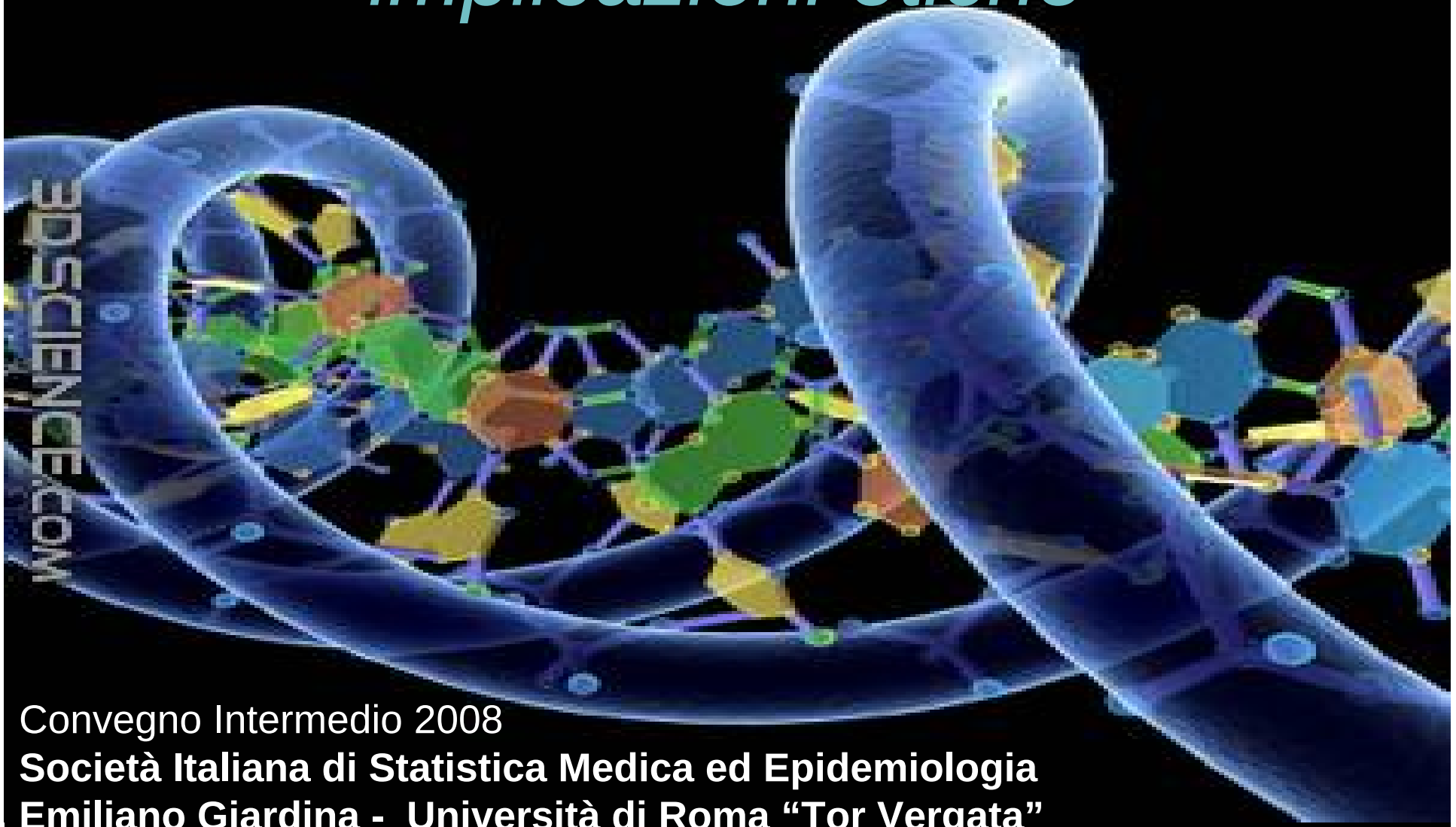
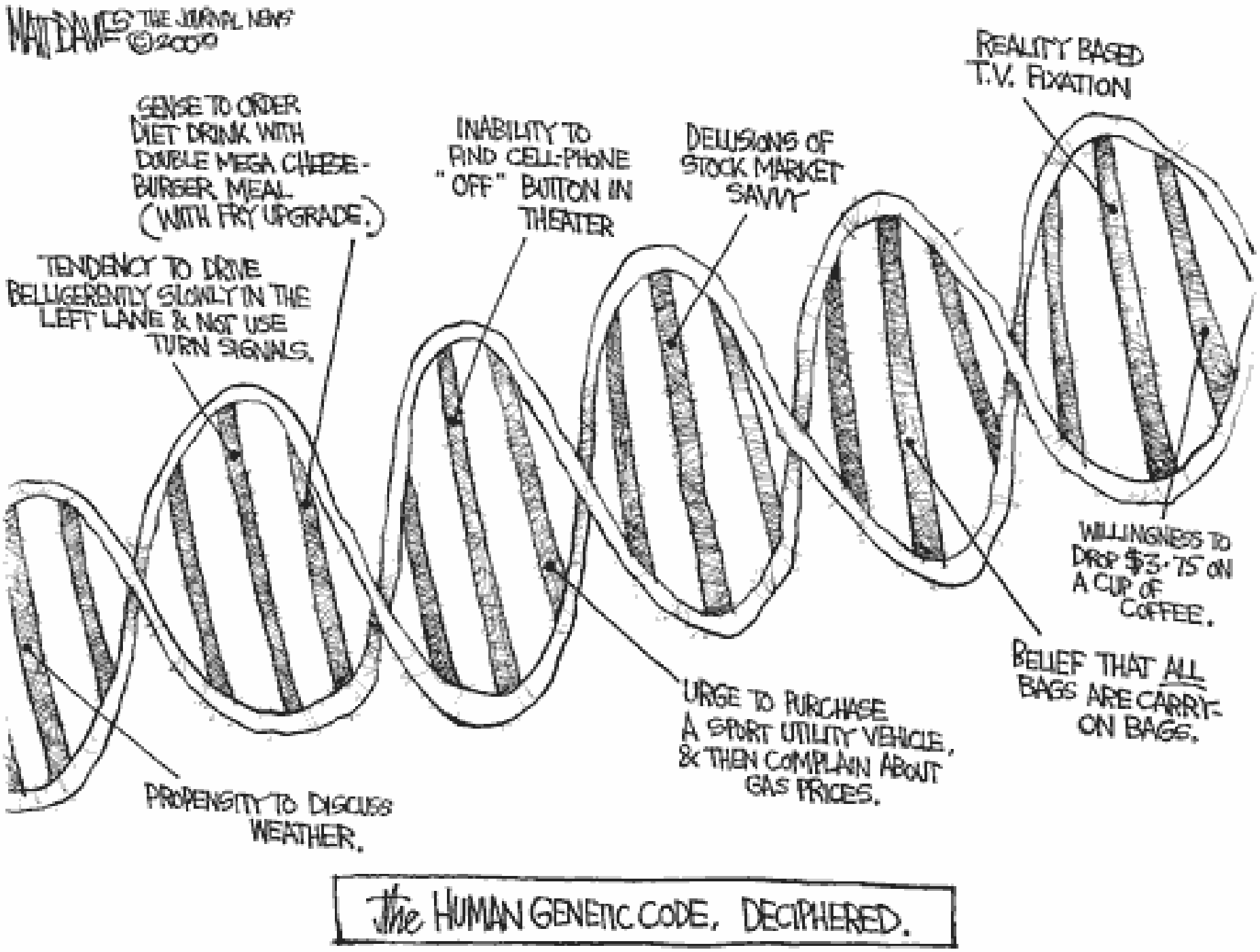
I test genetici: capacità predittiva ed implicazioni etiche



Convegno Intermedio 2008

Società Italiana di Statistica Medica ed Epidemiologia
Emiliano Giardina - Università di Roma "Tor Vergata"
emiliano.giardina@uniroma2.it

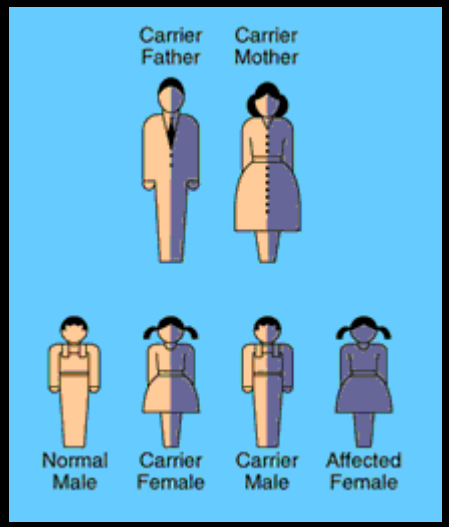
Roma, 20 Novembre 2008

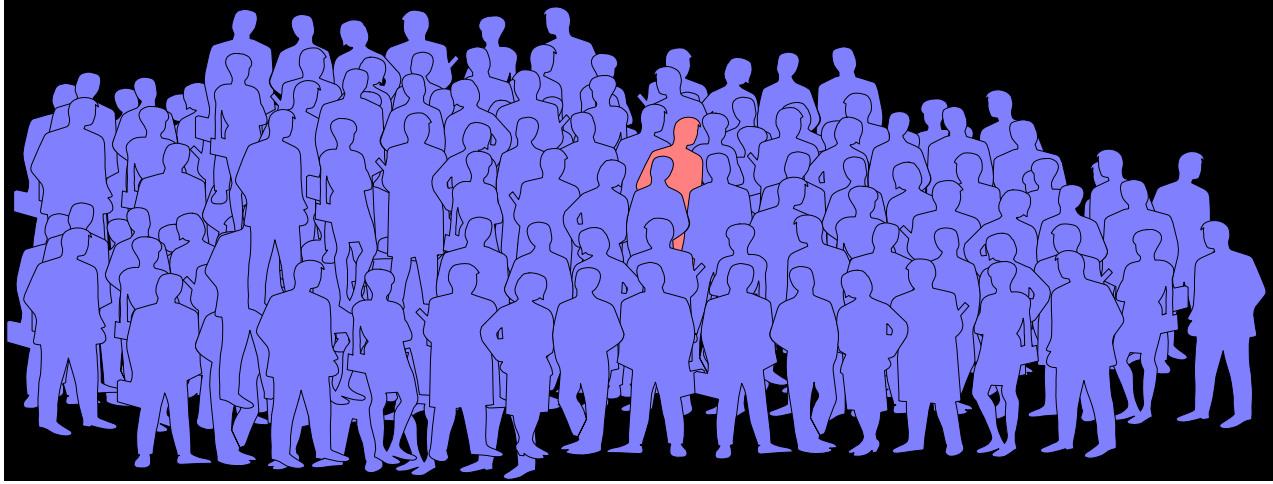

MATT DAVIES THE JOURNAL NEWS ©2009
REALITY BASED T.V. FIXATION
SENSE TO ORDER DIET DRINK WITH DOUBLE MEGA CHEESE-BURGER MEAL. (WITH FRY UPGRADE.)
INABILITY TO FIND CELL-PHONE "OFF" BUTTON IN THEATER
DELUSIONS OF STOCK MARKET SAVVY
TENDENCY TO DRIVE BELLIGERENTLY SLOWLY IN THE LEFT LANE & NOT USE TURN SIGNALS.
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.

