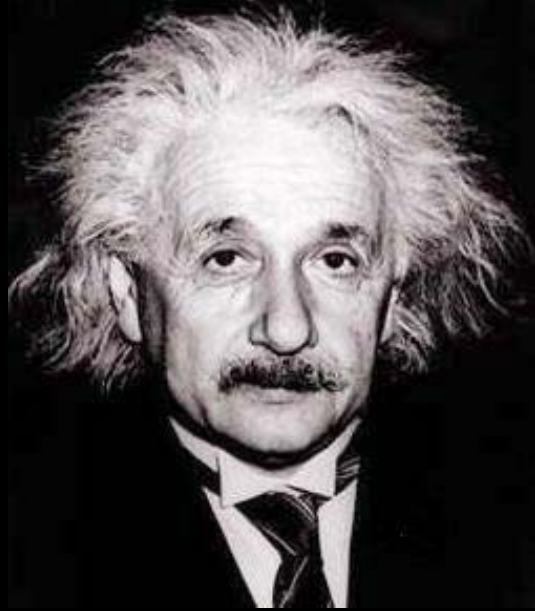
(Eschilo, *Prometeo incatenato*)



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

[11 Febbraio 2001-Bill Clinton]

Paradosso del valore C: la complessità non correla con la grandezza del genoma.



3.4×10^9 bp

Homo sapiens

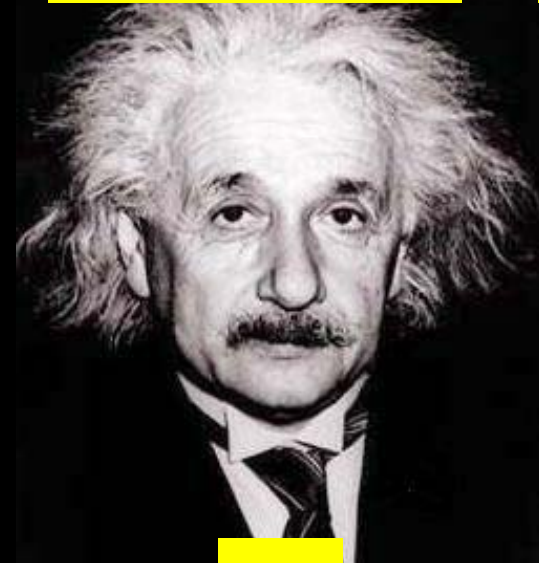


6.7×10^{11} bp

Amoeba dubia

Paradosso del valore K: La complessità non correla con il numero di cromosomi

Homo sapiens



46

Lysandra atlantica



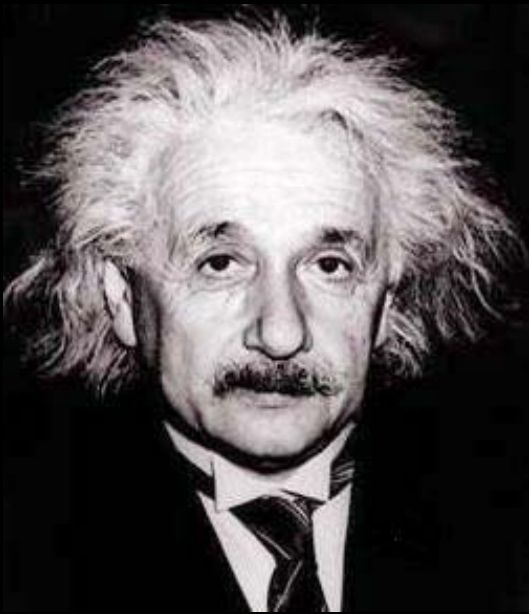
250

Ophioglossum reticulatum



1260

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



~24,000 genes



~50,000 genes

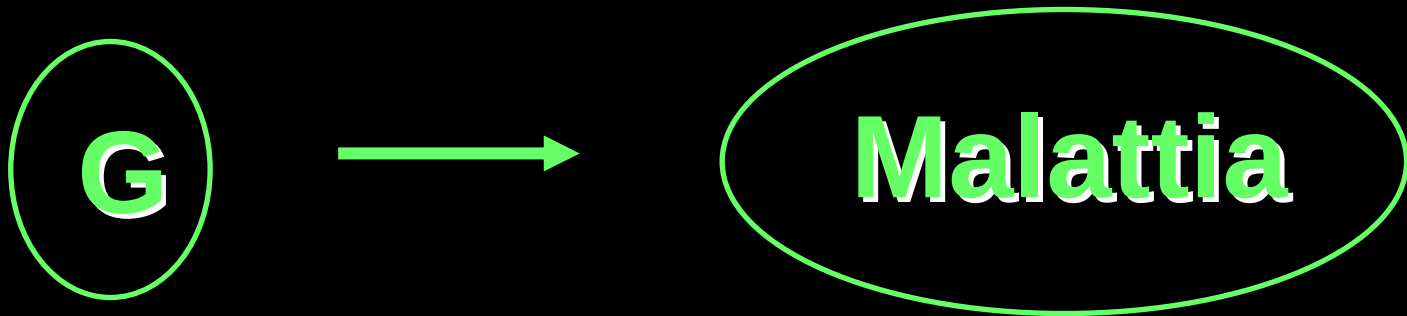


68



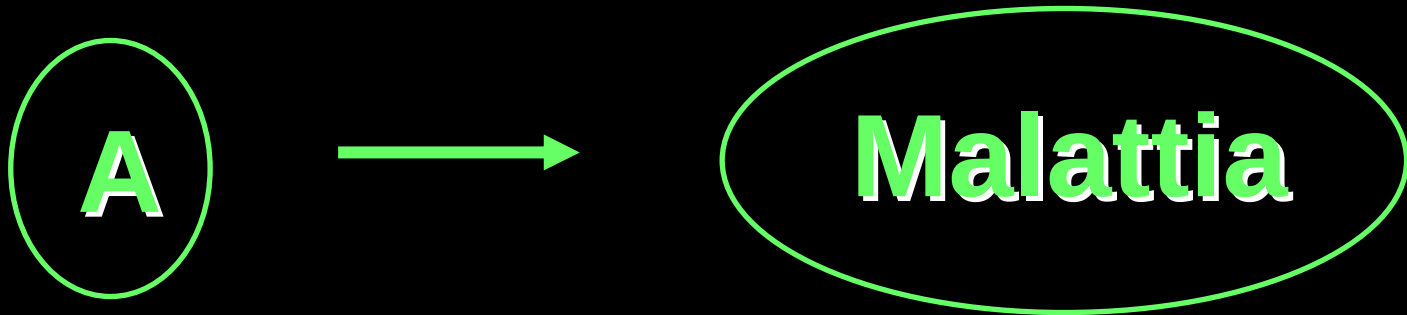
Genome Medical Futures

Malattia semplice



Esempi: Fibrosi Cistica, Distrofia Miotonica,
Atrofia Muscolare Spinale

Malattia semplice

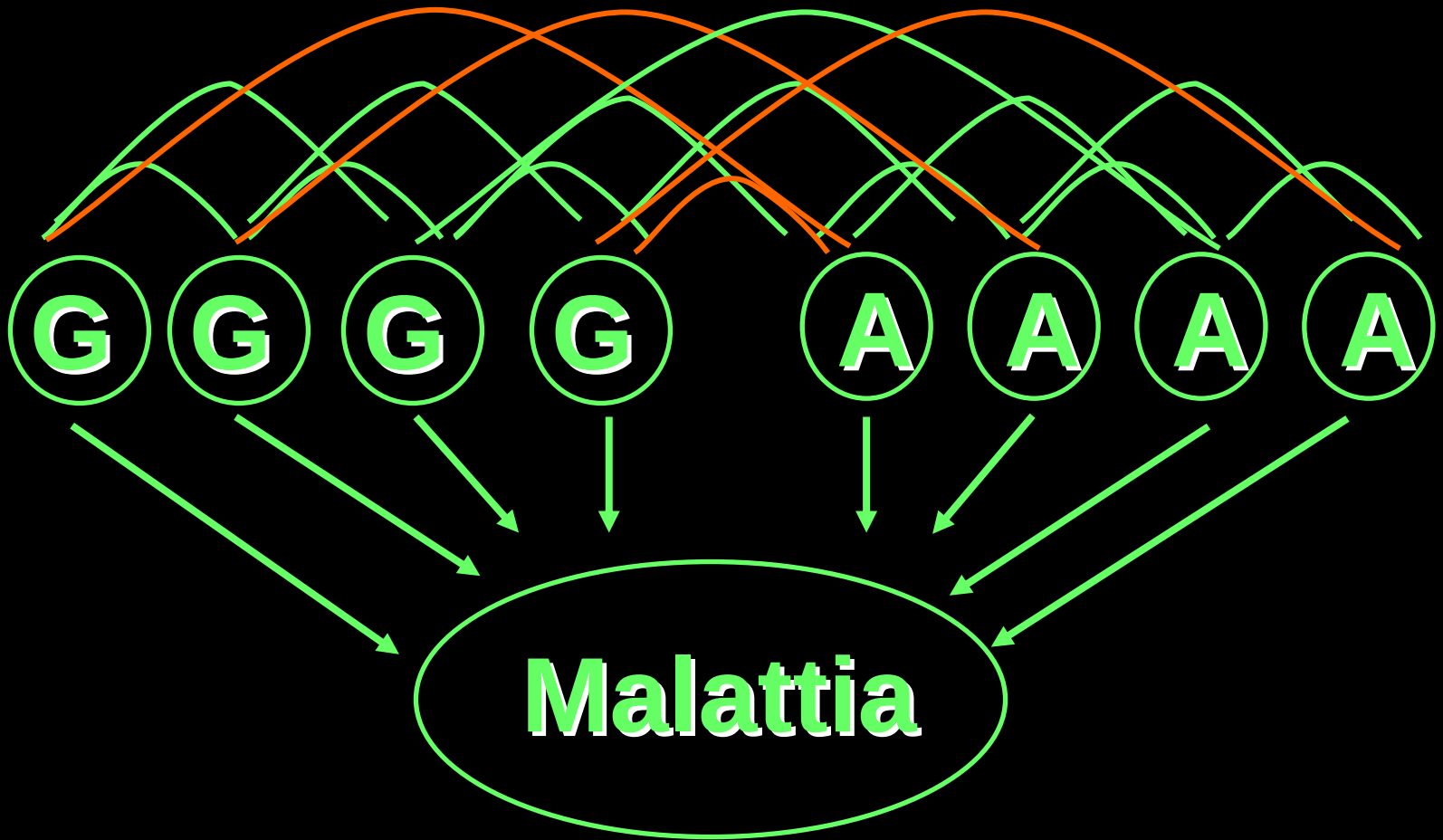


Esempi: infezioni virali, traumi

Malattie semplici

- Rare
- Dipendono, principalmente, da un singolo gene (Major Locus) **geni causativi**
- Seguono le leggi mendeliane di segregazione
- Mutazioni: evidenza di alleli rari

Malattie Complesse



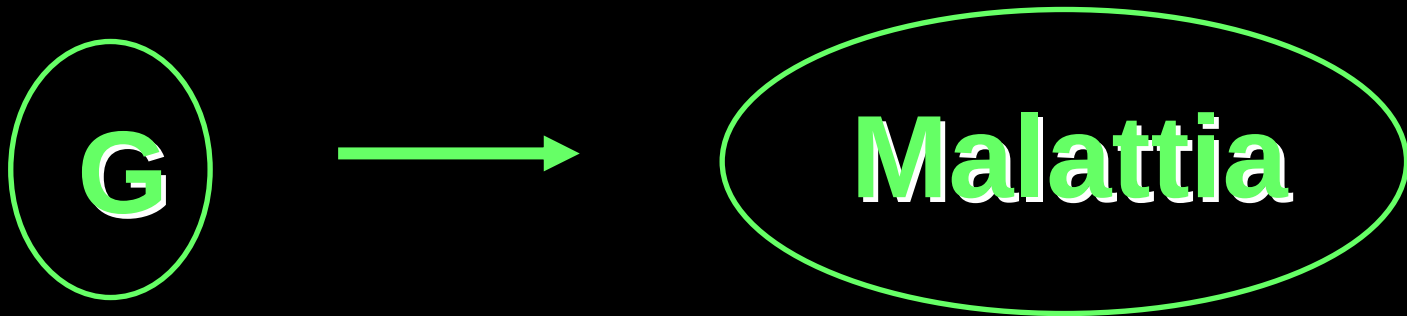
Malattie complesse

Soltanto gli individui geneticamente predisposti sviluppano la malattia, ma soltanto se esposti ai fattori ambientali scatenanti

Malattie complesse

Chi eredita alleli di suscettibilità ad una data malattia, non eredita la certezza di ammalarsi, bensì un **rischio maggiore** rispetto alla popolazione generale di svilupparla

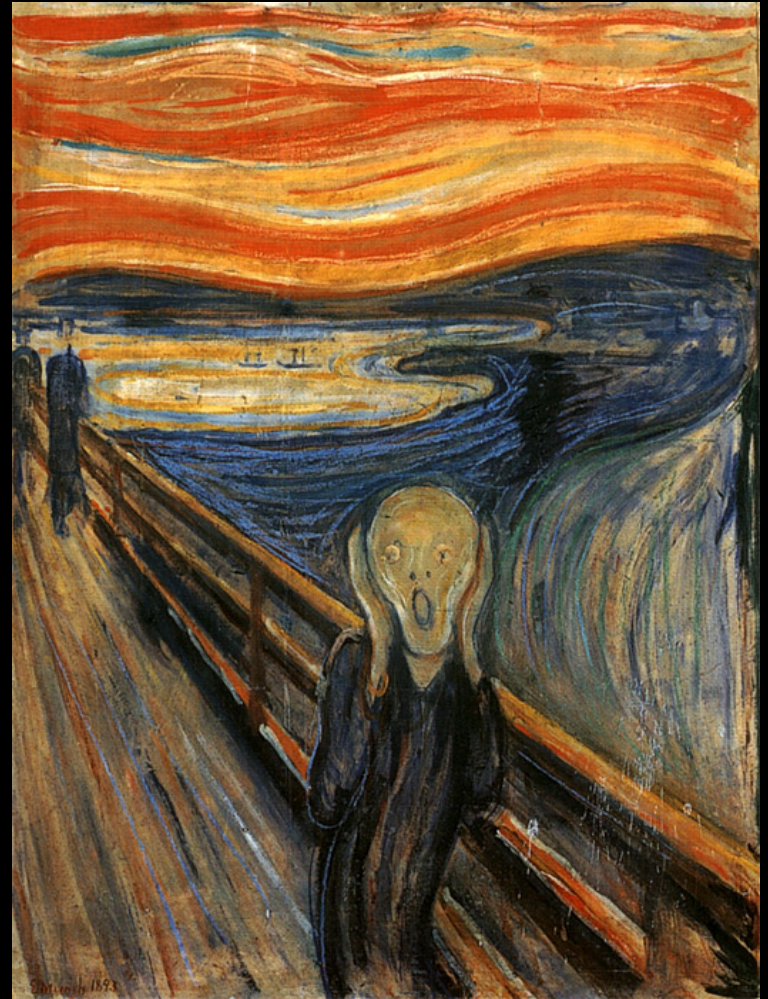
Malattia semplice



Esempi: Fibrosi Cistica, Distrofia Miotonica,
Atrofia Muscolare Spinale

LA PAURA

■ I TEST GENETICI PRENATALI QUALI MODERNA EUGENETICA



EUGENICS

EUGENICS IS THE
SELF DIRECTION

OF HUMAN EVOLUTION



LIKE A TREE

EUGENICS DRAWS ITS MATERIALS FROM MANY SOURCES AND ORGANIZES
THEM INTO AN HARMONIOUS ENTITY.

eugenetica

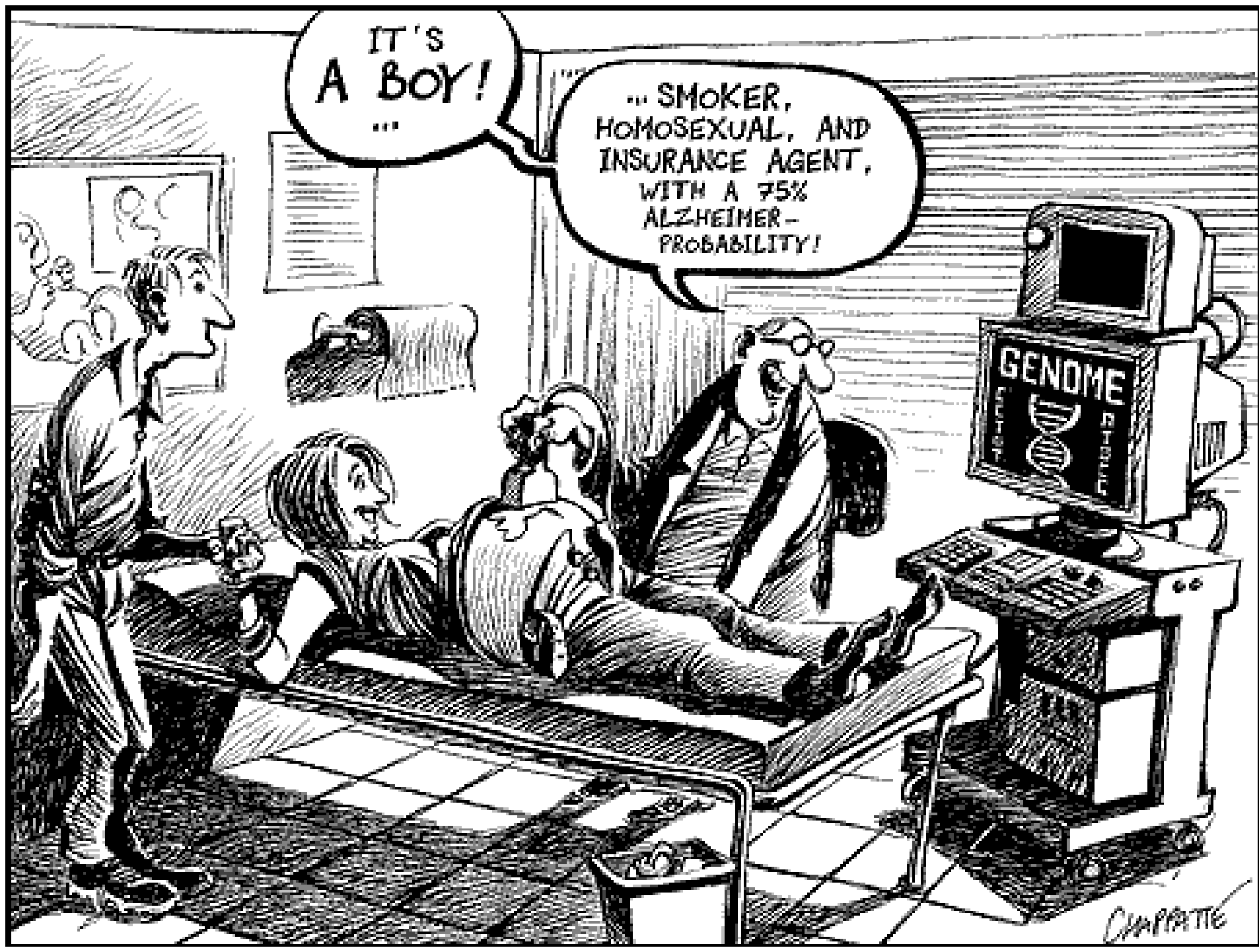
Da EU "buono" e da GENOS "razza, specie".

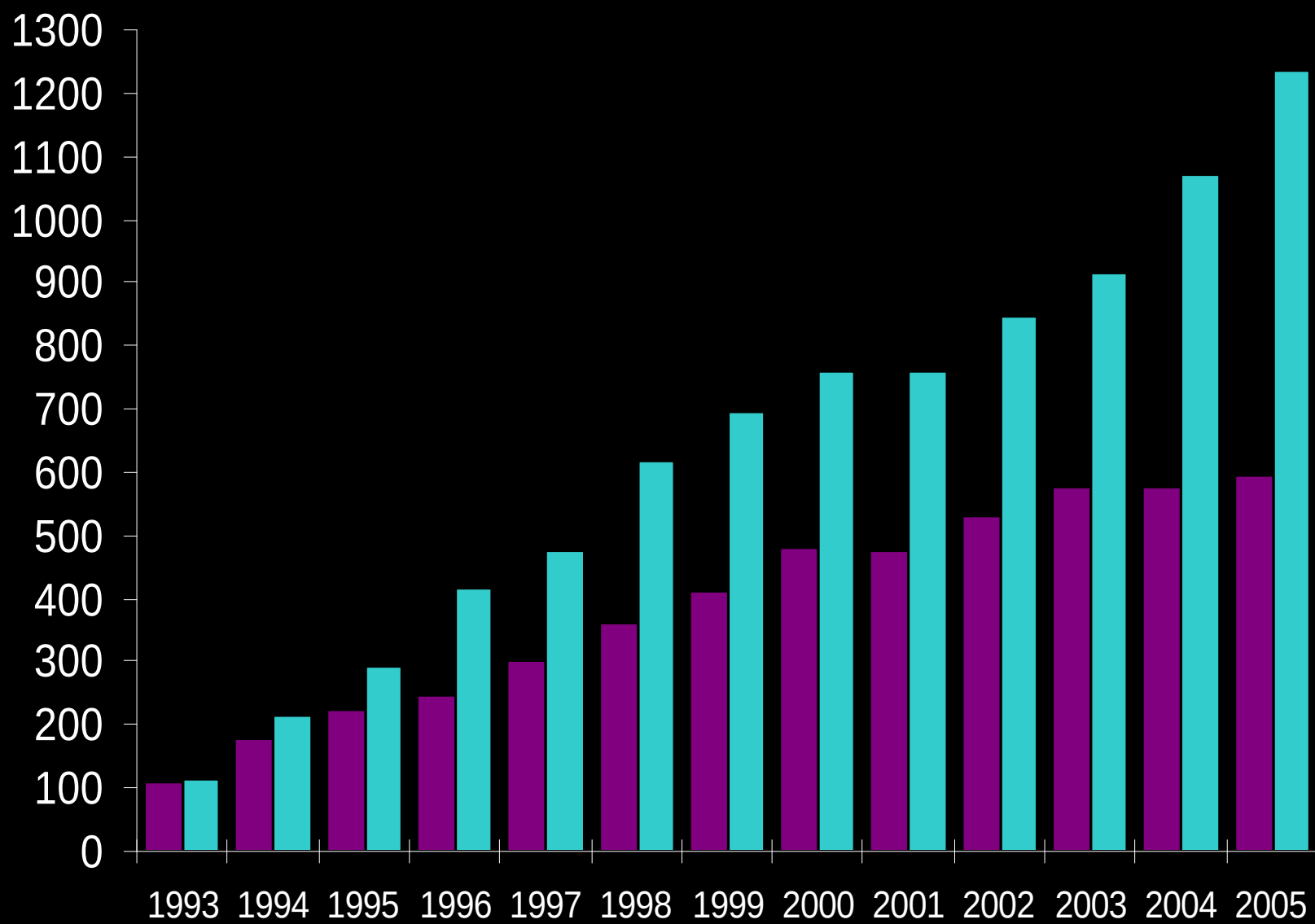
“pratica tesa al miglioramento della costituzione genetica della specie umana mediante incrocio selettivo”.



IT'S
A BOY!

... SMOKER,
HOMOSEXUAL, AND
INSURANCE AGENT,
WITH A 75%
ALZHEIMER -
PROBABILITY!





Genetic Testing: More, and More Complicated

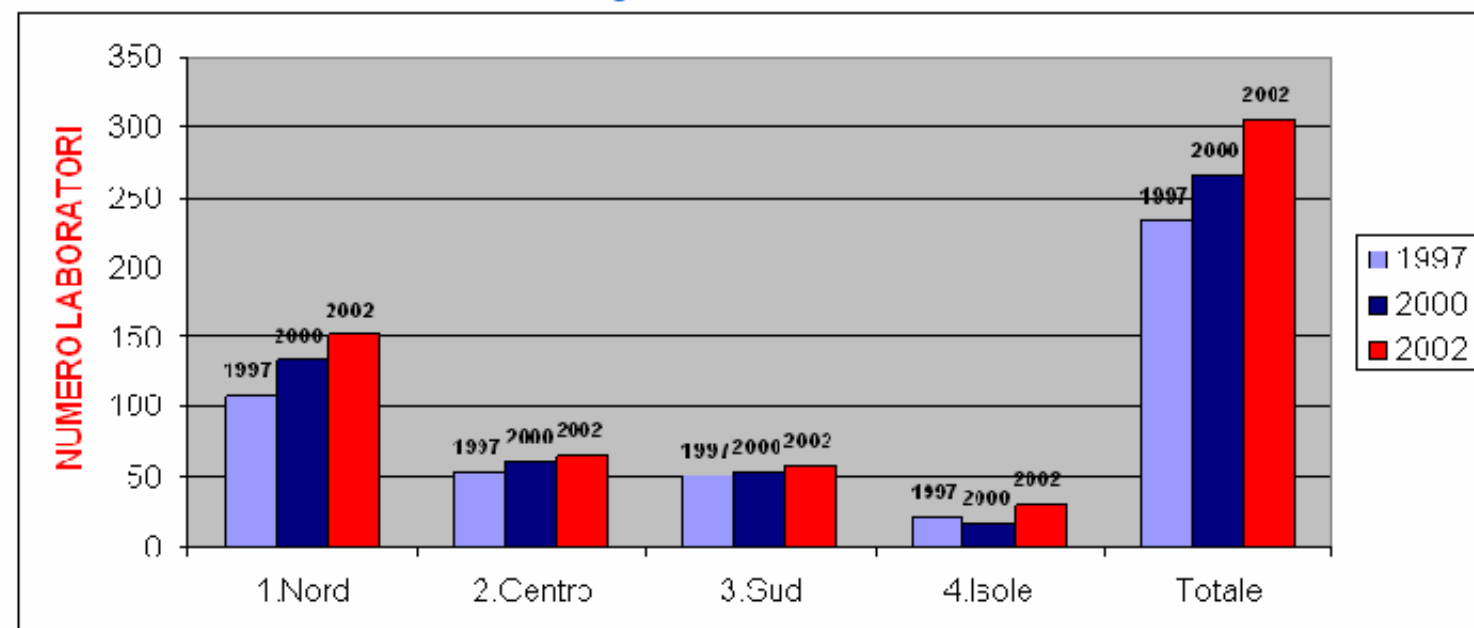
- Genetic tests available for >1400 diseases
 - 1129 clinical
 - 290 “research”
- Greater complexity and “actionability” of genetic tests
 - tests for multiple genes/gene products
 - test results informing clinical action
 - Chemotherapy
 - Choice of pharmaceutical
 - Dosage of pharmaceutical

Laboratori in Italia

Numero laboratori censiti nel 2002

	Laboratori di citogenetica	Laboratori di genetica molecolare	Totale Laboratori	Strutture cliniche
Totale	159	147	306	67
Divisione per area geografica				
Nord	78	73	151	30
Centro	36	30	66	18
Sud	29	29	58	13
Isole	16	15	31	6

Variazione del numero dei laboratori negli anni 1997,2000,2002



Test prenatali e postnatali



LA DIAGNOSI CITOGENETICA

	1997	2000	variazione (%)
▪ analisi prenatali	81.368	90.222	+ 10,8
▪ analisi postnatali	42.933	49.696	+ 15,7
totale	124.301	139.918	+ 12,5

LA DIAGNOSI MOLECOLARE

	1997	2000	variazione (%)
▪ analisi prenatali	2.473	8.238	+ 233,1
▪ analisi postnatali	47.894	107.472	+ 124,3
totale	50.367	115.710	+ 129,7

Anomalie cromosomiche rilevate alla nascita 0.65%

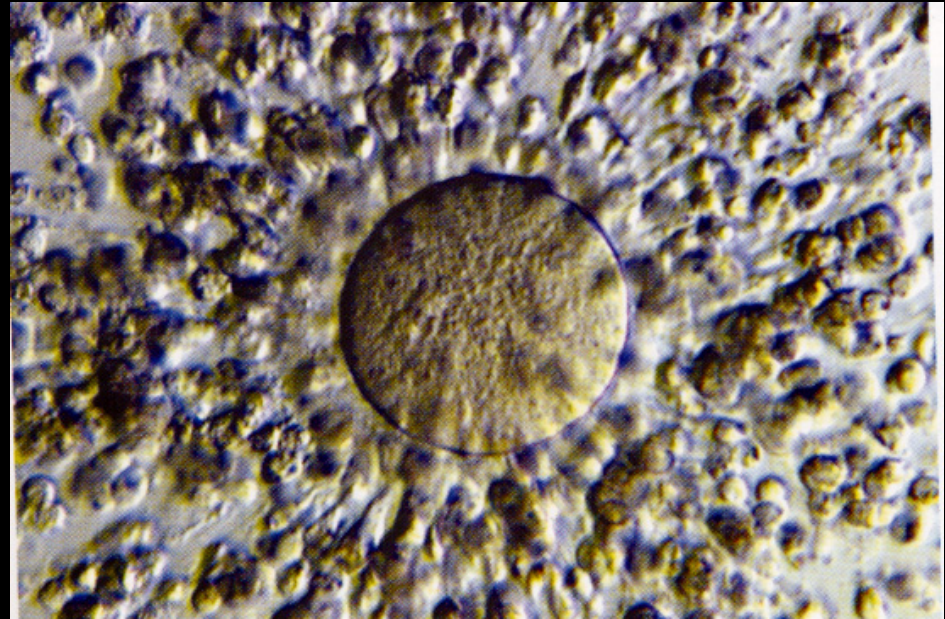
Incidenza / 10,000

nati

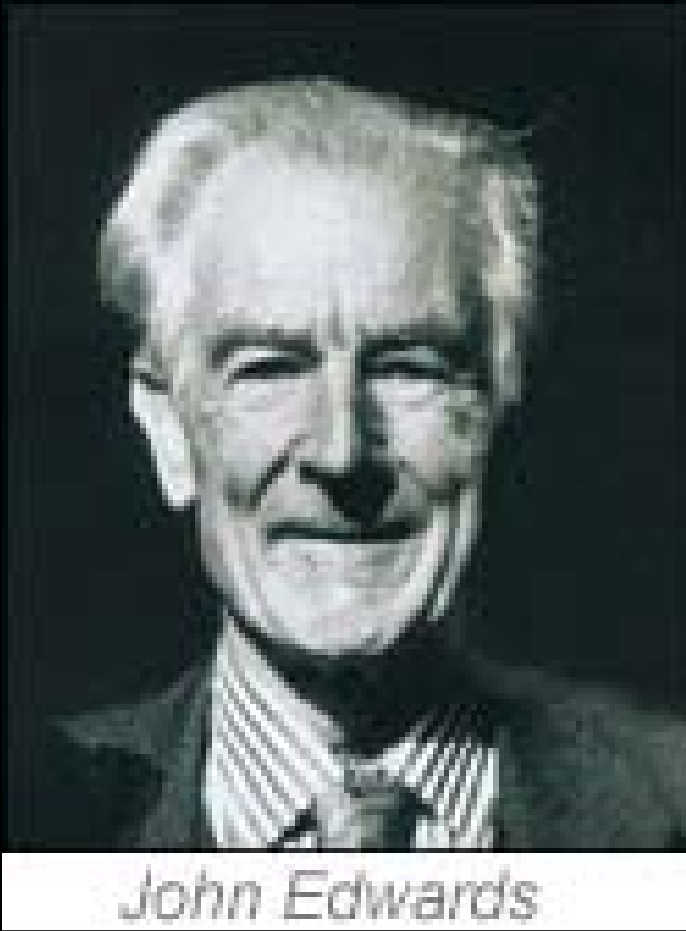
Trisomia 13	2
Trisomia 18	3
Trisomia 21	15
45,X	1
47,XXX	10
47,XXY	10
47,XYY	10
Sbilanciate	10
Bilanciate	30
Totale	90

Anomalie cromosomiche negli ovociti

Circa il 25 % degli ovociti presenta anomalie cromosomiche
(prevalentemente aneuploidie)



Prof. John Edwards



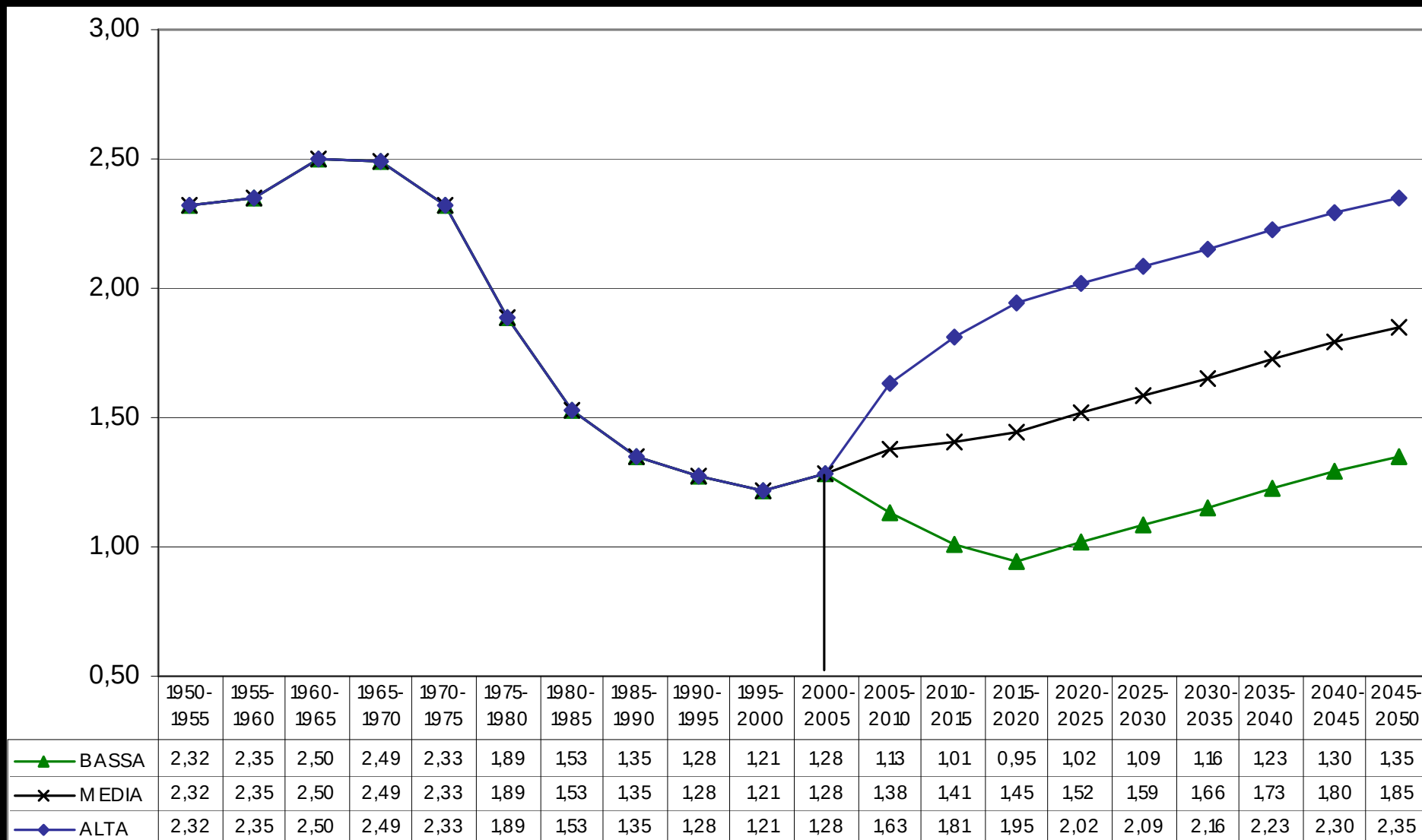
Professor of Genetics
at Oxford University
and
Fellow of the
Royal College of Physicians

QUOTE:

**“A normal male may
well produce
a whole of the gene
mutation catalogue
in every ejaculate”**



Numero medio di figli per donna in Italia, 1950-2050, secondo tre ipotesi di previsione

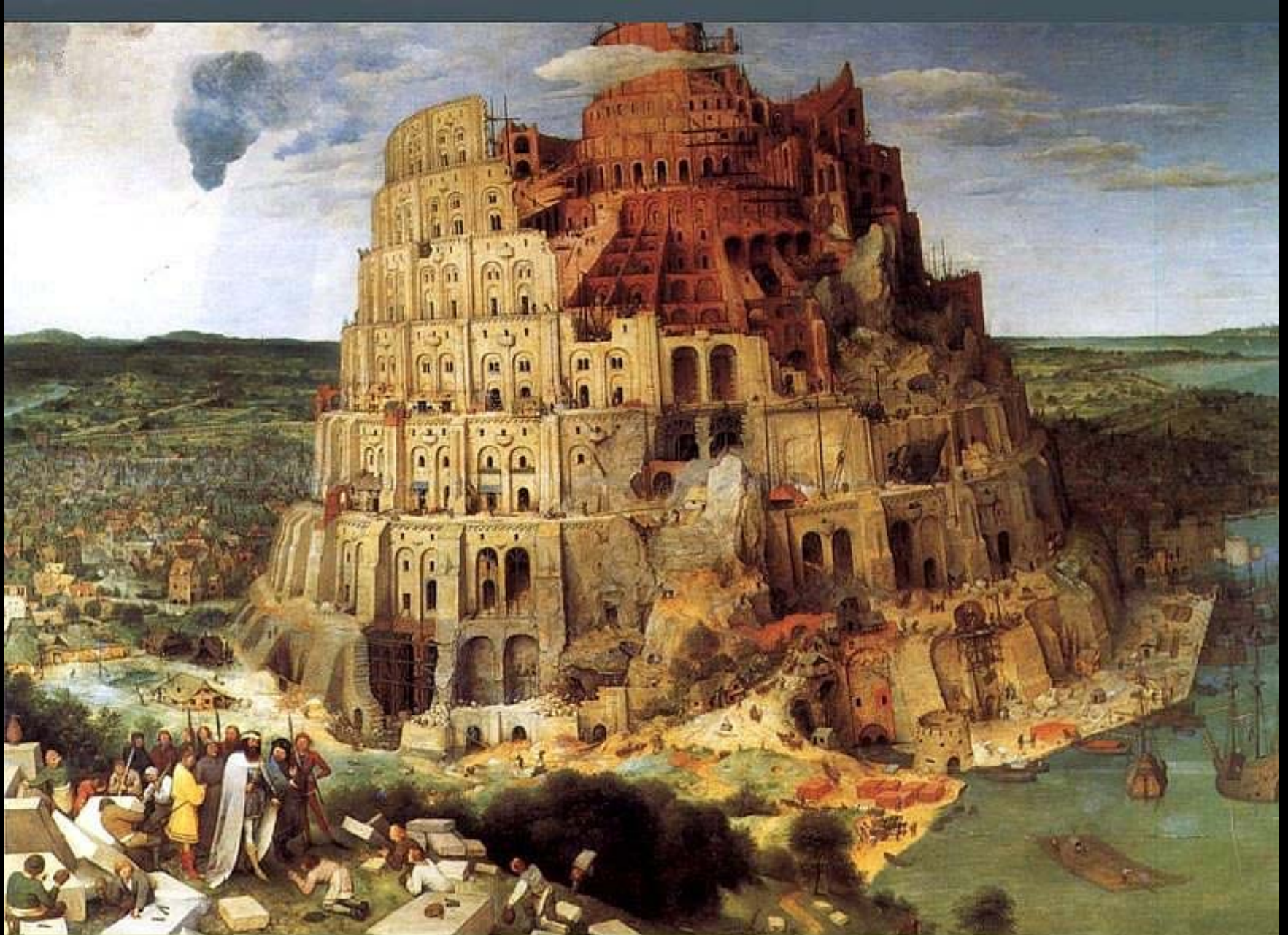


Rischio di specie

- 3% anomalia nel feto
- Non si abbatte aumentando il numero di test genetici eseguiti sul feto o sui genitori



Chiarezza: l'importanza delle definizioni



Per test genetico si intende l'analisi a scopo clinico di DNA, RNA, cromosomi, proteine, metaboliti o altri prodotti genici per evidenziare genotipi, mutazioni, fenotipi o cariotipi correlati o meno con patologie ereditabili umane. Questa definizione include gli screening prenatali, neonatali e dei portatori, così pure i test sulle famiglie a rischio. I risultati di queste indagini si possono applicare alla diagnosi ed alla prognosi di malattie ereditarie, alla predizione del rischio-malattia, all'identificazione dei portatori sani, alle correlazioni fenotipo-genotipo

OECD Guidelines

- **Informed consent to test** should be the norm and should be obtained in compliance with applicable legal, ethical, and professional standards.
- **Pre and post test counselling** should be available. It should be proportionate and appropriate to the characteristics of the test, the test limitations, the potential for harm, and the relevance of test results to individuals and their relatives.