(Galen, 130-200 CE)

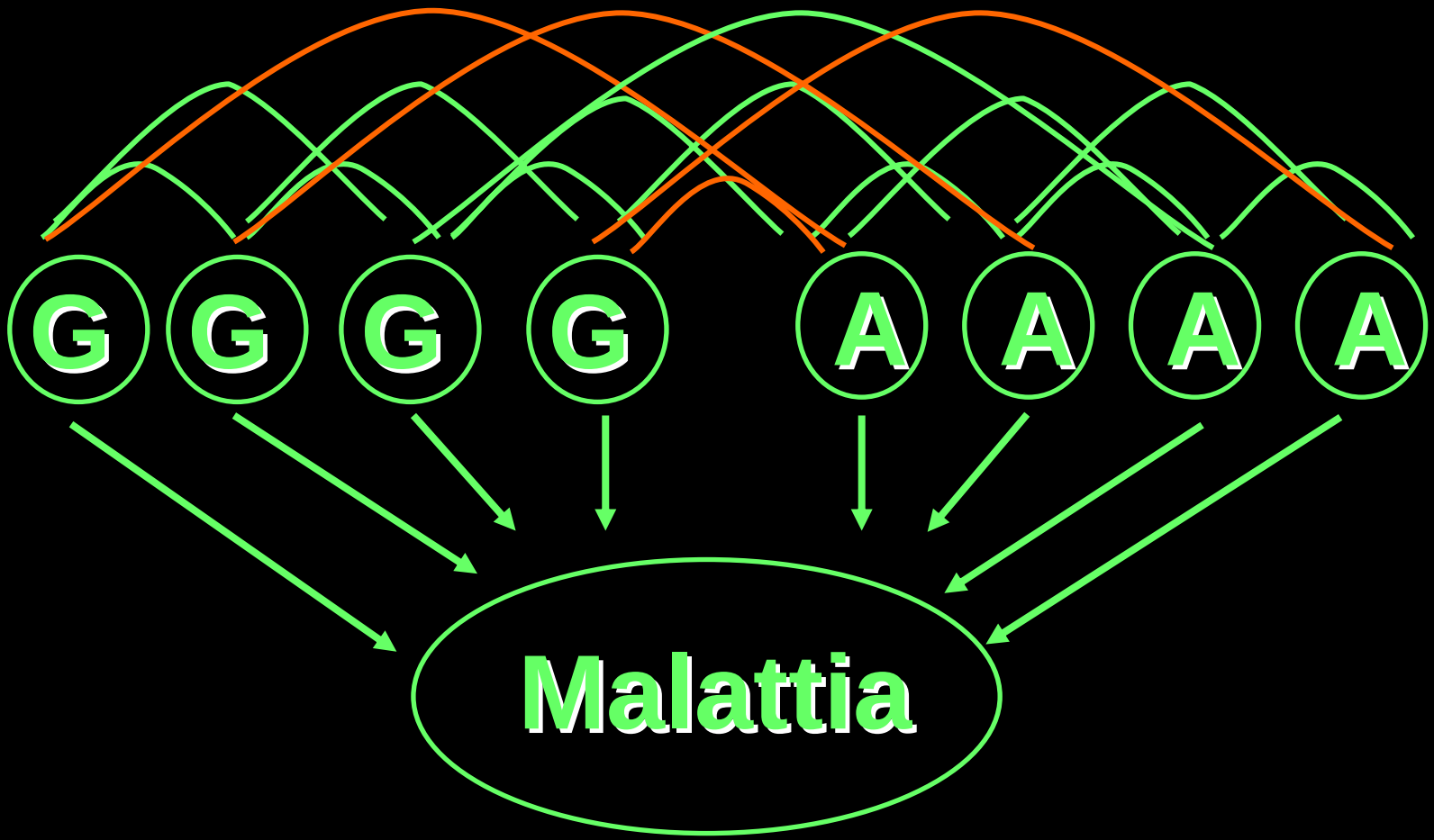
“But remember throughout that no cause is efficient without a predisposition of the body itself, otherwise, external factors which affect one would affect all.”