OECD Guidelines

Genetic counselling

is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

OECD Guidelines

Genetic counselling

This process integrates the following:

- **Interpretation** of family and medical histories to assess the chance of disease occurrence or recurrence.
- **Education** about inheritance, testing, management, prevention, resources and research.
- **Counselling** to promote informed choices and adaptation to the risk or condition.

OECD Guidelines

- Within jurisdictions where reports may be issued directly to patients, governments, regulatory and professional bodies should encourage all laboratories performing clinical molecular genetic tests to recommend that patients consult an appropriate clinician or health care professional **to help them understand** the implications of the test result.
- The interpretation of molecular genetic test results should be **appropriate** to the individual patient and clinical situation and should be based on objective evidence.

OECD Guidelines

- Internationally accepted **standard terminology and nomenclature** should be adopted and used consistently with respect to quality assurance systems.
- Reports should use applicable internationally accepted terminology and nomenclature including identification of reference sequences

Differenze...

“fatti in casa” vs. “kit”



- **Adverse economic consequences**
- **Absence of public access to information**
- **Disparities in quality**
- **Risk to public health**

Test prenatali e postnatali



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Solo la conoscenza rende liberi

La scienza come recupero dell'autonomia

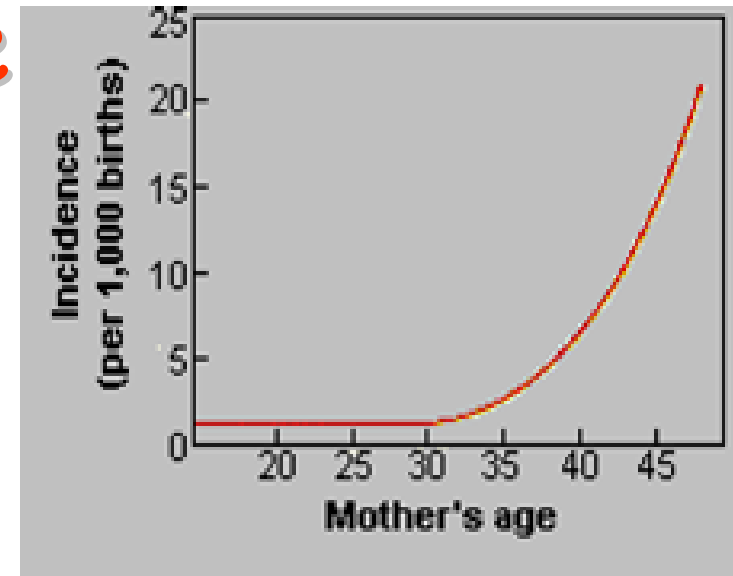


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(Eschilo, *Prometeo incatenato*)

La diagnosi prenatale

*La principale indicazione alla diagnosi prenatale è il monitoraggio del **cariotipo fetale**. In Italia questa analisi riguarda oltre il 98% delle diagnosi prenatali che utilizzano tecniche di laboratorio. Lo studio del cariotipo ha alcune precise indicazioni e ha negli amniociti il tessuto di elezione.*



CGH ARRAY

-4 -2 -1 0 +1 +2 +4

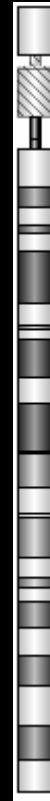
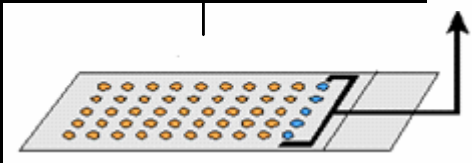
DNA Reference DNA Test

Reference
DNA-Cy3

Test
DNA-Cy5



Scanner

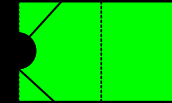


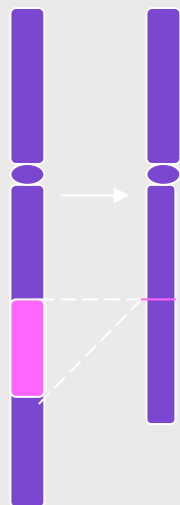
Cy5
Cy3

Red
Green

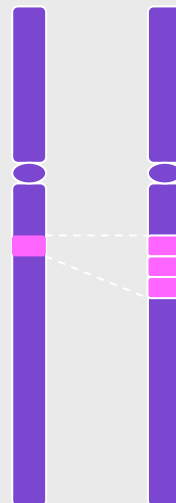
Amp
Del

Exp
Ref

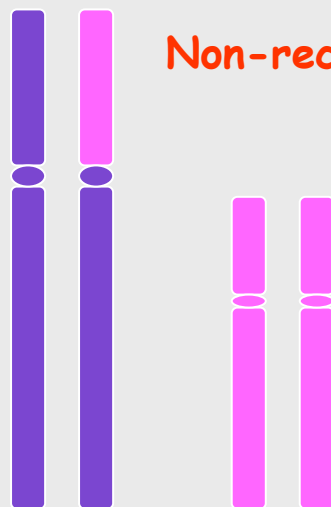




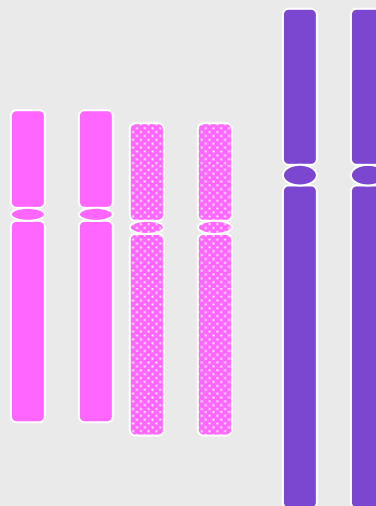
Deletions



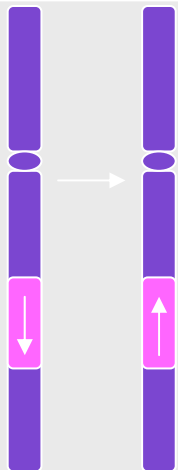
Gene Amplification



Non-reciprocal translocation



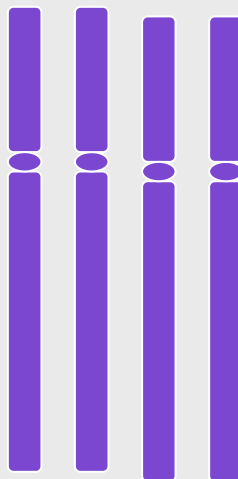
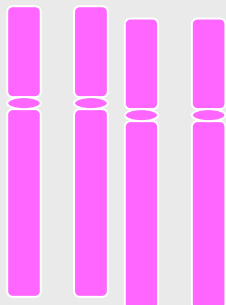
Aneuploidy



Inversions

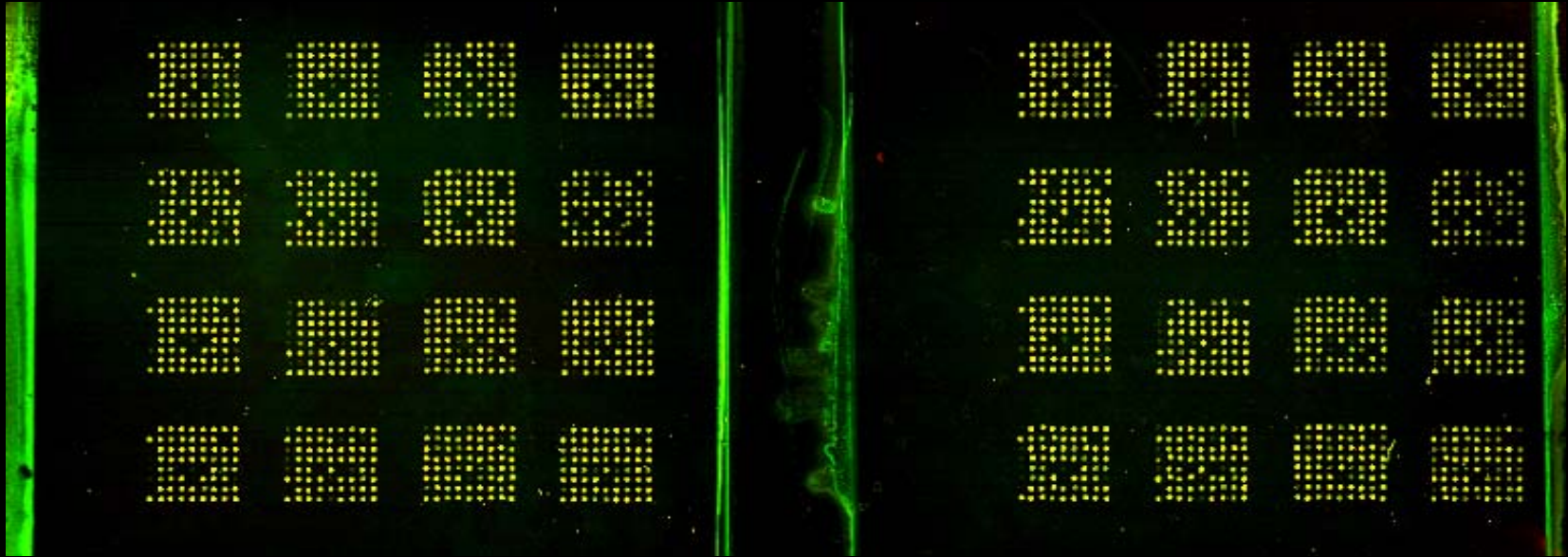


Balanced Translocation



Polyploid

MDTelArray (Technogenetics Srl)



- Ideato per la diagnostica pre e post natale.

- **167 cloni** che coprono le regioni critiche interessate da microdelezioni associate a **34 sindromi** che non possono essere diagnosticate con un cariotipo tradizionale

- **126 cloni** per le regioni subtelomeriche

Monosomy 1p36 Syndrome[(OMIM #607872) (1p36)]

Van der Woude Syndrome [(OMIM #119300) (1q32-q41)]

Nephronophthisis 1 [(OMIM #256100) (2q13)]

Brachydactyly-Mental Retardation Syndrome [(OMIM %600430) (2q37)]

Wolf Hirschhorn Syndrome[(OMIM #194190) (4p16.3)]

Cri-du-Chat Syndrome [(OMIM #123450) (5p15.2)]

Familial Adenomatous Polyposis of the Colon [(OMIM +175100) (5q21-q22)]

Sotos Syndrome[(OMIM #117550) (5q35)]

Saethre-Chotzen Syndrome [(OMIM #101400) (7p21.1)]

Williams-Beuren Syndrome[(OMIM #194050) (7q11.2)]

Kallmann Syndrome 2 [(OMIM #147950) (8p11.2-11.1)]

Langer-Giedion Syndrome [(OMIM #150230) (8q24.11-24.13)]

Monosomy 9p Syndrome[(OMIM #158170) (9p.14)]

HDR Syndrome [(OMIM #146255) (10p14)]

DiGeorge Syndrome/Velocardiofacial Syndrome Spectrum of Malformation 2 [(OMIM %601362) (10p13-10p14)]

Wagr Syndrome[(OMIM #194072) (11p13)]

Potocki –Shaffer Syndrome [(OMIM #601224) (11p11.2)]

Prader Willi Syndrome /Angelman Syndrome [(OMIM #176270/#105830) (15q11.2-q13)]

ATR-16 Syndrome[(OMIM #141750) (16pter-p13.3)]

Miller-Dieker Lissencephaly Syndrome [(OMIM #247200) (17p13.3)]

Charcot-Marie-Tooth Disease [(OMIM #118220) (17p12)]

Neuropathy, Hereditary, with Liability to Pressure Palsies [(OMIM #162500) (17p11.2)]

Smith-Magenis Syndrome [(OMIM #182290) (17p11.2)]

Neurofibromatosis Familial Spinal [(OMIM #162210) (17q11.2)]

Alagille Syndrome [(OMIM #118450) (20p12)]

DiGeorge Syndrome [(OMIM #188400) (22q11.2)]

Neurofibromatosis, Type II [(OMIM #101000) (22q12.2)]

Short Stature [(OMIM #604271) (Ypter-p11.2, Xpter-p22.32, 3q26.3)]

Steroid Sulfatase Deficiency [(OMIM +308100) (Xp22.32)]

Kallmann Syndrome 1 [(OMIM +308700) (Xp22.3)]

Muscular Dystrophy, Duchenne Type [(OMIM #310200) (Xp21.2)]

ATR-X Syndrome [(OMIM #301040) (Xq13)]

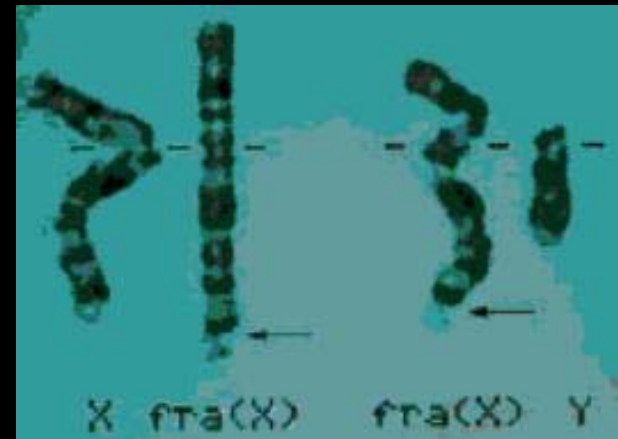
Pelizaeus-Merzbacher Disease [(OMIM #312080) (Xq22)]

XX Male Syndrome[(OMIM 278850)]

Sindrome dell'X fragile

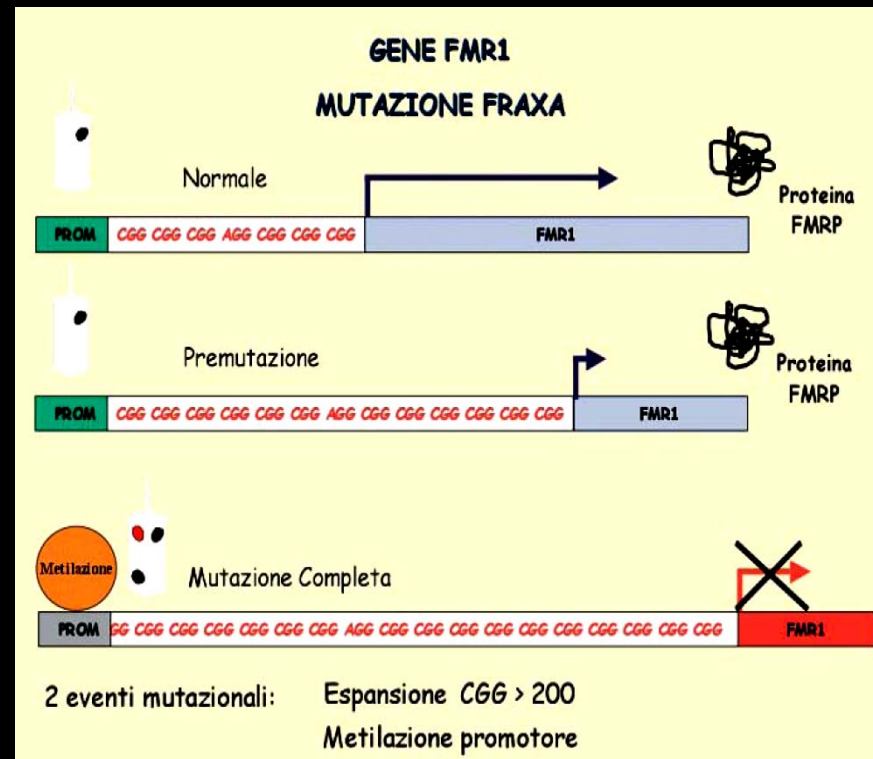
La sindrome del cromosoma X fragile è la forma più frequente di ritardo mentale ereditario, con una prevalenza stimata di 1:4000 maschi, è dovuta alla mutazione del gene *FMR1* localizzato in Xq27.3.

Questa mutazione (FRAXA) consiste in una amplificazione e successiva metilazione di una sequenza di triplette CGG, localizzata nella porzione trascritta ma non tradotta del primo esone del gene, ed è responsabile di un blocco della trascrizione.



Sindrome dell'X fragile

- Gli alleli normali hanno un numero di triplette compreso fra 5 e 44; negli alleli mutati questo numero è superiore a 200.
- Alleli con un numero di triplette compreso fra 56 e 200 (premutazioni) sono normalmente espressi ma risultano instabili, con forte tendenza alla transizione verso la mutazione completa nel corso della meiosi femminile.
- Alleli con un numero di triplette compreso fra 41 e 55 occupano una “zona grigia” di incerto



Sindrome dell'X fragile

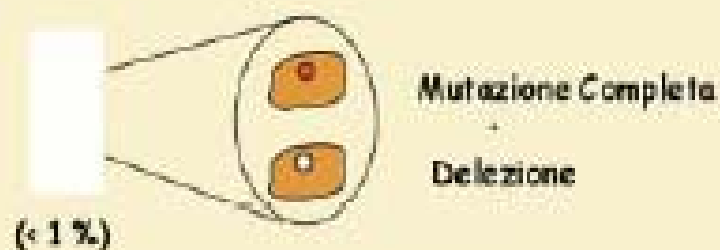
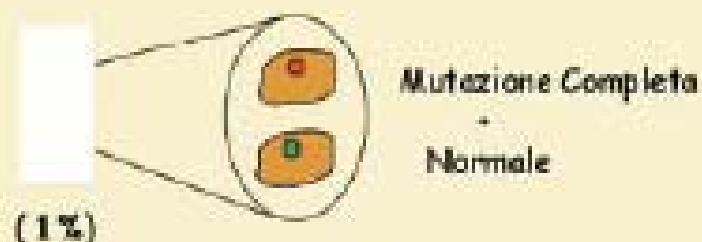
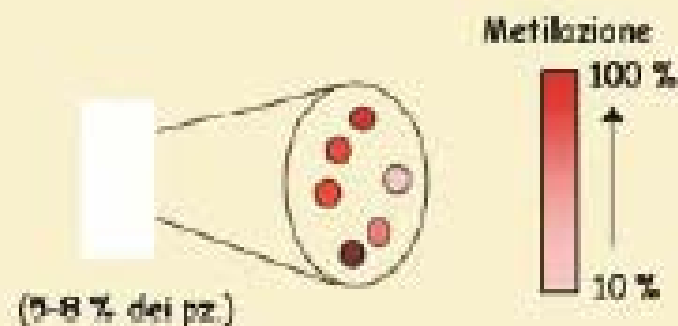
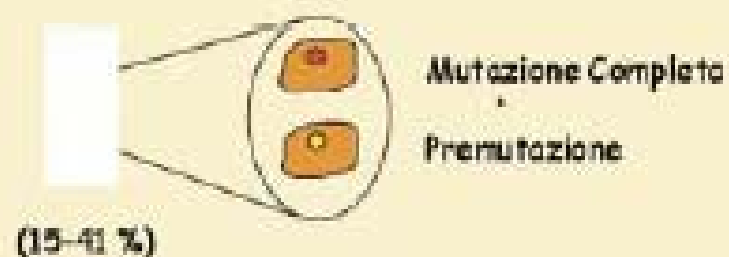
Il test genetico finalizzato alla diagnosi molecolare della sindrome dell'X Fragile viene eseguito mediante **Southern blot** e **PCR**.

Le due metodologie forniscono informazioni complementari: ciascun metodo non riconosce tutti i tipi di mutazione FRAXA con la stessa sensibilità; per questo motivo è generalmente riconosciuta la necessità di applicare in modo complementare entrambe le tecniche di indagine per l'identificazione dei soggetti normali, dei portatori sani, e degli affetti (comprese le

Mosaici

Mosaici di espansione

Mosaici di metilazione



Sindrome dell'X fragile

1. piccole premutazioni <100 CGG vengono riconosciute in Southern blot, ma devono essere analizzate anche in PCR per una più precisa valutazione del numero di repeats. (sulla base del numero delle ripetizioni CGG, dipende la valutazione del rischio procreativo di una donna portatrice)
1. per espansioni >100 CGG è sufficiente il risultato in Southern blot, riportando il risultato in termini di differenza di paia di basi (bp) rispetto all'allele normale (es. D= 250 bp oppure D>600 bp).
1. per espansioni al limite tra la premutazione e la mutazione è invece indispensabile testare lo stato di metilazione in Southern blot. (l'analisi dello stato di metilazione può aiutare a capire se l'espansione è da considerarsi premutazione o mutazione completa)

SOUTHERN blot

Cosa "VEDE" ?

- Sequenza Ripetuta *CGG*
- Metilazione Promotore *FMR1*



LIMITI

- Non consente la valutazione precisa del n. *CGG* inferiore a 100

(alleli intermedi e piccole premutazioni)

PCR

PCR

8

Cosa "VEDE"?

- Sequenza Ripetuta *CGG*
- Test Metilazione



LIMITI

- Non amplifica > 100 *CGG*
- Metilazione SOLO nei maschi
- Non "VEDE" i mosaici

Mosaici Mutazione/Normale
FALSI NEGATIVI

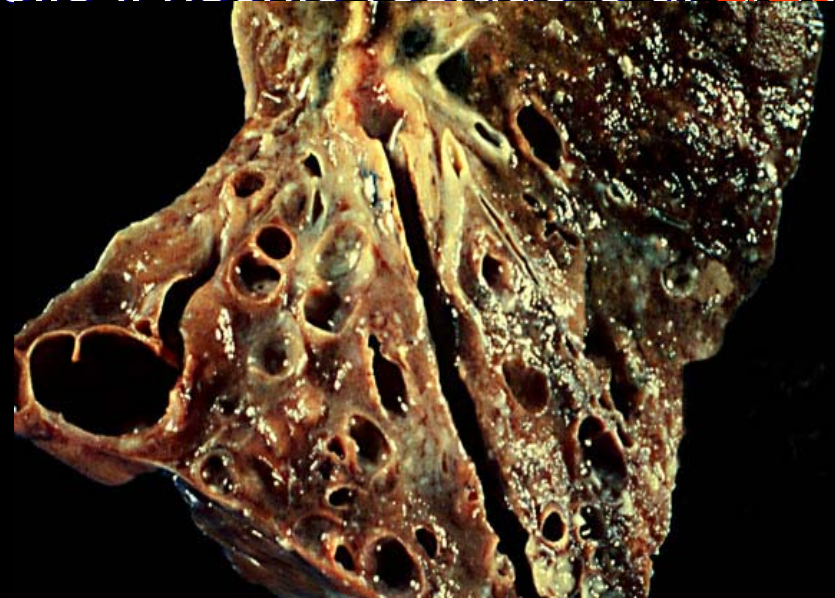
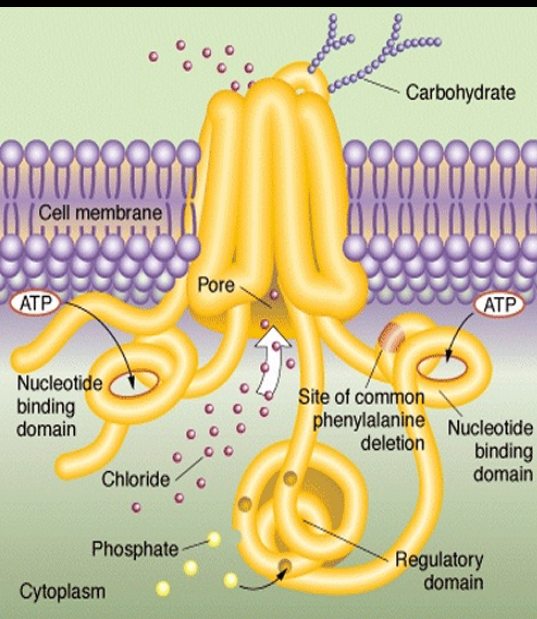
Sindrome dell'X fragile

- L'analisi in PCR non identifica mutazioni complete e le premutazioni che superano 100- 120 CGG non si amplificano.
- I maschi affetti da RM che presentano un mosaicismo mutazione completa/allele normale (1% circa dei soggetti con mutazione completa) possono sfuggire ad una corretta diagnosi se analizzati solo mediante PCR. Infatti se l'allele normale è presente anche in una piccola percentuale di cellule, si amplifica conducendo ad una diagnosi errata di normalità (falso negativo). Tali mosaici sono identificabili correttamente mediante analisi in Southern blot.
- Se in un maschio con RM si evidenzia mediante PCR una premutazione è indispensabile procedere con l'analisi in Southern blot per escludere un mosaicismo premutazione/mutazione completa (mosaicismo presente nel 15-20% dei soggetti con mutazione completa).
- Femmine eterozigoti per una premutazione (es. 30/170 CGG) e femmine omozigoti per un allele normale (es 30/30 CGG) possono generare lo stesso risultato in PCR: cioè l'identificazione di un solo allele di 30 CGG. Nel primo caso la preferenziale amplificazione dell'allele normale può impedire l'identificazione dell' allele premutato, nel secondo caso i due alleli di 30 CGG co-migrano. Per questo motivo in tutte le femmine se non sono evidenziabili due alleli distinti è indispensabile procedere all'analisi in Southern blot

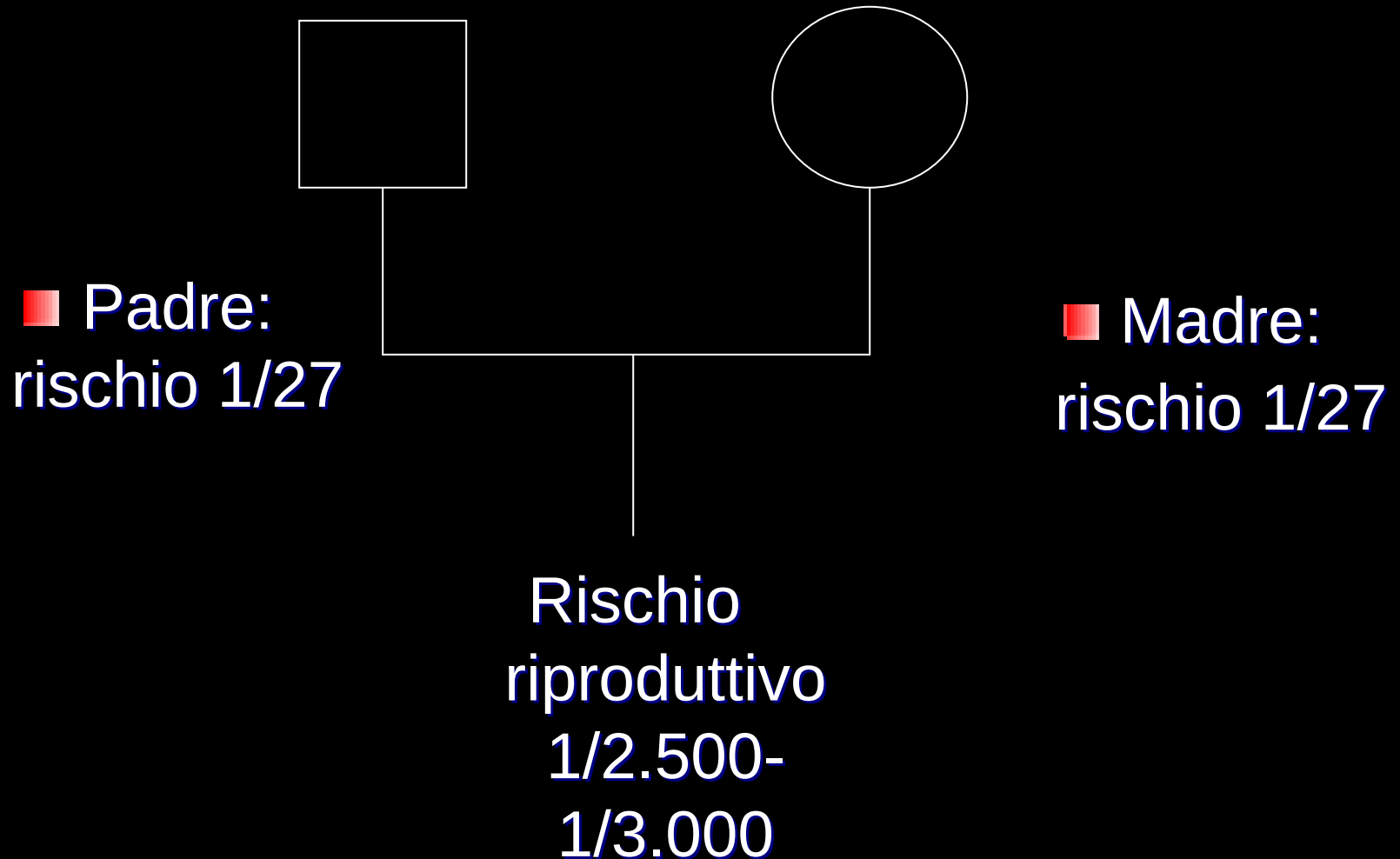
Frequenza di una patologia nella popolazione generale

L'esempio della fibrosi cistica

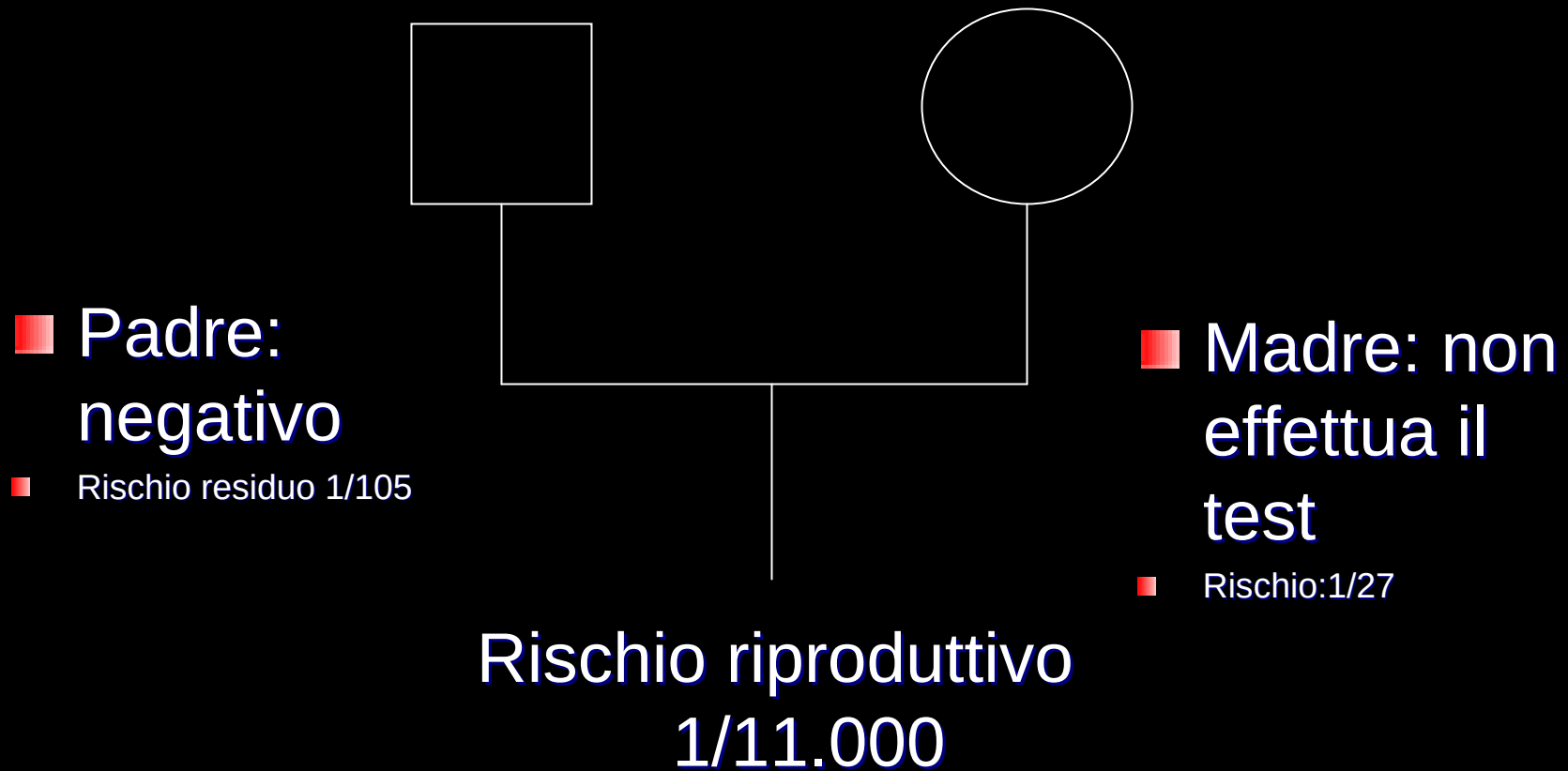
- Il rischio di essere portatore per un soggetto preso a caso nella popolazione generale è di **1/27**
- Dopo aver effettuato lo screening di I livello, all'individuo resta un rischio residuo di **1/105** di essere portatore
- Con uno screening di II livello il rischio residuo è di **1/261**



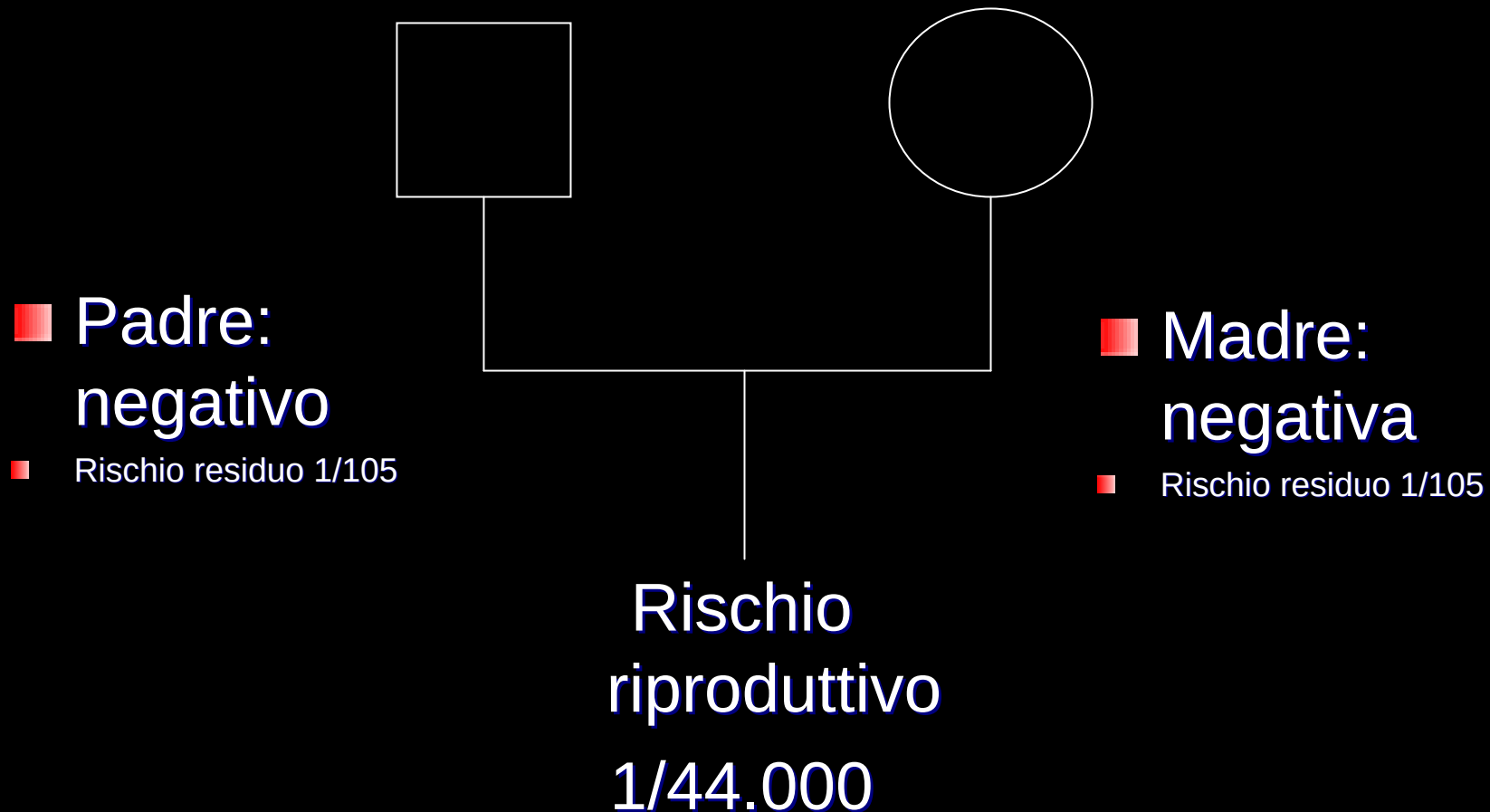
NO TEST

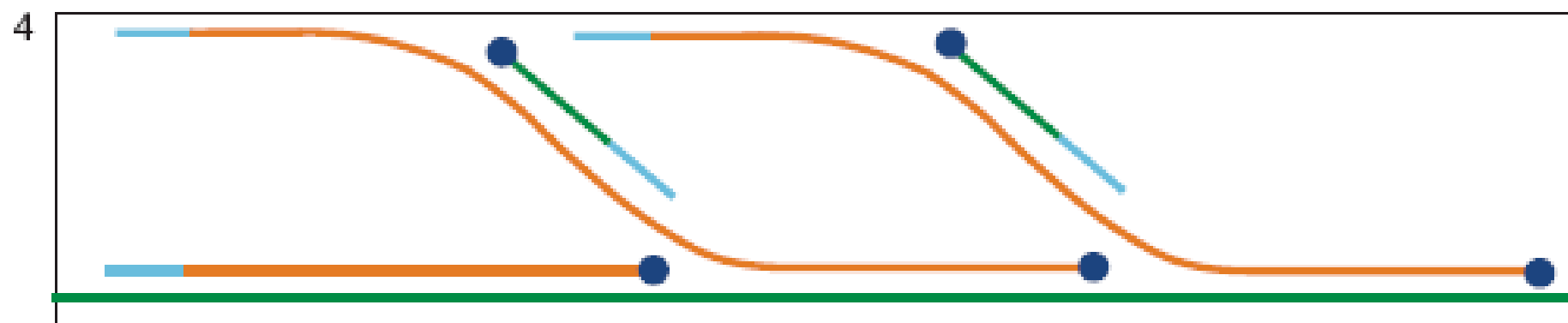
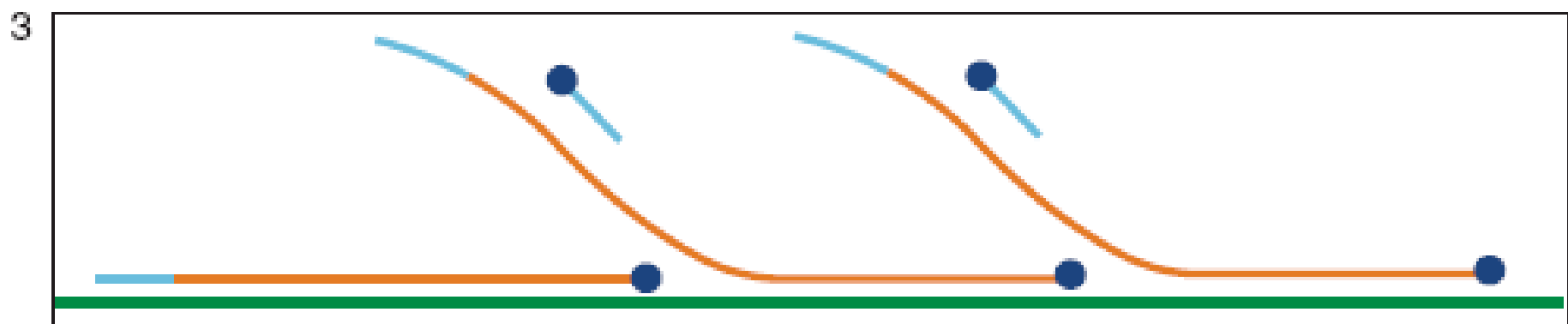
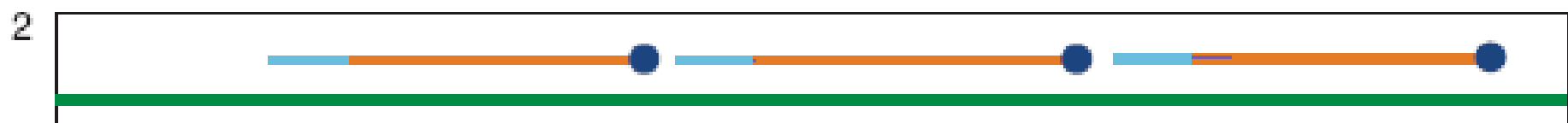


Test di I livello: primo caso

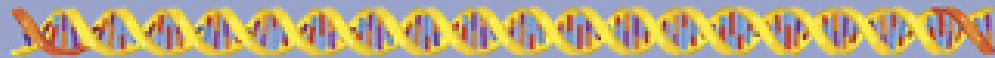
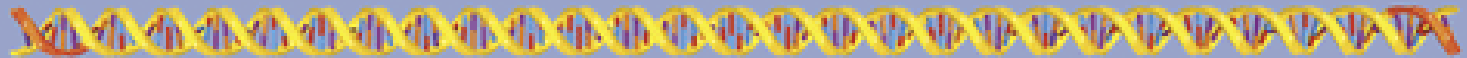


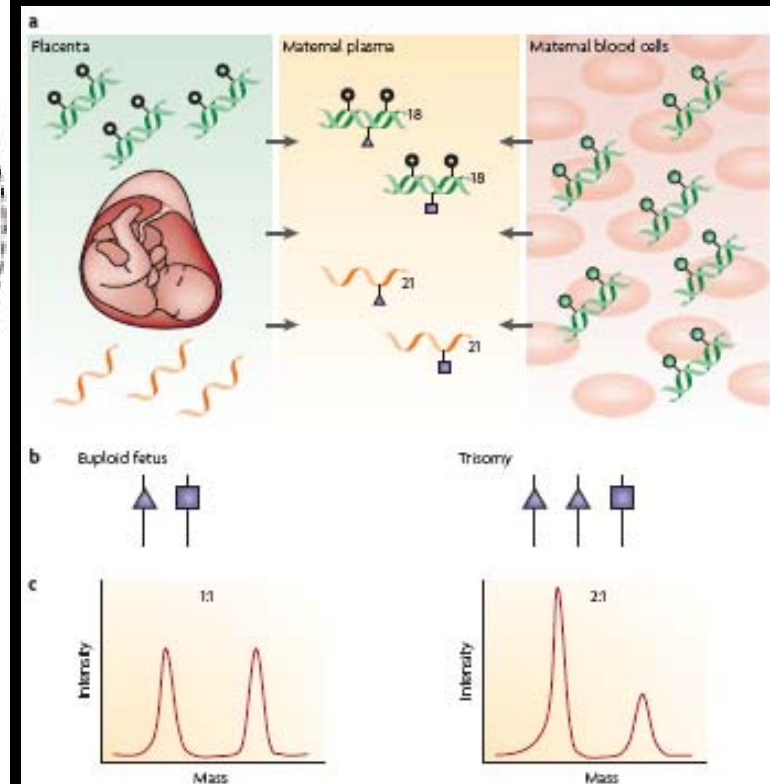
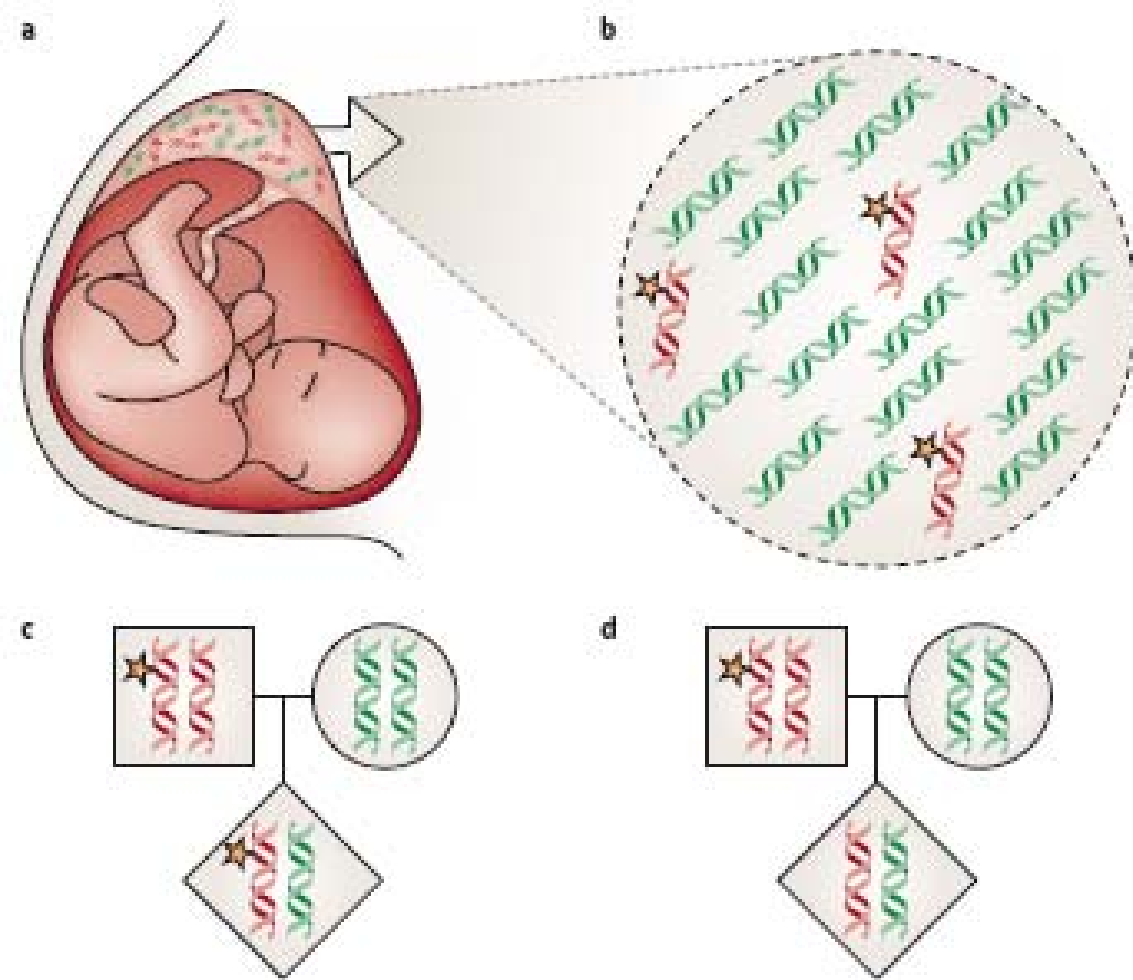
Test di I livello: secondo caso





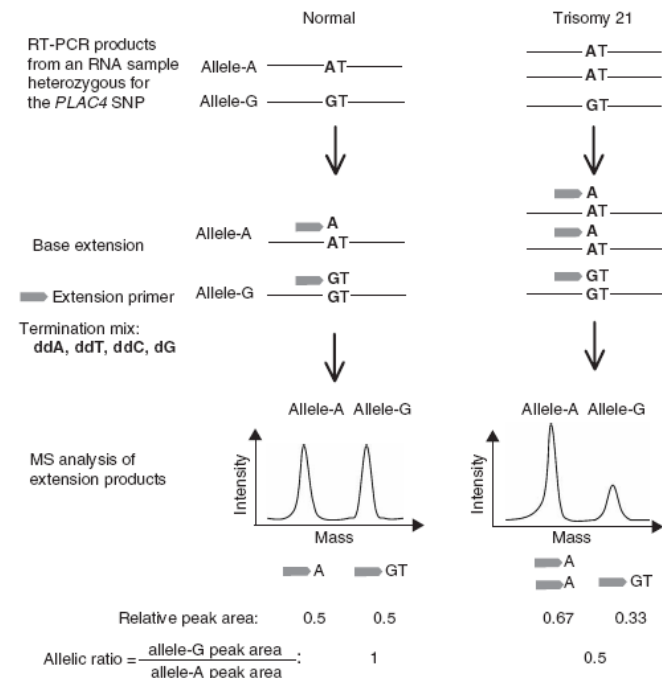
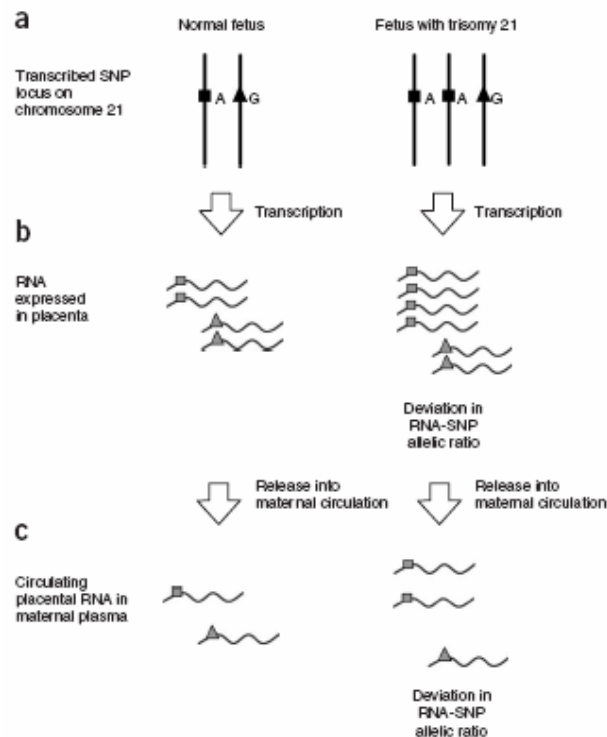
Multiple Displacement Amplification (MDA)





Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection

Y M Dennis Lo^{1,2,7}, Nancy B Y Tsui^{2,7}, Rossa W K Chiu^{1,2,7}, Tze K Lau³, Tse N Leung³, Macy M S Heung², Ageliki Gervassili⁴, Yongjie Jin⁵, Kypros H Nicolaides⁴, Charles R Cantor⁶ & Chunming Ding^{1,5,7}



LA PAURA

- IL DETERMINISMO GENETICO E LA DISCRIMINAZIONE BASATA SUL DNA
- VERSO UN NUOVO PROLETARIATO GENETICO...

SENSE TO ORDER
DIET DRINK WITH
DOUBLE MEGA CHEESE-
BURGER MEAL
(WITH FRY UPGRADE.)

TENDENCY TO DRIVE
BELLIGERENTLY SLOWLY IN THE
LEFT LANE & NOT USE
TURN SIGNALS.

INABILITY TO
FIND CELL-PHONE
"OFF" BUTTON IN
THEATER

DELUSIONS OF
STOCK MARKET
SAVVY

REALITY BASED
T.V. FIXATION

WILLINGNESS TO
DROP \$3.75 ON
A CUP OF
COFFEE.

BELIEF THAT ALL
BAGS ARE CARRY-
ON BAGS.

URGE TO PURCHASE
A SPORT UTILITY VEHICLE,
& THEN COMPLAIN ABOUT
GAS PRICES.

PROPENSITY TO DISCUSS
WEATHER.

The HUMAN GENETIC CODE, DECIPHERED.



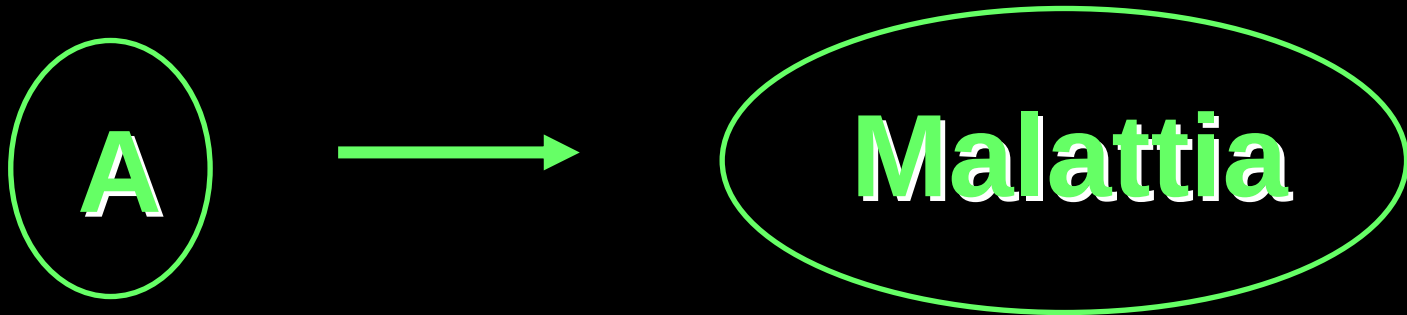
I gemelli Jim Springer e Jim Lewis, nati nel 1939 in Ohio, sono stati adottati da due famiglie diverse e nessuno dei due sapeva dell'esistenza dell'altro. Riuniti dopo decenni scoprirono: avevo lo stesso nome, avevano sposato una donna di nome Linda, avevano entrambi una seconda moglie, entrambe di nome Ann. I figli erano omonimi, entrambi si laurearono in legge e iniziarono a lavorare part-time come aiuto sceriffo. Tutti e due scelgono la Florida per trascorrere le ferie. Acquistano un cane che chiamano Toy. Fumano le stesse sigarette e bevono la stessa birra.

"Corriere del Medico" del 12 giugno del 1980

Gay Twins: A Case Study

In 1980, a man entered a gay bar while visiting another city and was surprised that many of the bar's patrons recognized him, yet called him by a name that was not his. The man wondered if he had a long-lost brother and began searching for such an individual. Upon meeting each other, the identical twins found that they'd both had childhood speech impediments, were both emotionally unstable, and had both realized they were gay around age fourteen. (The two later became lovers!)

Malattia semplice

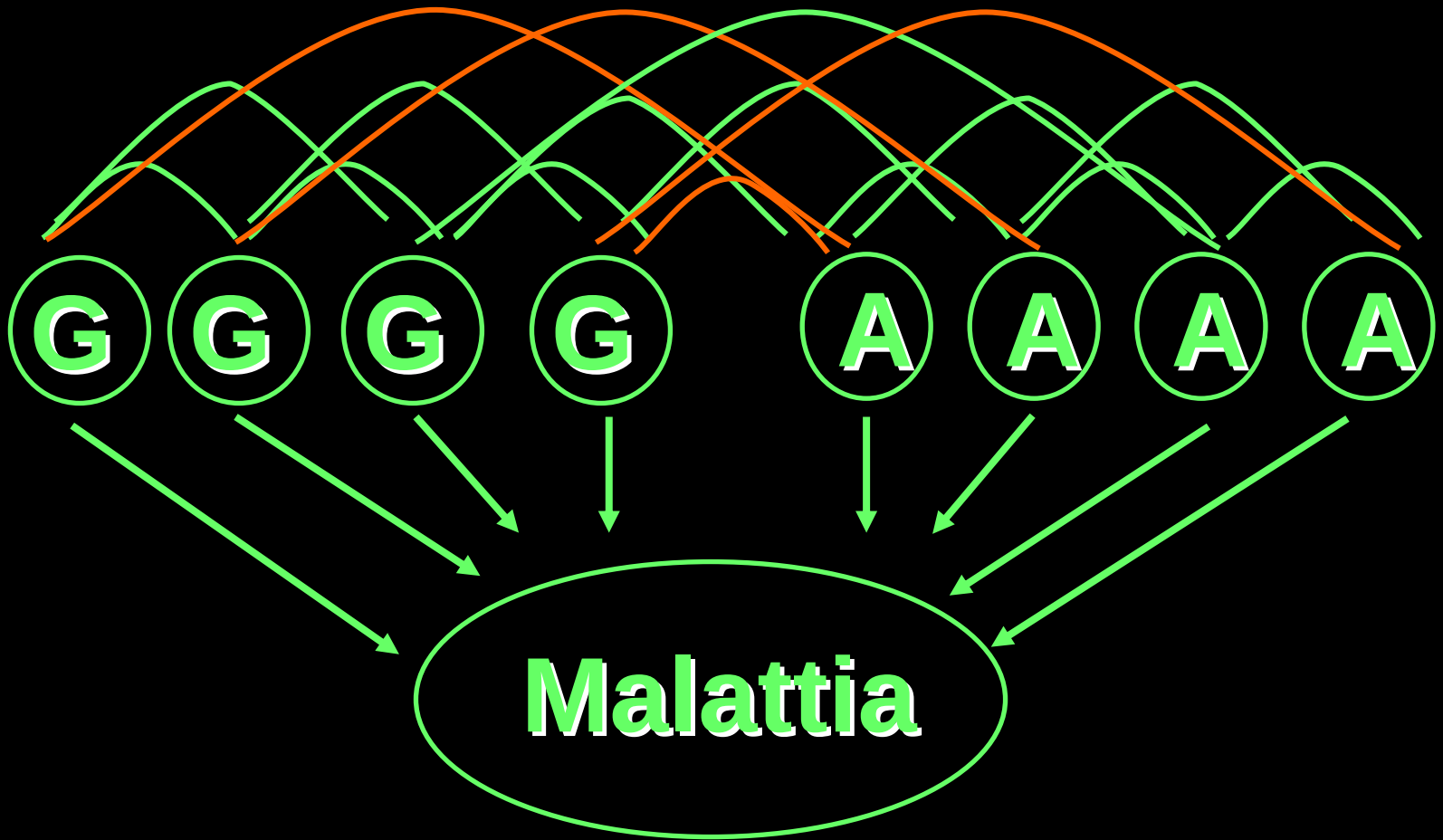


Esempi: infezioni virali, traumi

Malattie semplici

- Rare
- Dipendono, principalmente, da un singolo gene (Major Locus) **geni causativi**
- Seguono le leggi mendeliane di segregazione
- Mutazioni: evidenza di alleli rari

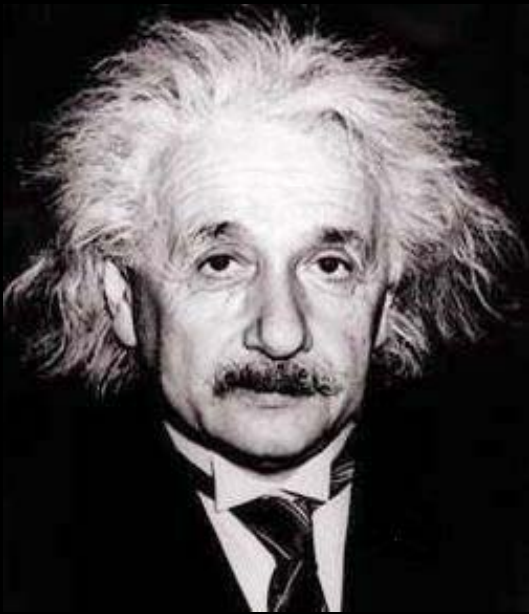
Malattie Complesse



“All diseases are genetic and I defy anyone to find a disease that isn't.”

[Paul Berg]

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



~24,000 geni



~50,000 geni

0.5%

99.9%



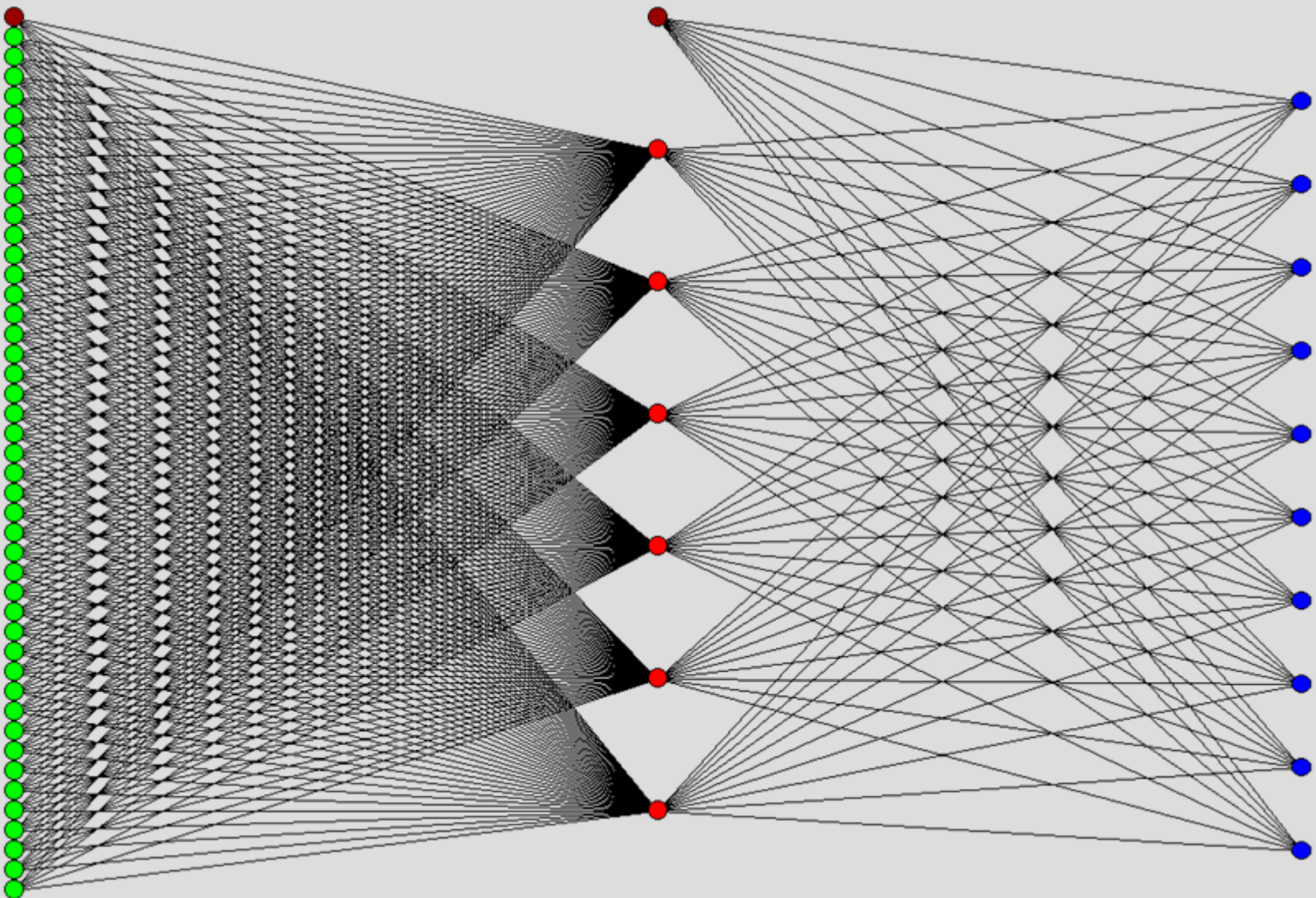


(Galen, 130-200 CE)

“But remember throughout that no cause is efficient without a predisposition of the body itself, otherwise, external factors which affect one would affect all.”



GENOMA



AMBIENTE



HEART
DISEASE

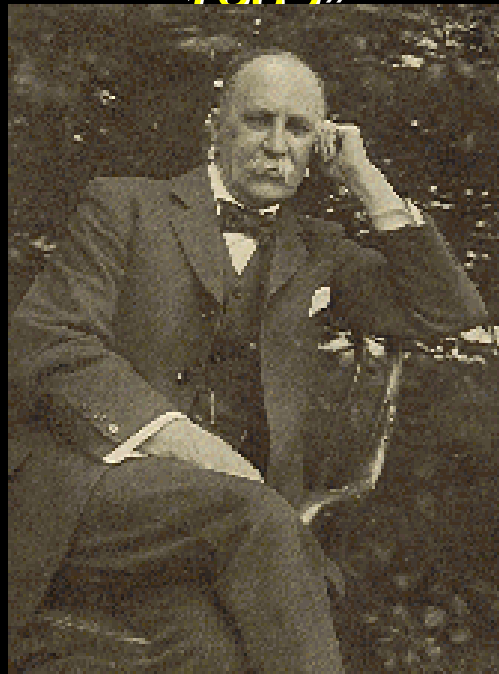
CANCER

STROKE

***“If were not for the great variability
between individuals, Medicine might
be a Science not an Art”***

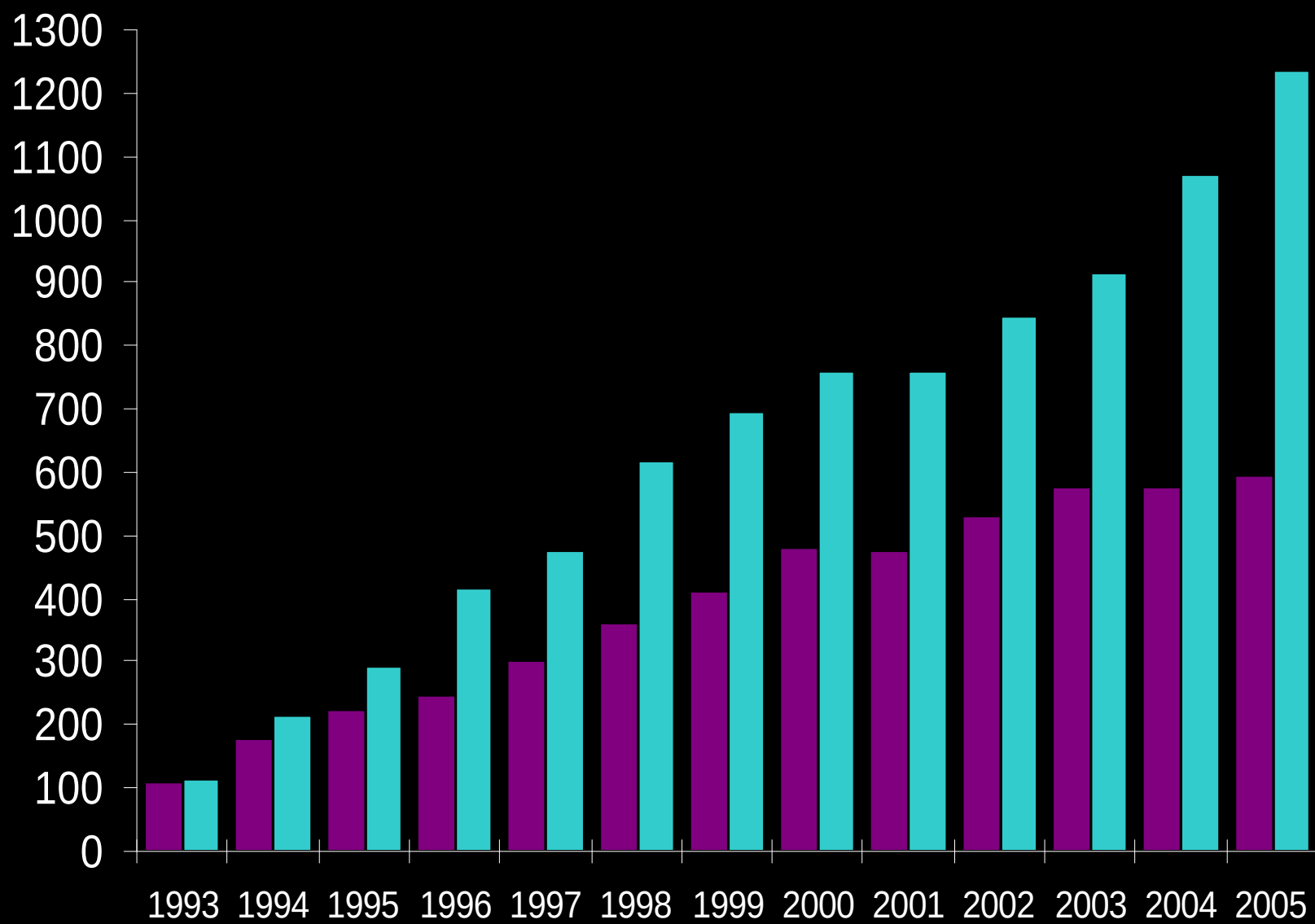
Sir William Osler

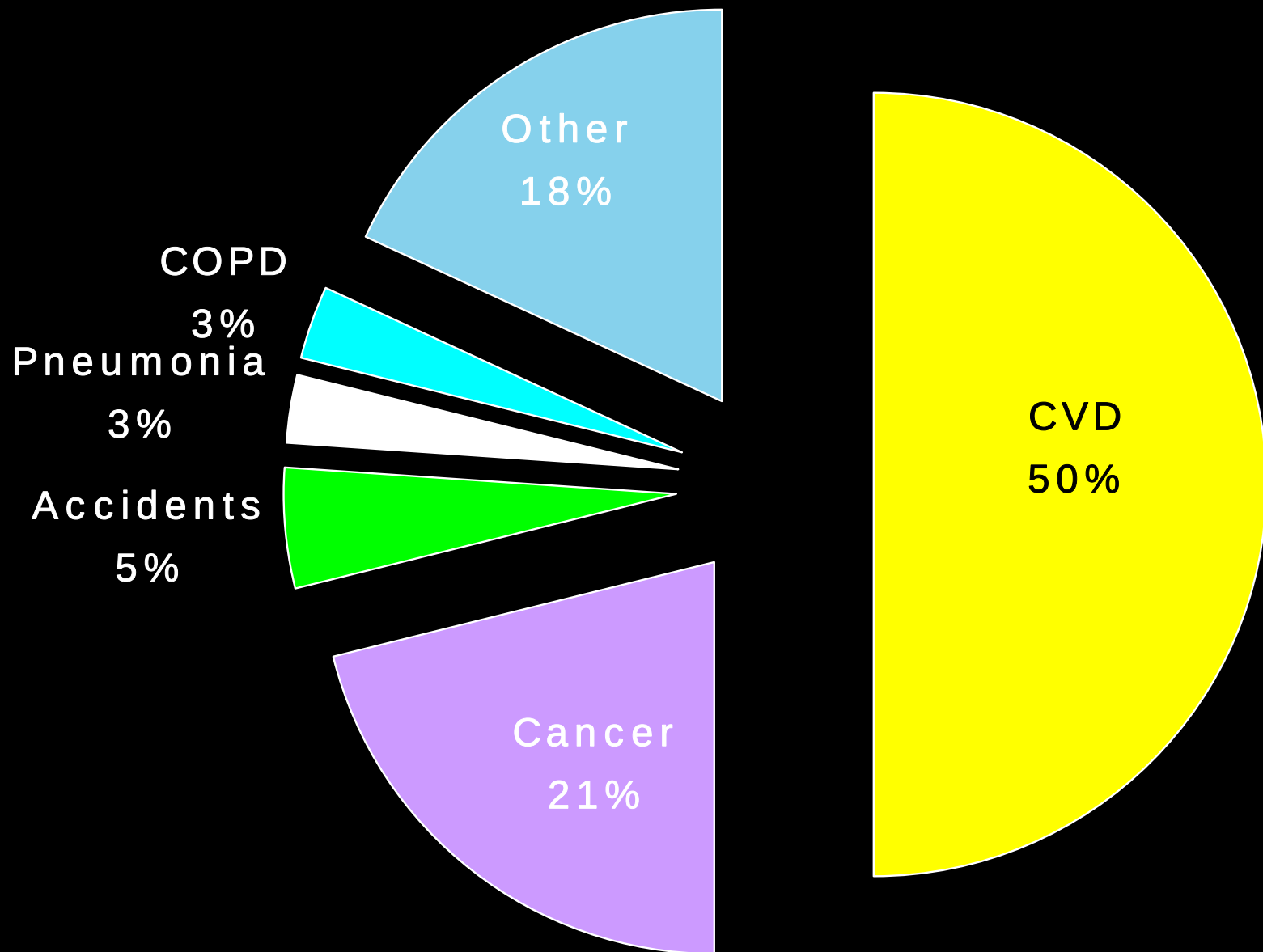
***“The principles and Practice of Medicine,
1902”***





LA VARIABILITA' INTER-INDIVIDUALE





Risk Factors

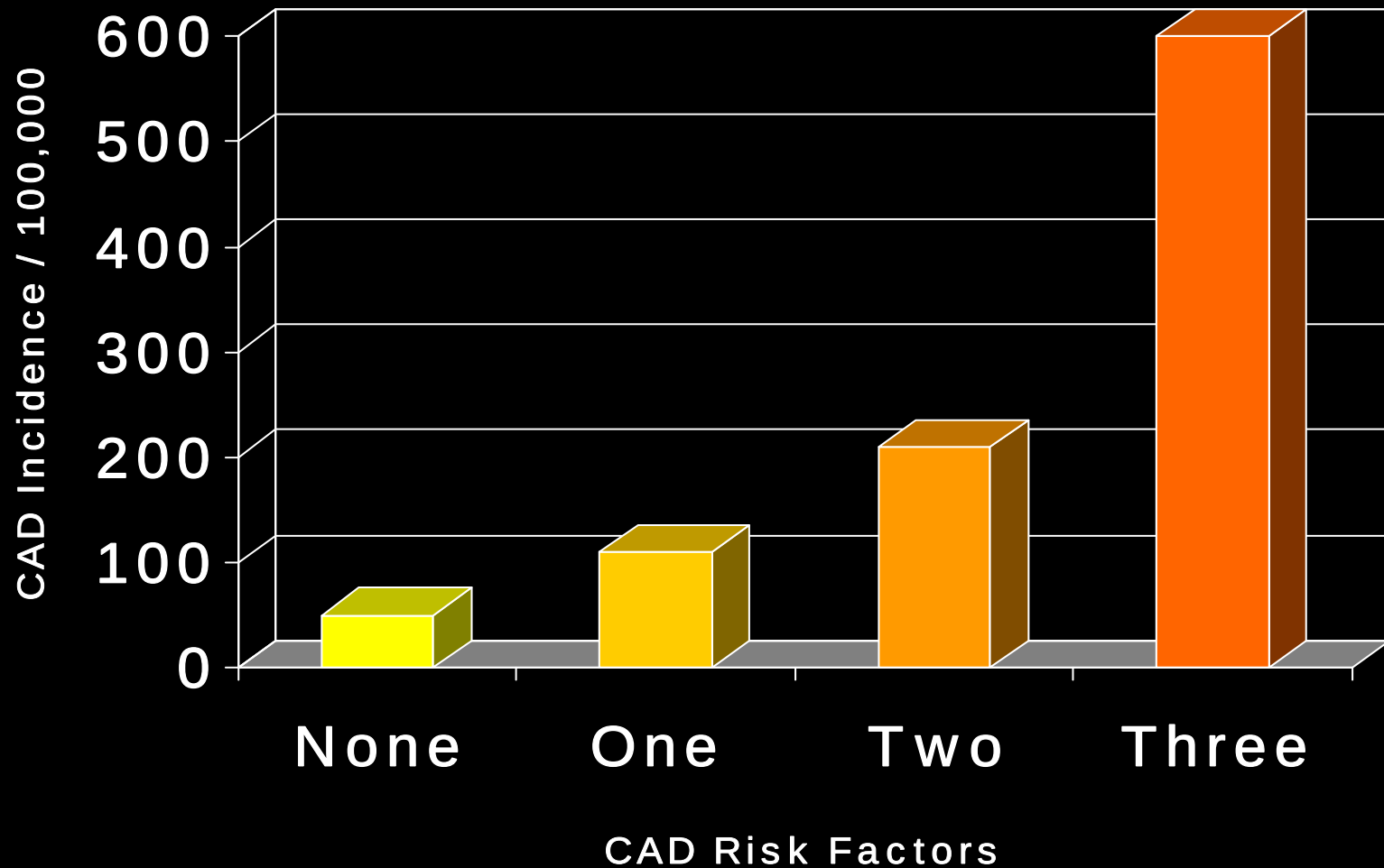
■ Modifiable

- Obesity
- Sedentary life
- Blood lipids
- Diet
- Hypertension
- Smoking
- Diabetes
- Tension & stress
- Education