Evoluzione del concetto di rischio

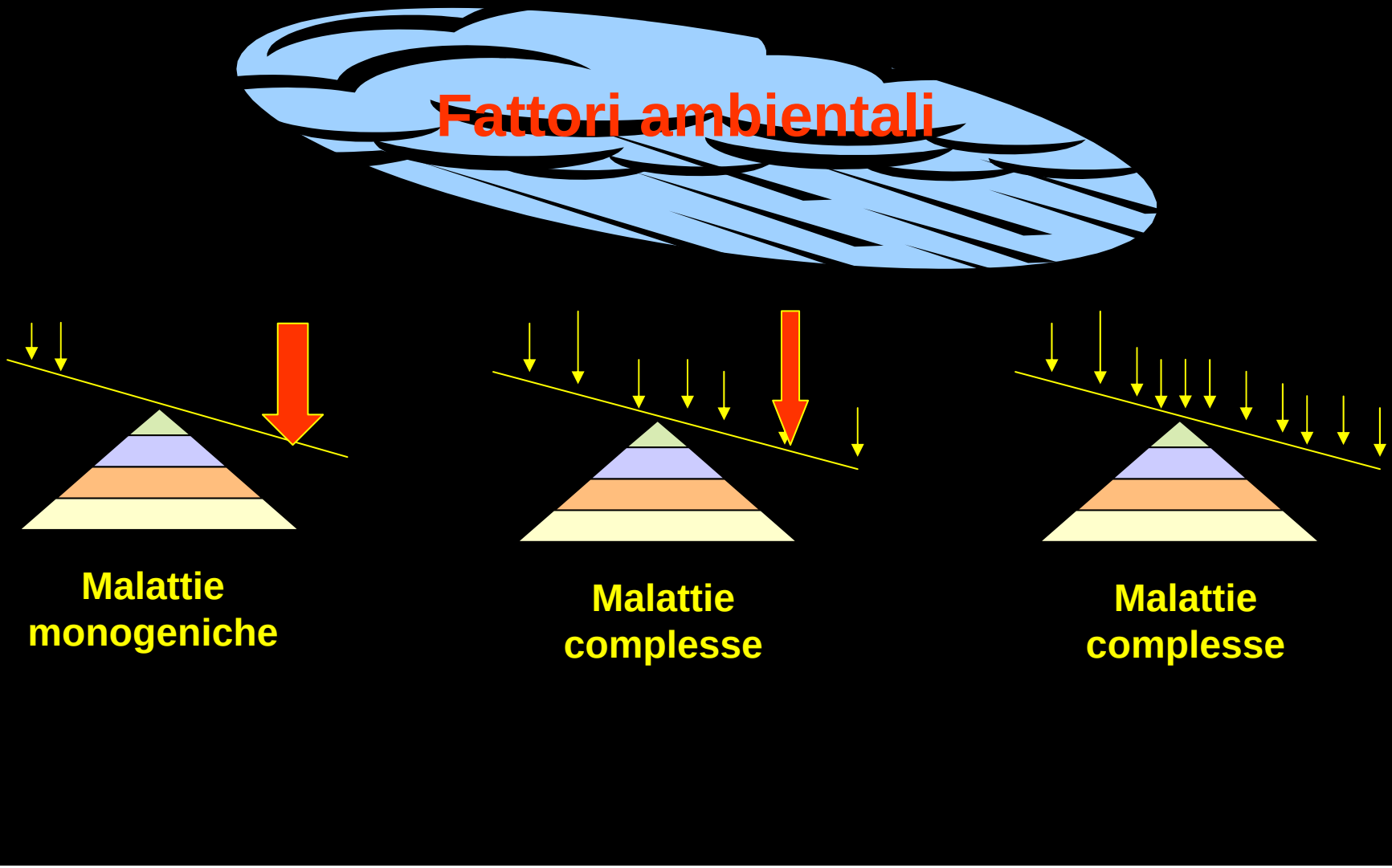


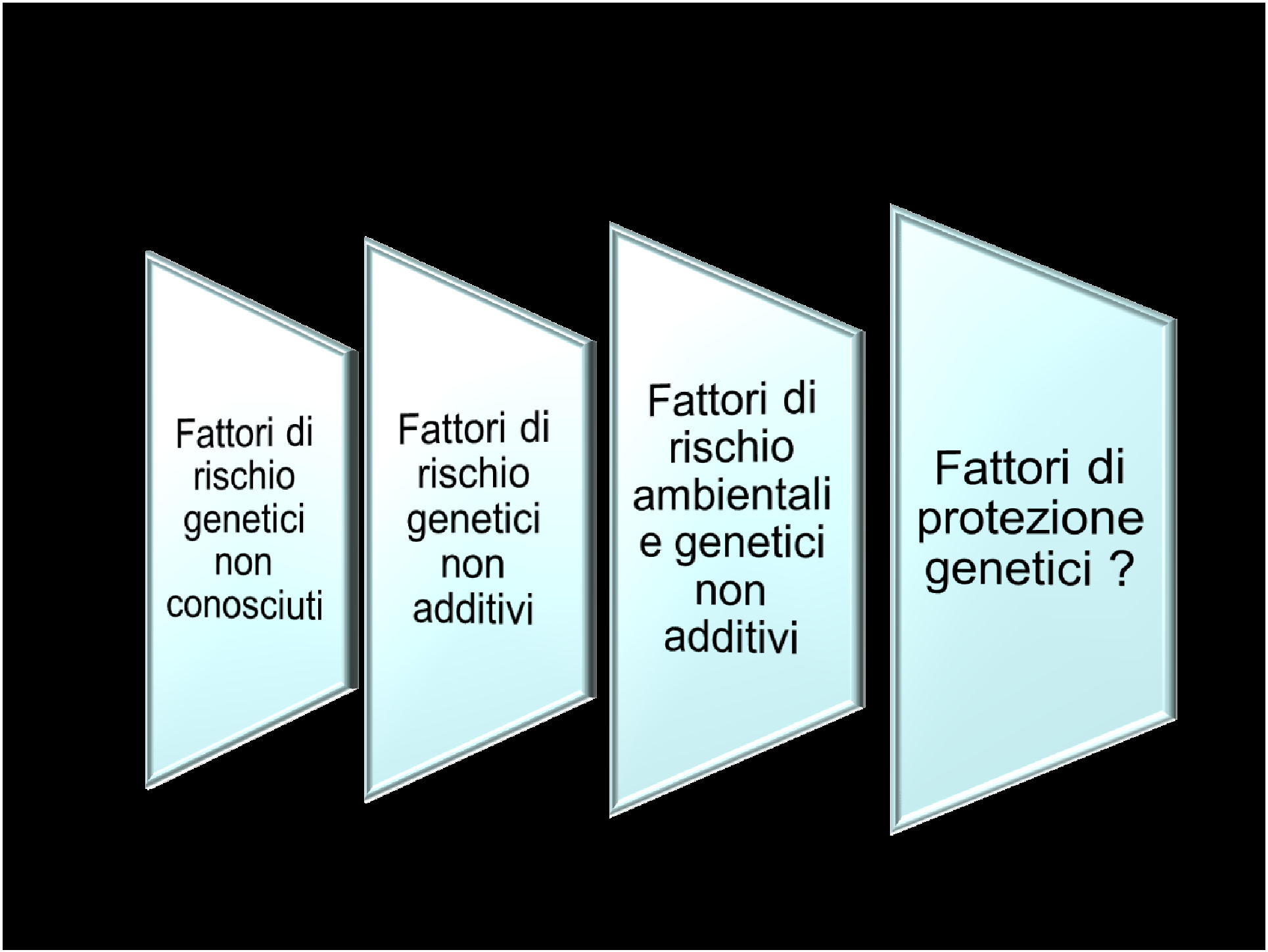


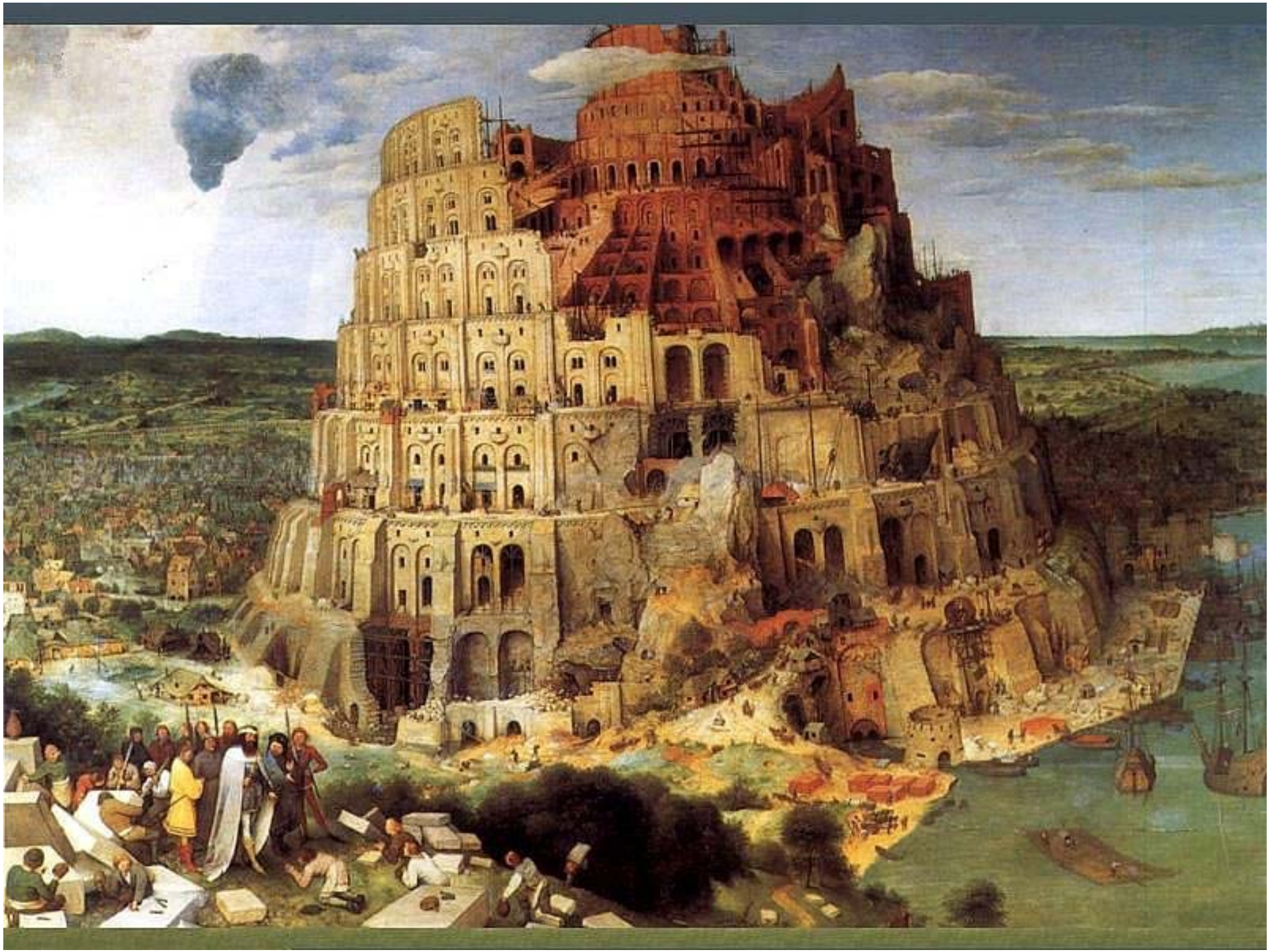
Malattie Complesse



Non esiste un modello unico per le malattie complesse

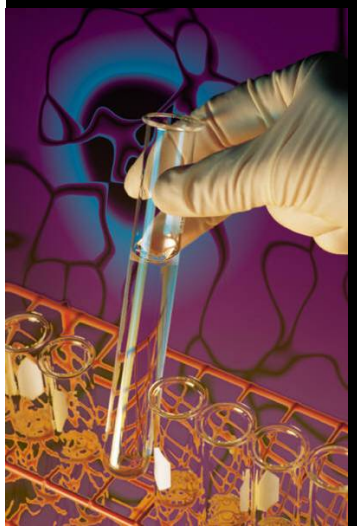



Fattori di rischio genetici non conosciuti
Fattori di rischio genetici non additivi
Fattori di rischio ambientali e genetici non additivi
Fattori di protezione genetici ?



Definizione di biomarker genomico

Qualsiasi caretteristica misurabile del DNA o del RNA che sia indicatore di un normale processo biologico, di un processo patogenetico, o della risposta ai farmaci o ad altri interventi biomedicali



Caratteristiche del biomarker genomico

- Un biomarker genomico potrebbe ad esempio riflettere :
  - la regolazione di un gene
  - L’espressione di un gene
  - La funzione di un gene

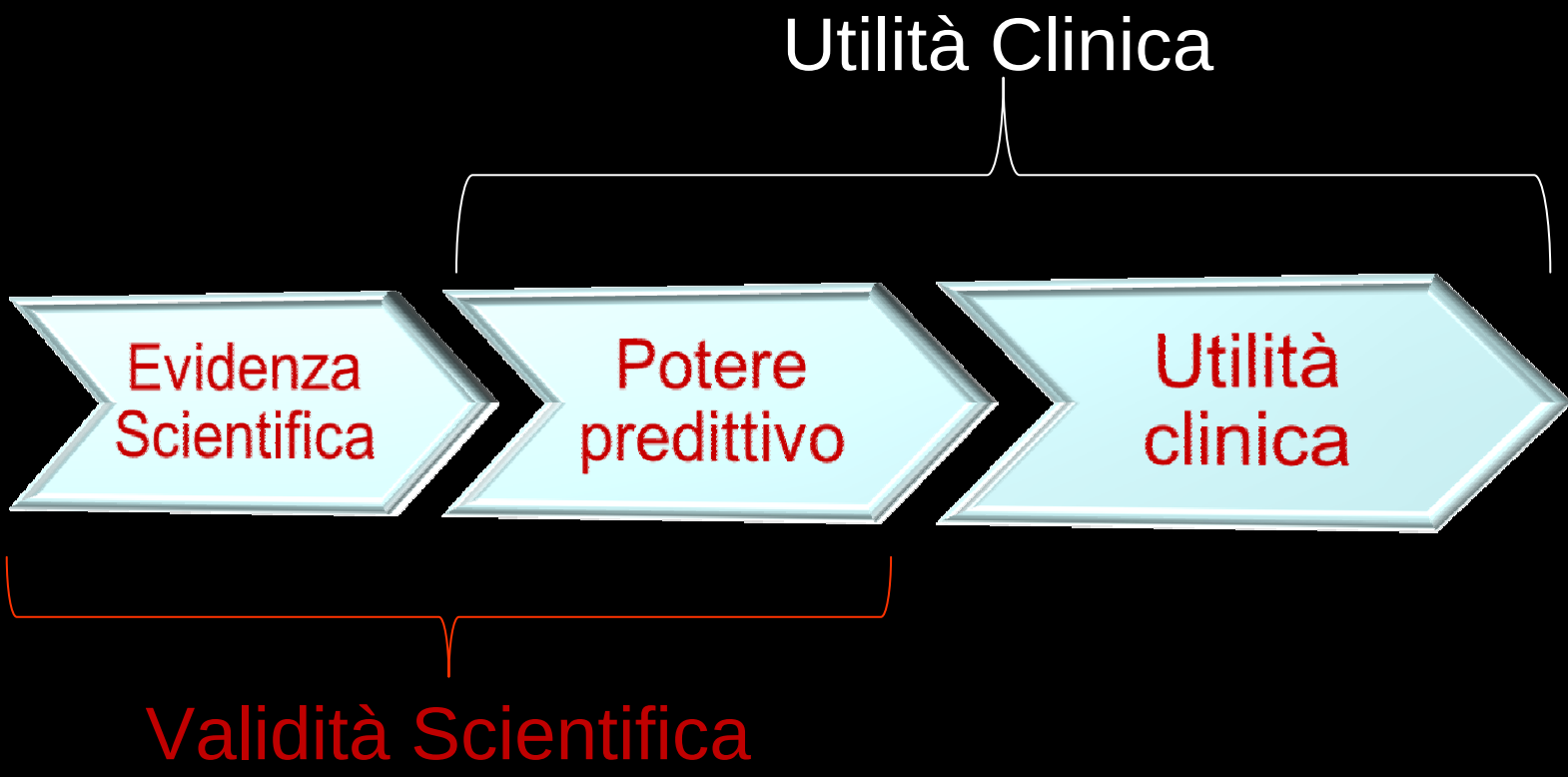
- Un biomarker genomico non comprende :
  - Proteomica
  - Metabolomica

Caratteristiche genetiche

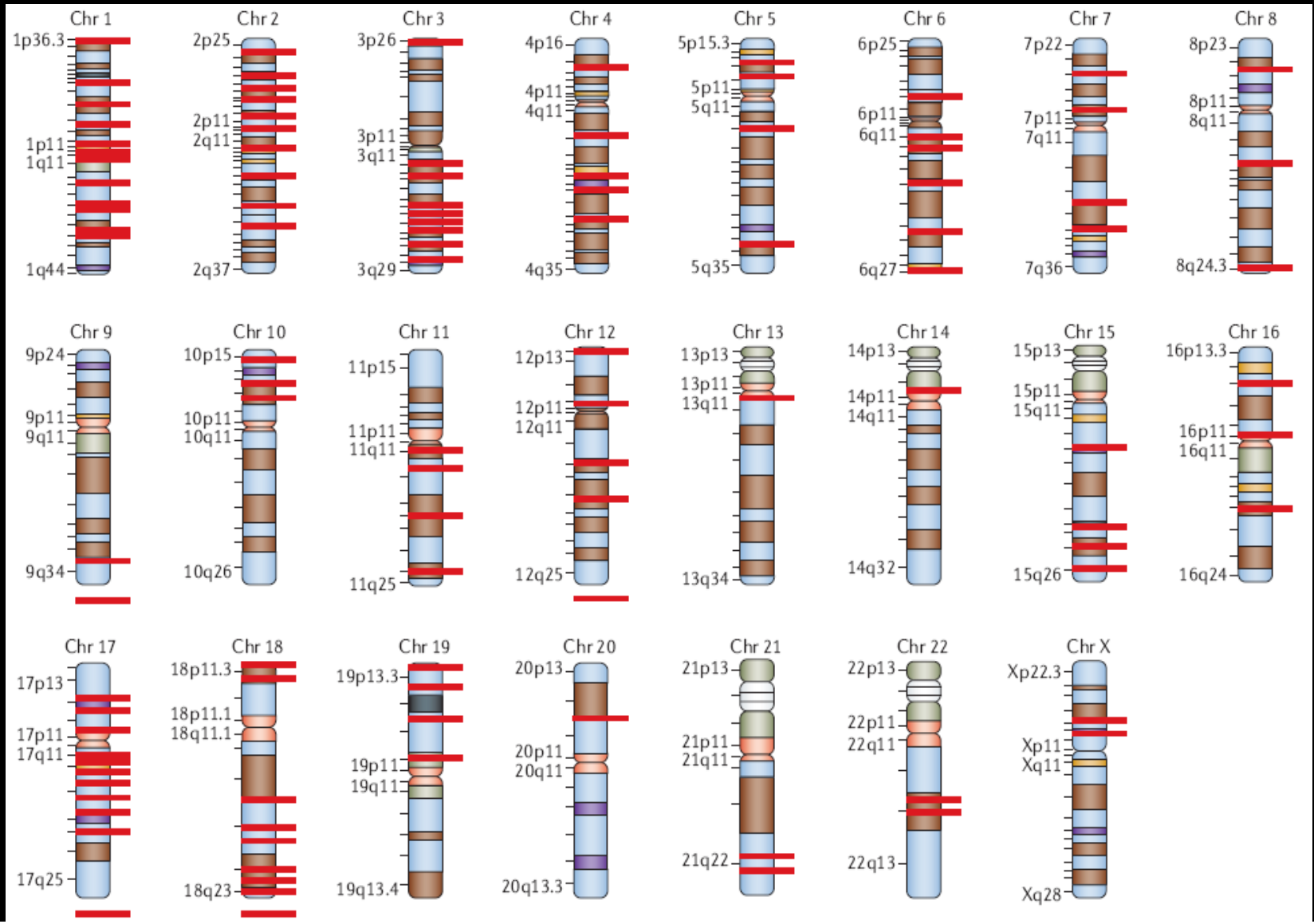
- Polimorfismi di Singolo Nucleotide (SNPs)
- Polimorfismi di lunghezza (STRs)
- Modificazioni epigenetiche del DNA
- Inserzioni
- Delezioni
- Polimorfismi del numero di copie
- Riarrangiamenti Citogenetici

Classificazione dei biomarker genomici

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


Utilità Clinica
Evidenza Scientifica
Potere predittivo
Utilità clinica
Validità Scientifica

Hypertension QTLs in the human genome



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

The Wellcome Trust Case Control Consortium*

NATURE Vol 447 7 June 2007

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	$\log_{10}$(BF), additive	$\log_{10}$(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

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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	$\log_{10}$(BF), additive	$\log_{10}$(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