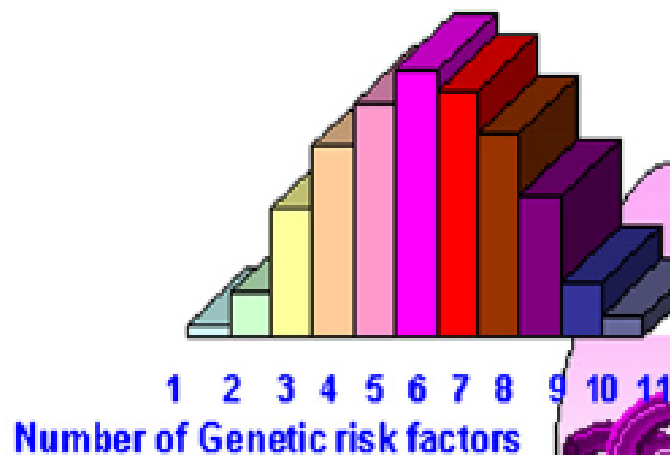
■ Non-Modifiable

- GENETICS *
 - Family History*
 - Race
 - Sex
- Age

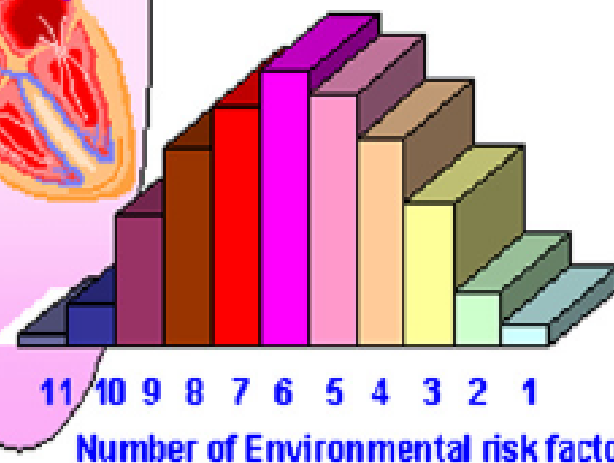
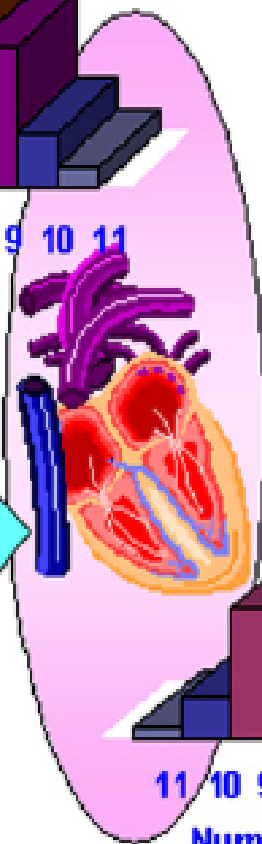
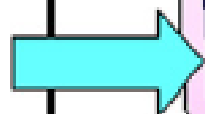
Interaction of Risk Factors



High Cholesterol genes Heart Failure genes
Low  **High**
 Clotting genes Blood Pressure genes Unknown genes

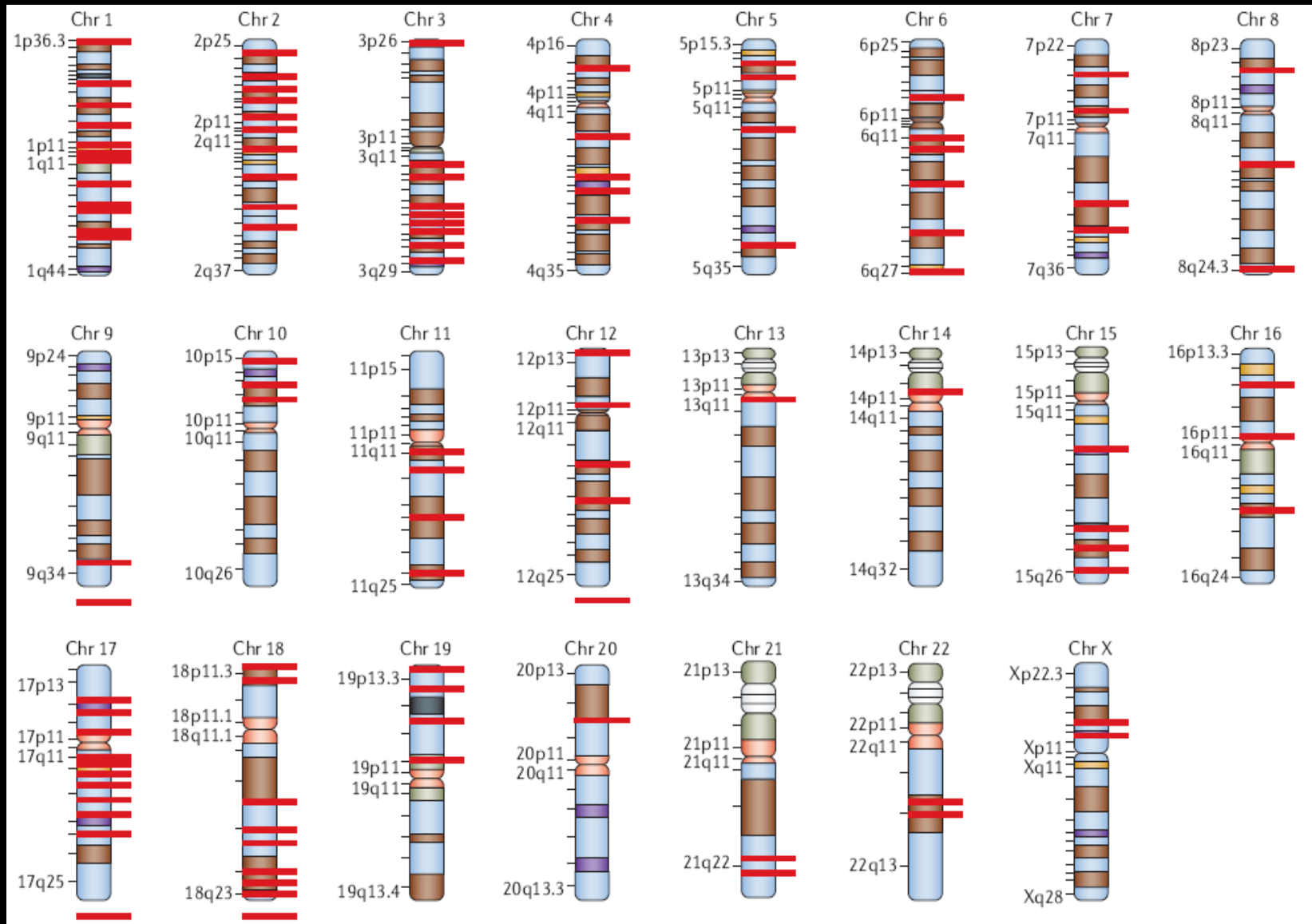


**High risk of early
 CHD ONLY
 in overlap - needs
 both environment
 AND
 genetic predisposition**



High  **Low**
 Blood pressure Obesity No Exercise
 Smoking Infection Diet Diabetes

Hypertension QTLs in the human genome



Gene Symbol	Variant	Genotype Comparison	Risk Variant Control Frequency	Odds Ratio (95% CI)	2-Tailed P Value	Genotype Frequency Difference
<i>ABCA1</i>	-477C/T ^{7,8}	TT vs CT or CC	0.222	1.13 (0.88-1.45)	.35	0.0215
<i>ABCA1</i>	Lys219Arg ^{9,10}	A vs G	0.274	1.02 (0.87-1.20)	.83	0.0041
<i>ACE1</i>	Indel ⁴	DD vs DI or II	0.286	1.07 (0.85-1.35)	.60	0.0139
<i>ADD1</i>	Gly460Trp ^{11,12}	T vs G	0.199	1.09 (0.91-1.32)	.35	0.0148
<i>ADRB2</i> §	Glu27Gln ¹³	G vs C	0.441	0.93 (0.80-1.08)	.34	-0.0186
<i>ADRB2</i>	Ile164Thr ¹³	CC vs CT	0.989	0.47 (0.20-1.13)	.10	-0.0117
<i>ADRB2</i>	Gly16Arg ¹³	A vs G	0.377	1.04 (0.89-1.20)	.67	0.0082
<i>ADRB3</i>	Arg64Trp ¹⁴	C vs T	0.077	0.99 (0.76-1.31)	>.99	-0.0004
<i>AGT</i>	Thr235Met ¹⁵	T vs C	0.572	1.04 (0.89-1.20)	.65	0.0086
<i>AGTR1</i>	A1166C ¹⁶	CC vs CA or AA	0.092	1.08 (0.76-1.53)	.72	0.0063
<i>ALOX5AP</i>	HAP B ¹⁷	HAP B vs non-B	0.062	1.12 (0.90-1.40)	.31	0.0120
<i>ALOX5AP</i>	HAP A ¹⁷	HAP A vs non-A	0.165	0.90 (0.75-1.10)	.32	-0.0130
<i>APOA1</i>	C83T ¹⁸	T vs C	0.173	0.99 (0.81-1.20)	.92	-0.0019
<i>APOA1</i>	-75G/A ¹⁹	A vs G	0.004	1.95 (0.68-5.54)	.23	0.0037
<i>APOE</i>	Arg158Cys ²⁰	CC vs CT or TT	0.023	1.61 (0.85-3.02)	.17	0.0134
<i>APOE</i>	-219T/G ²¹	T vs G	0.475	1.14 (0.99-1.32)	.08	0.0329
<i>BDKRB2</i>	-58C/T ²²	C vs T	0.590	0.93 (0.80-1.08)	.37	-0.0169
<i>CCL11</i> †	Thr23Ala ²³	C vs T	0.837	0.97 (0.80-1.19)	.80	-0.0036
<i>CCR2</i>	Val64Ile ²⁴	GG vs AG or AA	0.855	0.94 (0.70-1.25)	.71	-0.0082
<i>CCR5</i>	Indel ²⁵	I vs D	0.907	0.79 (0.62-1.00)	.05	-0.0224
<i>CD14</i>	-159C/T ²⁶	TT vs CT or CC	0.237	1.10 (0.86-1.39)	.46	0.0170
<i>CETP</i>	Intron1 G/A ²⁷	G vs A	0.568	0.93 (0.81-1.08)	.37	-0.0169
<i>CETP</i>	-629C/A ²⁸	C vs A	0.505	0.96 (0.83-1.11)	.60	-0.0104
<i>COMT</i> †	Val158Met ²⁹	GG or AG vs AA	0.222	1.11 (0.87-1.43)	.41	0.0193

Gene Symbol	Variant	Genotype Comparison	Risk Variant Control Frequency	Odds Ratio (95% CI)	2-Tailed P Value	Genotype Frequency Difference
<i>CX3CR1</i>	Ile249Val ^{30,31}	C vs T	0.729	0.96 (0.81-1.13)	.62	−0.0088
<i>CX3CR1</i>	Thr280Met ³⁰	G vs A	0.831	1.06 (0.87-1.29)	.58	0.0080
<i>CYP11B2</i> †	−344T/C ^{32,33}	C vs T	0.409	1.09 (0.94-1.26)	.27	0.0204
<i>CYP2C9</i>	Leu359Ile ^{34,35}	AC vs AA	0.094	0.76 (0.52-1.12)	.17	−0.0208
<i>CYP2C9</i> *†	Cys144Arg ^{34,35}	CC vs CT	0.798	1.01 (0.77-1.32)	.95	0.0019
<i>ENPP1</i>	Gln121Lys ³⁶	C vs A	0.130	1.07 (0.86-1.32)	.59	0.0076
<i>ESR1</i>	−401T/C ^{37,38}	TT vs CT or CC	0.285	1.06 (0.84-1.33)	.64	0.0118
<i>F12</i>	46C/T ³⁹	TT vs CT or CC	0.067	0.92 (0.60-1.40)	.75	−0.0051
<i>F13A1</i>	Val34Leu ⁴⁰	G vs T	0.753	1.02 (0.86-1.22)	.79	0.0045
<i>F2</i>	G20210A ^{40,41}	A vs G	0.017	0.92 (0.52-1.64)	.88	−0.0013
<i>F5</i>	Arg506Gln ⁴⁰	A vs G	0.025	0.93 (0.58-1.50)	.81	−0.0016
<i>F7</i> †	Arg353Gln ⁴²	G vs A	0.893	0.94 (0.74-1.19)	.63	−0.0062
<i>FGB</i>	−455A/G ⁴³	GG or AG vs AA	0.607	1.27 (1.03-1.58)	.03	0.0558
<i>GJA4</i>	C1019T ⁴⁴	T vs C	0.318	0.90 (0.77-1.06)	.22	−0.0215
<i>GP1BA</i>	−5T/C ⁴⁴⁻⁴⁶	T vs C	0.882	0.94 (0.75-1.17)	.57	−0.0071
<i>GRL</i>	Asn363Ser ⁴⁷	AG vs AA	0.073	0.79 (0.52-1.19)	.29	−0.0146
<i>HFE</i>	Cys282Tyr ⁴⁸	A vs G	0.065	0.98 (0.73-1.32)	.94	−0.0010
<i>HTR2A</i> *	Ser102Ser ⁴⁹	TT vs CT or CC	0.156	1.12 (0.84-1.48)	.47	0.0154
<i>ICAM1</i>	Lys469Glu ⁵⁰	A vs G	0.557	1.09 (0.94-1.27)	.26	0.0214
<i>IL1B</i>	−511C/T ⁵¹	CC vs CT or TT	0.445	1.14 (0.92-1.41)	.24	0.0328
<i>IL6</i>	−174G/C ^{52,53}	C vs G	0.403	1.05 (0.91-1.22)	.50	0.0127
<i>IRS1</i>	Arg971Gly ⁵⁴	A vs G	0.059	0.96 (0.70-1.32)	.81	−0.0023
<i>ITGA2</i>	Phe807Phe ^{55,56}	A vs G	0.391	1.03 (0.88-1.19)	.73	0.0063
<i>ITGB3</i>	Leu33Pro ⁴	C vs T	0.164	0.85 (0.70-1.05)	.14	−0.0203
<i>LIPC</i>	−514T/C ^{57,58}	T vs C	0.240	0.85 (0.71-1.01)	.07	−0.0286
<i>LPL</i>	Asp9Asn ⁵⁹	AG vs GG	0.026	1.43 (0.78-2.63)	.29	0.0107
<i>LRP1</i>	Thr3261Thr ⁶⁰	GG or AG vs AA	0.107	1.02 (0.73-1.42)	.93	0.0018

Gene Symbol	Variant	Genotype Comparison	Risk Variant Control Frequency	Odds Ratio (95% CI)	2-Tailed P Value	Genotype Frequency Difference
LTA	A252G ^{61,62}	GG vs AG or AA	0.116	0.86 (0.62-1.20)	.40	−0.0147
LTA	Thr26Asn ^{61,62}	AA vs AC or CC	0.119	0.82 (0.59-1.14)	.27	−0.0191
MGP	Thr83Ala ⁶³	G vs A	0.385	1.00 (0.86-1.16)	>.99	0.0000
MGP	−7A/G ⁶³	G vs A	0.636	1.00 (0.86-1.16)	.97	−0.0010
MMP3	Indel ^{64,65}	DD vs DI or II	0.284	0.82 (0.65-1.05)	.13	−0.0375
MTHFR [*]	Ala222Val ⁶⁶	TT vs CT or CC	0.100	1.32 (0.95-1.84)	.10	0.0283
MTP	−493G/T ^{67,68}	T vs G	0.255	1.01 (0.86-1.20)	.86	0.0028
MTR	Asp919Gly ⁶⁹	A vs G	0.804	1.03 (0.85-1.24)	.78	0.0043
NPPA	Ter29ArgArg ⁷⁰	CC vs CT or TT	0.023	1.20 (0.61-2.32)	.62	0.0044
OLR1	Lys167Asn ⁷¹	C vs G	0.916	0.82 (0.63-1.05)	.12	−0.0169
p22-PHOX‡	His72Tyr ^{72,73}	CC vs CT or TT	0.337	1.13 (0.91-1.39)	.28	0.0299
PAI1	Indel ^{43,44}	DD vs DI or II	0.309	1.00 (0.80-1.25)	>.99	−0.0005
PECAM1	Leu125Val ^{74,75}	GG vs CG or CC	0.288	0.94 (0.75-1.19)	.64	−0.0120
PECAM1	Ser563Asn ^{74,75}	A vs G	0.498	0.97 (0.84-1.13)	.71	−0.0072
PON1	Gln192Arg ⁷⁶	A vs G	0.705	1.01 (0.86-1.18)	.97	0.0010
PON2	Cys311Ser ⁷⁷	CC vs CG or GG	0.556	1.10 (0.89-1.35)	.40	0.0223
PPARG	Ala12Pro ⁷⁸	C vs G	0.129	0.83 (0.66-1.03)	.10	−0.0200
PTGS2	−765G/C ⁷⁹	C vs G	0.168	0.85 (0.69-1.04)	.11	−0.0219
RECQL2	Arg1367Cys ⁸⁰	T vs C	0.758	0.80 (0.68-0.94)	.01	−0.0433
SELE	Leu554Phe ⁷⁵	T vs C	0.036	1.17 (0.80-1.71)	.44	0.0059
SELE	Ser128Arg ⁷⁵	C vs A	0.103	0.91 (0.71-1.16)	.45	−0.0086
SELP	Thr715Pro ⁸¹	A vs C	0.902	0.93 (0.73-1.18)	.58	−0.0068
TFPI	Val264Met ⁸²	AG vs GG	0.050	0.80 (0.49-1.32)	.44	−0.0096
THBD	−33G/A ⁸³	AG vs GG	0.002	2.39 (0.25-23.0)	.63	0.0022
THBD	Ala25Thr ⁸⁴	AG vs GG	0.011	1.29 (0.50-3.35)	.64	0.0030
THBD	Ala455Val ⁸⁵	CC vs CT or TT	0.659	1.05 (0.85-1.31)	.65	0.0114
THBS1	Asn700Ser ⁸⁶	GG vs AG or AA	0.021	0.81 (0.38-1.72)	.70	−0.0039
THBS2‡	3'UTR T/G ⁸⁷	TT or GT vs GG	0.950	0.51 (0.34-0.79)	.002	−0.0432
THBS4	Ala387Pro ⁸⁷	GG or CG vs CC	0.939	1.00 (0.65-1.53)	>.99	−0.0002
THPO	A5713G ⁸⁸	GG vs AG or AA	0.264	1.20 (0.95-1.51)	.13	0.0368
TLR4	Gly299Asp ⁸⁹	A vs G	0.942	1.02 (0.75-1.40)	.94	0.0011
TNF	−308G/A ⁹⁰	A vs G	0.158	0.86 (0.70-1.06)	.17	−0.0188
TNFRSF1A	Arg92Gln ⁹¹	AG vs GG	0.050	0.80 (0.49-1.32)	.44	−0.0096

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

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Bipolar disorder

Coronary artery disease

Crohn's disease

Hypertension

Rheumatoid arthritis

Type 1 diabetes

Type 2 diabetes

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

Table 3 | Regions of the genome showing the strongest association signals

Collection	Chromosome	Region (Mb)	SNP	Trend P value	Genotypic P value	$\log_{10}(\text{BF})$, additive	$\log_{10}(\text{BF})$, general	Risk allele	Minor allele	Heterozygote odds ratio	Homozygote odds ratio	Control MAF	Case MAF
Standard analysis													
BD	16p12	23.3–23.62	rs420259	2.19×10^{-04}	6.29×10^{-08}	1.96	4.79	A	G	2.08 (1.60–2.71)	2.07 (1.6–2.69)	0.282	0.248
CAD	9p21	21.93–22.12	rs1333049	1.79×10^{-14}	1.16×10^{-13}	11.66	11.19	C	C	1.47 (1.27–1.70)	1.9 (1.61–2.24)	0.474	0.554
CD	1p31	67.3–67.48	rs11805303	6.45×10^{-13}	5.85×10^{-12}	10.07	9.41	T	T	1.39 (1.22–1.58)	1.86 (1.54–2.24)	0.317	0.391
CD	2q37	233.92–234	rs10210302	7.10×10^{-14}	5.26×10^{-14}	11.11	11.28	T	C	1.19 (1.01–1.41)	1.85 (1.56–2.21)	0.481	0.402
CD	3p21	49.3–49.87	rs9858542	7.71×10^{-07}	3.58×10^{-08}	4.24	5.22	A	A	1.09 (0.96–1.24)	1.84 (1.49–2.26)	0.282	0.331
CD	5p13	40.32–40.66	rs17234657	2.13×10^{-13}	1.99×10^{-12}	10.41	9.89	G	G	1.54 (1.34–1.76)	2.32 (1.59–3.39)	0.125	0.181
CD	5q33	150.15–150.31	rs1000113	5.10×10^{-08}	3.15×10^{-07}	5.36	5.01	T	T	1.54 (1.31–1.82)	1.92 (0.92–4.00)	0.067	0.098
CD	10q21	64.06–64.31	rs10761659	2.68×10^{-07}	1.75×10^{-06}	4.69	4.13	G	A	1.23 (1.05–1.45)	1.55 (1.3–1.84)	0.461	0.406
CD	10q24	101.26–101.32	rs10883365	1.41×10^{-08}	5.82×10^{-08}	5.91	5.48	G	G	1.2 (1.03–1.39)	1.62 (1.37–1.92)	0.477	0.537
CD	16q12	49.02–49.4	rs17221417	9.36×10^{-12}	3.98×10^{-11}	8.93	8.47	G	G	1.29 (1.13–1.46)	1.92 (1.58–2.34)	0.287	0.356
CD	18p11	12.76–12.91	rs2542151	4.56×10^{-08}	2.03×10^{-07}	5.42	5.00	G	G	1.3 (1.14–1.48)	2.01 (1.46–2.76)	0.163	0.208
RA	1p13	113.54–114.16	rs6679677	4.90×10^{-26}	5.55×10^{-25}	22.36	21.99	A	A	1.98 (1.72–2.27)	3.32 (1.93–5.69)	0.096	0.168
RA	6	MHC	rs6457617*	3.44×10^{-76}	5.18×10^{-75}	74.84	73.18	T	T	2.36 (1.97–2.84)	5.21 (4.31–6.30)	0.489	0.685
T1D	1p13	113.54–114.16	rs6679677	1.17×10^{-26}	5.43×10^{-26}	23.07	22.83	A	A	1.82 (1.59–2.09)	5.19 (3.15–8.55)	0.096	0.169
T1D	6	MHC	rs9272346*	2.42×10^{-134}	5.47×10^{-134}	141.9	142.2	A	G	5.49 (4.83–6.24)	18.52 (27.03–12.69)	0.387	0.150
T1D	12q13	54.64–55.09	rs11171739	1.14×10^{-11}	9.71×10^{-11}	8.89	8.24	C	C	1.34 (1.17–1.54)	1.75 (1.48–2.06)	0.423	0.493
T1D	12q24	109.82–111.49	rs17696736	2.17×10^{-15}	1.51×10^{-14}	12.53	11.88	G	G	1.34 (1.16–1.53)	1.94 (1.65–2.29)	0.424	0.506
T1D	16p13	10.93–11.37	rs12708716	9.24×10^{-08}	4.92×10^{-07}	5.15	4.70	A	G	1.19 (0.97–1.45)	1.55 (1.27–1.89)	0.350	0.297
T2D	6p22	20.63–20.84	rs9465871	1.02×10^{-06}	3.34×10^{-07}	4.15	3.98	C	C	1.18 (1.04–1.34)	2.17 (1.6–2.95)	0.178	0.218
T2D	10q25	114.71–114.81	rs4506565	5.68×10^{-13}	5.05×10^{-12}	10.14	9.43	T	T	1.36 (1.2–1.54)	1.88 (1.56–2.27)	0.324	0.395
T2D	16q12	52.36–52.41	rs9939609	5.24×10^{-08}	1.91×10^{-07}	5.35	5.05	A	A	1.34 (1.17–1.52)	1.55 (1.3–1.84)	0.398	0.453
Multi-locus analysis													
T1D	4q27	123.26–123.92	rs6534347	4.48×10^{-07}	1.83×10^{-06}	5.15	4.69	A	A	1.30 (1.10–1.55)	1.49 (1.25–1.78)	0.351	0.402
T1D	12p13	9.71–9.86	rs3764021	7.19×10^{-05}	5.08×10^{-08}	2.12	4.55	C	T	1.57 (1.38–1.79)	1.48 (1.25–1.75)	0.467	0.426
Sex differentiated analysis													
RA	7q32	130.80–130.84	rs11761231	3.91×10^{-07}	1.37×10^{-06}	-	-	G	A	1.44 (1.19–1.75)	1.64 (1.35–1.99)	0.375	0.327
Combined cases													
RA+T1D	10p15	6.07–6.17	rs2104286	5.92×10^{-08}	2.52×10^{-07}	5.26	4.45	T	C	1.35 (1.11–1.65)	1.62 (1.34–1.97)	0.286	0.245

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

Table 4 | Regions of the genome showing moderate evidence of association

Collection	Chromosome	Region (Mb)	SNP	Trend P value	Genotypic P value	$\log_{10}(\text{BF})$, additive	$\log_{10}(\text{BF})$, general	Risk allele	Minor allele	Heterozygote odds ratio	Homozygote odds ratio	Control MAF	Case MAF
HT	12p12	24.86–24.95	rs7961152	7.39×10^{-06}	3.03×10^{-05}	3.29	2.51	A	A	1.16 (1.01–1.32)	1.47 (1.25–1.74)	0.415	0.461
HT	12q23	100.52–100.58	rs11110912	9.18×10^{-06}	1.94×10^{-05}	3.27	3.11	G	G	1.33 (1.18–1.51)	1.34 (0.96–1.86)	0.165	0.200
HT	13q21	66.90–67.04	rs1937506	9.23×10^{-06}	4.53×10^{-05}	3.25	2.85	G	A	1.33 (1.04–1.69)	1.60 (1.26–2.02)	0.289	0.248
HT	15q26	94.60–94.67	rs2398162	7.85×10^{-06}	5.67×10^{-06}	3.33	3.40	A	G	0.97 (0.76–1.25)	1.31 (1.03–1.67)	0.258	0.218
RA	1p36	2.44–2.77	rs6684865	5.37×10^{-06}	3.14×10^{-05}	3.47	2.97	G	A	1.27 (1.02–1.56)	1.54 (1.25–1.90)	0.338	0.294
RA	1p31	80.16–80.36	rs11162922	1.80×10^{-06}	-	4.11	3.80	A	G	1.27 (0.41–4.01)	2.00 (0.64–6.20)	0.072	0.048
RA	4p15	24.99–25.13	rs3816587	7.65×10^{-03}	9.25×10^{-06}	0.50	2.64	C	C	0.91 (0.80–1.04)	1.35 (1.14–1.59)	0.406	0.434
RA	6q23	138.00–138.06	rs6920220	4.99×10^{-06}	1.58×10^{-05}	3.49	3.17	A	A	1.20 (1.06–1.36)	1.72 (1.33–2.22)	0.223	0.263
RA	7q32	130.80–130.84	rs11761231	1.74×10^{-06}	2.65×10^{-06}	3.92	3.42	C	T	1.44 (1.19–1.75)	1.64 (1.35–1.99)	0.375	0.327
RA	10p15	6.07–6.16	rs2104286	7.02×10^{-06}	2.52×10^{-05}	3.37	2.57	T	C	1.41 (1.10–1.81)	1.68 (1.31–2.14)	0.286	0.244
RA	13q12	19.845–19.855	rs9550642	8.44×10^{-06}	3.90×10^{-05}	3.35	3.02	A	A	1.34 (1.15–1.56)	2.23 (1.21–4.13)	0.084	0.112
RA	21q22	41.430–41.465	rs2837960	3.45×10^{-02}	1.68×10^{-06}	0.05	2.70	G	G	0.95 (0.83–1.08)	2.30 (1.64–3.23)	0.171	0.188
RA	22q13	35.870–35.885	rs743777	7.92×10^{-06}	1.15×10^{-06}	3.29	3.52	G	G	1.09 (0.97–1.24)	1.72 (1.40–2.11)	0.292	0.336
T1D	1q42	221.92–222.17	rs2639703	8.46×10^{-06}	1.74×10^{-05}	3.25	3.06	C	C	1.15 (1.02–1.30)	1.61 (1.31–1.99)	0.276	0.318
T1D	4q27	123.02–123.92	rs17388568	5.01×10^{-07}	3.27×10^{-06}	4.42	3.89	A	A	1.26 (1.11–1.42)	1.58 (1.27–1.95)	0.260	0.307
T1D	5q14	86.20–86.50	rs2544677	8.23×10^{-06}	4.43×10^{-05}	3.32	2.70	C	G	1.34 (1.00–1.79)	1.65 (1.24–2.18)	0.242	0.204
T1D	5q31	132.64–132.67	rs17166496	6.06×10^{-01}	5.20×10^{-06}	−0.97	3.25	C	G	0.77 (0.68–0.87)	1.09 (0.92–1.29)	0.391	0.386
T1D	10p15	6.07–6.18	rs2104286	7.96×10^{-06}	4.32×10^{-05}	3.31	2.88	T	C	1.30 (1.02–1.65)	1.57 (1.25–1.99)	0.286	0.245
T1D	12p13	9.71–9.80	rs11052552	1.02×10^{-04}	7.24×10^{-07}	2.22	3.80	G	T	1.49 (1.28–1.73)	1.43 (1.21–1.69)	0.486	0.446
T1D	18p11	12.76–12.91	rs2542151	1.89×10^{-06}	1.16×10^{-05}	3.91	3.52	G	G	1.30 (1.15–1.47)	1.62 (1.17–2.24)	0.163	0.201
T2D	1p31	66.04–66.36	rs4655595	2.68×10^{-06}	1.33×10^{-05}	3.81	3.47	G	G	1.37 (1.17–1.59)	2.33 (1.23–4.42)	0.080	0.108
T2D	2q24	160.90–161.17	rs6718526	2.40×10^{-06}	1.16×10^{-05}	3.86	3.35	C	T	1.49 (1.05–2.11)	1.86 (1.32–2.63)	0.209	0.171
T2D	3p14	55.24–55.32	rs358806	4.77×10^{-01}	3.05×10^{-06}	−0.83	2.72	A	A	0.86 (0.75–0.97)	1.78 (1.34–2.36)	0.198	0.204
T2D	4q27	122.92–123.02	rs7659604	2.1×10^{-02}	9.42×10^{-06}	0.13	2.74	T	T	1.35 (1.19–1.54)	1.09 (0.91–1.30)	0.380	0.403
T2D	10q11	43.43–43.63	rs9326506	7.78×10^{-06}	2.99×10^{-05}	3.27	2.92	C	C	1.28 (1.11–1.48)	1.46 (1.24–1.72)	0.492	0.538
T2D	12q13	49.50–49.87	rs12304921	5.37×10^{-02}	7.07×10^{-06}	−0.09	2.68	G	G	2.50 (1.53–4.09)	1.94 (1.20–3.15)	0.145	0.159
T2D	12q15	69.58–69.96	rs1495377	1.31×10^{-06}	6.52×10^{-06}	4.01	3.15	G	G	1.28 (1.11–1.49)	1.51 (1.28–1.78)	0.497	0.547
T2D	15q24	72.24–72.50	rs2930291	7.72×10^{-06}	4.40×10^{-05}	3.30	2.42	G	A	1.25 (1.04–1.51)	1.50 (1.24–1.82)	0.377	0.332
T2D	15q25	78.12–78.36	rs2903265	9.57×10^{-06}	4.98×10^{-05}	3.24	2.53	G	A	1.18 (0.93–1.49)	1.47 (1.17–1.86)	0.284	0.243

Research

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Framingham Heart Study 100K project: genome-wide associations for cardiovascular disease outcomes

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Phenotype	Definition	Number of individuals	Number with event	Adjustment*
Major CVD	Myocardial infarction, coronary insufficiency, CHD death, or atherothrombotic stroke	1345	142	Age, sex; Multivariable: Age, sex, smoking, diabetes, systolic BP, anti-hypertensive therapy, total cholesterol
Major CHD	Myocardial infarction, coronary insufficiency, or CHD death	1345	118	Same as Major CVD
Heart failure	Heart failure, hospitalized or non-hospitalized	1345	73	Same as Major CVD except BMI added, total cholesterol removed
Atrial fibrillation	Atrial fibrillation or atrial flutter on ECG	1341	151	Age, sex; Multivariable: Age, sex, diabetes, systolic BP, anti-hypertensive therapy, valve disease

Table 4: Association Results for Pre-Specified Candidate Genes

Candidate gene	Total number of SNPs*	SNPs with p value < 0.05	Phenotype	GEE p value	FBAT p value
Major CVD/Major CHD					
<i>ALOX5</i>	5	0			
<i>ALOX5AP</i>	23	rs7983138	Major CHD	0.011	0.373
		rs2985183	Major CHD	0.014	0.455
		rs7984952	Major CHD	0.015	0.266
		rs117395	Major CHD	0.016	0.568
		rs4603405	Major CHD	0.018	0.257
		rs10507391	Major CHD	0.028	0.660
		rs10507391	Major CVD	0.043	0.878
		rs7995384	Major CHD	0.049	0.967
<i>GJA4</i>	14	rs618675	Major CHD	0.004	0.169
		rs10489658	Major CHD	0.004	0.145
		rs618675	Major CVD	0.009	0.464
		rs10493062	Major CHD	0.011	0.051
		rs768586	Major CHD	0.016	0.135
		rs10489658	Major CVD	0.025	0.237
		rs10489656	Major CHD	0.520	0.030
		rs10489656	Major CVD	0.538	0.044
		rs2093185	Major CVD	0.547	0.019
		rs6686484	Major CHD	1.000	0.031

LGALS2	1	0			
LTA	2	0			
LTA4H	22	rs10492225	Major CHD	0.013	0.080
MEF2A	5	rs2033546	Major CVD	0.004	0.006
		rs2863274	Major CVD	0.006	0.006
		rs2033546	Major CHD	0.016	0.013
		rs2863274	Major CHD	0.062	0.021
MMP3	17	rs2096767	Major CVD	0.028	0.506
		rs2096767	Major CHD	0.032	0.610
		rs566125	Major CVD	0.042	0.079
SERPINE1	2	0			
PCSK9	11	rs2114580	Major CHD	0.010	0.075
		rs2114580	Major CVD	0.026	0.057
		rs2317951	Major CVD	0.076	0.002
		rs2317951	Major CHD	0.077	0.002
		rs2317948	Major CHD	0.478	0.029
		rs2317948	Major CVD	0.584	0.026
THBS2	7	rs911839	Major CVD	0.192	0.035
		rs911839	Major CHD	0.255	0.032
THBS4	16	rs264986	Major CHD	0.443	0.048
VAMP8	5	0			

Atrial fibrillation

ACE	3	0			
AGT	13	rs758216		0.041	0.204
GJA5	13	0			
KCNE2	14	0			
KCNH2	6	0			
KCNJ2	23	rs10512574		0.140	0.041
KCNQ1	5	rs10488674		0.136	0.046
KCNE1	20	rs7277304		0.745	0.047
		rs9305551		0.119	0.018

Heart failure

ABCC9	8	0			
ACTC	15	rs752876		0.065	0.040

Nonvalidation of Reported Genetic Risk Factors for Acute Coronary Syndrome in a Large-Scale Replication Study

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COMPELLING EVIDENCE FROM twin and epidemiological studies suggests a genetic basis for atherosclerotic heart disease and acute coronary syndromes (ACS), including unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI).^{1,2} To date, numerous candidate genes have been implicated, mainly by case-control studies, as potential cardiovascular risk factors, but few, if any, have been established definitively.³⁻⁵ Factors undermining the validity of previous reports include inappropriately small sample sizes, multiple subgroup comparisons, and publication bias.⁴

Before use in clinical care, potential genetic risk factors would ideally be replicated en masse in large, well-characterized patient populations.⁶ To date, no such comprehensive validation of genetic variants potentially associated with ACS or atherosclerosis has been reported.

Accordingly, we first sought to identify genetic associations with ACS by systematically searching the medical literature for variants reported in association with MI, unstable angina, or atherosclerosis. We then attempted to validate these putative genetic risks in a large case-control study.

Context Given the numerous, yet inconsistent, reports of genetic variants being associated with acute coronary syndromes (ACS), there is a need for comprehensive validation of ACS susceptibility genotypes.

Objective To perform an extensive validation of putative genetic risk factors for ACS.

Design, Setting, and Participants Through a systematic literature search of articles published before March 10, 2005, we identified genetic variants previously reported as significant susceptibility factors for atherosclerosis or ACS. Restricting our analysis to white patients to reduce confounding from racial admixture, we identified 811 patients who presented from March 2001 through June 2003 with ACS at 2 Kansas City, Mo, university-affiliated hospitals. During 2005-2006, we genotyped the 811 patients along with 650 age- and sex-matched controls for 85 variants in 70 genes and attempted to replicate previously reported associations. We further explored possible associations without prior assumption of specific risk models and used the Sign test to search for weak associations.