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Gene Symbol	Variant	Genotype Comparison	Risk Variant Control Frequency	Odds Ratio (95% CI)	2-Tailed *P* Value	Genotype Frequency Difference
ABCA1	−477C/T[7,8]	TT vs CT or CC	0.222	1.13 (0.88-1.45)	.35	0.0215
ABCA1	Lys219Arg[9,10]	A vs G	0.274	1.02 (0.87-1.20)	.83	0.0041
ACE1	indel[4]	DD vs DI or II	0.286	1.07 (0.85-1.35)	.60	0.0139
ADD1	Gly460Trp[11,12]	T vs G	0.199	1.09 (0.91-1.32)	.35	0.0148
ADRB2§	Glu27Gln[13]	G vs C	0.441	0.93 (0.80-1.08)	.34	−0.0186
ADRB2	Ile164Thr[13]	CC vs CT	0.989	0.47 (0.20-1.13)	.10	−0.0117
ADRB2	Gly16Arg[13]	A vs G	0.377	1.04 (0.89-1.20)	.67	0.0082
ADRB3	Arg64Trp[14]	C vs T	0.077	0.99 (0.76-1.31)	>.99	−0.0004
AGT	Thr235Met[15]	T vs C	0.572	1.04 (0.89-1.20)	.65	0.0086
AGTR1	A1166C[16]	CC vs CA or AA	0.092	1.08 (0.76-1.53)	.72	0.0063
ALOX5AP	HAP B[17]	HAP B vs non-B	0.062	1.12 (0.90-1.40)	.31	0.0120
ALOX5AP	HAP A[17]	HAP A vs non-A	0.165	0.90 (0.75-1.10)	.32	−0.0130
APOA1	C83T[18]	T vs C	0.173	0.99 (0.81-1.20)	.92	−0.0019
APOA1	−75G/A[19]	A vs G	0.004	1.95 (0.68-5.54)	.23	0.0037
APOE	Arg158Cys[20]	CC vs CT or TT	0.023	1.61 (0.85-3.02)	.17	0.0134
APOE	−219T/G[21]	T vs G	0.475	1.14 (0.99-1.32)	.08	0.0329
BDKRB2	−58C/T[22]	C vs T	0.590	0.93 (0.80-1.08)	.37	−0.0169
CCL11†	Thr23Ala[23]	C vs T	0.837	0.97 (0.80-1.19)	.80	−0.0036
CCR2	Val64Ile[24]	GG vs AG or AA	0.855	0.94 (0.70-1.25)	.71	−0.0082
CCR5	Indel[25]	I vs D	0.907	0.79 (0.62-1.00)	.05	−0.0224
CD14	−159C/T[26]	TT vs CT or CC	0.237	1.10 (0.86-1.39)	.46	0.0170
CETP	intron1 G/A[27]	G vs A	0.568	0.93 (0.81-1.08)	.37	−0.0169
CETP	−629C/A[28]	C vs A	0.505	0.96 (0.83-1.11)	.60	−0.0104
COMT†	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
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

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

Thomas M. Morgan, MD
Harlan M. Krumholz, MD, MS
Richard P. Lifton, MD, PhD
John A. Spertus, MD, MPH

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 identifed 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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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.

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

Author Affiliations: Department of Genetics, Howard Hughes Medical Institute (Drs Morgan and Lifton), Robert Wood Johnson Clinical Scholars Program and Department of Internal Medicine (Dr Krumholz), Yale University School of Medicine, New Haven, Conn, and Mid-America Heart Institute and University of Missouri-Kansas City, Mo (Dr Spertus). Dr Morgan is now with the Department of Pediatrics, Division of Genetics and Genomic Medicine, Washington University School of Medicine, St Louis, Mo.
Corresponding Author: Thomas M. Morgan, MD, Washington University School of Medicine, McDonnell Pediatric Research Bldg, 3103, 660 Euclid Ave, St Louis, MO 63110, (email: morgan_t@kids.wustl.edu) or Richard P. Lifton, MD, PhD, Yale University School of Medicine, 295 Congress Ave, New Haven, CT 06510 (richard.lifton@yale.edu).

Gene	Variant	Genotype	No. (%) Cases	No. (%) Controls	2-Tailed *P* Value
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	I/D	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	
ALOX5AP	HAP A	A	124 (15.9)	122 (17.4)	.35
		non-A	654 (84.1)	584 (82.6)	
			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)	
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)	

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Gene	Variant	Genotype	No. (%) Cases	No. (%) Controls	2-Tailed *P* Value
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)	
LTA	A252G	AA	394 (49.1)	282 (429)	.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)	

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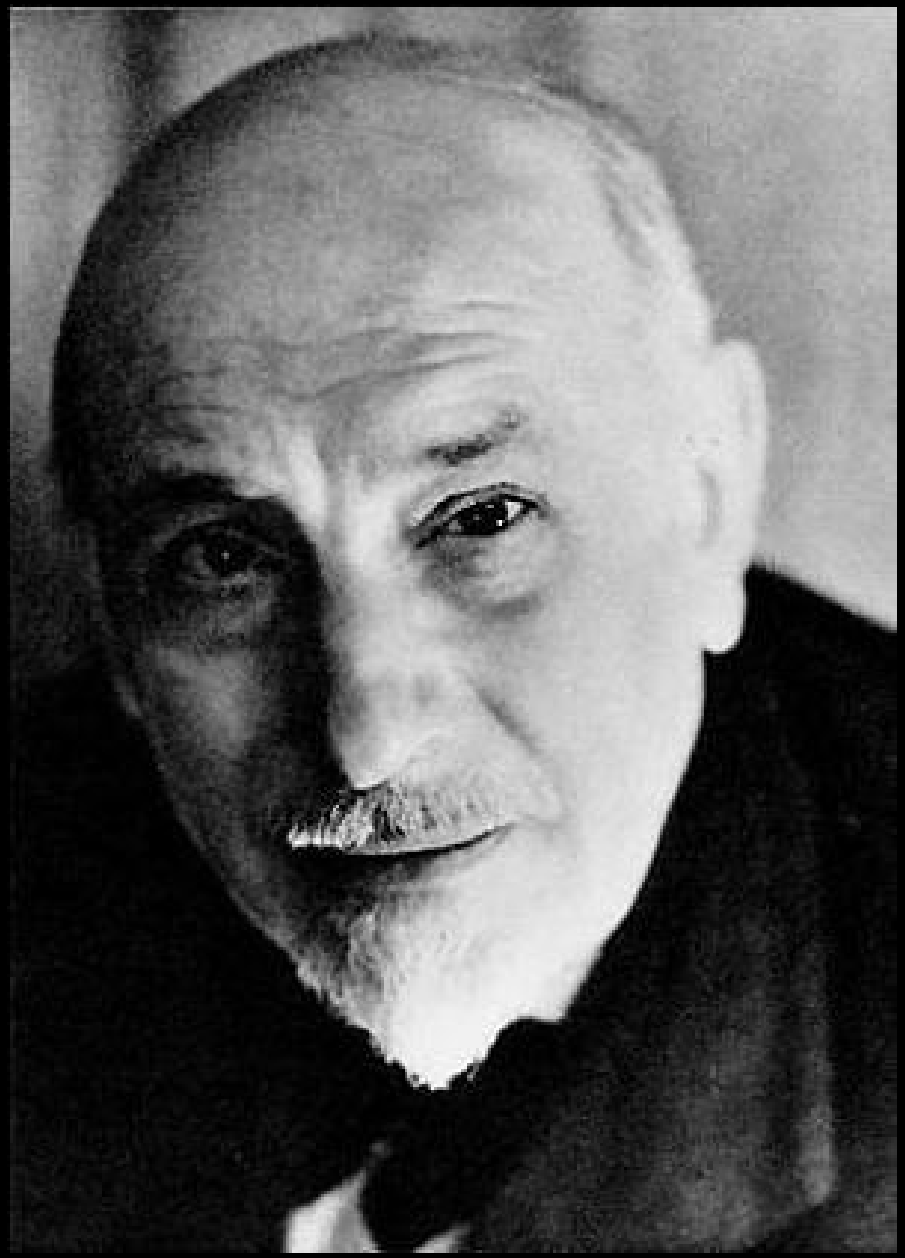
Gene	Variant	Genotype	No. (%) Cases	No. (%) Controls	2-Tailed *P* Value
PTGS2	−765G/C	CC	15 (1.9)	21 (3.3)	.17
		CG	202 (25.5)	174 (27.1)	
		GG	576 (72.6)	447 (69.6)	
RECQL2	Arg1367Cys	CC	66 (8.2)	38 (5.8)	.03
		CT	326 (40.5)	239 (36.7)	
		TT	412 (51.2)	375 (57.5)	
SELE	Leu554Phe	CC	740 (91.9)	611 (92.9)	.47
		CT	63 (7.8)	47 (7.1)	
		TT	2 (0.2)	0	
SELE	Ser128Arg	AA	658 (82.0)	528 (80.4)	.71
		AC	137 (17.1)	123 (18.7)	
		CC	7 (0.9)	6 (0.9)	
SELP	Thr715Pro	AA	646 (80.2)	530 (80.8)	.22
		AC	150 (18.6)	124 (18.9)	
		CC	9 (1.1)	2 (0.3)	
TFPI	Val264Met	AA	758 (95.9)	625 (95.0)	.45
		AG	32 (4.1)	33 (5.0)	
		GG	0	0	
THBD	−33G/A	AA	801 (99.6)	638 (99.8)	.63
		AG	3 (0.4)	1 (0.2)	
		GG	0	0	
THBD	Ala25Thr	AA	794 (98.6)	652 (98.9)	.64
		AG	11 (1.4)	7 (1.1)	
		GG	0	0	
THBD	Ala455Val	CC	531 (67.0)	433 (65.9)	.91
		CT	237 (29.9)	203 (3.9)	
		TT	24 (3.0)	21 (3.2)	
THBS1	Asn700Ser	AA	614 (76.3)	507 (77.2)	.74
		AG	177 (22.0)	136 (20.7)	
		GG	14 (1.7)	14 (2.1)	
THBS2	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)	
THBS4	Ala387Pro	CC	49 (6.1)	40 (6.1)	.85
		CG	268 (33.4)	229 (34.8)	
		GG	486 (60.5)	389 (59.1)	
THPO	A5713G	AA	187 (23.3)	159 (24.2)	.30
		AG	374 (46.6)	324 (49.4)	
		GG	241 (30.0)	173 (26.4)	
TLR4	Gly299Asp	AA	702 (88.7)	579 (88.4)	.89
		AG	88 (11.1)	76 (11.6)	
		GG	1 (0.1)	0	
TNF	−308G/A	AA	17 (2.1)	14 (2.2)	.27
		AG	189 (23.5)	176 (27.2)	
		GG	597 (74.3)	457 (70.6)	
TNFRSF1A	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)!!!!



Studi consorziati (banche DNA)

Familiarità

Epistasi

Fattori protettivi

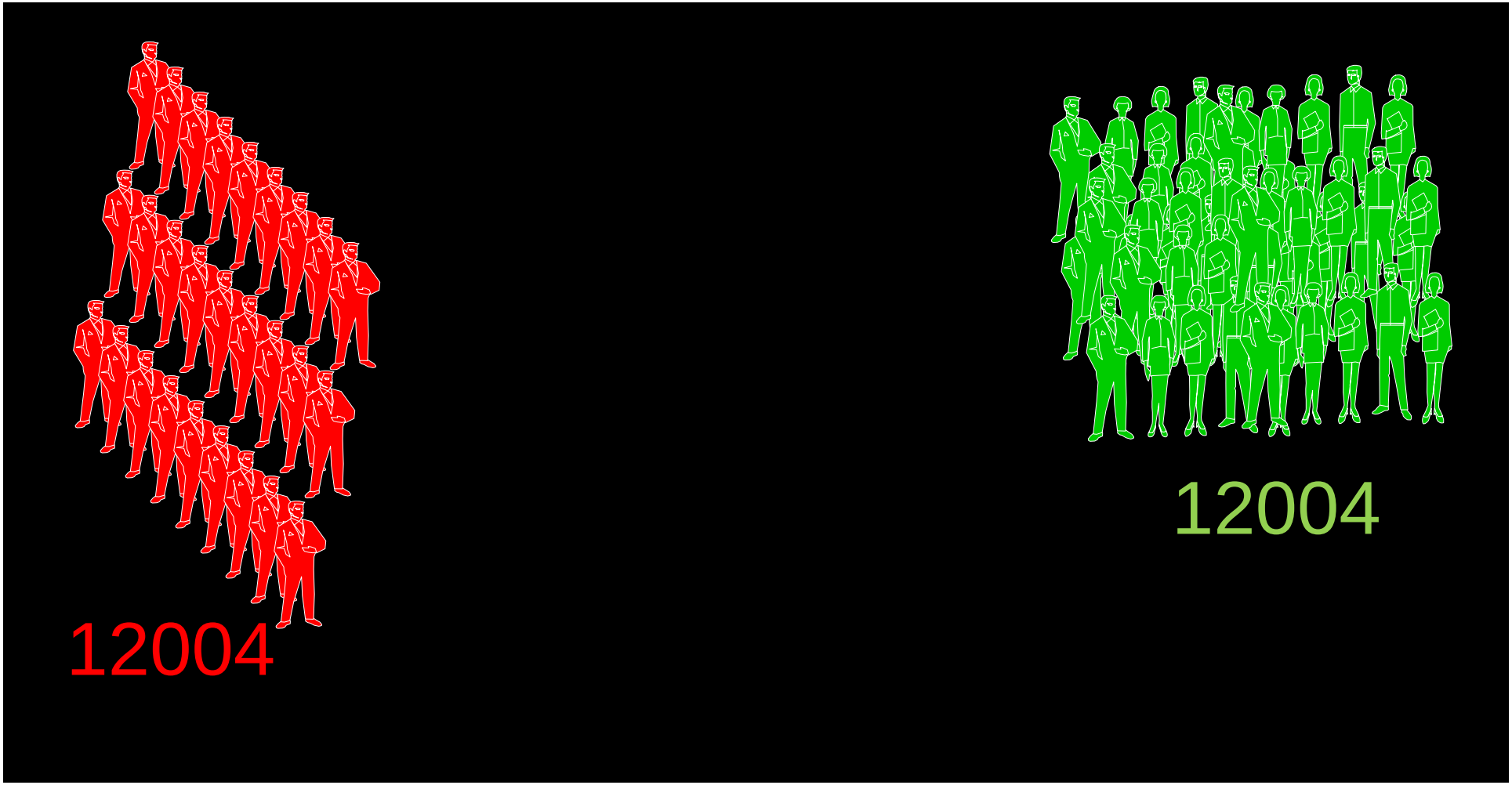
Variabilità fattori ambientali

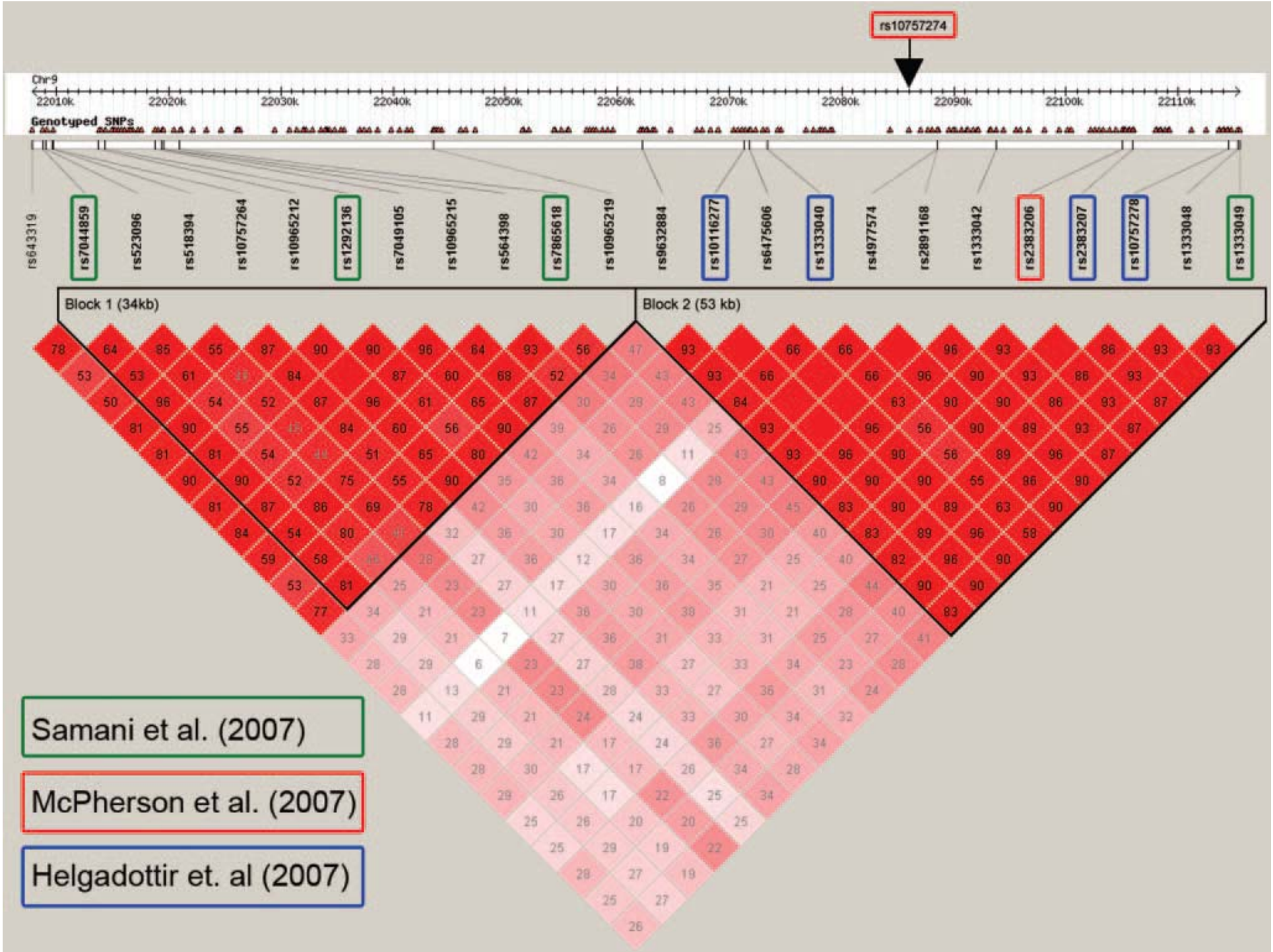
Eterogeneità fattotri genetici

Genetics

Repeated Replication and a Prospective Meta-Analysis of the Association Between Chromosome 9p21.3 and Coronary Artery Disease

(*Circulation*. 2008;117:1675-1684.)




rs10757274
Chr 9
22010k
22020k
22030k
22040k
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22060k
22070k
22080k
22090k
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22110k
Genotyped SNPs
rs643319
rs7044859
rs523096
rs518394
rs10757264
rs10965212
rs1292136
rs7049105
rs10965215
rs564398
rs7865618
rs10965219
rs9632884
rs10116277
rs6475606
rs1333040
rs4977574
rs2891168
rs1333042
rs2383206
rs2383207
rs10757278
rs1333048
rs1333049
Block 1 (34kb)
Block 2 (53 kb)
Samani et al. (2007)
McPherson et al. (2007)
Helgadottir et. al (2007)

Table 4. Allelic Effect of the rs1333049-C Allele According to the Haplotypic Backgrounds Derived From rs7044859, rs1292136, and rs7865618

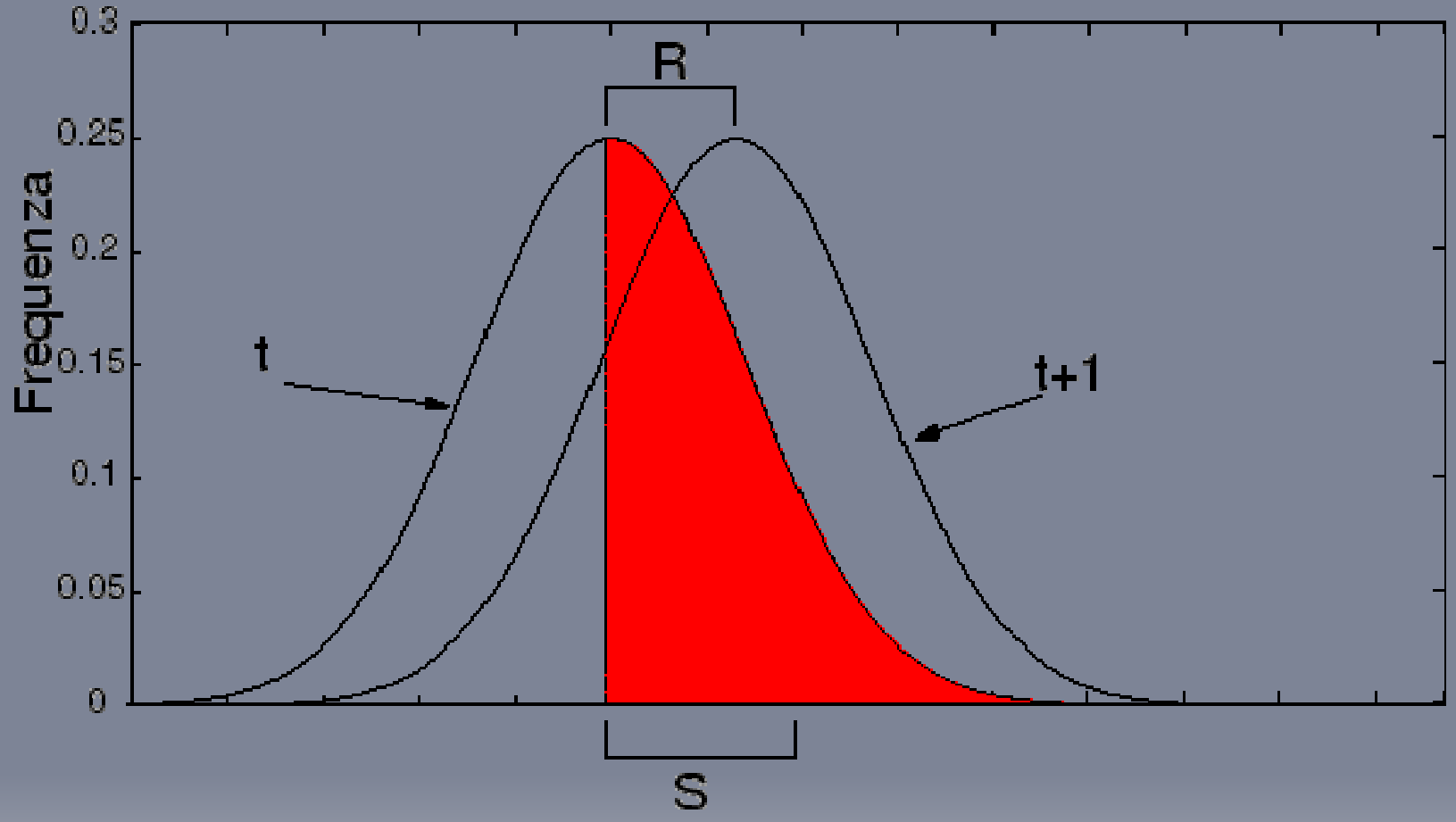
	Haplotypic Background		
Study	TTA	TTG	ACA
GerMIFS II	0.91 (0.51–1.65)	1.05 (0.73–1.50)	1.35 (1.03–1.76)
UK MI study	0.72 (0.39–1.34)	1.31 (0.93–1.85)	1.37 (1.05–1.79)
Left Main Disease study	0.79 (0.38–1.63)	0.93 (0.61–1.42)	1.31 (0.89–1.92)
MONICA/KORA study	1.58 (0.92–2.73)	1.20 (0.82–1.75)	1.27 (0.96–1.68)
PopGen	0.96 (0.55–1.69)	1.12 (0.84–1.48)	1.73 (1.39–2.16)
Test for homogeneity across studies	0.36	0.78	0.39
Pooled OR (95% CI)	0.99 (0.76–1.30)	1.12 (0.96–1.31)	1.44 (1.27–1.62)
	0.94	0.14	4.08×10^{-9}

Allelic OR (95% CI) associated with the rs1333049-C allele according to the 3 haplotypic backgrounds by which it was carried: TTA-, TTG-, and ACA-. These backgrounds are composed of the alleles at the rs7044859 (T/A), rs1292136 (C/T), and rs7865618 (A/G) SNPs.