Main Outcome Measures Compare each prespecified gene variant associated with ACS risk among cases and controls. A surplus of associations would imply that some are associated with ACS.

Results Of 85 variants tested, only 1 putative risk genotype (−455 promoter variant in β -fibrinogen) was nominally statistically significant ($P = .03$). Only 4 additional genes were positive in model-free analysis. Neither number of associations was more frequent than expected by chance, given the number of comparisons. Finally, only 41 of 84 predefined risk variants were even marginally more frequent in cases than in controls (with 1 tie), representing a 48.8% "win rate" (95% confidence interval, 38.1%-59.5%) for the collective risk genotypes ($P = .91$, Sign test).

Conclusions Our null results provide no support for the hypothesis that any of the 85 genetic variants tested is a susceptibility factor for ACS. These results emphasize the need for robust replication of putative genetic risk factors before their introduction into clinical care.

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METHODS

Candidate Genes

We searched PubMed and bibliographies of original and review articles for manuscripts published before March 10, 2005, that reported statistically significant associations between specific genotypes and coronary atherosclerosis or ACS (A list of the articles is available on request from the authors). MEDLINE search terms

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Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
ABCA1	-477C/T	CC	191 (24.6)	182 (28.3)	.27
		CT	396 (51.0)	319 (49.5)	
		TT	189 (24.4)	143 (22.2)	
ABCA1	Lys219Arg	AA	65 (8.2)	46 (7.1)	.69
		AG	311 (39.3)	263 (40.6)	
		GG	416 (52.5)	338 (52.2)	
ACE1	VD	DD	233 (30.0)	185 (28.6)	.84
		DI	389 (50.1)	329 (50.9)	
		II	154 (19.8)	132 (20.4)	
ADD1	Gly460Trp	GG	456 (60.7)	419 (64.9)	.08
		GT	269 (35.8)	197 (30.5)	
		TT	26 (3.5)	30 (4.6)	
ADRB2	Glu27Gln†	CC	266 (34.5)	217 (34.8)	.14
		CG	358 (46.5)	264 (42.3)	
		GG	146 (19.0)	143 (22.9)	
ADRB2	Ile164Thr	CC	789 (97.8)	652 (98.9)	.11
		CT	18 (2.2)	7 (1.1)	
		TT	0	0	
ADRB2	Gly16Arg	AA	128 (16.3)	100 (15.2)	.87
		AG	348 (44.3)	294 (44.8)	
		GG	309 (39.4)	262 (39.9)	
ADRB3	Arg64Trp	CC	6 (0.7)	1 (0.2)	.21
		CT	111 (13.8)	99 (15.1)	
		TT	687 (85.4)	557 (84.8)	
AGT	Thr235Met	CC	143 (17.8)	107 (16.5)	.27
		CT	387 (48.3)	340 (52.6)	
		TT	272 (33.9)	200 (30.9)	
AGTR1	A1166C	AA	388 (48.1)	332 (50.8)	.61
		AC	339 (42.1)	262 (40.1)	
		CC	79 (9.8)	60 (9.2)	
ALOX5AP	HAP B	B	50 (6.5)	41 (5.8)	.31
		non-B	734 (93.5)	661 (94.2)	
		NA	NA	NA	
ALOX5AP	HAP A	A	124 (15.9)	122 (17.4)	.35
		non-A	654 (84.1)	584 (82.6)	
		NA	NA	NA	
APOA1	C83T	AA	23 (3.0)	25 (3.8)	.59
		AG	219 (28.3)	175 (26.9)	
		GG	532 (68.7)	450 (69.2)	
APOA1	-75G/A	AA	1 (0.1)	0	.51
		AG	10 (1.3)	5 (0.8)	
		GG	784 (98.6)	638 (99.2)	
APOE	Arg158Cys	CC	29 (3.6)	15 (2.3)	.14
		CT	209 (26.1)	154 (23.5)	
		TT	562 (70.3)	487 (74.2)	
APOE	-219T/G	GG	194 (24.2)	177 (27.3)	.21
		GT	403 (50.2)	327 (50.5)	
		TT	206 (25.7)	144 (22.2)	
BDKRB2	-58C/T	CC	263 (32.8)	221 (33.6)	.43
		CT	394 (49.1)	335 (50.9)	
		TT	145 (18.1)	102 (15.5)	

Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
CCL11	Thr23Ala‡	CC	539 (68.2)	456 (70.0)	.20
		CT	239 (30.3)	178 (27.3)	
		TT	12 (1.5)	17 (2.6)	
CCR2	Val64Ile	AA	7 (0.9)	6 (0.9)	.91
		AG	116 (14.4)	89 (13.6)	
		GG	681 (84.7)	561 (85.5)	
CCR5	Indel	II	631 (78.4)	540 (82.4)	.15
		ID	162 (20.1)	108 (16.5)	
		DD	12 (1.5)	7 (1.1)	
CD14	-159C/T	CC	204 (25.4)	193 (29.5)	.22
		CT	395 (49.2)	306 (46.8)	
		TT	204 (25.4)	155 (23.7)	
CETP	Intron1 G/A	AA	168 (20.9)	135 (20.6)	.44
		AG	387 (48.1)	297 (45.3)	
		GG	250 (31.1)	224 (34.1)	
CETP	-629C/A	AA	205 (25.6)	171 (26.4)	.31
		AC	400 (49.9)	298 (46.1)	
		CC	197 (24.6)	178 (27.5)	
COMT	Val158Met‡	AA	231 (29.8)	181 (28.1)	.39
		AG	358 (46.1)	321 (49.8)	
		GG	187 (24.1)	143 (22.2)	
CX3CR1	Ile249Val	CC	410 (51.1)	353 (53.6)	.43
		CT	336 (41.9)	254 (38.6)	
		TT	56 (7.0)	51 (7.8)	
CX3CR1	Thr280Met	AA	18 (2.2)	13 (2.0)	.65
		AG	223 (27.7)	195 (29.8)	
		GG	565 (70.1)	447 (68.2)	
CYP11B2	-344T/C‡	CC	163 (20.6)	109 (16.6)	.12
		CT	352 (44.6)	319 (48.6)	
		TT	275 (34.8)	229 (34.9)	
CYP2C9	Leu359Ile	AA	708 (92.7)	568 (90.6)	.17
		AC	56 (7.3)	59 (9.4)	
		CC	0	0	
CYP2C9	Cys144Arg*‡	CC	589 (80.0)	491 (79.8)	.95
		CT	147 (20.0)	124 (20.2)	
		TT	0	0	
ENPP1	Gln121Lys	AA	600 (74.3)	498 (75.7)	.84
		AC	192 (23.8)	149 (22.6)	
		CC	15 (1.9)	11 (1.7)	
ESR1	-401T/C	CC	145 (18.0)	143 (21.8)	.20
		CT	421 (52.3)	326 (49.7)	
		TT	239 (29.7)	187 (28.5)	
F12	46C/T	CC	459 (58.0)	371 (56.6)	.84
		CT	283 (35.8)	241 (36.7)	
		TT	49 (6.2)	44 (6.7)	
F13A1	Val34Leu	GG	443 (56.8)	354 (55.8)	.93
		GT	296 (37.9)	247 (39.0)	
		TT	41 (5.3)	33 (5.2)	
F2	G20210A	AA	1 (0.1)	1 (0.2)	.94
		AG	23 (2.9)	20 (3.0)	
		GG	783 (97.0)	635 (96.8)	

Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
F5	Arg506Gln	AA	1 (0.1)	1 (0.2)	.95
		AG	36 (4.5)	31 (4.7)	
		GG	769 (95.4)	623 (95.1)	
F7	Arg353Gln†	AA	16 (2.0)	6 (0.9)	.22
		AG	148 (18.7)	129 (19.6)	
		GG	629 (79.3)	522 (79.5)	
FGB	-455A/G	AA	24 (3.0)	26 (4.0)	.08
		AG	247 (30.7)	229 (35.3)	
		GG	533 (66.3)	394 (60.7)	
GJA4	C1019T	CC	401 (50.6)	311 (47.5)	.47
		CT	313 (39.5)	272 (41.5)	
		TT	78 (9.8)	72 (11.0)	
GP1BA	-5T/C	CC	13 (1.7)	8 (1.2)	.75
		CT	168 (21.6)	138 (21.1)	
		TT	597 (76.7)	509 (77.7)	
GRL	Asn363Ser	AA	756 (94.1)	608 (92.7)	.29
		AG	47 (5.9)	48 (7.3)	
		GG	0	0	
HFE	Cys282Tyr	AA	3 (0.4)	1 (0.2)	.70
		AG	96 (12.0)	83 (12.6)	
		GG	703 (87.7)	574 (87.2)	
HTR2A	Ser102Ser*	CC	286 (36.5)	275 (42.0)	.11
		CT	363 (46.4)	278 (42.4)	
		TT	134 (17.1)	102 (15.6)	
ICAM1	Lys469Glu	AA	270 (34.0)	195 (30.2)	.30
		AG	379 (47.7)	329 (51.0)	
		GG	145 (18.3)	121 (18.8)	
IL1B	-511C/T	CC	359 (47.7)	289 (44.5)	.40
		CT	311 (41.4)	292 (44.9)	
		TT	82 (10.9)	69 (10.6)	
IL6	-174G/C	CC	142 (17.6)	106 (16.1)	.73
		CG	386 (48.0)	319 (48.5)	
		GG	277 (34.4)	233 (35.4)	
IRS1	Arg971Gly	AA	3 (0.4)	3 (0.5)	.98
		AG	84 (10.6)	69 (10.9)	
		GG	704 (89.0)	562 (88.6)	
ITGA2	Phe807Phe	AA	123 (15.3)	108 (16.4)	.40
		AG	394 (48.9)	298 (45.4)	
		GG	288 (35.8)	251 (38.2)	
ITGB3	Leu33Pro	CC	20 (2.5)	14 (2.2)	.12
		CT	188 (23.6)	182 (28.3)	
		TT	588 (73.9)	446 (69.5)	
LIPC	-514T/C	CC	506 (62.9)	369 (56.8)	.03
		CT	256 (31.8)	250 (38.5)	
		TT	42 (5.2)	31 (4.8)	
LPL	Asp9Asn	AG	29 (3.7)	17 (2.6)	.29
		GG	765 (96.3)	641 (97.4)	
		GG	0	0	
LRP1	Thr3261Thr	AA	367 (46.9)	283 (43.2)	.31
		AG	330 (42.2)	302 (46.1)	
		GG	85 (10.9)	70 (10.7)	

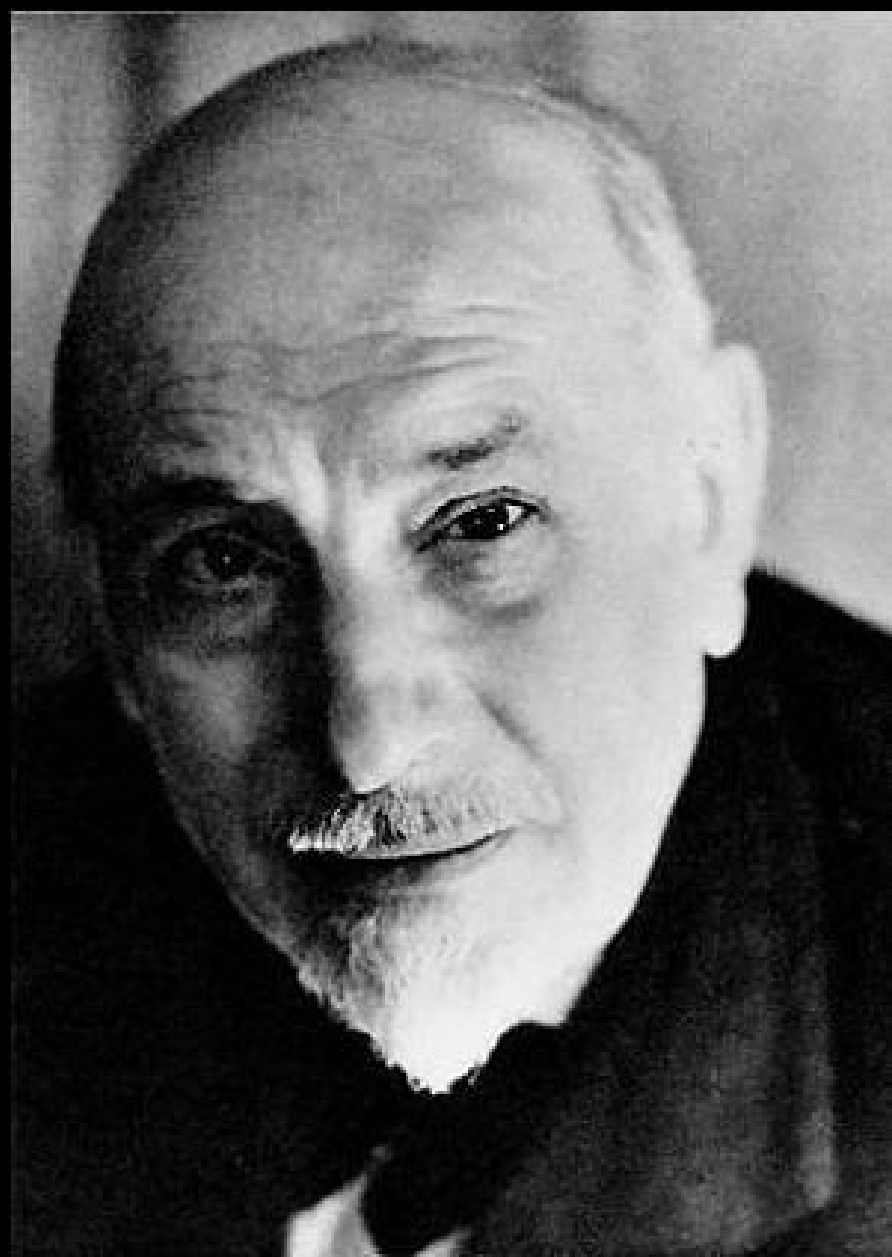
Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
LTA	A252G	AA	394 (49.1)	282 (42.9)	.06
		AG	327 (40.8)	299 (45.5)	
		GG	81 (10.1)	76 (11.6)	
LTA	Thr26Asn	AA	80 (10.0)	78 (11.6)	.07
		AC	331 (41.4)	297 (45.3)	
		CC	389 (48.6)	280 (42.7)	
MGP	Thr83Ala	AA	308 (38.3)	257 (39.1)	.79
		AG	374 (46.5)	294 (44.7)	
		GG	123 (15.3)	106 (16.1)	
MGP	-7A/G	AA	110 (13.6)	95 (14.5)	.77
		AG	368 (45.7)	288 (43.8)	
		GG	328 (40.7)	274 (41.7)	
MMP3	Indel	DD	194 (24.7)	176 (28.4)	.27
		DI	386 (49.1)	294 (47.5)	
		II	206 (26.2)	149 (24.1)	
MTHFR	Ala222Val*	CC	350 (44.1)	272 (41.3)	.06
		CT	341 (43.0)	320 (48.6)	
		TT	102 (12.9)	66 (10.0)	
MTP	-493G/T	GG	449 (55.8)	371 (56.5)	.95
		GT	297 (36.9)	237 (36.1)	
		TT	59 (7.3)	49 (7.5)	
MTR	Asp919Gly	AA	529 (66.0)	423 (65.7)	.88
		AG	239 (29.8)	190 (29.5)	
		GG	34 (4.2)	31 (4.8)	
NPPA	Ter29ArgArg	CC	22 (2.8)	15 (2.3)	.83
		CT	190 (23.9)	159 (24.7)	
		TT	583 (73.3)	471 (73.0)	
OLR1	Lys167Asn	CC	649 (80.8)	543 (83.7)	.26
		CG	146 (18.2)	103 (15.9)	
		GG	8 (1.0)	3 (0.5)	
P22-PHOX	His72Tyr§	CC	347 (47.0)	288 (44.0)	.002
		CT	271 (36.7)	293 (44.7)	
		TT	121 (16.4)	74 (11.3)	
PAI1	Indel	DD	249 (30.9)	203 (30.9)	.77
		DI	398 (49.4)	314 (47.9)	
		II	159 (19.7)	139 (21.2)	
PECAM1	Leu125Val	CC	187 (23.3)	155 (23.6)	.82
		CG	395 (49.1)	312 (47.6)	
		GG	222 (27.6)	189 (28.8)	
PECAM1	Ser563Asn	AA	200 (25.0)	163 (25.5)	.92
		AG	386 (48.3)	312 (48.8)	
		GG	214 (26.8)	165 (25.8)	
PON1	Gln192Arg	AA	396 (49.6)	324 (49.3)	>.99
		AG	337 (42.2)	279 (42.5)	
		GG	66 (8.3)	54 (8.2)	
PON2	Cys311Ser	CC	464 (57.9)	366 (55.6)	.50
		CG	298 (37.2)	251 (38.1)	
		GG	40 (5.0)	41 (6.2)	
PPARG	Ala12Pro	CC	637 (79.2)	492 (75.9)	.22
		CG	159 (19.8)	145 (22.4)	
		GG	8 (1.0)	11 (1.7)	

Gene	Variant	Genotype	No. (%)		2-Tailed <i>P</i> Value
			Cases	Controls	
<i>PTGS2</i>	-765G/C	CC	15 (1.9)	21 (3.3)	.17
		CG	202 (25.5)	174 (27.1)	
		GG	576 (72.6)	447 (69.6)	
<i>RECQL2</i>	Arg1367Cys	CC	66 (8.2)	38 (5.8)	.03
		CT	326 (40.5)	239 (36.7)	
		TT	412 (51.2)	375 (57.5)	
<i>SELE</i>	Leu554Phe	CC	740 (91.9)	611 (92.9)	.47
		CT	63 (7.8)	47 (7.1)	
		TT	2 (0.2)	0	
<i>SELE</i>	Ser128Arg	AA	658 (82.0)	528 (80.4)	.71
		AC	137 (17.1)	123 (18.7)	
		CC	7 (0.9)	6 (0.9)	
<i>SELP</i>	Thr715Pro	AA	646 (80.2)	530 (80.8)	.22
		AC	150 (18.6)	124 (18.9)	
		CC	9 (1.1)	2 (0.3)	
<i>TFPI</i>	Val264Met	AA	758 (95.9)	625 (95.0)	.45
		AG	32 (4.1)	33 (5.0)	
		GG	0	0	
<i>THBD</i>	-33G/A	AA	801 (99.6)	638 (99.8)	.63
		AG	3 (0.4)	1 (0.2)	
		GG	0	0	
<i>THBD</i>	Ala25Thr	AA	794 (98.6)	652 (98.9)	.64
		AG	11 (1.4)	7 (1.1)	
		GG	0	0	
<i>THBD</i>	Ala455Val	CC	531 (67.0)	433 (65.9)	.91
		CT	237 (29.9)	203 (3.9)	
		TT	24 (3.0)	21 (3.2)	

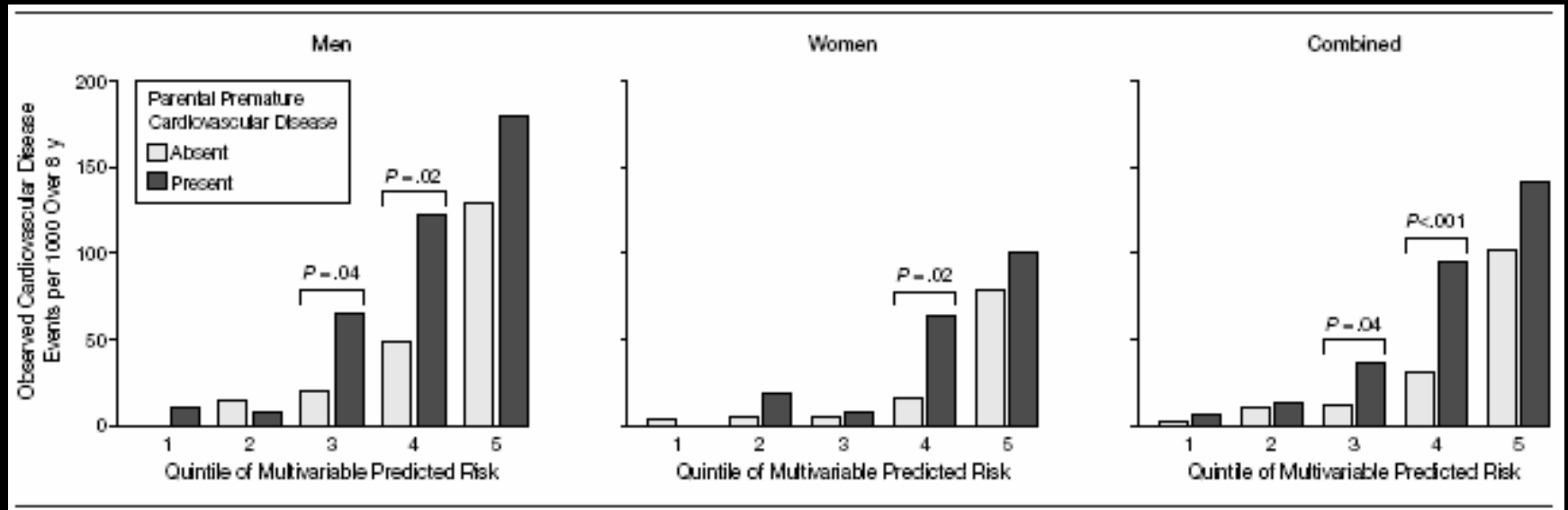
Gene	Variant	Genotype	No. (%)		2-Tailed <i>P</i> Value
			Cases	Controls	
<i>THBS1</i>	Asn700Ser	AA	614 (76.3)	507 (77.2)	.74
		AG	177 (22.0)	136 (20.7)	
		GG	14 (1.7)	14 (2.1)	
<i>THBS2</i>	3'UTR T/G‡	GG	74 (9.4)	33 (5.0)	.001
		GT	250 (31.6)	251 (38.4)	
		TT	466 (59.0)	370 (56.6)	
<i>THBS4</i>	Ala387Pro	CC	49 (6.1)	40 (6.1)	.85
		CG	268 (33.4)	229 (34.8)	
		GG	486 (60.5)	389 (59.1)	
<i>THPO</i>	A5713G	AA	187 (23.3)	159 (24.2)	.30
		AG	374 (46.6)	324 (49.4)	
		GG	241 (30.0)	173 (26.4)	
<i>TLR4</i>	Gly299Asp	AA	702 (88.7)	579 (88.4)	.89
		AG	88 (11.1)	76 (11.6)	
		GG	1 (0.1)	0	
<i>TNF</i>	-308G/A	AA	17 (2.1)	14 (2.2)	.27
		AG	189 (23.5)	176 (27.2)	
		GG	597 (74.3)	457 (70.6)	
<i>TNFRSF1A</i>	Arg92Gln	AA	784 (97.0)	627 (95.4)	.13
		AG	24 (3.0)	30 (4.6)	
		GG	0	0	

*Hardy-Weinberg equilibrium deviation in controls, $P < .05$ ($n = 3$).
† $P < .001$ ($n = 1$).
‡Hardy-Weinberg equilibrium deviation in cases, $P < .05$ ($n = 5$).
§ $P < .001$ ($n = 2$).

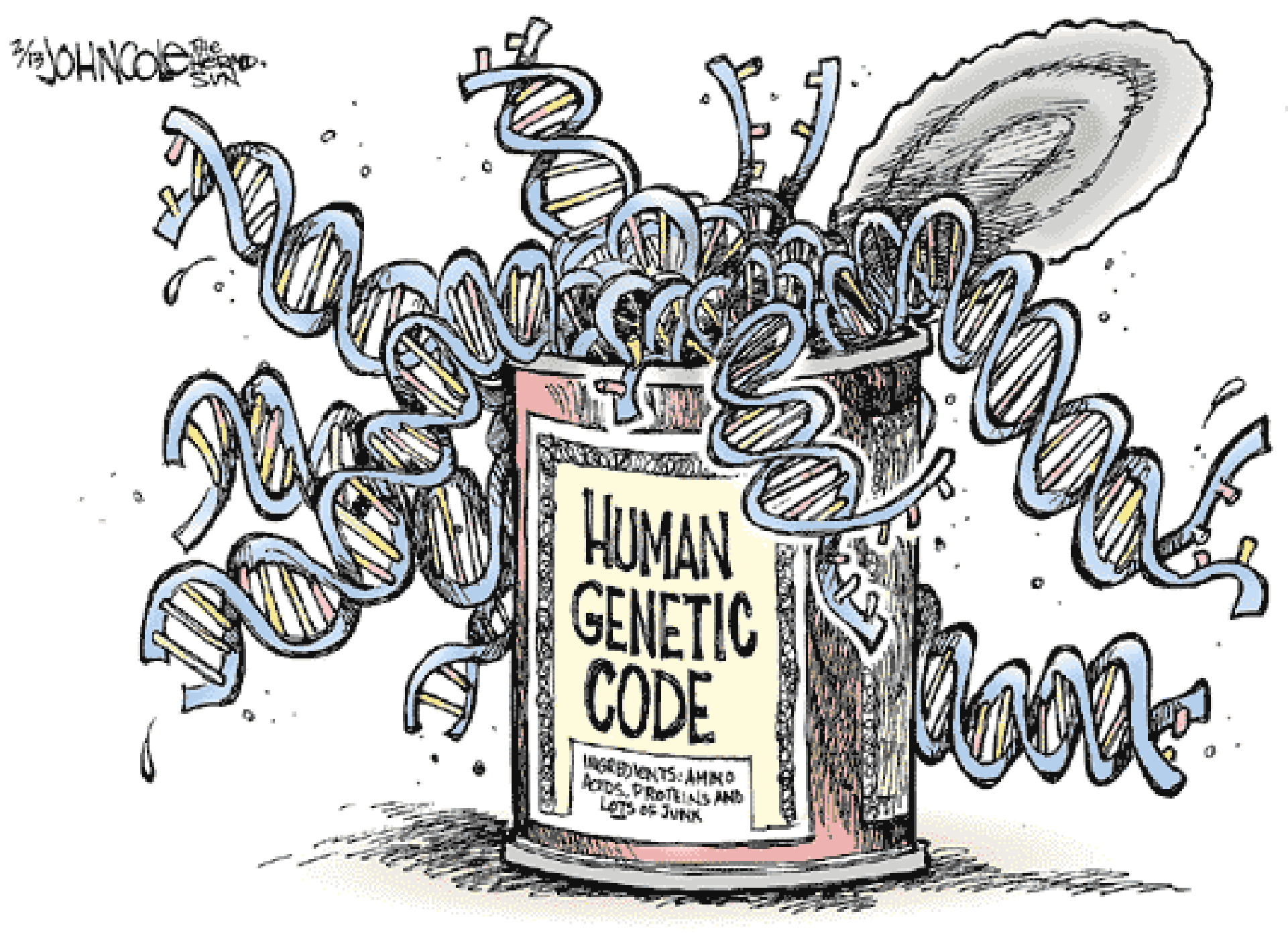
Risultati: Solo Trombospondina 2 (VEGF)
Lipasi epatica (HDL)!!!!



Familiarità



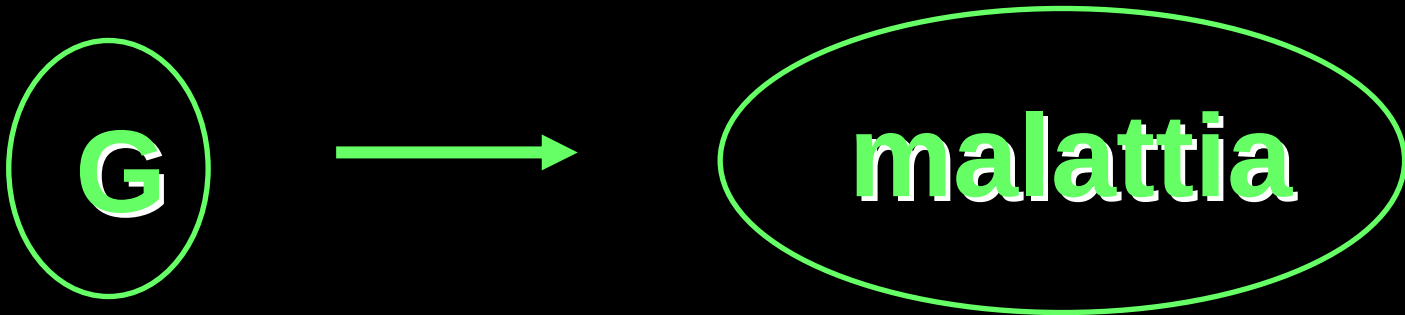
Offspring Cardiovascular Disease Event Rates by Predicted Risk and Presence of Premature Parental CVD



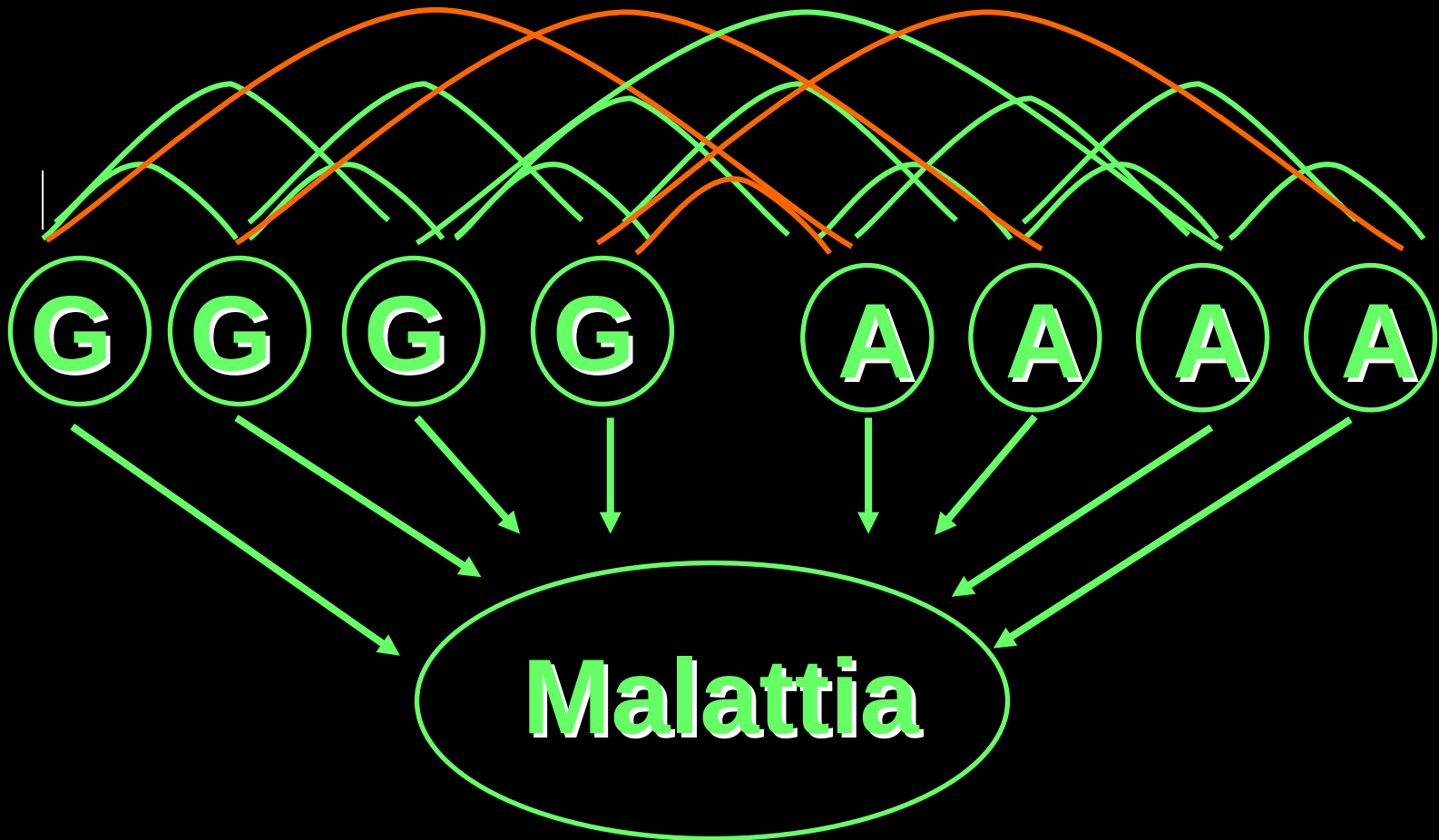


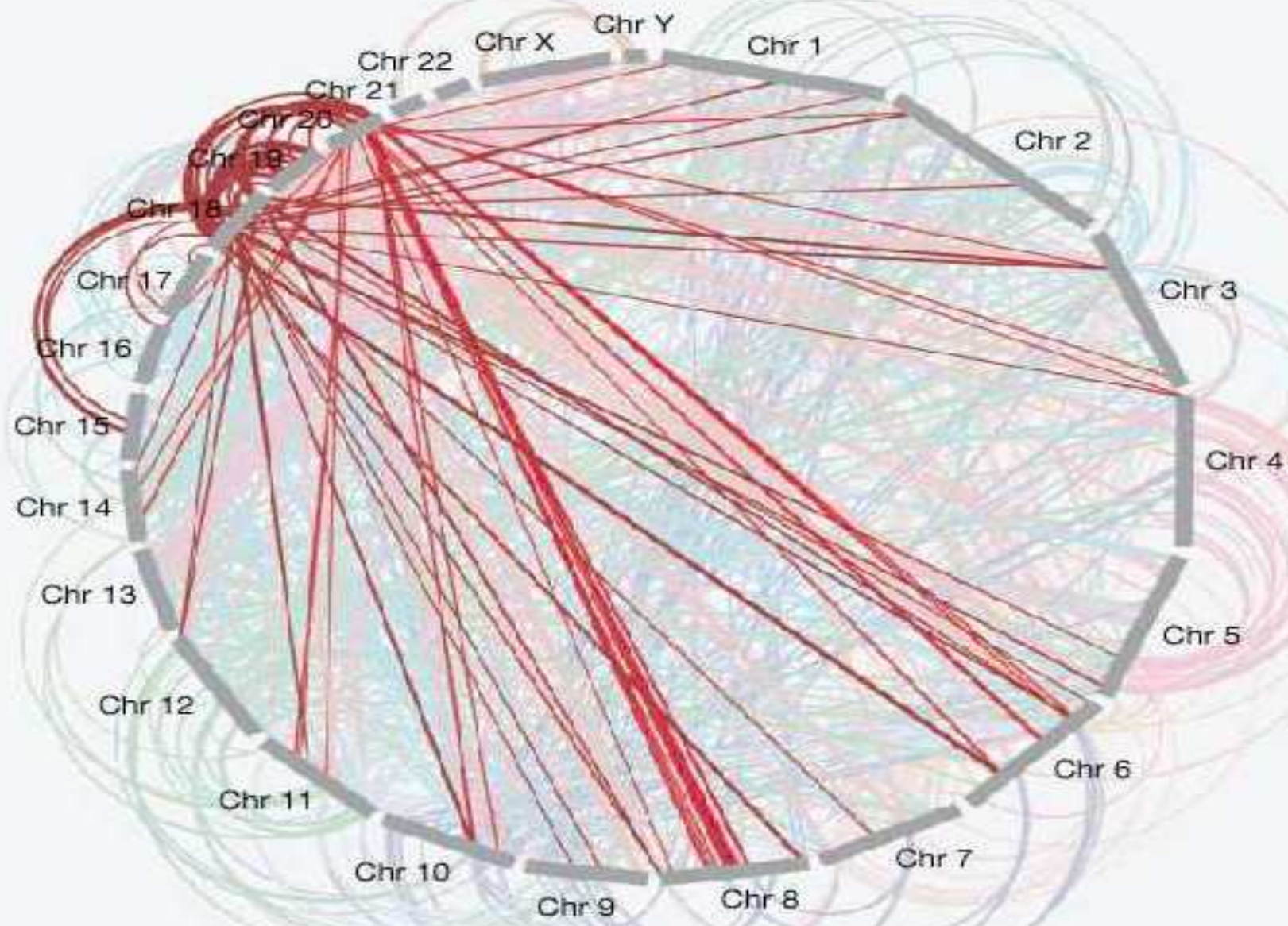
Mente genetica in un'era genomica

Malattia monogenica



Malattia complessa







Epistasi

CNVs

Elaborazione rischio



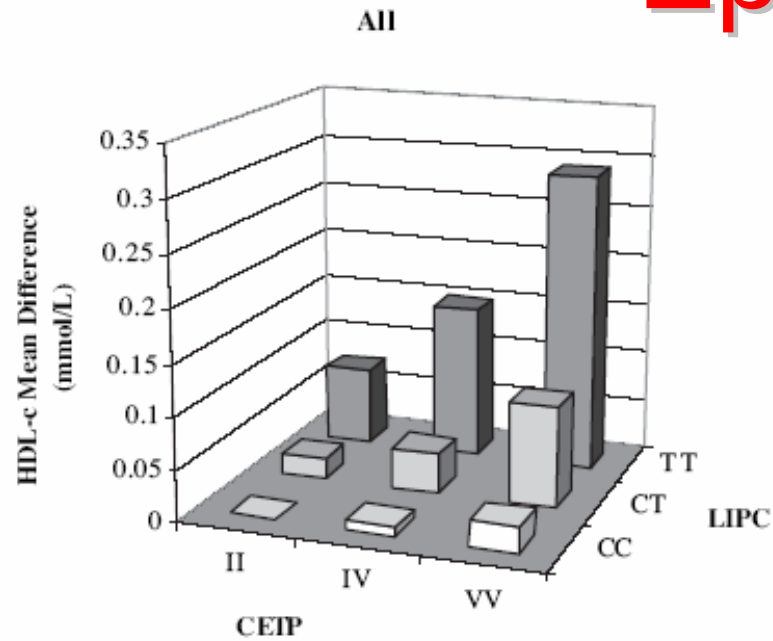
Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
ABCA1	-477C/T	CC	191 (24.6)	182 (28.3)	.27
		CT	396 (51.0)	319 (49.5)	
		TT	189 (24.4)	143 (22.2)	
ABCA1	Lys219Arg	AA	65 (8.2)	46 (7.1)	.69
		AG	311 (39.3)	263 (40.6)	
		GG	416 (52.5)	338 (52.2)	
ACE1	VD	DD	233 (30.0)	185 (28.6)	.84
		DI	389 (50.1)	329 (50.9)	
		II	154 (19.8)	132 (20.4)	
ADD1	Gly460Trp	GG	456 (60.7)	419 (64.9)	.08
		GT	269 (35.8)	197 (30.5)	
		TT	26 (3.5)	30 (4.6)	
ADRB2	Glu27Gln†	CC	266 (34.5)	217 (34.8)	.14
		CG	358 (46.5)	264 (42.3)	
		GG	146 (19.0)	143 (22.9)	
ADRB2	Ile164Thr	CC	789 (97.8)	652 (98.9)	.11
		CT	18 (2.2)	7 (1.1)	
		TT	0	0	
ADRB2	Gly16Arg	AA	128 (16.3)	100 (15.2)	.87
		AG	348 (44.3)	294 (44.8)	
		GG	309 (39.4)	262 (39.9)	
ADRB3	Arg64Trp	CC	6 (0.7)	1 (0.2)	.21
		CT	111 (13.8)	99 (15.1)	
		TT	687 (85.4)	557 (84.8)	
AGT	Thr235Met	CC	143 (17.8)	107 (16.5)	.27
		CT	387 (48.3)	340 (52.6)	
		TT	272 (33.9)	200 (30.9)	
AGTR1	A1166C	AA	388 (48.1)	332 (50.8)	.61
		AC	339 (42.1)	262 (40.1)	
		CC	79 (9.8)	60 (9.2)	
ALOX5AP	HAP B	B	50 (6.5)	41 (5.8)	.31
		non-B	734 (93.5)	661 (94.2)	
		NA	NA	NA	
ALOX5AP	HAP A	A	124 (15.9)	122 (17.4)	.35
		non-A	654 (84.1)	584 (82.6)	
		NA	NA	NA	
APOA1	C83T	AA	23 (3.0)	25 (3.8)	.59
		AG	219 (28.3)	175 (26.9)	
		GG	532 (68.7)	450 (69.2)	
APOA1	-75G/A	AA	1 (0.1)	0	.51
		AG	10 (1.3)	5 (0.8)	
		GG	784 (98.6)	638 (99.2)	
APOE	Arg158Cys	CC	29 (3.6)	15 (2.3)	.14
		CT	209 (26.1)	154 (23.5)	
		TT	562 (70.3)	487 (74.2)	
APOE	-219T/G	GG	194 (24.2)	177 (27.3)	.21
		GT	403 (50.2)	327 (50.5)	
		TT	206 (25.7)	144 (22.2)	
BDKRB2	-58C/T	CC	263 (32.8)	221 (33.6)	.43
		CT	394 (49.1)	335 (50.9)	
		TT	145 (18.1)	102 (15.5)	

Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
CCL11	Thr23Ala‡	CC	539 (68.2)	456 (70.0)	.20
		CT	239 (30.3)	178 (27.3)	
		TT	12 (1.5)	17 (2.6)	
CCR2	Val64Ile	AA	7 (0.9)	6 (0.9)	.91
		AG	116 (14.4)	89 (13.6)	
		GG	681 (84.7)	561 (85.5)	
CCR5	Indel	II	631 (78.4)	540 (82.4)	.15
		ID	162 (20.1)	108 (16.5)	
		DD	12 (1.5)	7 (1.1)	
CD14	-159C/T	CC	204 (25.4)	193 (29.5)	.22
		CT	395 (49.2)	306 (46.8)	
		TT	204 (25.4)	155 (23.7)	
CETP	Intron1 G/A	AA	168 (20.9)	135 (20.6)	.44
		AG	387 (48.1)	297 (45.3)	
		GG	250 (31.1)	224 (34.1)	
CETP	-629C/A	AA	205 (25.6)	171 (26.4)	.31
		AC	400 (49.9)	298 (46.1)	
		CC	197 (24.6)	178 (27.5)	
COMT	Val158Met‡	AA	231 (29.8)	181 (28.1)	.39
		AG	358 (46.1)	321 (49.8)	
		GG	187 (24.1)	143 (22.2)	
CX3CR1	Ile249Val	CC	410 (51.1)	353 (53.6)	.43
		CT	336 (41.9)	254 (38.6)	
		TT	56 (7.0)	51 (7.8)	
CX3CR1	Thr280Met	AA	18 (2.2)	13 (2.0)	.65
		AG	223 (27.7)	195 (29.8)	
		GG	565 (70.1)	447 (68.2)	
CYP11B2	-344T/C‡	CC	163 (20.6)	109 (16.6)	.12
		CT	352 (44.6)	319 (48.6)	
		TT	275 (34.8)	229 (34.9)	
CYP2C9	Leu359Ile	AA	708 (92.7)	568 (90.6)	.17
		AC	56 (7.3)	59 (9.4)	
		CC	0	0	
CYP2C9	Cys144Arg*‡	CC	589 (80.0)	491 (79.8)	.95
		CT	147 (20.0)	124 (20.2)	
		TT	0	0	
ENPP1	Gln121Lys	AA	600 (74.3)	498 (75.7)	.84
		AC	192 (23.8)	149 (22.6)	
		CC	15 (1.9)	11 (1.7)	
ESR1	-401T/C	CC	145 (18.0)	143 (21.8)	.20
		CT	421 (52.3)	326 (49.7)	
		TT	239 (29.7)	187 (28.5)	
F12	46C/T	CC	459 (58.0)	371 (56.6)	.84
		CT	283 (35.8)	241 (36.7)	
		TT	49 (6.2)	44 (6.7)	
F13A1	Val34Leu	GG	443 (56.8)	354 (55.8)	.93
		GT	296 (37.9)	247 (39.0)	
		TT	41 (5.3)	33 (5.2)	
F2	G20210A	AA	1 (0.1)	1 (0.2)	.94
		AG	23 (2.9)	20 (3.0)	
		GG	783 (97.0)	635 (96.8)	

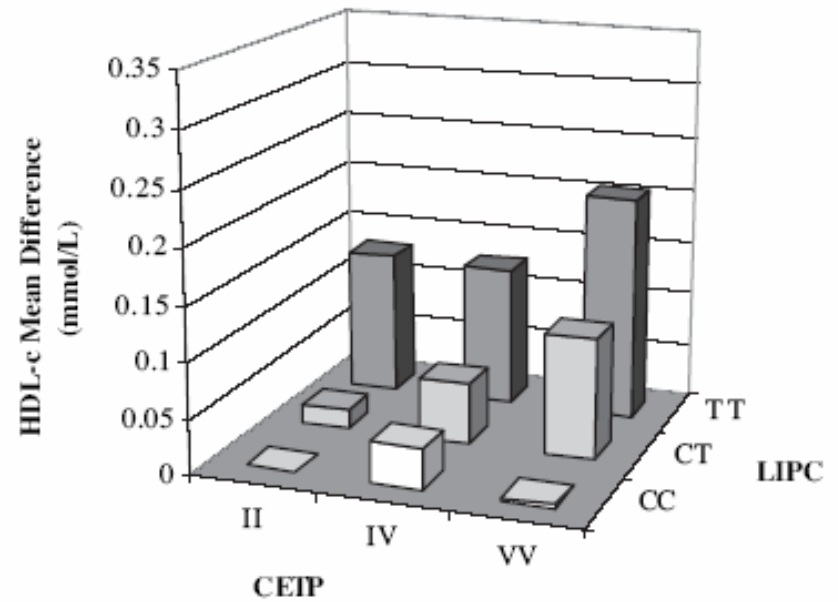
Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
F5	Arg506Gln	AA	1 (0.1)	1 (0.2)	.95
		AG	36 (4.5)	31 (4.7)	
		GG	769 (95.4)	623 (95.1)	
F7	Arg353Gln†	AA	16 (2.0)	6 (0.9)	.22
		AG	148 (18.7)	129 (19.6)	
		GG	629 (79.3)	522 (79.5)	
FGB	-455A/G	AA	24 (3.0)	26 (4.0)	.08
		AG	247 (30.7)	229 (35.3)	
		GG	533 (66.3)	394 (60.7)	
GJA4	C1019T	CC	401 (50.6)	311 (47.5)	.47
		CT	313 (39.5)	272 (41.5)	
		TT	78 (9.8)	72 (11.0)	
GP1BA	-5T/C	CC	13 (1.7)	8 (1.2)	.75
		CT	168 (21.6)	138 (21.1)	
		TT	597 (76.7)	509 (77.7)	
GRL	Asn363Ser	AA	756 (94.1)	608 (92.7)	.29
		AG	47 (5.9)	48 (7.3)	
		GG	0	0	
HFE	Cys282Tyr	AA	3 (0.4)	1 (0.2)	.70
		AG	96 (12.0)	83 (12.6)	
		GG	703 (87.7)	574 (87.2)	
HTR2A	Ser102Ser*	CC	286 (36.5)	275 (42.0)	.11
		CT	363 (46.4)	278 (42.4)	
		TT	134 (17.1)	102 (15.6)	
ICAM1	Lys469Glu	AA	270 (34.0)	195 (30.2)	.30
		AG	379 (47.7)	329 (51.0)	
		GG	145 (18.3)	121 (18.8)	
IL1B	-511C/T	CC	359 (47.7)	289 (44.5)	.40
		CT	311 (41.4)	292 (44.9)	
		TT	82 (10.9)	69 (10.6)	
IL6	-174G/C	CC	142 (17.6)	106 (16.1)	.73
		CG	386 (48.0)	319 (48.5)	
		GG	277 (34.4)	233 (35.4)	
IRS1	Arg971Gly	AA	3 (0.4)	3 (0.5)	.98
		AG	84 (10.6)	69 (10.9)	
		GG	704 (89.0)	562 (88.6)	
ITGA2	Phe807Phe	AA	123 (15.3)	108 (16.4)	.40
		AG	394 (48.9)	298 (45.4)	
		GG	288 (35.8)	251 (38.2)	
ITGB3	Leu33Pro	CC	20 (2.5)	14 (2.2)	.12
		CT	188 (23.6)	182 (28.3)	
		TT	588 (73.9)	446 (69.5)	
LIPC	-514T/C	CC	506 (62.9)	369 (56.8)	.03
		CT	256 (31.8)	250 (38.5)	
		TT	42 (5.2)	31 (4.8)	
LPL	Asp9Asn	AG	29 (3.7)	17 (2.6)	.29
		GG	765 (96.3)	641 (97.4)	
		GG	0	0	
LRP1	Thr3261Thr	AA	367 (46.9)	283 (43.2)	.31
		AG	330 (42.2)	302 (46.1)	
		GG	85 (10.9)	70 (10.7)	

Gene	Variant	Genotype	No. (%)		2-Tailed P Value
			Cases	Controls	
LTA	A252G	AA	394 (49.1)	282 (42.9)	.06
		AG	327 (40.8)	299 (45.5)	
		GG	81 (10.1)	76 (11.6)	
LTA	Thr26Asn	AA	80 (10.0)	78 (11.6)	.07
		AC	331 (41.4)	297 (45.3)	
		CC	389 (48.6)	280 (42.7)	
MGP	Thr83Ala	AA	308 (38.3)	257 (39.1)	.79
		AG	374 (46.5)	294 (44.7)	
		GG	123 (15.3)	106 (16.1)	
MGP	-7A/G	AA	110 (13.6)	95 (14.5)	.77
		AG	368 (45.7)	288 (43.8)	
		GG	328 (40.7)	274 (41.7)	
MMP3	Indel	DD	194 (24.7)	176 (28.4)	.27
		DI	386 (49.1)	294 (47.5)	
		II	206 (26.2)	149 (24.1)	
MTHFR	Ala222Val*	CC	350 (44.1)	272 (41.3)	.06
		CT	341 (43.0)	320 (48.6)	
		TT	102 (12.9)	66 (10.0)	
MTP	-493G/T	GG	449 (55.8)	371 (56.5)	.95
		GT	297 (36.9)	237 (36.1)	
		TT	59 (7.3)	49 (7.5)	
MTR	Asp919Gly	AA	529 (66.0)	423 (65.7)	.88
		AG	239 (29.8)	190 (29.5)	
		GG	34 (4.2)	31 (4.8)	
NPPA	Ter29ArgArg	CC	22 (2.8)	15 (2.3)	.83
		CT	190 (23.9)	159 (24.7)	
		TT	583 (73.3)	471 (73.0)	
OLR1	Lys167Asn	CC	649 (80.8)	543 (83.7)	.26
		CG	146 (18.2)	103 (15.9)	
		GG	8 (1.0)	3 (0.5)	
P22-PHOX	His72Tyr§	CC	347 (47.0)	288 (44.0)	.002
		CT	271 (36.7)	293 (44.7)	
		TT	121 (16.4)	74 (11.3)	
PAI1	Indel	DD	249 (30.9)	203 (30.9)	.77
		DI	398 (49.4)	314 (47.9)	
		II	159 (19.7)	139 (21.2)	
PECAM1	Leu125Val	CC	187 (23.3)	155 (23.6)	.82
		CG	395 (49.1)	312 (47.6)	
		GG	222 (27.6)	189 (28.8)	
PECAM1	Ser563Asn	AA	200 (25.0)	163 (25.5)	.92
		AG	386 (48.3)	312 (48.8)	
		GG	214 (26.8)	165 (25.8)	
PON1	Gln192Arg	AA	396 (49.6)	324 (49.3)	>.99
		AG	337 (42.2)	279 (42.5)	
		GG	66 (8.3)	54 (8.2)	
PON2	Cys311Ser	CC	464 (57.9)	366 (55.6)	.50
		CG	298 (37.2)	251 (38.1)	
		GG	40 (5.0)	41 (6.2)	
PPARG	Ala12Pro	CC	637 (79.2)	492 (75.9)	.22
		CG	159 (19.8)	145 (22.4)	
		GG	8 (1.0)	11 (1.7)	

Epistasi



Males



Females

Cholesterol ester transfer protein (I405V)

Hepatic lipase (-514>T)

POLIMORFISMI GENETICI

Polimorfismi di lunghezza



Polimorfismi di sequenza



Copy Number Variation



Absence of links between SNPs and variable drug-response phenotypes

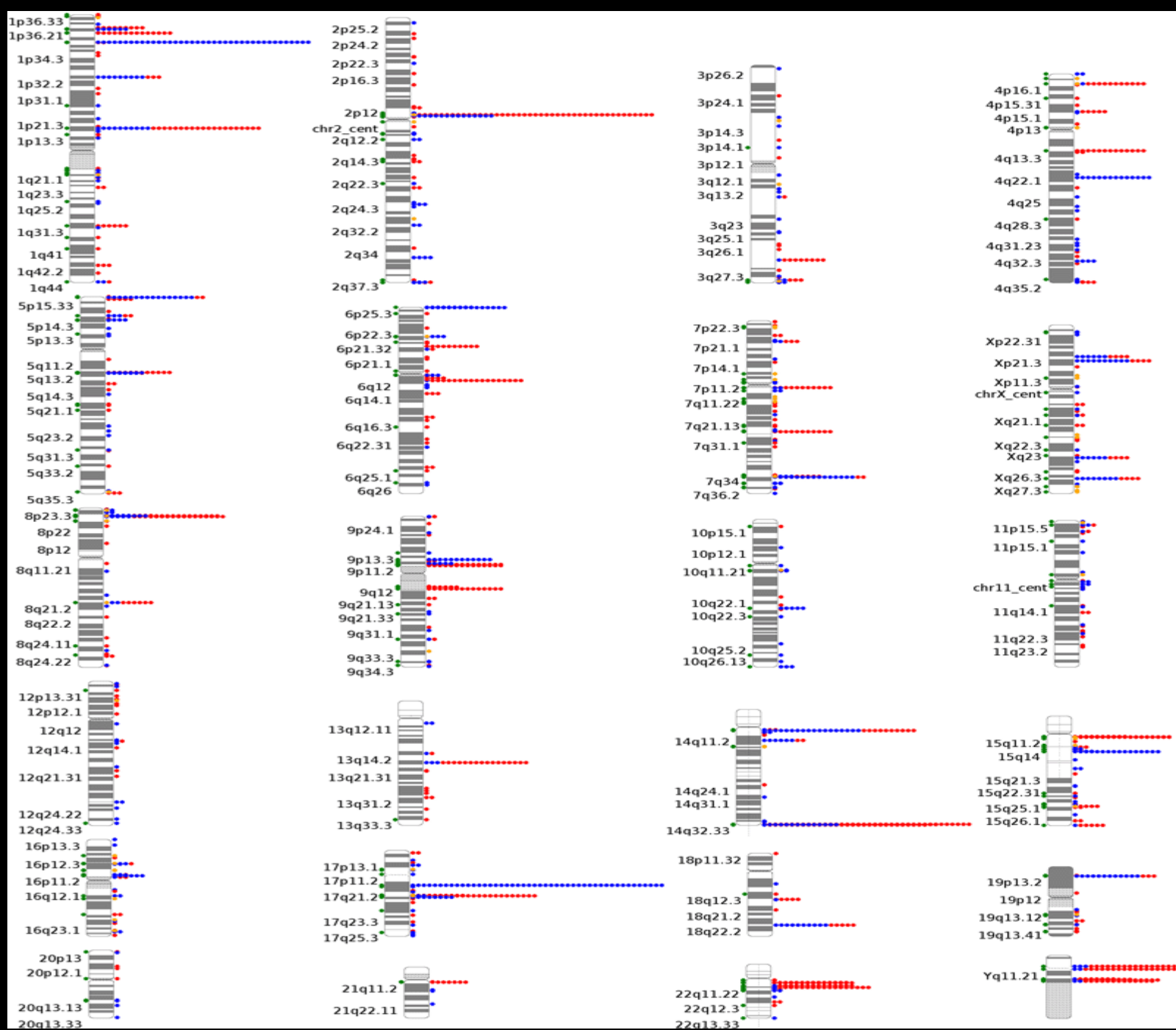
MORE SNPs?

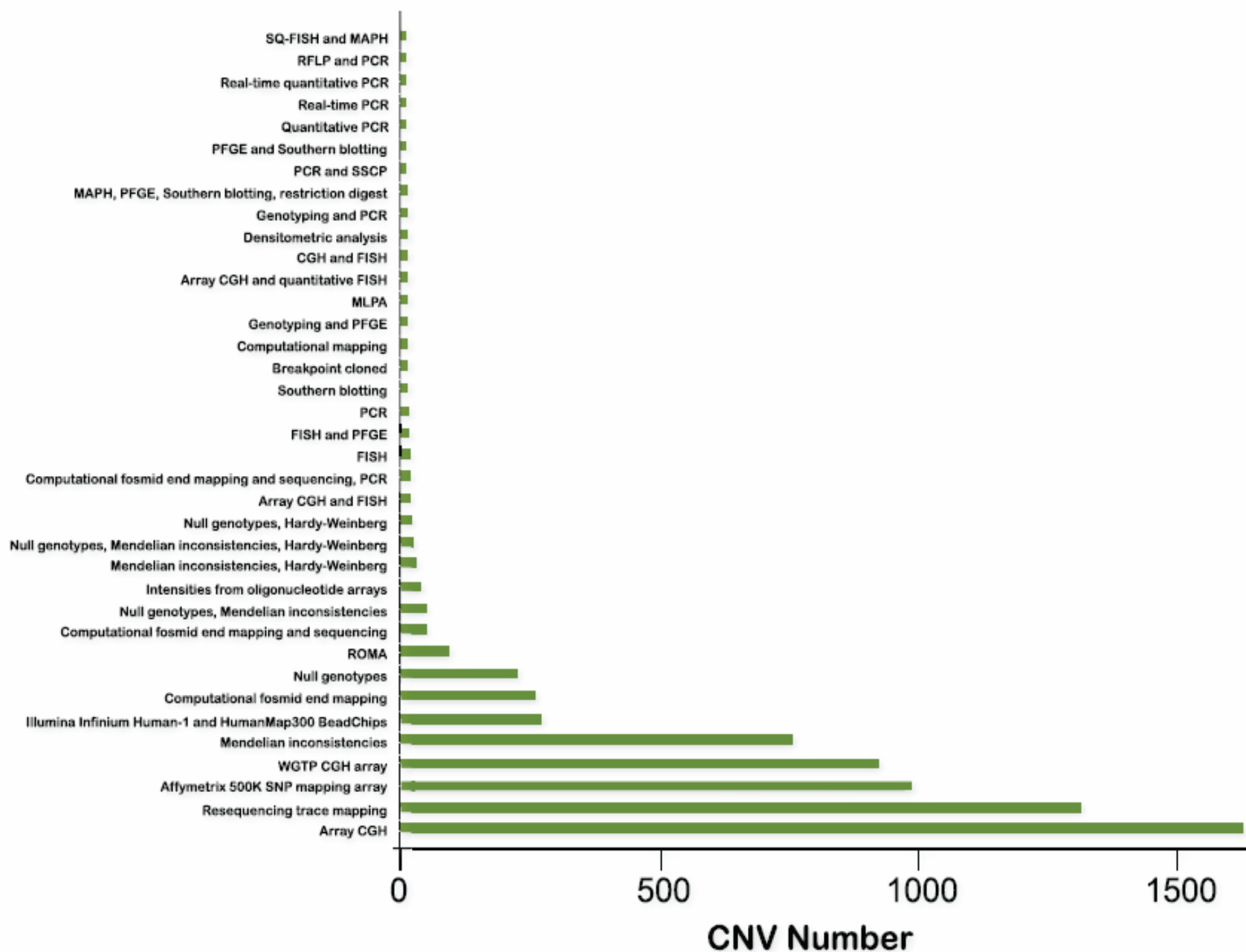
SNPs DO NOT REPRESENT ALL THE GENOME VARIATION

Copy Number Variants (CNVs)

a new source of human variation !







L'errore del determinismo genetico

Si ritiene l'informazione genetica qualcosa di definitivo, fatale, un'ineluttabile forma di informazione piuttosto che un informazione di tipo probabilistico che viene continuamente bilanciata da altri fattori.

(A. Buchanan & al, *Pharmacogenetics. Ethical and Regulatory Issues in Research and Clinical Practice. Report of the Consortium on Pharmacogenetics. Findings and Recommendations*, 2002, p. 10-11).

ALLORA?

Sebbene il rischio determini un'incertezza meno ambigua qualora sia quantificabile, la rilevanza medica di questo non può **mai** essere adeguatamente valutata senza prendere in considerazione il particolare **contesto** entro cui avviene.

I timori riguardo l'informazione genetica sono influenzati dalla percezione che tutti i dati genetici contengano informazioni vitali per il “portatore” e per i suoi discendenti (“determinismo genetico”).

Tuttavia, noi non siamo il semplice prodotto dei nostri geni: le nostre caratteristiche dipendono da una complessa interazione tra fattori genetici ed ambientali.

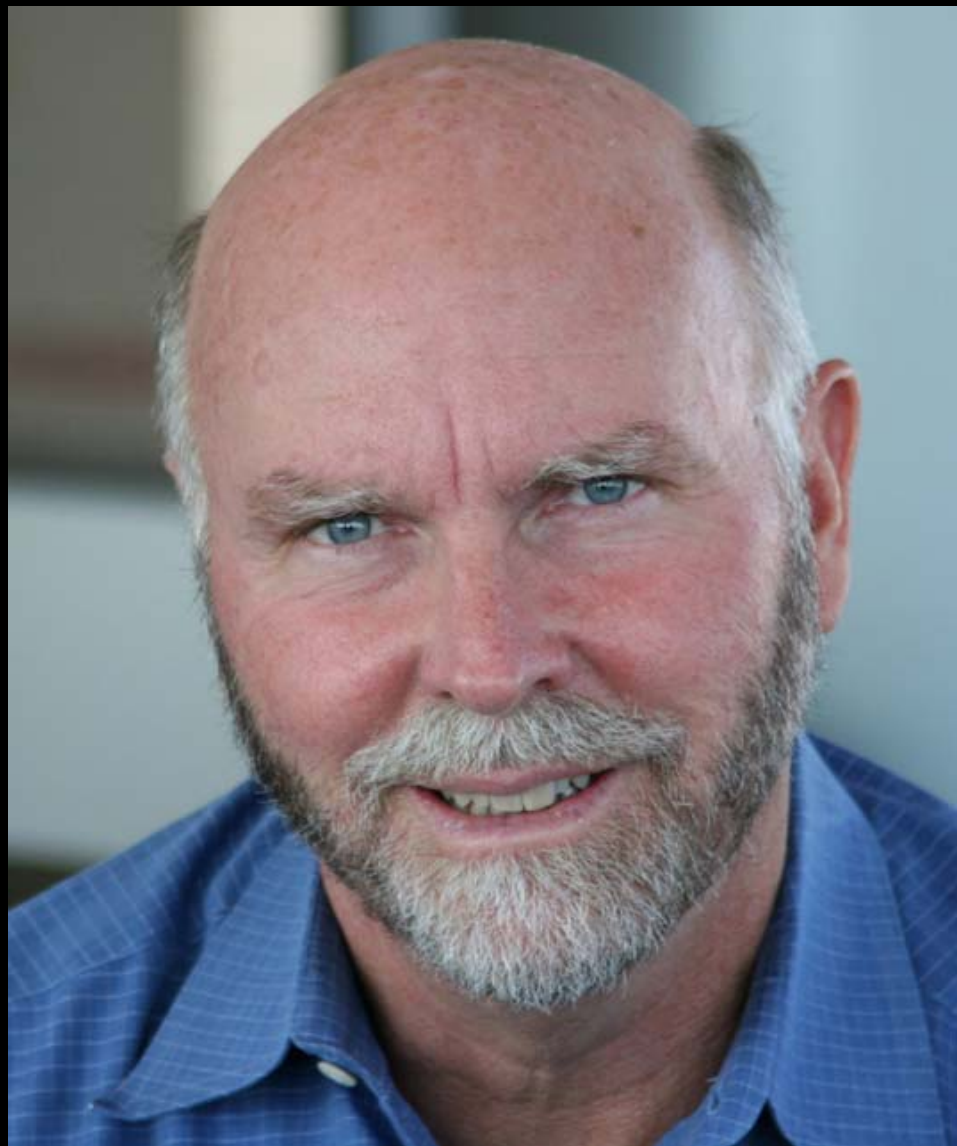
- 3,213,401 sostituzioni;
- 53,823 variazioni (2-200 bp);
- 292,102 delezioni/inserzioni;

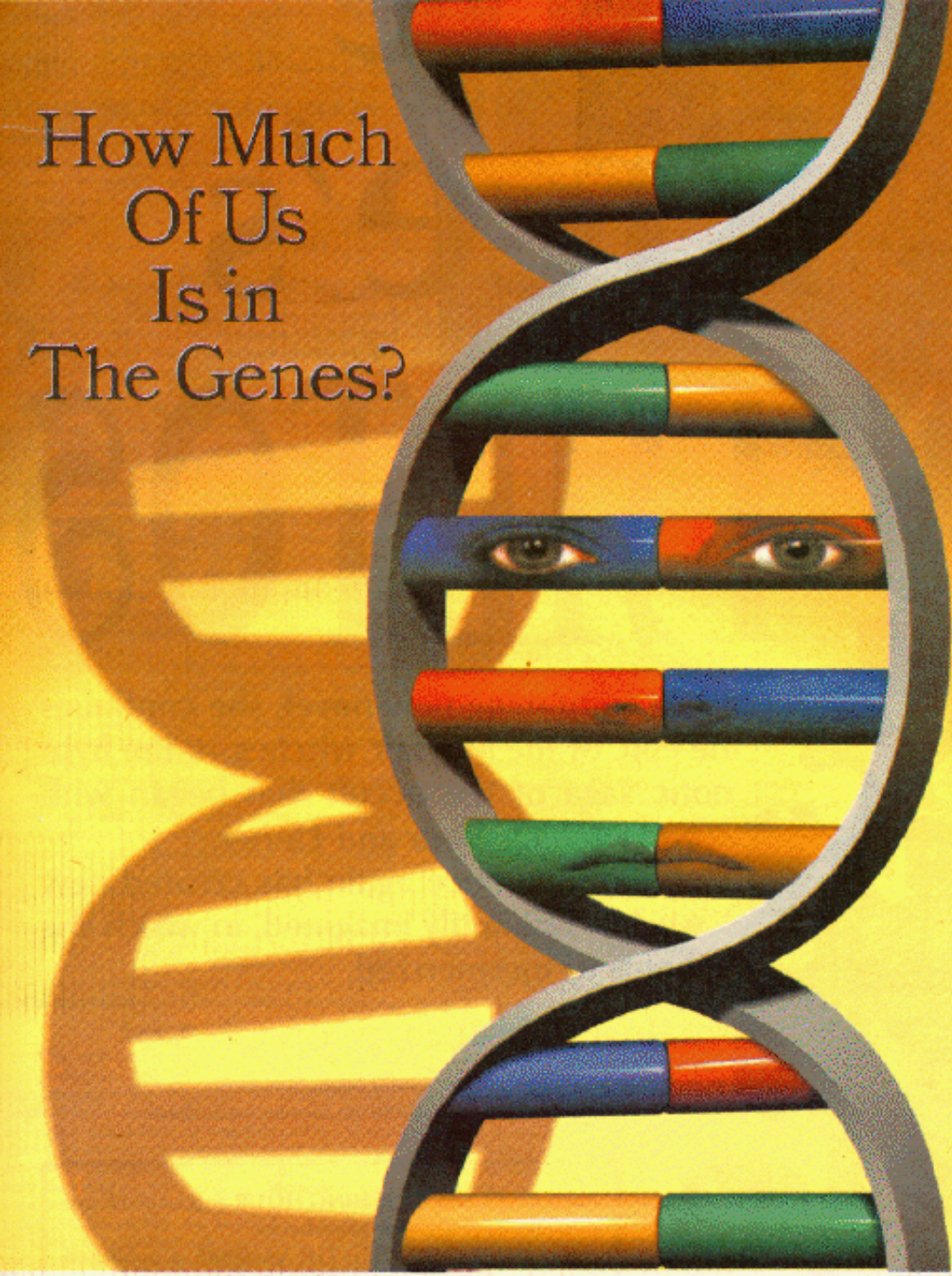
Table 13. Genotypes for Some Traits in the HuRef Donor

Gene	SNP	Genotype	Phenotype Associated Allele/Haplotypes	Associated Common Trait	Confidence of Genotype	
					Genotype in Phased Haplotype	Probability Missing Heterozygous Allele Based on Coverage
<i>Clock</i>	rs1801260(3111 C/T)	T/T	C/C	Evening preference		1.00
<i>Per2</i>	S662G	S662S	S662G	Advanced sleep phase syndrome (ASPA)		0.01
<i>LCT</i>	rs4988235(C/T ₁₉₈₁₉)	T/T	C/C	Adult-type hypolactasia		0.00
	rs182549(G/A ₂₀₉₈)	A/A	G/G	Adult-type hypolactasia		0.07
<i>OCA2</i>	rs1800401	C/C	C/C(Arg305Arg)	Link to blue eye, fair skin color	+	0.22
	rs1800407	G/G	G/G(Arg419Arg)	Link to blue eye, fair skin color	+	0.22
	rs7495174	T/T		rs7495174(T/T), rs6497268(rs4778241)G/G and rs11855019 (rs4778138) T/T are in one major haplotype block TGT/TGT link to blue eye	+	0.68
	rs6497268(rs4778241)	G/G			+	0.13
<i>ABCC11</i>	rs11855019 (rs4778138)	T/T				0.38
	rs17822931 (538G → A)	G/G	A: dry type; G/A&G/G wet type.	Human earwax type(AA,Dry; G/A&G/G are wet type)	+	0.07
<i>SLC6A3</i>	40-bp VNTR in 3'UTR	10/10 allele	9/9 allele	Substance abuse		0.38
<i>DRD4</i>	DRD4 II Exon	4-repeat (short form)	Long forms (6–11 repeat) are associated with higher Novelty Seeking scores and more prevalent in substance abusers than short form (2–5 repeat).	Novelty seeking		1.00
	3 VNTR polymorphism					
	rs180095 (DRD4-521C/T, promoter)	C/C	C/C genotype exhibited the highest novelty seeking scores	Novelty seeking		0.38
<i>DRD3</i>	rs6280 (DRD3 BstI polymorphism)	A/A (allele 1)	Allele 1 (aGC:5) showed significantly lower Novelty Seeking scores compared to patients without this allele. Allele 2(gGCG) was associated with increased rates of obsessive personality disorder symptomatology	Novelty seeking		0.07
<i>DRD2</i>	rs1800497(DRD2Tag1A polymorphism, 3' down stream)	A2 allele, G/G	A1 allele(A)is more prevalence in alcohol-dependent males than A2 allele(G).	Alcohol-dependent		0.04
<i>CHRNA4</i>	rs2273504	G/G	G	Tobacco addiction protection	+	0.68
	rs2273502	C/C	C		+	1.00
	rs1044396	T/T	T		+	1.00
	rs1044397	A/A	A			1.00
	rs3827020	T/T	T			1.00
	rs2236196	A/A	A			0.07
	rs16969968	G/G	A	Tobacco addiction		1.00
<i>CHRNA5</i>	rs684513	C/C	C			0.38
	rs637137	T/T	T		+	0.22
	rs3749078	G/G	G	Tobacco addiction		0.02
	rs1051730	G/G	A			0.13
<i>CHRNA3</i>	rs578776	A/A	G		+	0.38
	rs3813567	A/A	A	Tobacco addiction	+	1.00
	rs2304297	G/G	G	Tobacco addiction		0.22
<i>CHRNA6</i>	rs4952	C/C	C	Tobacco addiction	+	0.22
	rs6474413	C/T	T		+	
	rs10958726	G/T	T		+	

Table 13. Continued.

Gene	SNP	Genotype	Phenotype Associated Allele/Haplotypes	Associated Common Trait	Confidence of Genotype	
					Genotype in Phased Haplotype	Probability Missing Heterozygous Allele Based on Coverage
CHRD	rs3791729	A/G	A	Tobacco addiction	+	
	rs2767	A/G	G		+	
	rs2276560	T/T	T			0.04
	rs6749955	T/T	T		+	0.01
GABAR2	rs1435252	C/C	T/C	Tobacco addiction	+	0.38
	rs3780422	G/A	A/A			
	rs2779562	T/T	T/C			1.00
	rs3750344	A/A	A/A			0.63
MAOA	MAOA-uVNTR	Hemizyosity 4 copies	3.5 or 4 copies nMAOA-uVNTR transcribed 2 to 10 times more efficiently than those with 3 or 5 copies. Low MAOA activity allele were much more likely to develop antisocial behavior, conduct disorder.	Antisocial behavior, conduct disorder,		
COMT	rs13306281	G/G (Val158Val)	(A/A)158Met/158Met	Alcoholism		0.07
TNFSF4	rs1234315	C/T	T	Myocardial infarction and severity of coronary artery stenosis		
	rs3850641	A/A	G			1.00
	rs1234313	A/G	A		+	
	rs3861950	T/T	N			1.00
CYBA	rs1234312	C/C	N	Coronary artery disease and hypertension	+	0.22
	rs4673	C/T	T/T		+	
	rs1049255	A/G	A/A		+	
	rs9932581	G/A	G/G		+	
GNB3	rs6489738 (rs5443)	C/T	T	Hypertension, obesity, insulin-resistance and left ventricular hypertrophy	+	
MMP3	rs3025058	SA/SA	SA/SA	Acute myocardial infarction	+	0.04
CD36		Germine mutation not found	Missense mutation, small or gross indels	Lipoprotein lipase deficiency, hypertriglyceridaemia,		
LPL		Germine mutation not found	Missense/nonsense, splicing, regulatory and small or gross indels	Lipoprotein lipase deficiency, hypertriglyceridaemia,		
NOS3	rs1799983	G/G(glu/glu)	T(asp)	Myocardial infarction and stenosed arteries	+	0.13
	rs207044	T/T	C			0.04
	rs1800779	A/A	G		+	0.04
	rs1800783	T/T	A			0.22
	27bp repeat in Intron 4	Homozygous 5 copies, long form,	Short form (4 tandem 27-bp repeats)			0.38
	CA repeats in Intron 13	30 CA repeats	13 CA repeat			1.00
KL	rs9536314	G/T	T/T	Coronary artery disease, and stroke	+	
	rs9527025	G/C	C/C		+	
SORL1	rs661057	T/T	T	Alzheimer disease	+	0.38
	rs668387	C/C	C			0.07
	rs689021	G/G	G		+	0.13
	rs641120	C/C	C			0.13
	rs12285364	C/C	T			0.63
	rs2070045	T/T	G			0.01



A 3D illustration of a DNA double helix. The sugar-phosphate backbones are grey and spiral around each other. The rungs, representing base pairs, are made of colored cylinders: red, blue, green, and orange. In the center of the helix, two human eyes are visible, looking out from between the rungs. The background is a warm, yellowish-orange gradient with a faint, larger-scale DNA helix pattern.

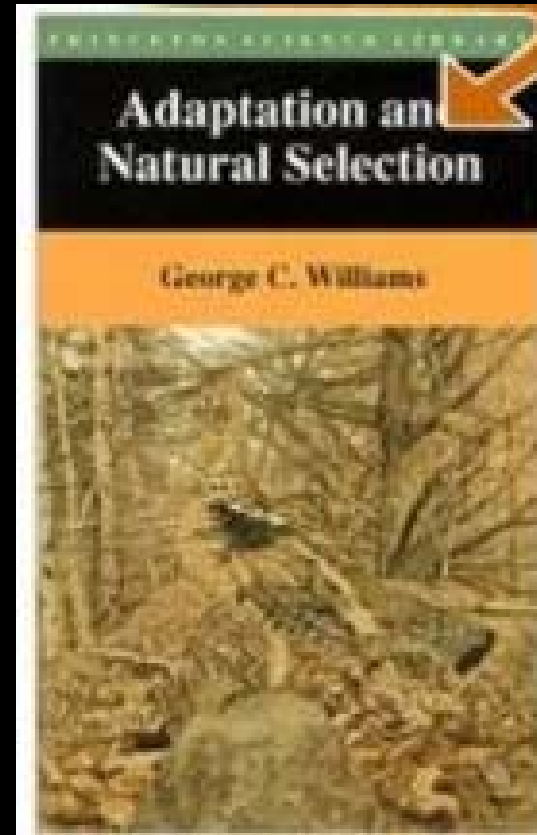
How Much
Of Us
Is in
The Genes?

*I maestri
sono inclini
ad attribuire
l'intelligenza
dei propri
figli ai geni
e quella dei
propri allievi
all'ambiente*

[Roger D. Master]



George C. Williams



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

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

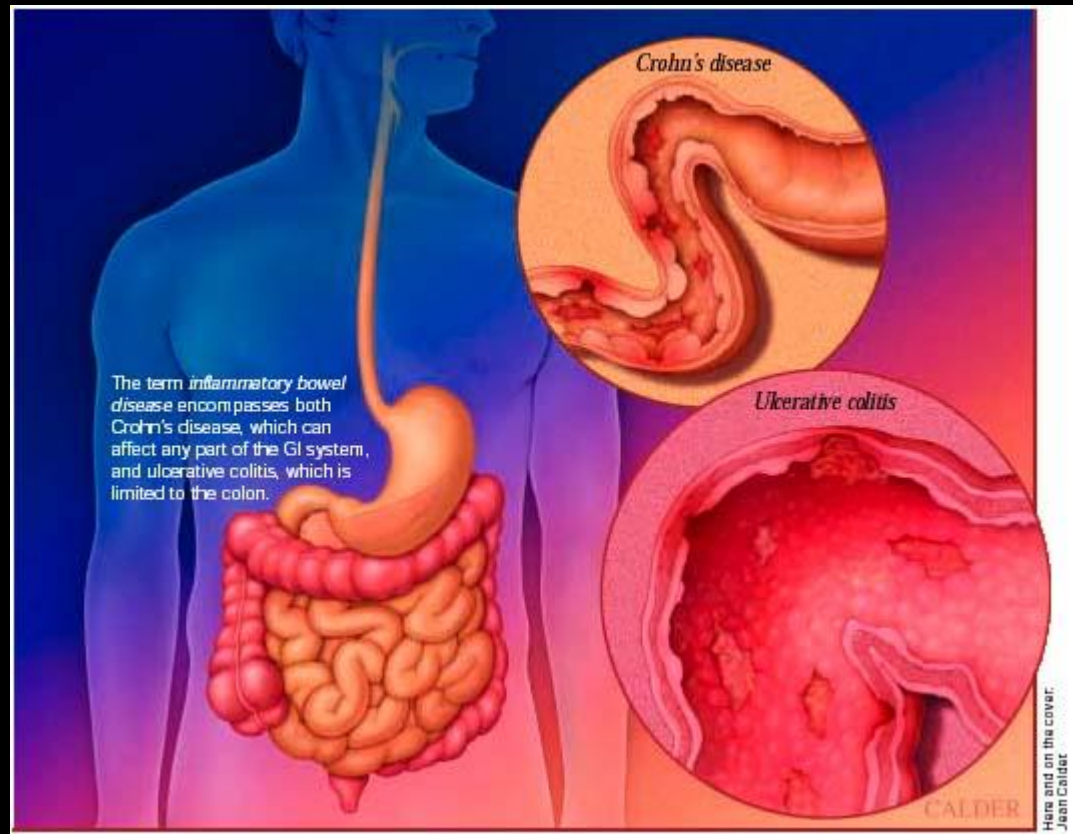
L' esempio delle IBDs

- 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.

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”

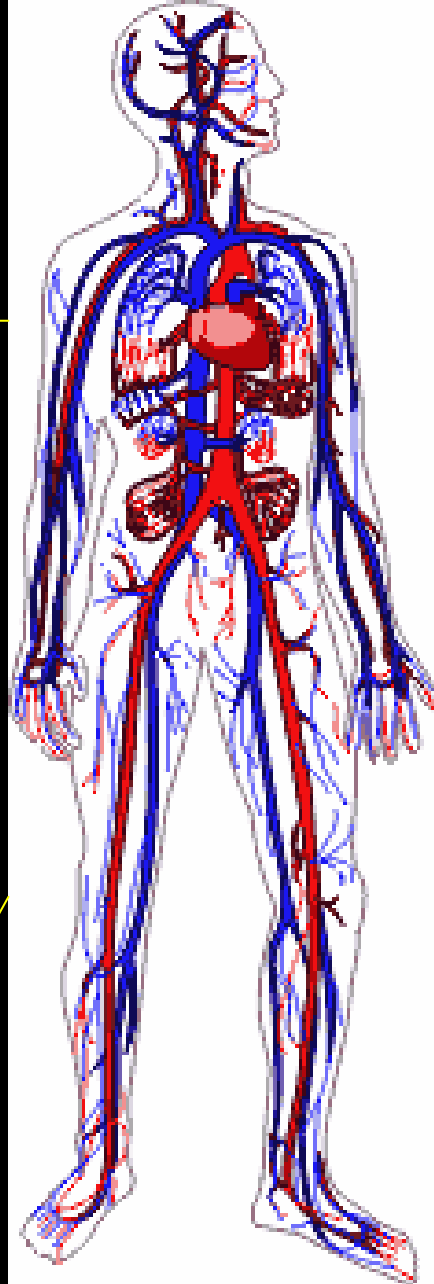
ictus

Cancro mammella

Diabete

Obesità

Patologie dell'intestino



Depressioni-manie

Infarto del miocardio

Ipertensione

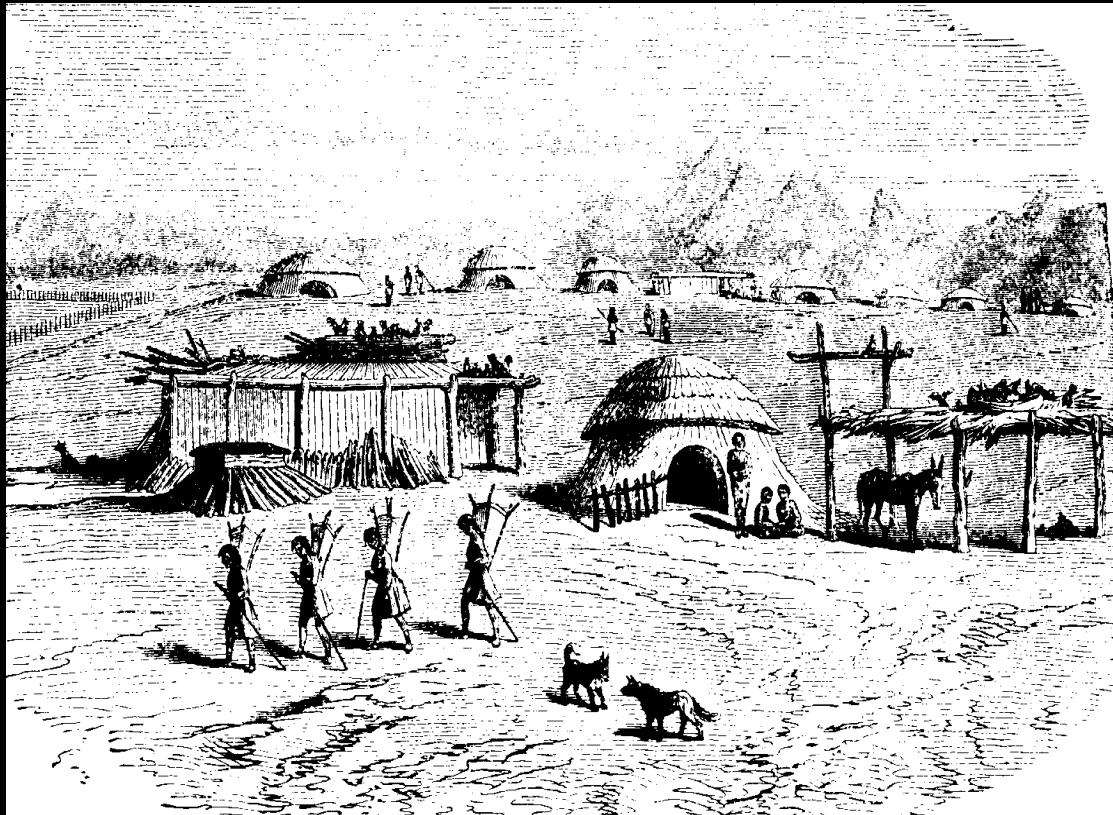
ipercolesterolemia

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



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

L'esempio dell'ipertensione

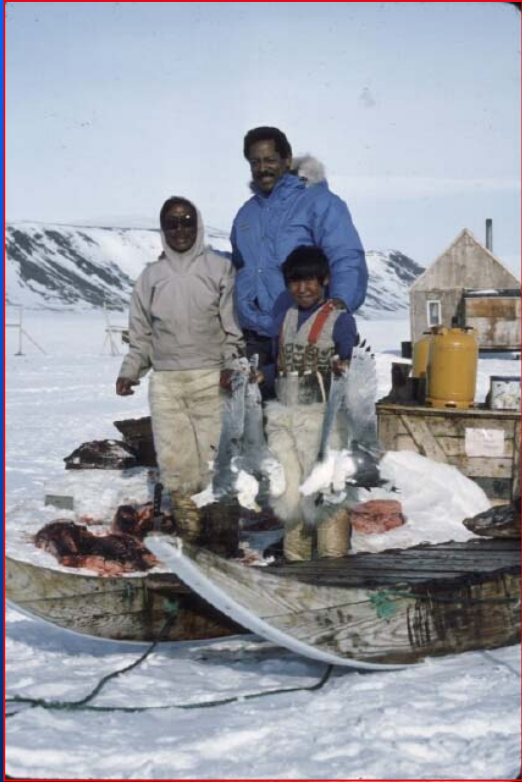


Yanomamo indians
(Brasile)

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



Genetic-dietary interactions



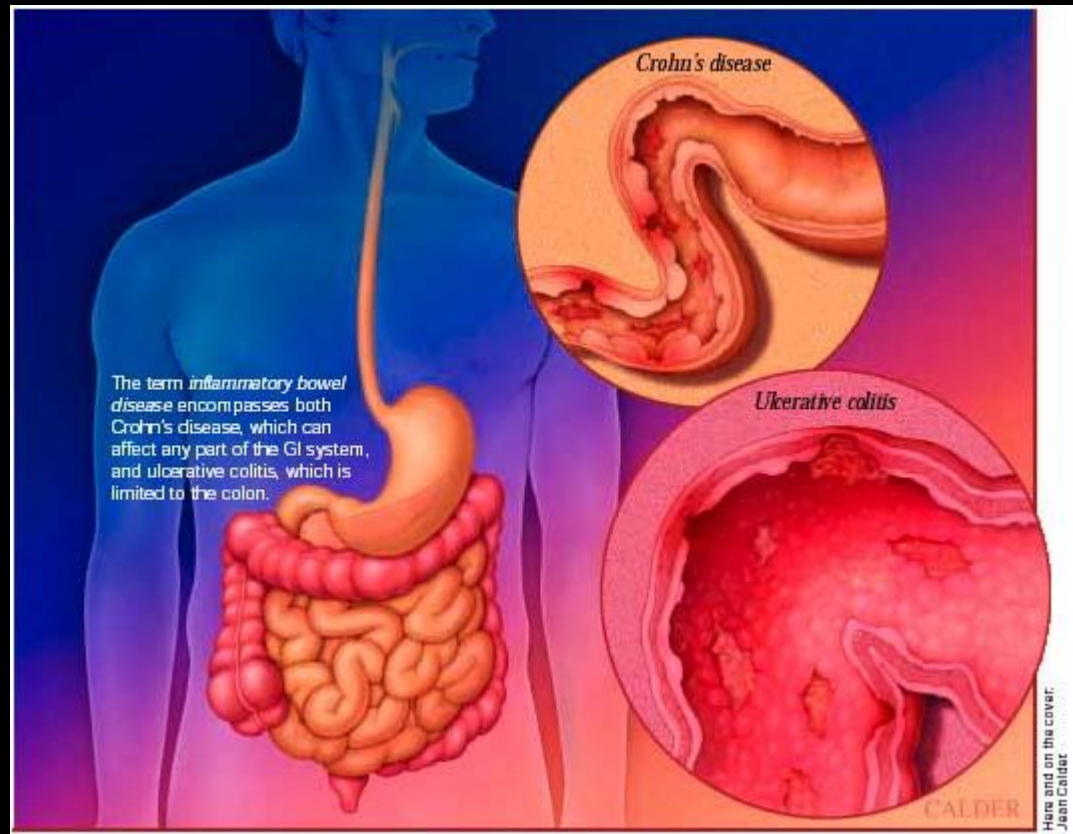
Arctic Eskimos have relatively poor repression of cholesterol synthesis in response to a high-fat, high cholesterol diet

Masai



- High fat intake
- Cholesterol levels tend to be relatively low.
- Unusually efficient negative feedback regulation of cholesterol synthesis.

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”

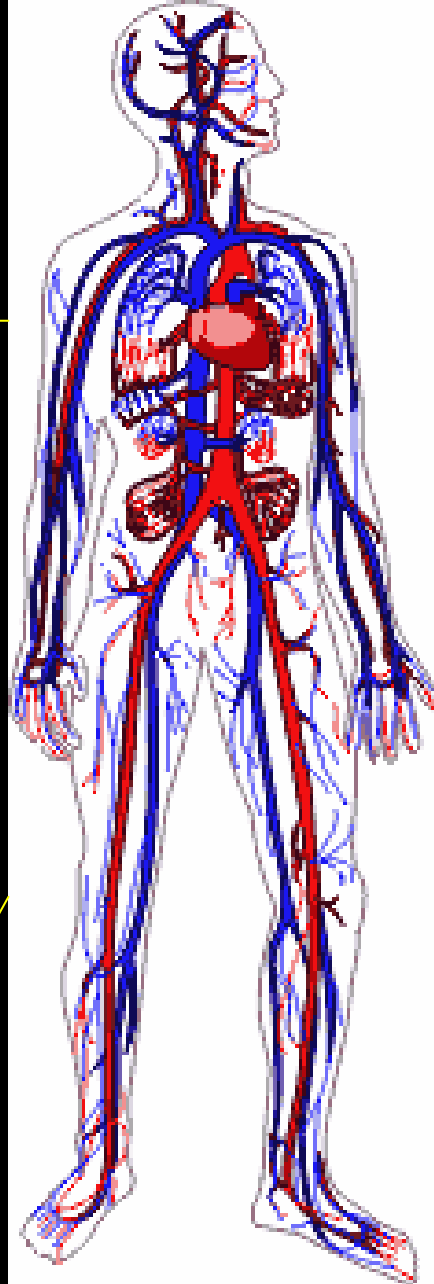
ictus

Cancro mammella

Diabete

Obesità

Patologie dell'intestino



Depressioni-manie

Infarto del miocardio

Ipertensione

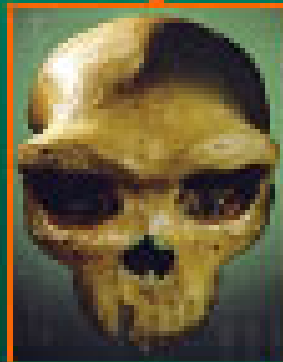
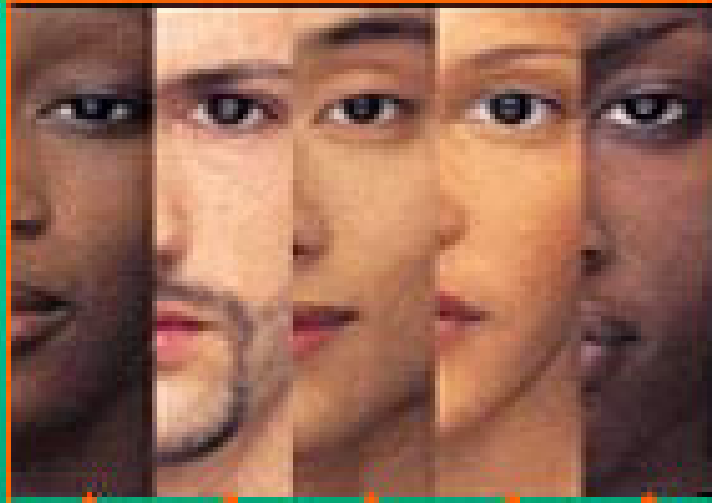
ipercolesterolemia

Schizofrenia

La coca-colonizzazione anche negli zoo...



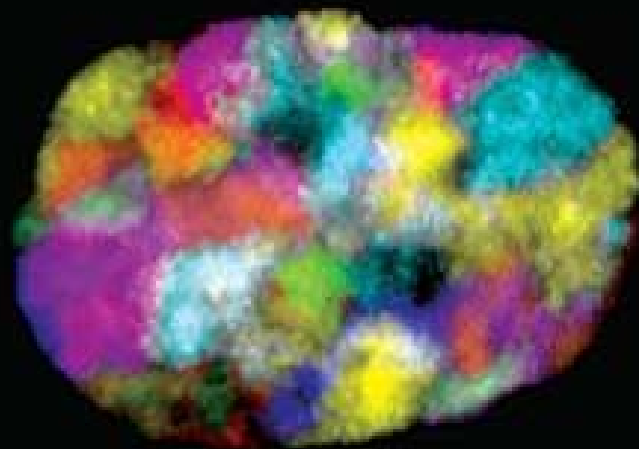
**Variazione
=
Adattabilità**



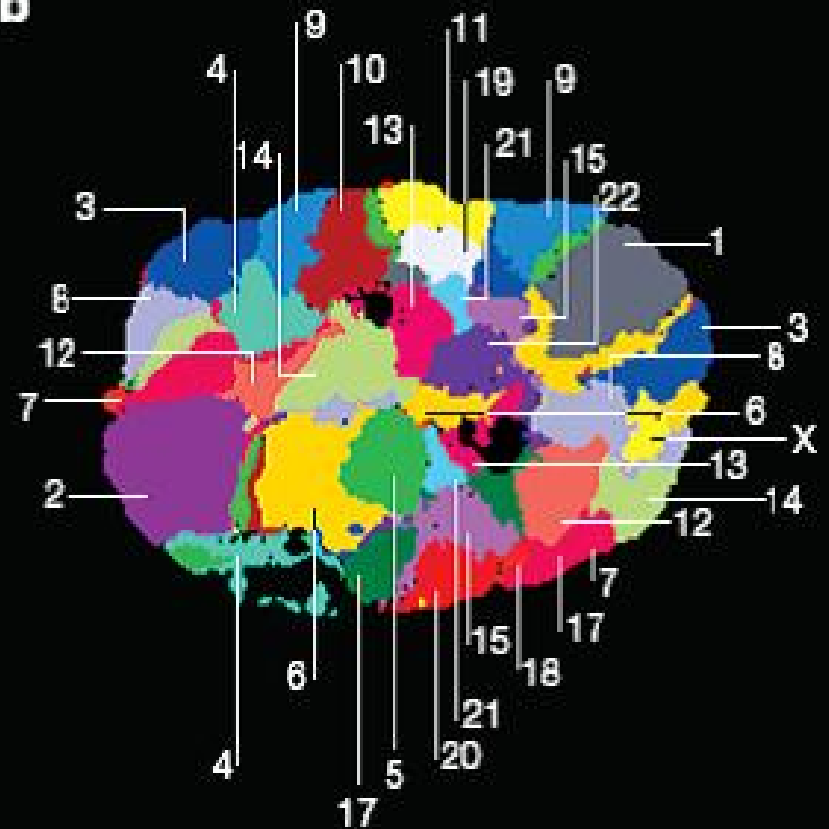
Geografia del DNA



a



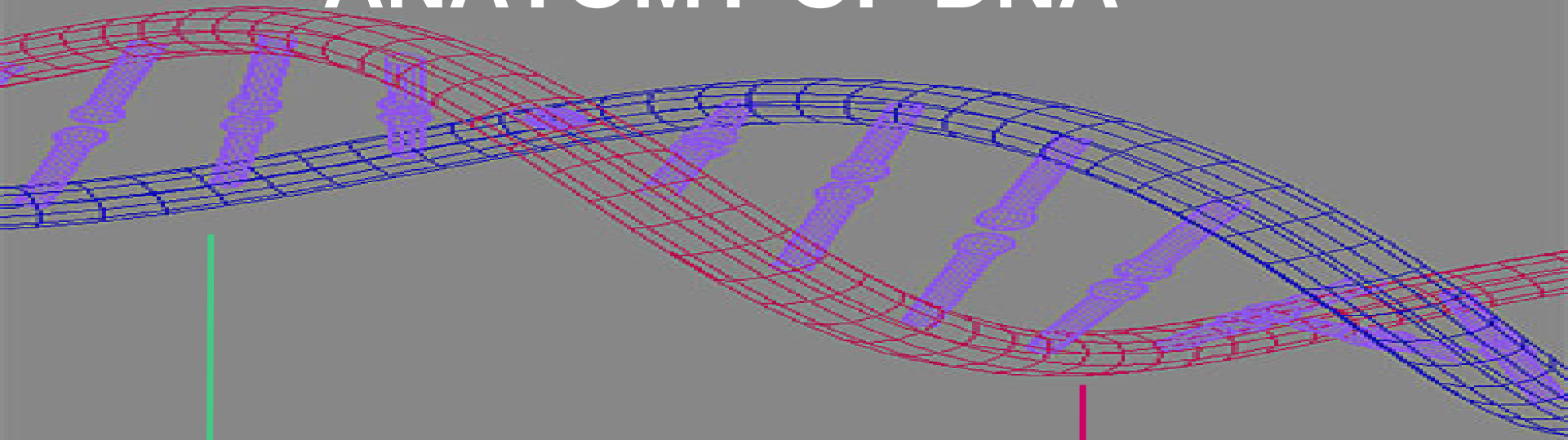
b



This is a reproduction of Leonardo da Vinci's famous drawing, 'Vitruvian Man'. It depicts a male figure with long, curly hair and a beard, standing with arms and legs extended to touch the boundaries of a circle and a square. The figure is shown in two superimposed positions: one with arms and legs extended horizontally, and another with arms and legs extended vertically. The drawing is a detailed anatomical study, showing the musculature of the body. The background is a light, textured surface, and the entire figure is enclosed within a square frame.

A vertical collage of classical sculptures, including figures like Apollo and Artemis, arranged in a circular pattern against a dark background with a glowing central light source. The sculptures are rendered in various colors, including purple, blue, and gold, and are set against a background of vertical light streaks. The overall composition is symmetrical and visually striking.

ANATOMY OF DNA



**CORE BIOLOGY FUNCTION GENES
NO NEED FOR GREAT VARIABILITY
BLOCKED REGIONS**

**ENVIRONMENTAL/INTERACTION GENES
NEED FOR GREAT VARIABILITY
POLYMORPHIC REGIONS**

**IL DNA NON PUO' DIRCI CHI
SIAMO, CHI SAREMO O DA
DOVE VENIAMO.**

Consapevolezza

“E’ molto più importante sapere quale paziente ha una malattia, piuttosto che quale tipo di malattia ha un paziente”

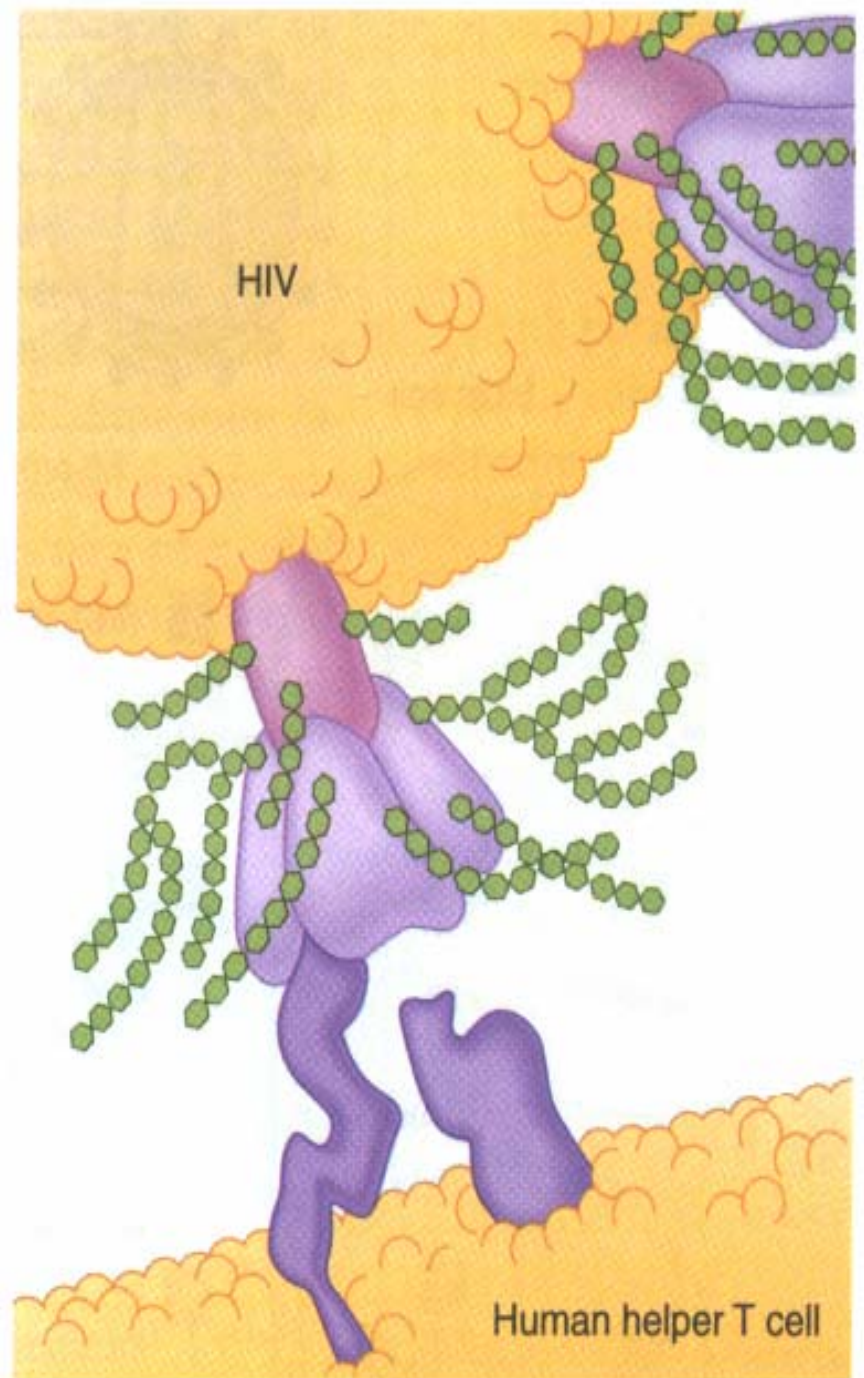
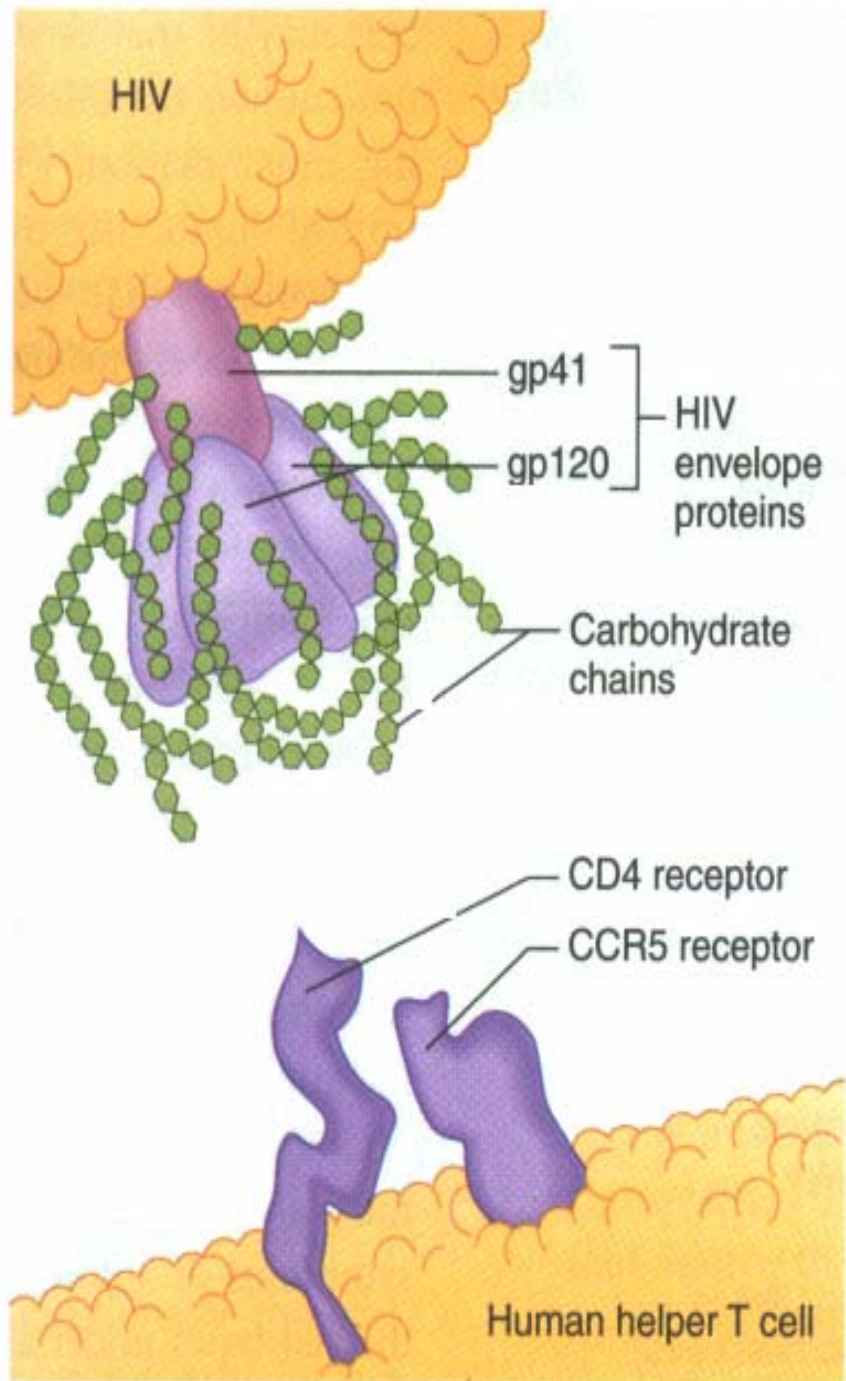
Caleb Parry



TEST PRESINTOMATICI E INDESIDERABILITA'

**I TEST GENETICI PORTANO
INFORMAZIONI POTENZIALMENTE
NON DESIDERATE.**

Questo non è esclusivo dei test genetici: un routinario controllo radiografico o un test del sangue può evidenziare un tumore asintomatico anche in stadio avanzato.



Test genetico predittivo

Offre la possibilità di prevedere in un individuo il rischio statistico di sviluppare una malattia o di rispondere a un intervento terapeutico sulla base della determinazione del genotipo per una o più mutazioni geniche

Quando fare un test genetico predittivo?

- Il test e' disponibile
- Il rischio e' accertato
- Vi sono indicazioni per la selezione del gruppo di persone che possono sottoporsi al test
- Sono note possibili misure per la riduzione del rischio



68



Genome Medical Futures

ECCEZIONALISMO GENETICO E IL CONCETTO DI RISCHIO

Si ritiene che la natura particolare della genetica dia origine a un **rischio più grande** o a rischi di natura differente dai normali concetti di rischio noti da tempo in medicina.

L'errore dell' eccezionalismo genetico

Si ritiene che questi rischi non possano essere riportati e regolamentati chiaramente dai principi di etica e da leggi specifiche; la genetica medica è caratterizzata da un *eccezionalismo regolatorio*.

L'errore della sovrastima statistica dell'incertezza

Il rischio fa parte dell'incertezza,
ma può essere quantificato.

Tuttavia, la quantificazione del
rischio non implica la sua
abolizione, soltanto il fatto che noi
acquisiamo la capacità di definire
e quantificare, in termini
probabilistici, le possibilità di
eventi diversi.

Questa forma di incertezza
quantificabile non è tuttavia la sola
forma di incertezza con cui la medicina
(inclusa la genetica medica) deve
confrontarsi. Ogni *non-quantificabile
forma di incertezza*, così come la
genuina ignoranza, deve sempre
essere tenuta in grande
considerazione.

Un altro problema connesso con il concetto di rischio è che la percezione dello stesso potrebbe anche **differire considerevolmente tra gli individui**. Per esempio, due persone con un rischio di 1 a 100 potrebbero vedere la stessa situazione in modi differenti:

- Molto alto – gioca alla lotteria ogni settimana con possibilità di vittoria 1 su decine di milioni. Si aspetta di essere **quell'uno**.

- basso - 99% delle volte non avviene

E allora quali i rischi dell'analisi genetica ?

Test diagnostici e predittivi

- Privacy e riservatezza
- Conseguenze in ambito assicurativo e lavorativo
- Rischio di discriminazione e stigmatizzazione
- Impatto psicologico (“morbidificazione”) sul soggetto e sulla famiglia
- Ancora poco chiaro il significato di probabilità e di rischio

Soluzioni

- Regolatorie
- Tecniche, per i predittivi non esistono (bassa penetranza)
- Non esiste: siamo tutti mutanti!
- Da oltre 150 anni i medici chiedono informazioni sulla genealogia.

Il problema

- ***Ogni anno, gli effetti collaterali o le reazioni avverse ai farmaci uccidono circa 100,000 pazienti americani.***
- ***Più di 2 milioni di pazienti hanno reazioni avverse serie.***
- ***Una dose uguale per tutti può essere pericolosa!!!***

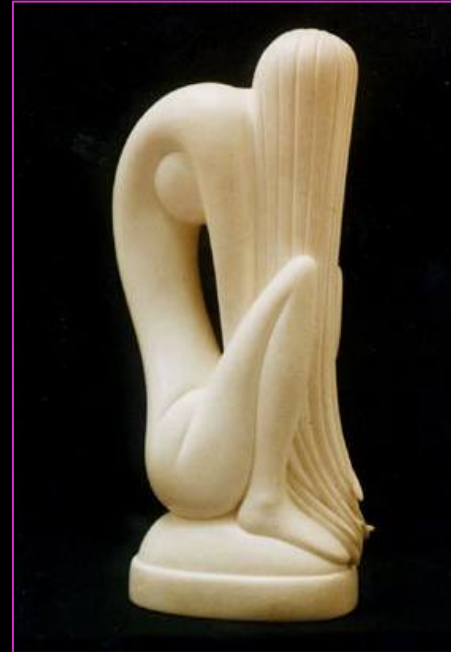
"All substances are poisons;
there is none which is not a
poison. The right **DOSE**
differentiates a poison from a
remedy."