SCIENTIFIC EVIDENCE
≠
CLINICAL UTILITY


35
36
74
50
79
48
24
14
40
49


tombola

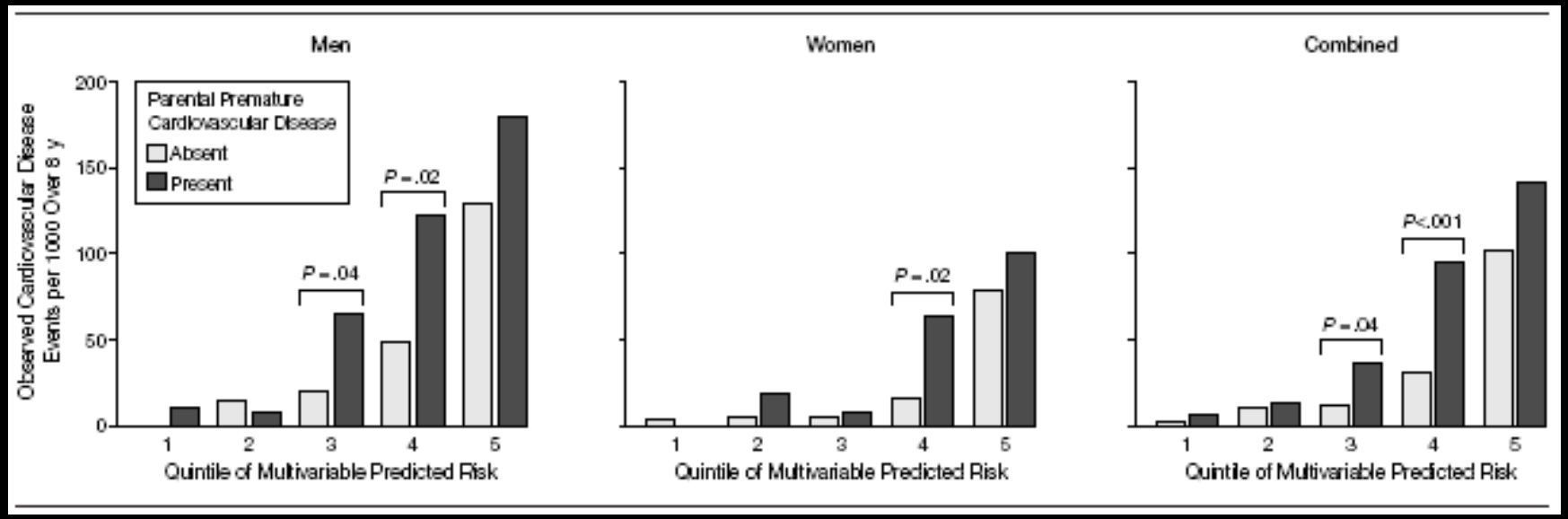

0.3
0.25
0.2
0.15
0.1
0.05
0
Frequenza
R
S
t
t+1

Rischio relativo: rapporto tra la frequenza di una malattia multifattoriale in un consanguineo della persona affetta e la frequenza della stessa malattia nella popolazione generale.

$$\lambda_r = \frac{\text{frequenza della malattia nei consanguinei di grado r della persona affetta}}{\text{frequenza della malattia nella popolazione generale}}$$

r = grado di consanguineità

Familiarità



Donald et al., 2004

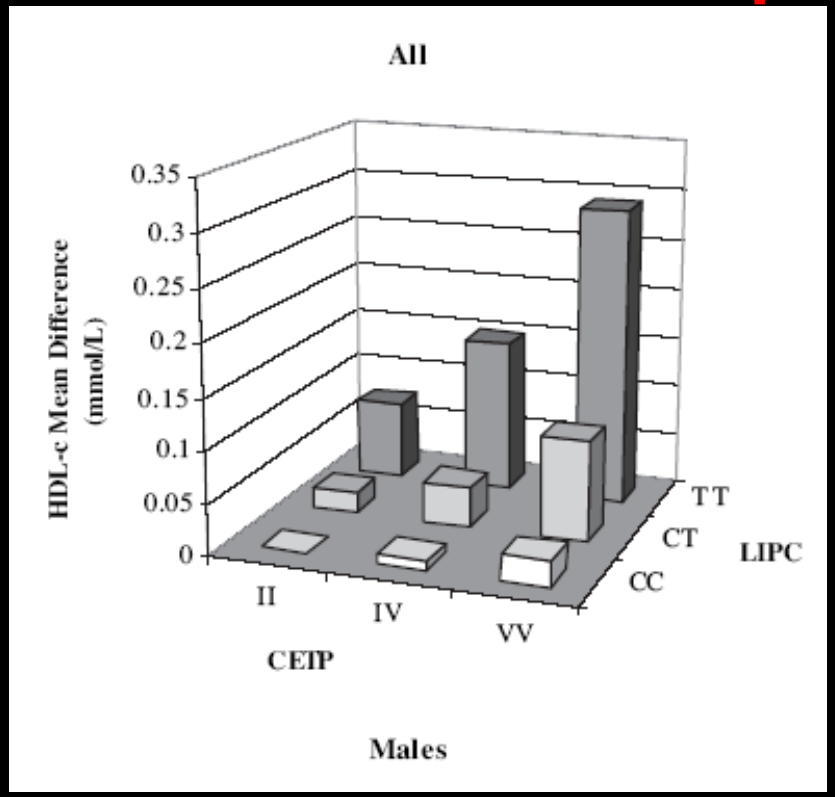
Gene	Variant	Genotype	No. (%) Cases	No. (%) Controls	2-Tailed *P* Value
ABCA1	−477C/T	CC	191 (24.6)	182 (28.3)	.27
		CT	396 (51.0)	319 (49.5)	
		TT	189 (24.4)	143 (22.2)	
ABCA1	Lys219Arg	AA	65 (8.2)	46 (7.1)	.69
		AG	311 (39.3)	263 (40.6)	
		GG	416 (52.5)	338 (52.2)	
ACE1	I/D	DD	233 (30.0)	185 (28.6)	.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	
ALOX5AP	HAP A	A	124 (15.9)	122 (17.4)	.35
		non-A	654 (84.1)	584 (82.6)	
			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)	
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)	

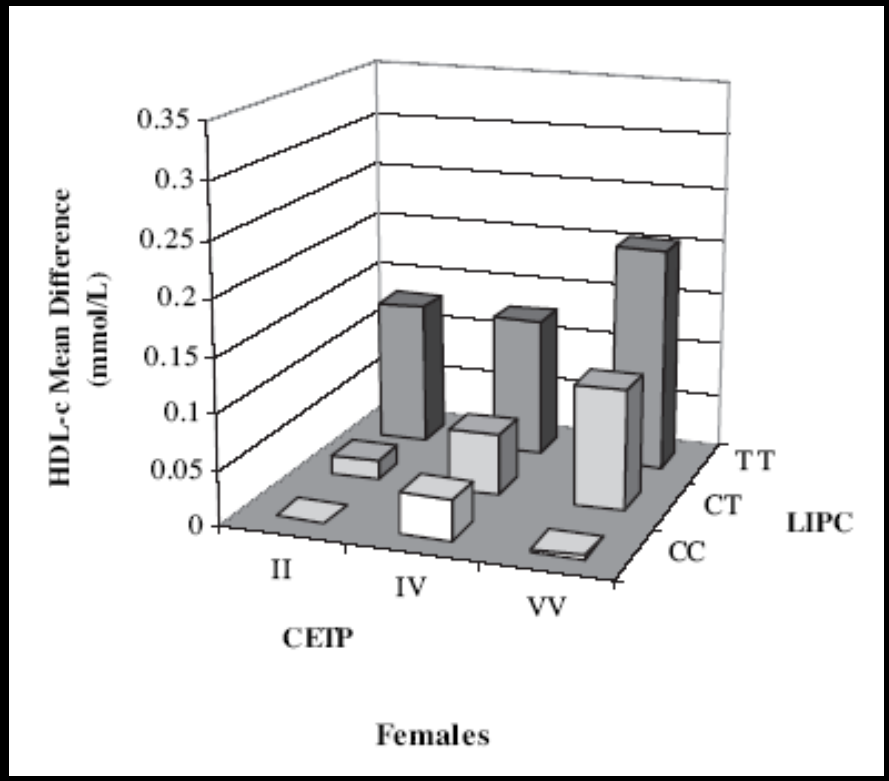
Gene	Variant	Genotype	No. (%) Cases	No. (%) Controls	2-Tailed *P* Value
F5	Arg506Gln	AA	1 (0.1)	1 (0.2)	.95
		AG	36 (4.5)	31 (4.7)	
		GG	769 (95.4)	623 (95.1)	
F7	Arg353Gln‡	AA	16 (2.0)	6 (0.9)	.22
		AG	148 (18.7)	129 (19.6)	
		GG	629 (79.3)	522 (79.5)	
FGB	−455A/G	AA	24 (3.0)	26 (4.0)	.08
		AG	247 (30.7)	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)	
LTA	A252G	AA	394 (49.1)	282 (429)	.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)	

Il CETP è coinvolto nel metabolismo dei lipidi, mediando lo scambio di lipidi tra lipoproteine mediante il trasferimento di esteri del colesterolo dalle HDL alle lipoproteine ricche di trigliceridi, con conseguente riduzione dei livelli di HDL. Il polimorfismo dell'introne 1 del gene CETP G279A aumenta le concentrazioni del CETP e riduce i livelli di HDL a favore di LDL e VLDL.

Col nome di *lipasi* ci si riferisce a un gruppo di enzimi che scindono i grassi mediante l'idrolisi dei trigliceridi dividendoli cioè in glicerolo e acidi grassi.

Epistasi


All
HDL-c Mean Difference (mmol/L)
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
II
IV
VV
CEIP
TT
CT
CC
LIPC
Males


HDL-c Mean Difference (mmol/L)
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
II
IV
VV
CEIP
TT
CT
CC
LIPC
Females

	AA	Aa	aa
BB	+	-	-
Bb	-	+	-
bb	-	-	+

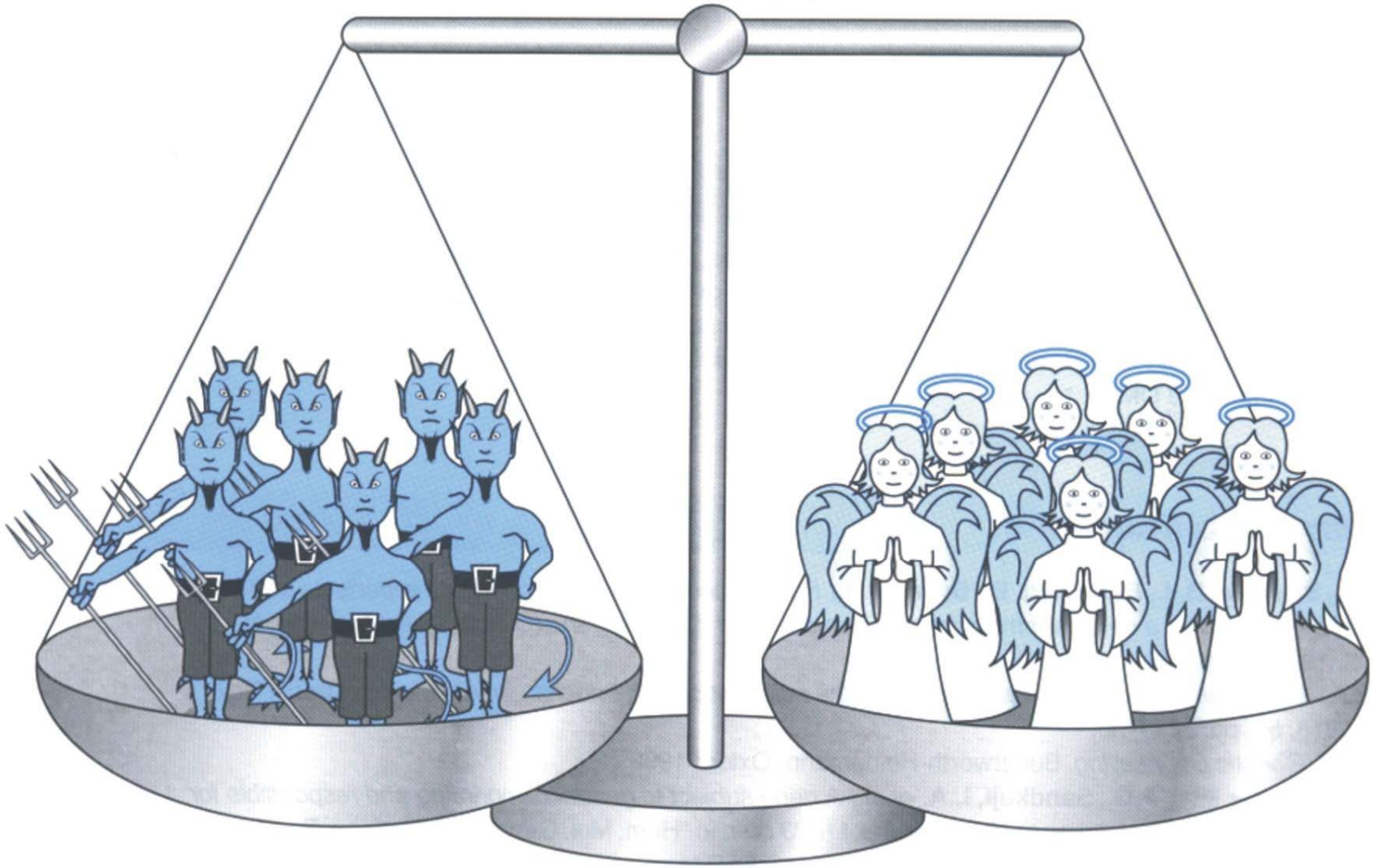
Human Case-Control Study

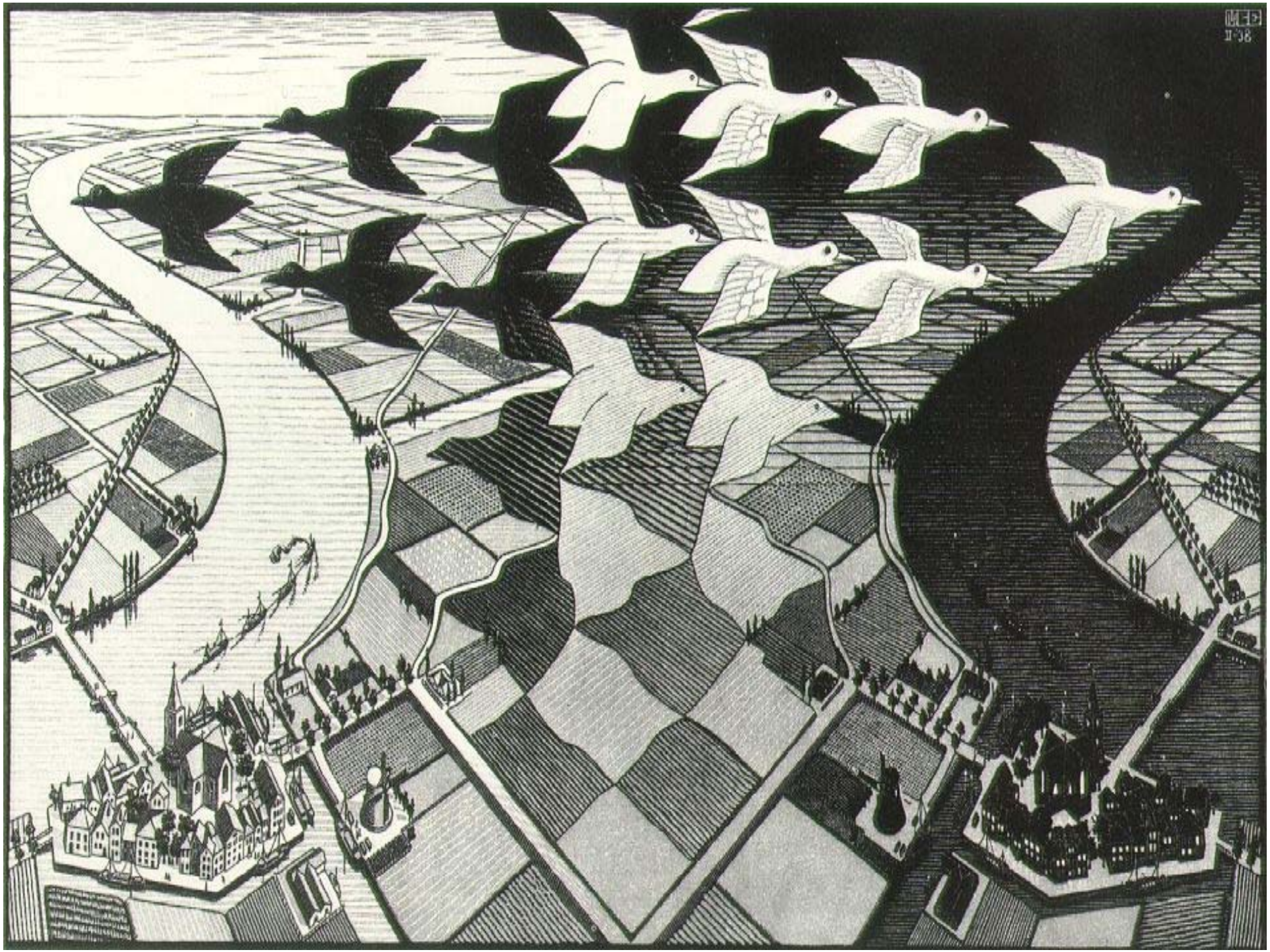
Controls

	AA	Aa	aa	
BB	0	100	100	200
Bb	100	200	100	400
bb	100	100	0	200
	200	400	200	800

Cases

	AA	Aa	aa	
BB	200	0	0	200
Bb	0	400	0	400
bb	0	0	200	200
	200	400	200	800




M.C.E.
1938

AMD

- Causa principale di cecità nella popolazione al di sopra dei 50’anni di età, nei paesi sviluppati

- 8 milioni di affetti in USA;
- 14 milioni previsti nel 2020;
- Ereditabilità : oltre il 71%

CFH	O.R.
heterozygous	2.1-4.6
homozygous	3.3-7.4

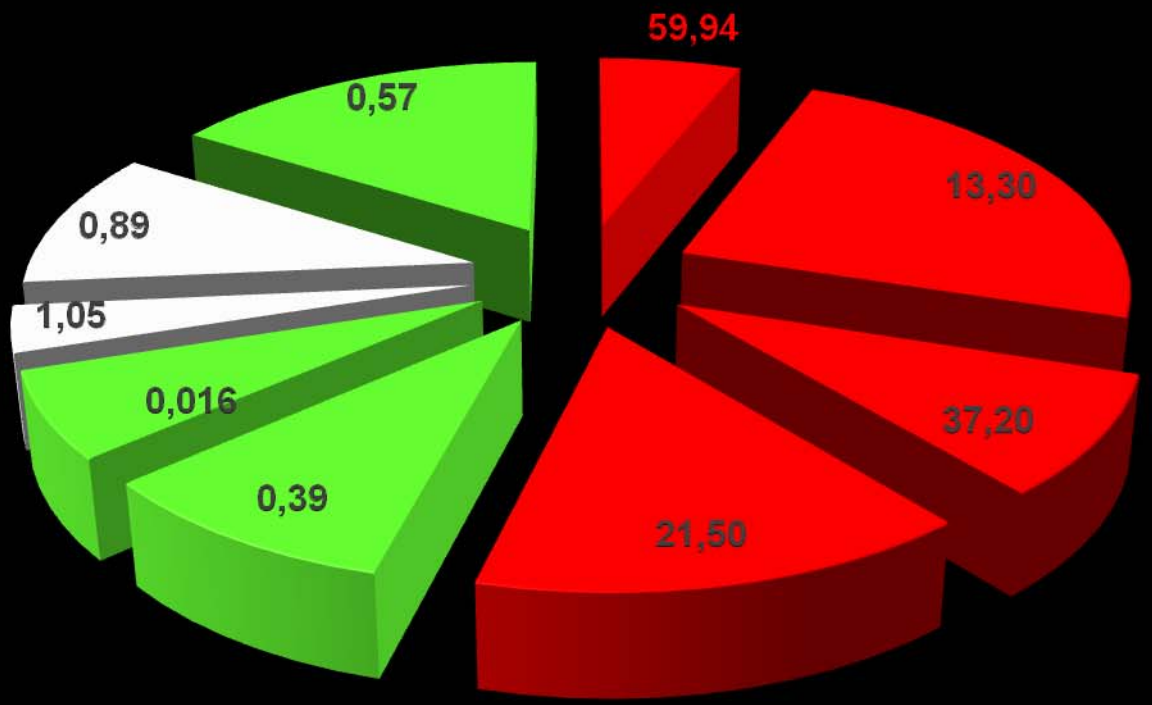
Jager at al., *NEJM*, 2008

ARMS2	O.R.
heterozygous	2.9
homozygous	8.1

Authors	AMD				Control				CC/TT		TC/TT	
	N	Genotype			*N*	Genotype			OR	(95% CI)	OR	(95% CI)
		TT	*TC*	*CC*		*TT*	*TC*	*CC*				
Conley (37)	168	22	81	65	108	54	40	14	11.40	5.32, 24.39	4.97	2.66, 9.27
Edwards (38)	395	85	186	124	190	81	83	26	4.54	2.70, 7.65	2.14	1.43, 3.18
Hageman (39)	952	192	454	306	403	181	169	53	5.44	3.82, 7.76	2.53	1.93, 3.31
Klein (40)	95	14	39	42	48	17	25	6	8.50	2.80, 25.79	1.89	0.80, 4.51
Magnusson (41)	1330	264	644	422	1265	470	613	182	4.13	3.28, 5.20	1.87	1.55, 2.25
Rivera (44)[a]	1166	199	530	437	946	355	475	116	6.72	5.14, 8.79	1.99	1.61, 2.46
Souied (42)	141	30	63	48	91	47	33	11	6.84	3.07, 15.21	2.99	1.61, 5.57
Zareparsi (43)	616	86	311	219	275	114	136	25	11.61	7.05, 19.14	3.03	2.15, 4.23
Pooled OR									6.32	4.25, 9.48	2.50	1.96, 3.30
λ (95% CI)										0.50 (0.34, 0.71)		

Thakkinstian et al., 2006

O.R. per combinazioni genotipiche



PREDICTIVE MEDICINE

+

INNOVATIVE MEDICINES

↓

PATIENT-TARGETED THERAPIES

Right Medicine

Right Patient

Right Disease

Right Time

Right Dose

Right Response

I test che devono/possono essere fatti
I biomarker farmacogenomici validi

- **L'FDA ha finora identificato 28 "valid genomic biomarkers in the context of approved drug labels"**
- **Il test genomico è "richiesto" per la sommistrazione di 4 farmaci**
- **Il test genomico è "raccomandato" per 10 farmaci**
- **Per 14 farmaci sono contenute informazioni**

Test obbligatori

Trastuzumab* (breast cancer)	Her2 expression	**Test required** Her2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy
Cetuximab* (colorectal carcinoma)	EGFR expression	**Test required** Indicated in the treatment of EGFR expressing colorectal carcinoma..
Dasatinib * (acute lymphoblastic leukemia)	Philadelphia chromosome presence	**Test required** Indicated for Philadelphia chromosome positive acute lymphoblastic leukemia
Maraviroc (HIV-1 infection)	*CCR5 - Chemokine C-C motif receptor*	**Test required** Indicated for treatment experienced adult patients infected with only CCR5-tropic HIV-1 detectable…

Test raccomandati

Irinotecan* (metastatic carcinoma of colon and rectum)	UGT1A1 mutations	**Test recommended** Individuals who are homozygous for the UGT1A*28 allele are at increased risk for neutropenia following initiation of camptosar treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A*28 allele. Heterozygous patients may be at increased risk of neutropenia; however clinical results have been variable and such patients have been shown to tolerate normal starting doses"
Abacavir	HLA-B*5701 allele presence	**Test recommended** *Risk Factor: HLA-B*5701 Allele:* Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir
Atorvastatine (hypercholesterolemia)	Deficit and/or mutation of LDL receptor	**Test recommended** Dose adjustment for homozygous and heterozygous familail hypercholesterolemia

Test raccomandati 2

Warfarin (anticoagulant)	Protein C deficiency	**Test recommended** Deficiency in protein C or S has been assocoated with tissue necrosis following warfarin administration
Warfarin (anticoagulant)	Vitamin K epoxide reductase (VKORC1) Variants	**Test recommended** Certain SNPs in the VKORC1 gene have been associated with lower dose requirements for warfarin.
Warfarin (anticoagulant)	*CYP2C9 Variants*	**Test recommended** Increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles.

Test raccomandati 3

Rasburicase (plasma uric acid levels in cancer patients)	G6PD deficiency	**Test recommended** Can cause sever hemolisis in patients with G6PD deficiency
Valproic acid (treatment of seizures)	Urea Cycle Disorder (UCD) deficiency	**Test recommended** Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in pts with urea cycle disorder, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered…
Azathioprine (renal transplantation, rheumatoid arthritis)	TPMT variants	**Test recommended** TPMT deficiency or lower activity incresse risk of myelotoxicity. TPMP testing is recommended and consideration be given to either genotype or phenotype patienyts foir TPMT
Carbamazepine (hepilepsy)	HLA-B*1502	**Test recommended for at risk popolations** Should not be used in patients HLA-B*1502 positive…Tested patients found to be negative are thought to have a low risk for SJS/TEN

European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 January 2008
Doc.Ref. EMEA/CHMP/37314/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
POST-AUTHORISATION SUMMARY OF POSITIVE OPINION*
for
ZIAGEN

International Non-proprietary Name (INN): Abacavir Sulfate

On 24 January 2008 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion** to recommend the variation to the terms of the marketing authorisation for the medicinal product Ziagen. The Marketing Authorisation Holder for this medicinal product is Glaxo Group Limited.