Areolus Phillipus
Theophrastus
Bombastus
von Hohenheim

Paracelsus (1493-1541)



La reale frustrante realtà della moderna
medicina è che i dottori sanno che i
farmaci che loro prescrivono non
hanno sempre effetti terapeutici



Molecole alla prova di efficacia

tipo di farmaco

efficacia

antipertensivi

Inferiore al 60%

antidepressivi

Inferiore al 50%

antipsicotici

Inferiore al 40%

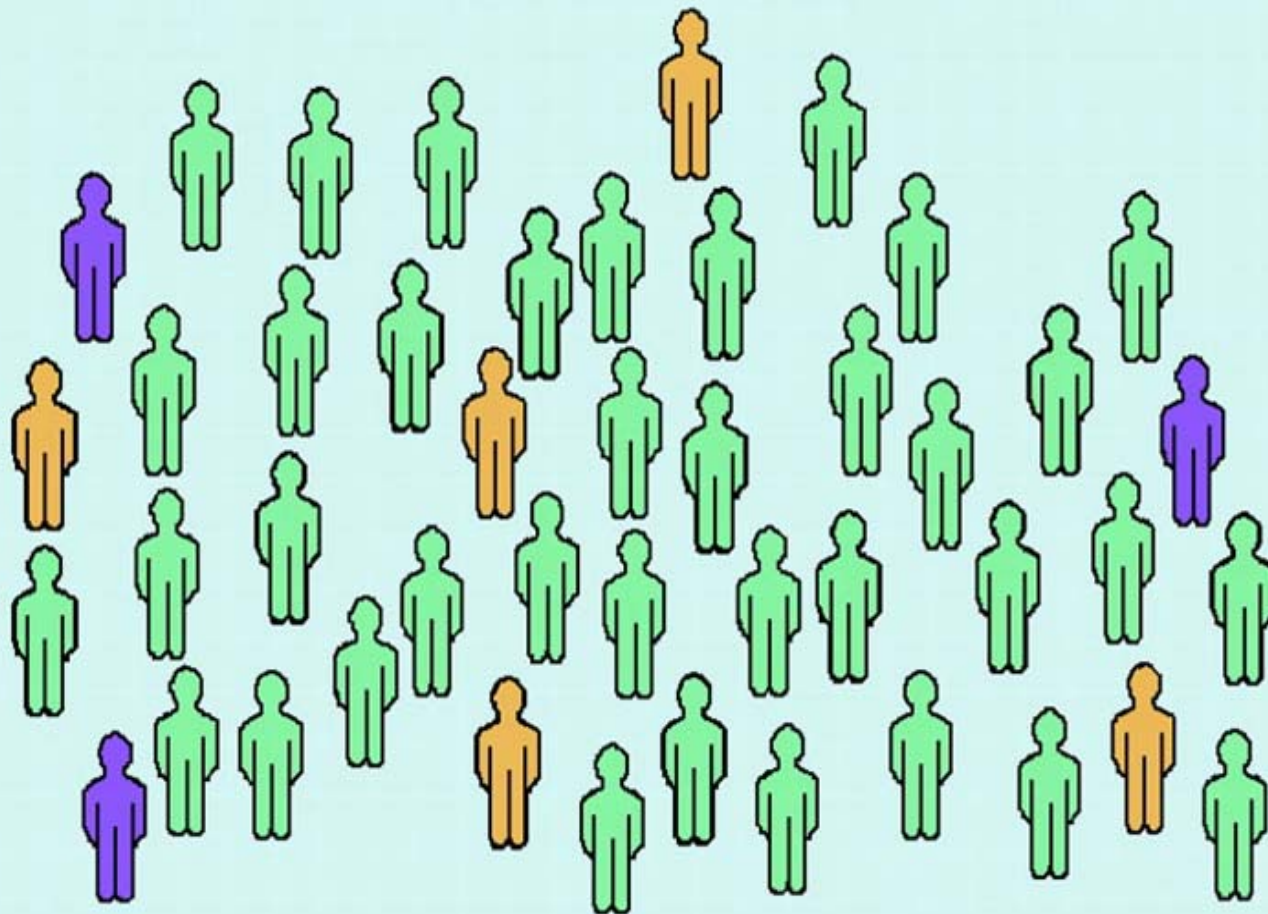
Stevens–Johnson Syndrome



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

*La capacità di predire quale
farmaco è più appropriato per un
particolare paziente dovrebbe
rappresentare l'obiettivo più
ambizioso della medicina
genomica*

Pazienti con la stessa diagnosi



responsivi



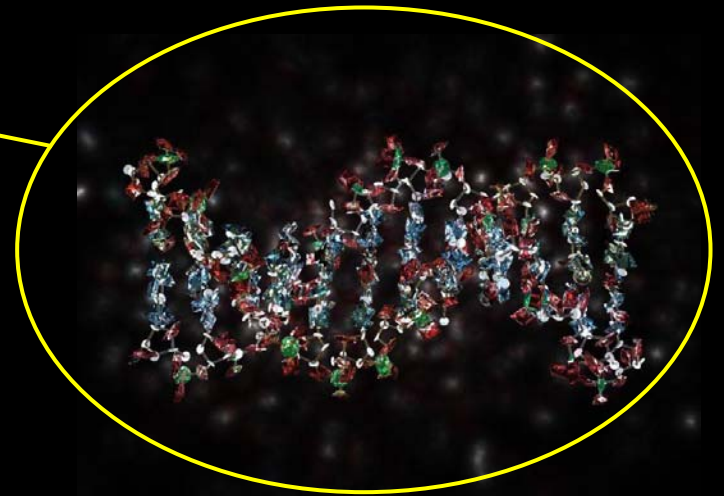
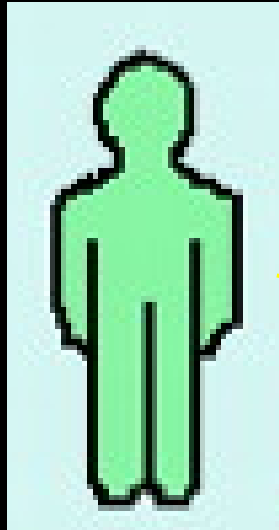
**non
responsivi**

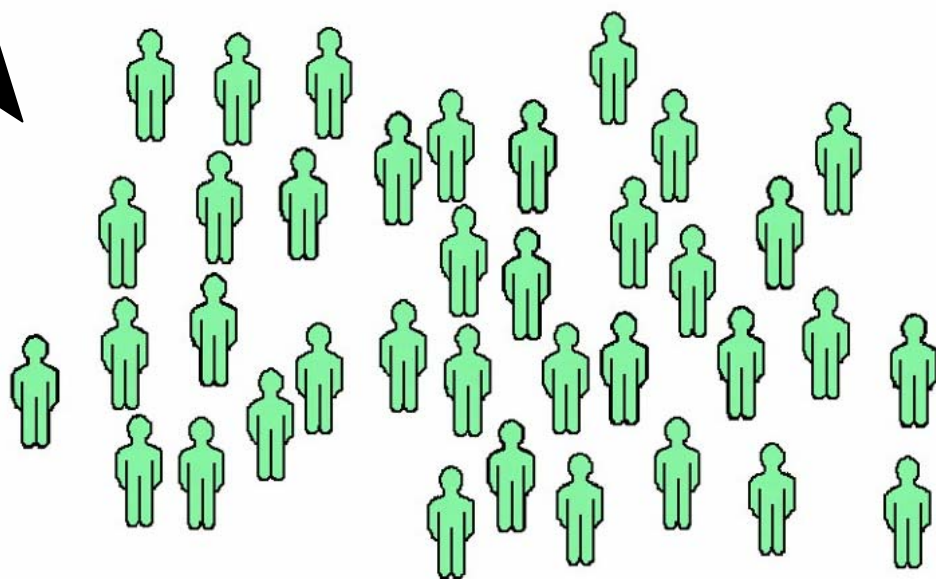
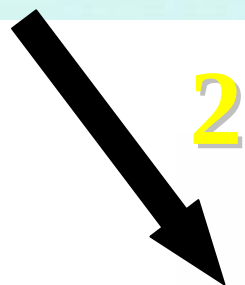
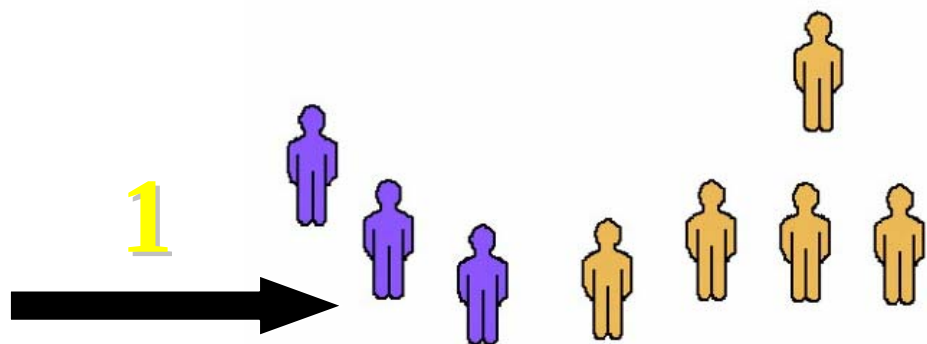
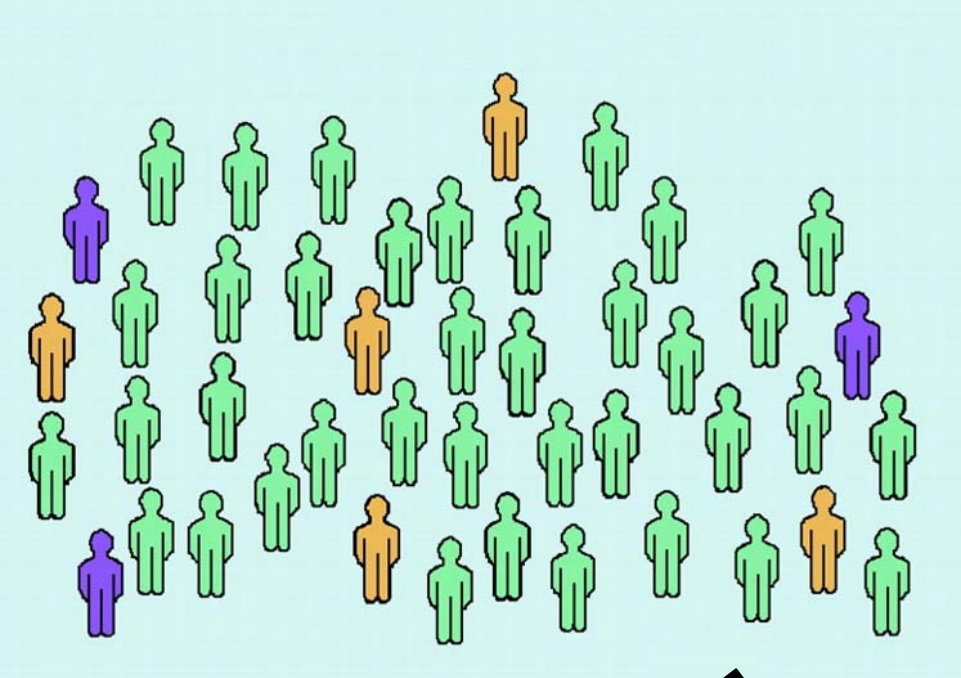


**reazioni
avverse**



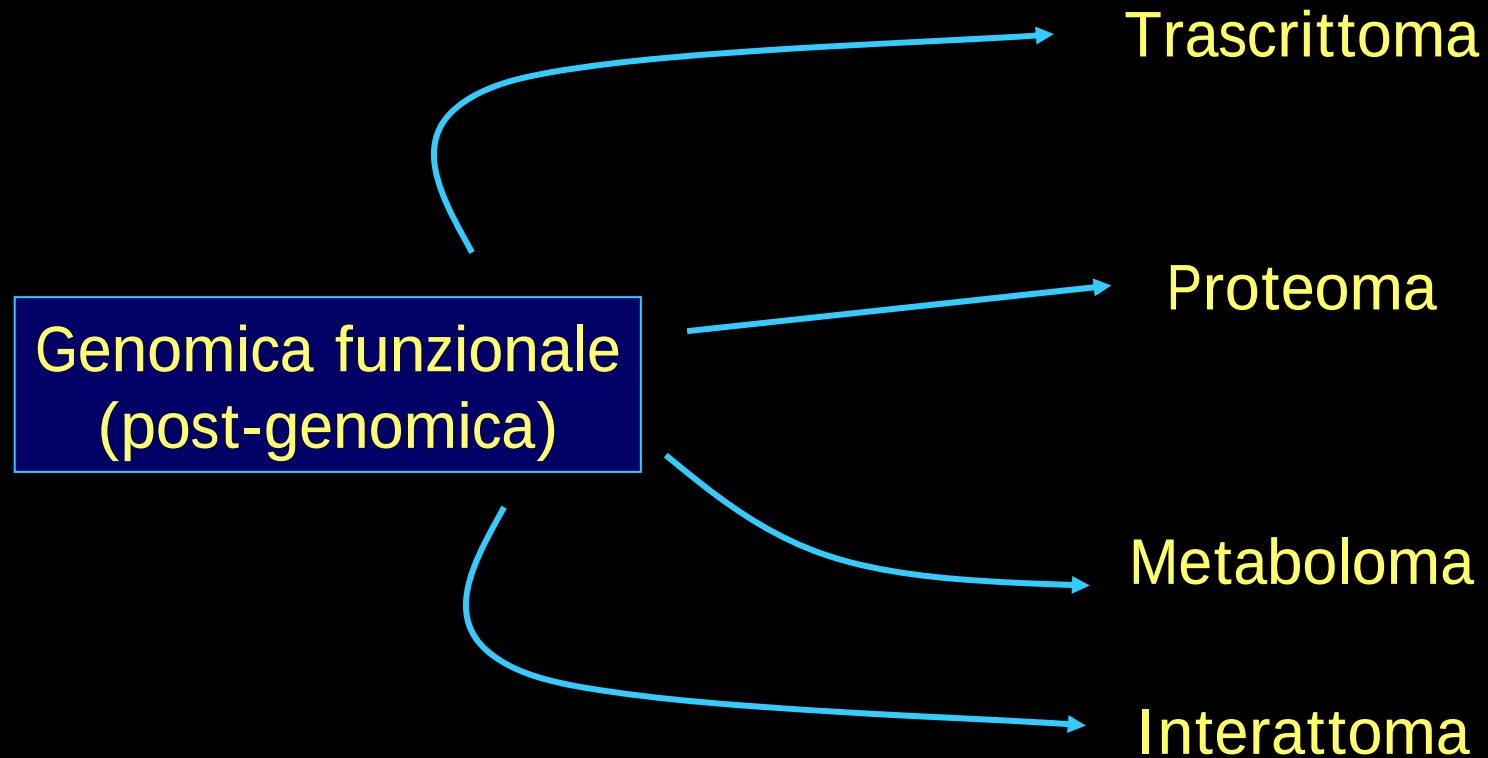
Caratterizzazione genetica dei pazienti





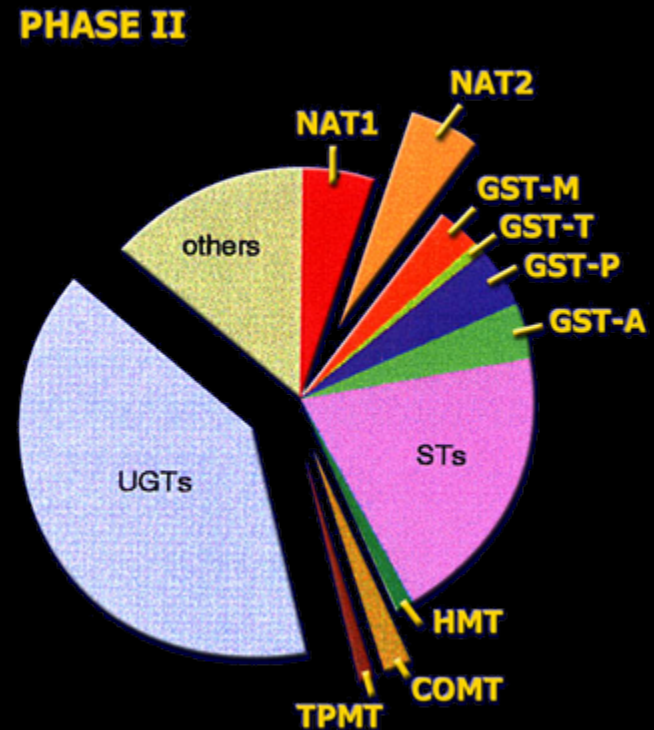
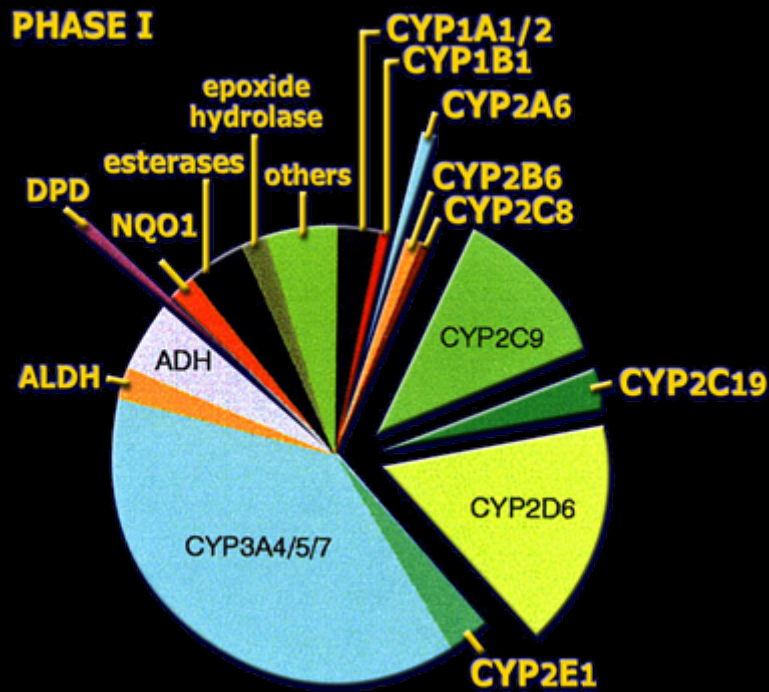


La ricerca della patogenesi delle malattie nell'era genomica

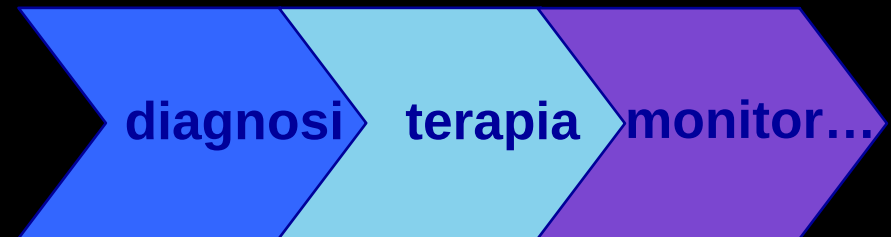


L'obiettivo della genomica funzionale è capire come tutti i geni identificati e catalogati dallo Human Genome Project interagiscono tra loro per regolare la fisiologia molecolare di un organismo, cambiando tuttavia il raggio di analisi: l'indagine non si sofferma su un gene alla volta ma su un numero molto elevato di geni/proteine in dipendenza delle tecnologie utilizzate

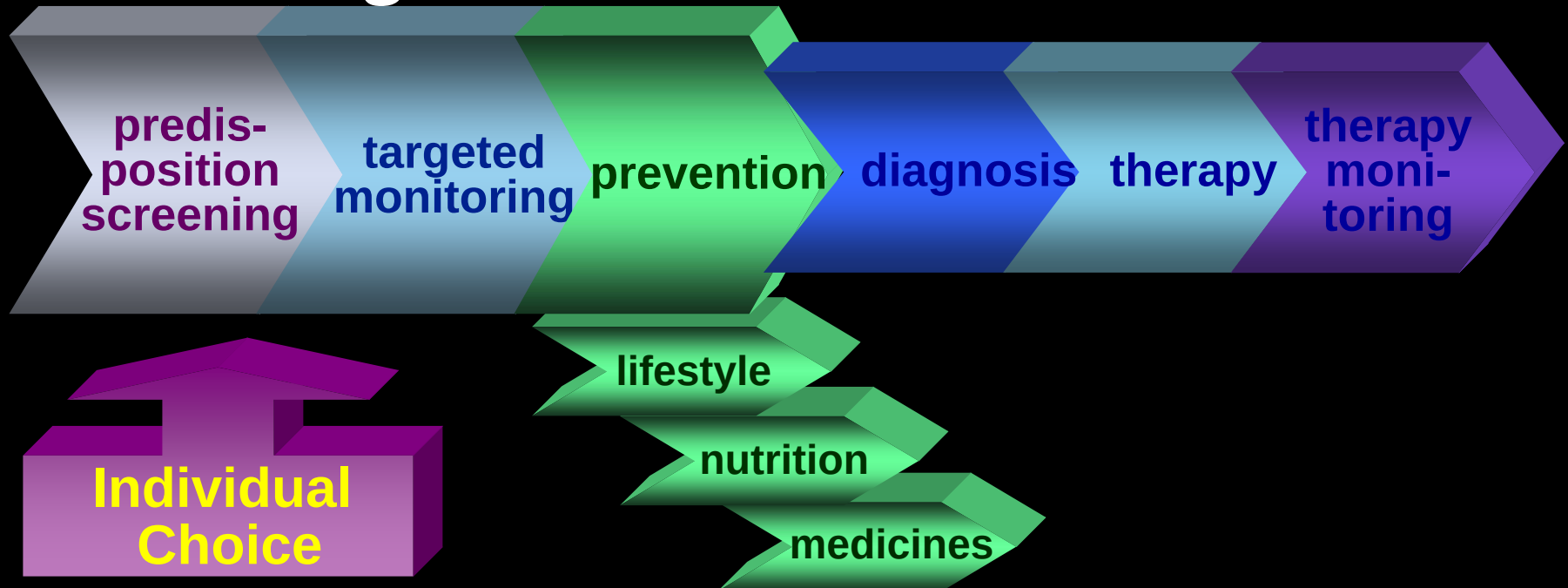
Principali enzimi che esibiscono un polimorfismo implicato nel metabolismo dei farmaci



oggi...



...uno sguardo al futuro



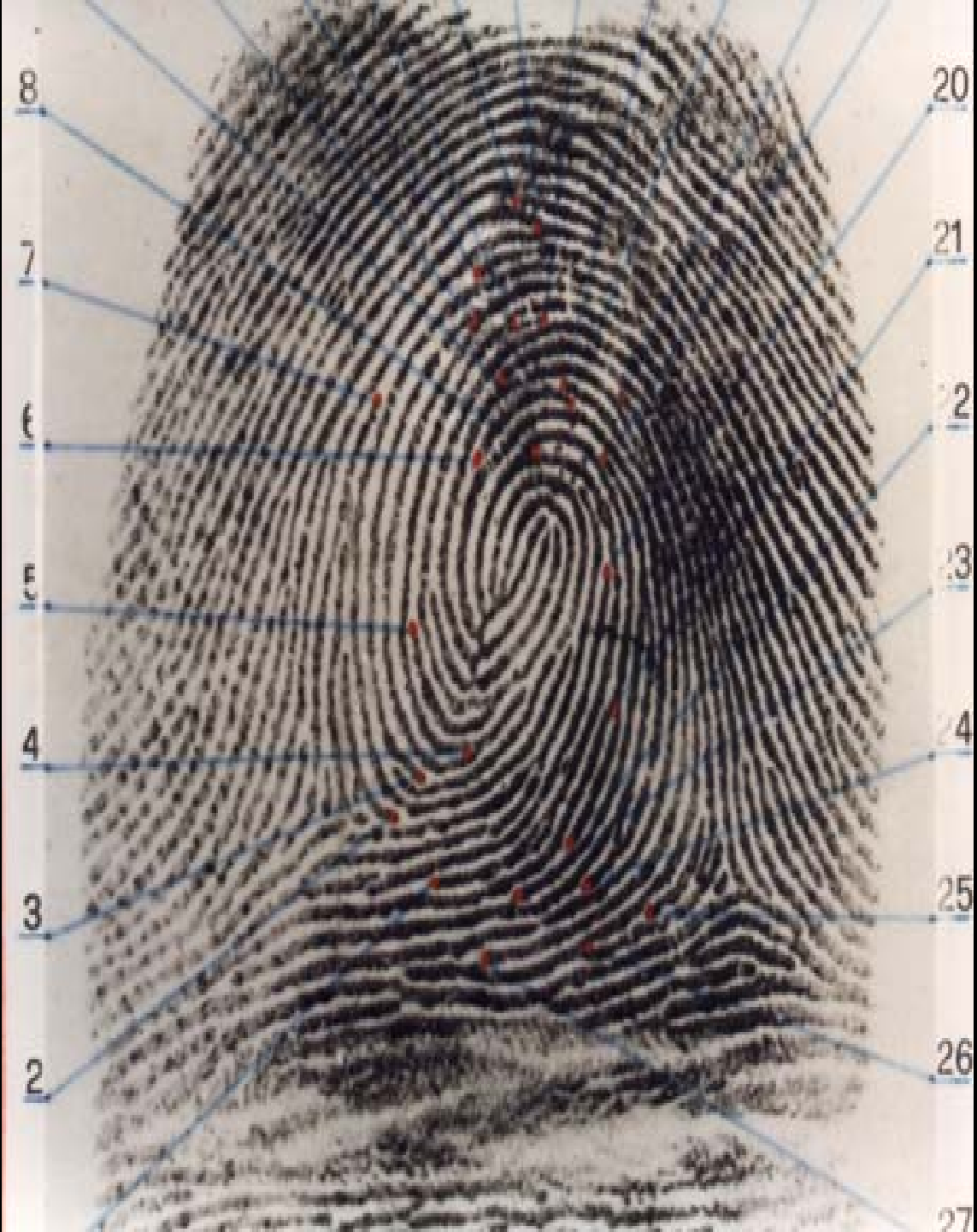
LA PAURA

- Banche dati del DNA per tutti, solo per chi non rispetta la legge?
- Saremo tutti schedati e verrà negata la nostra privacy.

Test per la variabilità interindividuale ed UNICITA'

I test genetici identificano le persone
in modo inequivocabile.

Anche le impronte digitali o altri dati
personali hanno un simile potere di
informazione (tutti gli esami richiedono
un campione biologico identificabile ed
identificato).



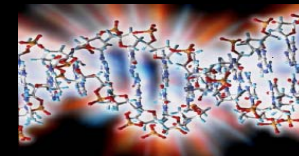


LA VARIABILITA' INTER-INDIVIDUALE

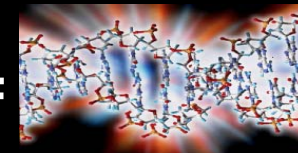
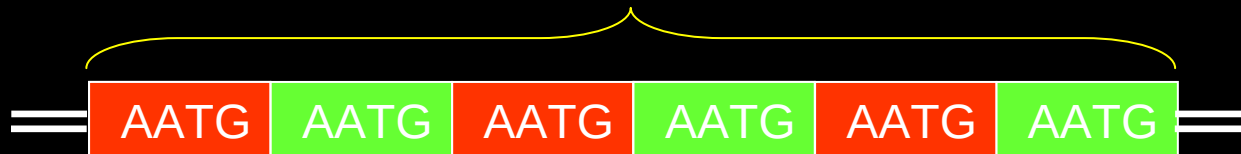
- 1985: Alec Jeffreys trova regioni di DNA contenenti sequenze ripetute in tandem, e scopre che il numero dell'unità ripetuta può differire da individuo ad individuo.



4 ripetizioni



6 ripetizioni



Nasce la genetica forense moderna!!!

... l'arte dell'investigazione deve essere capace di riconoscere un elevato numero di fatti, che sono casuali ma vitali. Pertanto la tua energia e la tua attenzione devono essere dissipate invece che concentrate.

[Sherlock Holmes, the Reigate Puzzle]



Sherlock Holmes was not a golfer.



...studiando l'evoluzione del gene
della mioglobina tra uomo e foca



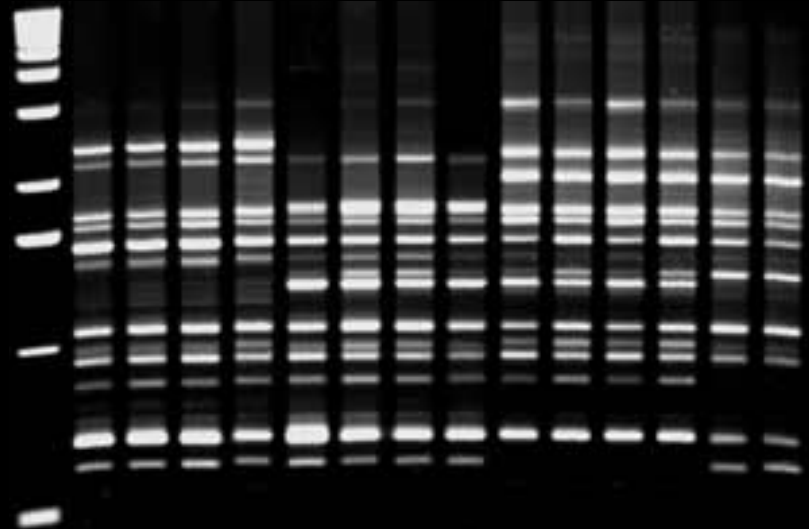
Il primo caso

- Il 22/11/83 Lynda Mann è stata trovata violentata e strangolata nei pressi di Narborough, vicino Leicester.
- Il colpevole non fu trovato ma fu raccolto un campione di sperma

- Il 2 agosto del 1986, in un cespuglio nei pressi di Leicestershire, venne ritrovato il corpo di una studentessa di 15 anni, Dawn Ashworth, violentata e strangolata
- Richard Buckland, il giovane usciere dell'ospedale locale, confessò solo il secondo delitto.

Alec Jeffreys

- Confermò che entrambi i campioni di sperma provenivano dalla stessa persona!
- Caso chiuso. No!: i campioni non appartenevano a Buckland...

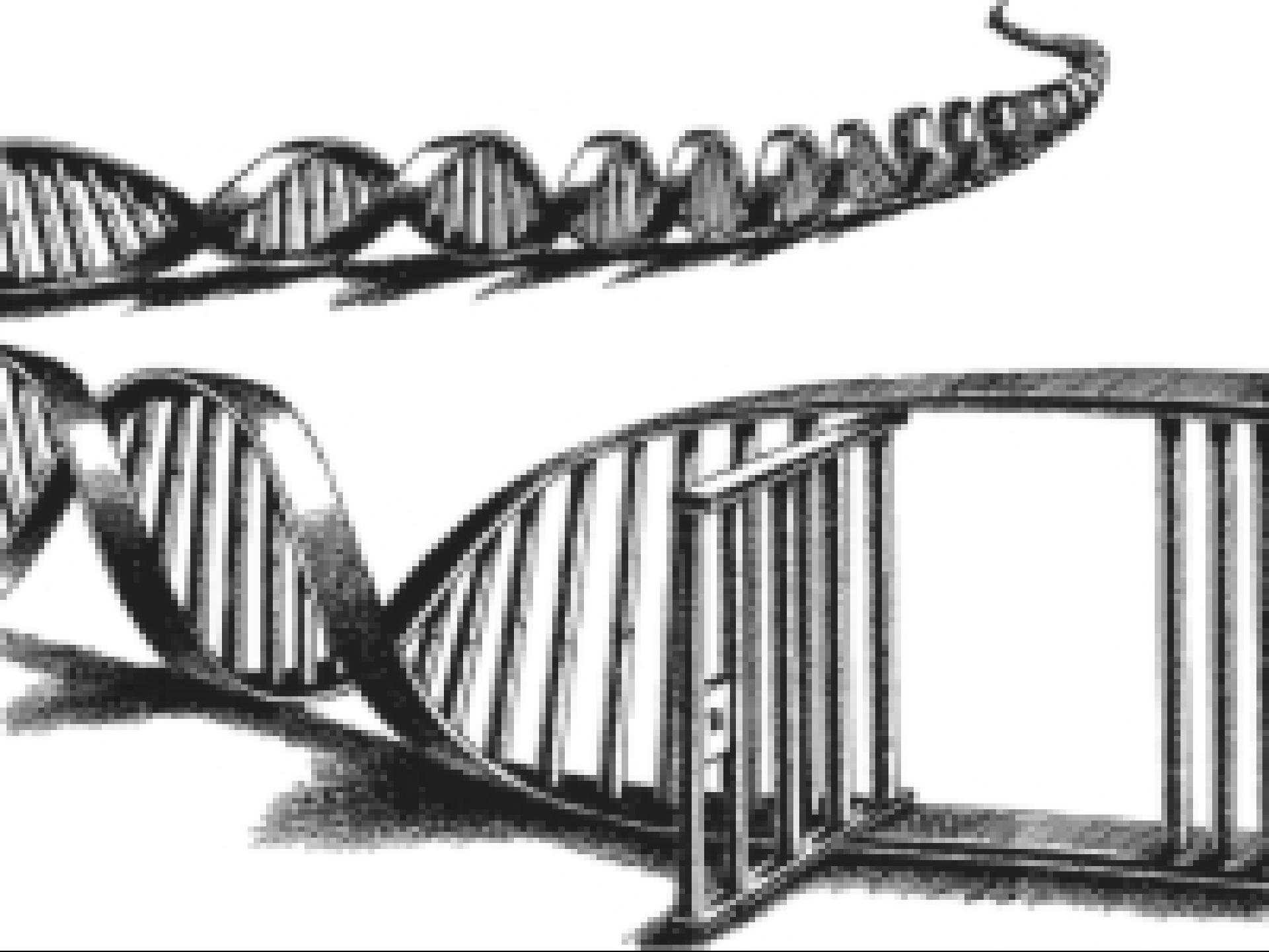




Parte una tremenda caccia all'uomo: 5500 uomini furono tipizzati. Nessun risultato.



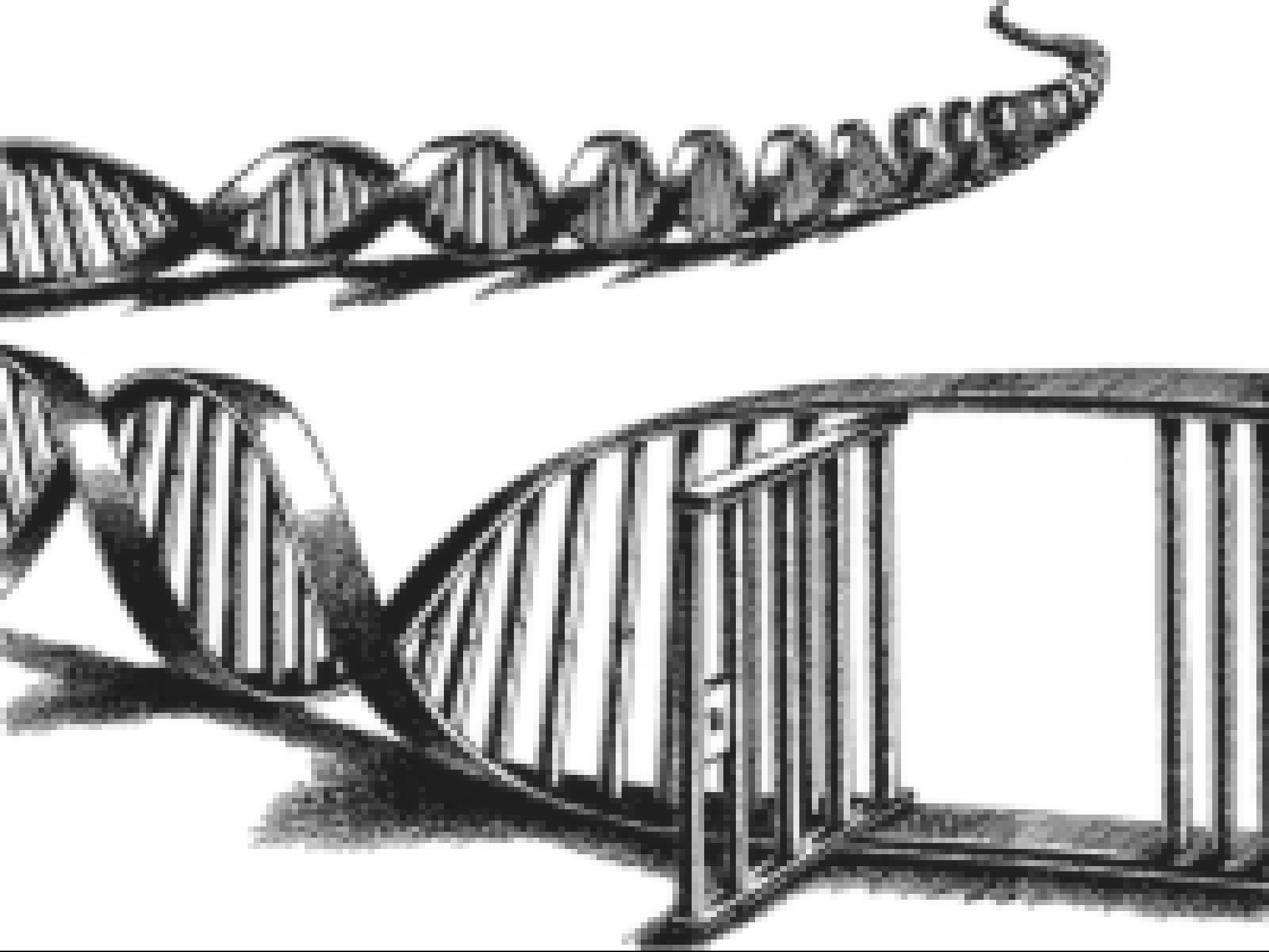
1988 Colinn Pitchfork





MY
GENOME
MADE ME
DO IT!

STAYSKAL
2000 TAMPA
TRIBUNE



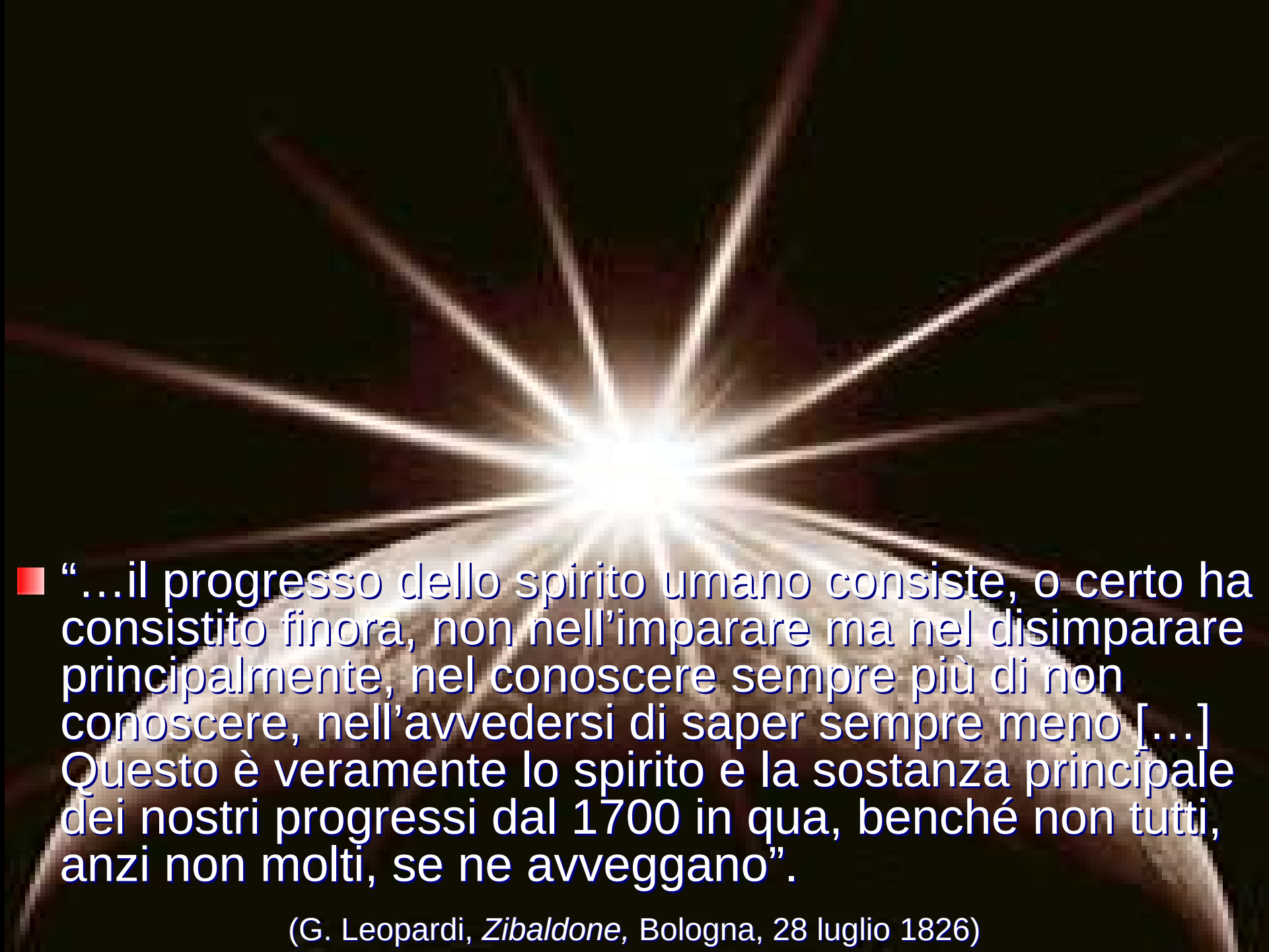
Leonardo Da Vinci: Solo lo stupore conosce

“...vago di vedere la gran copia delle varie e strane forme fatte dalla artificiosa natura, raggiratomì alquanto infra gli ombrosi scogli, pervenni all’entrata di una gran caverna...e stato alquanto, subito sorser in me due cose: paura e desiderio: paura per la minacciante spilonca, desiderio per vedere se là dentro fosse alcuna miracolosa cosa”.

(Leonardo Da Vinci, *Scritti letterari*)

**What to do not to look to the wrong
direction?**





■ “...il progresso dello spirito umano consiste, o certo ha consistito finora, non nell’imparare ma nel disimparare principalmente, nel conoscere sempre più di non conoscere, nell’avvedersi di saper sempre meno [...] Questo è veramente lo spirito e la sostanza principale dei nostri progressi dal 1700 in qua, benché non tutti, anzi non molti, se ne avveggano”.

(G. Leopardi, *Zibaldone*, Bologna, 28 luglio 1826)