The CHMP adopted a change to the indication as follows:

*"Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing."*

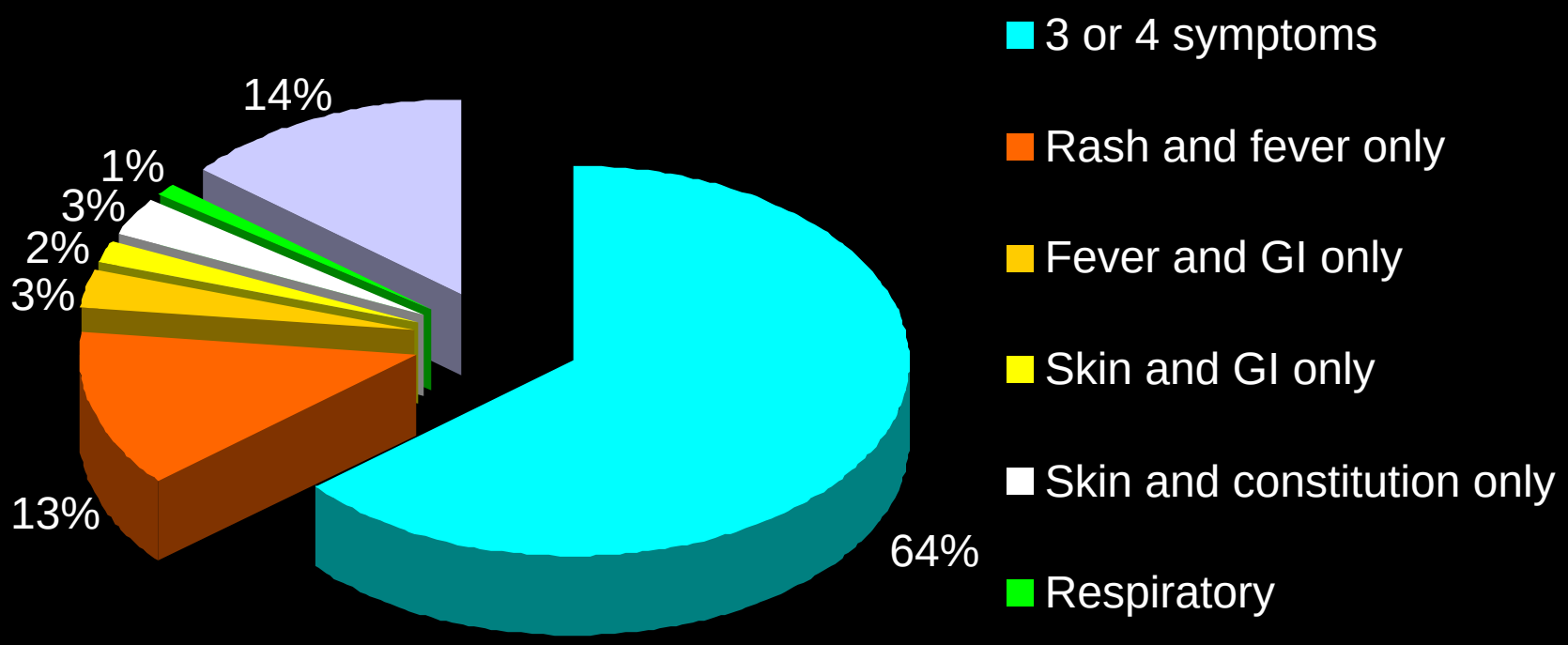
ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

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

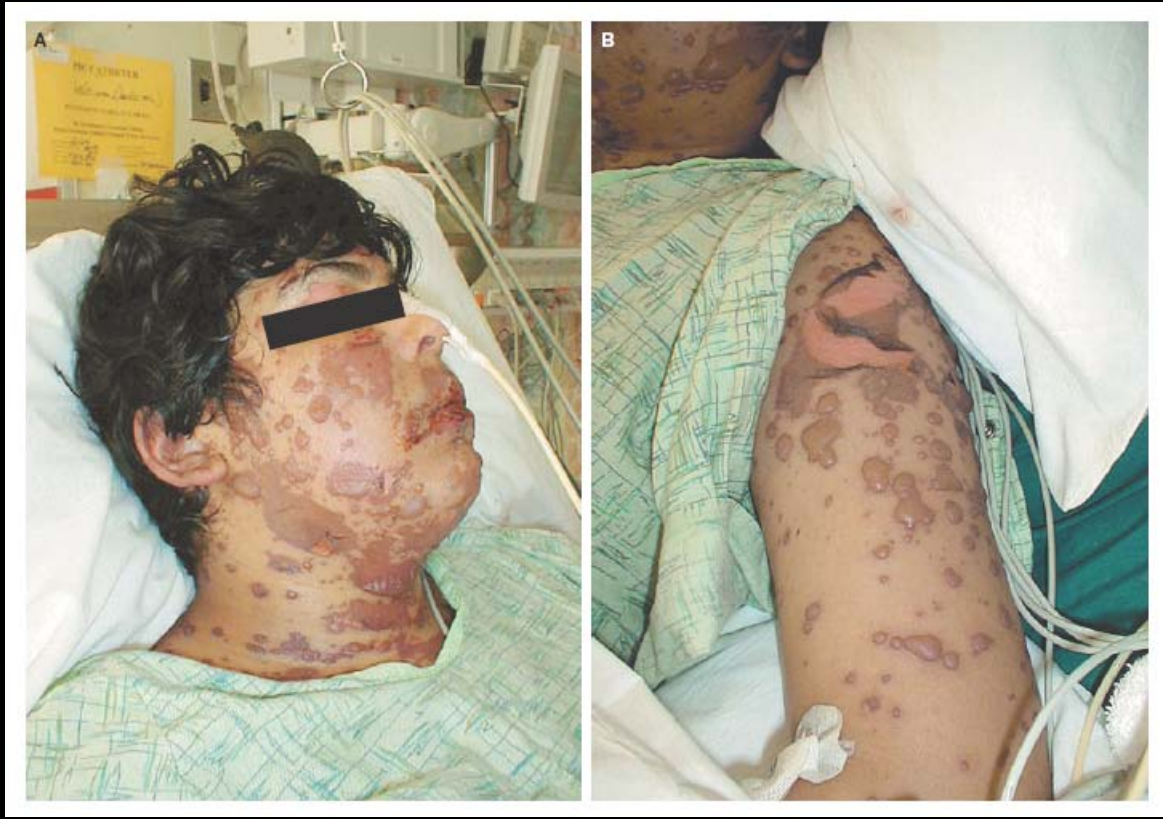
Combinazione di sintomi comunemente riportati con ipersensibilità (n=1,306)



Sintomi multipli sono tipicamente presenti nella maggioranza dei casi di ipersensibilità

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

Stevens–Johnson Syndrome

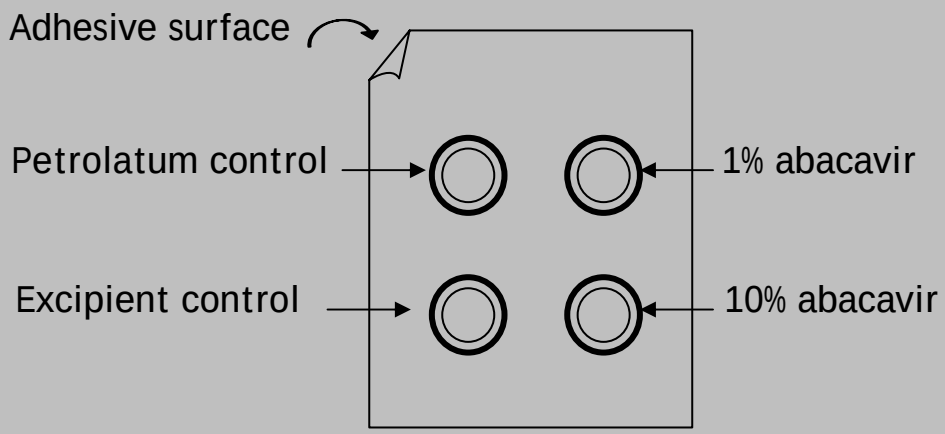


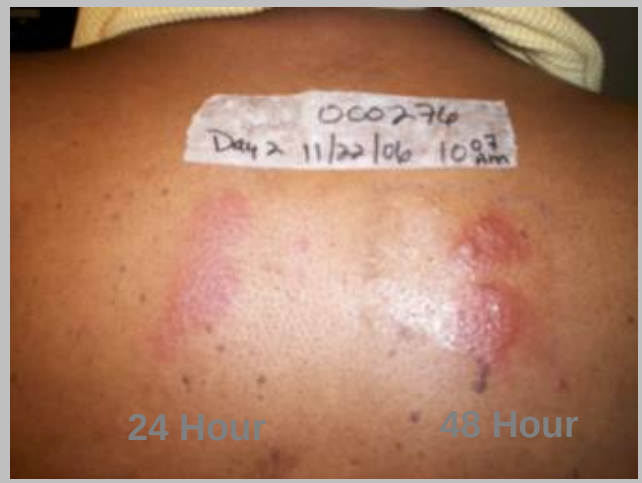
carbamazepine (CBZ), lamotrigine (LTG), phenobarbital (PHB), phenytoin (PHT), or valproic acid (VPA)

Abacavir Skin Patch Testing

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

Schematic top view of skin patch

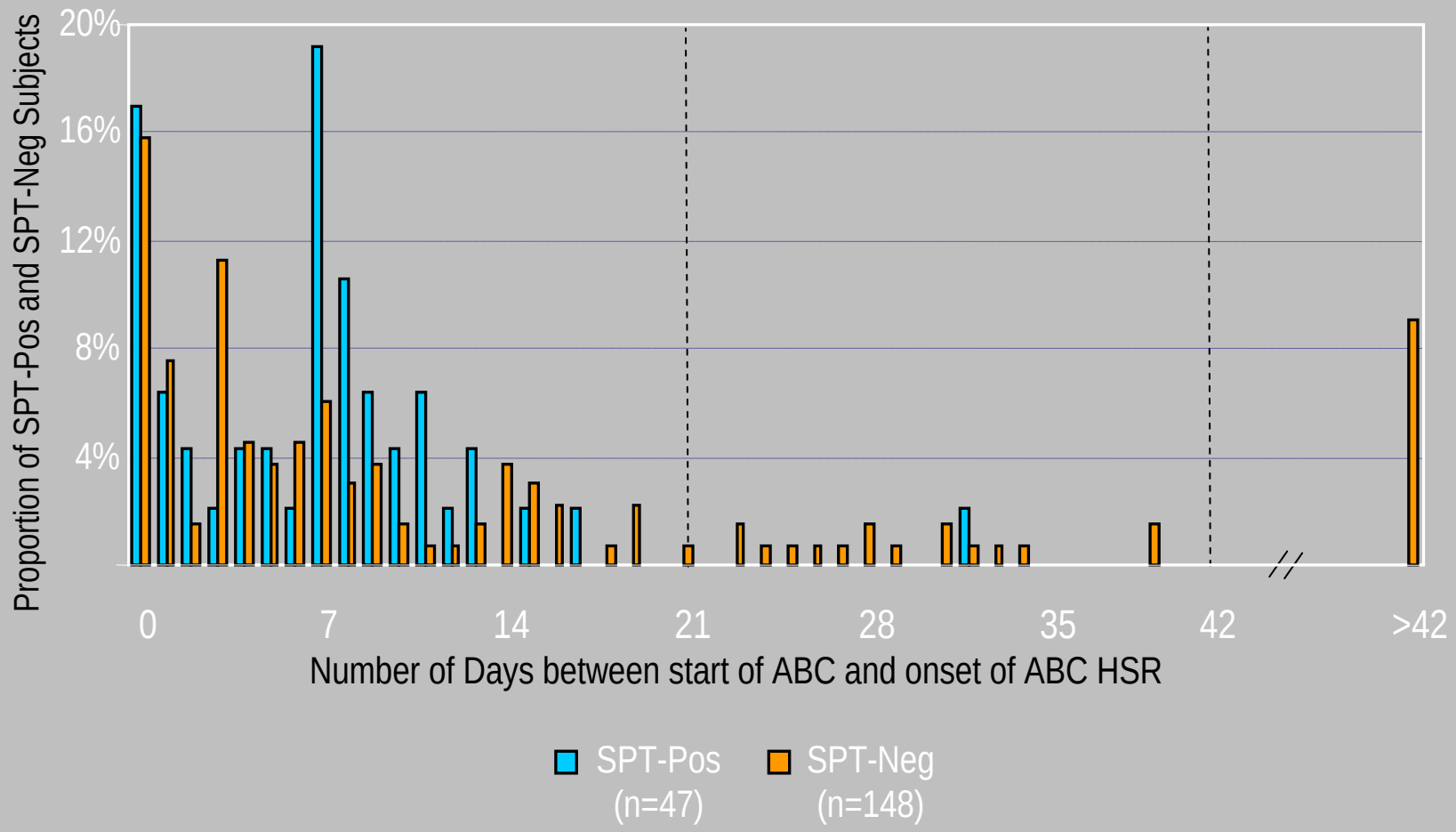




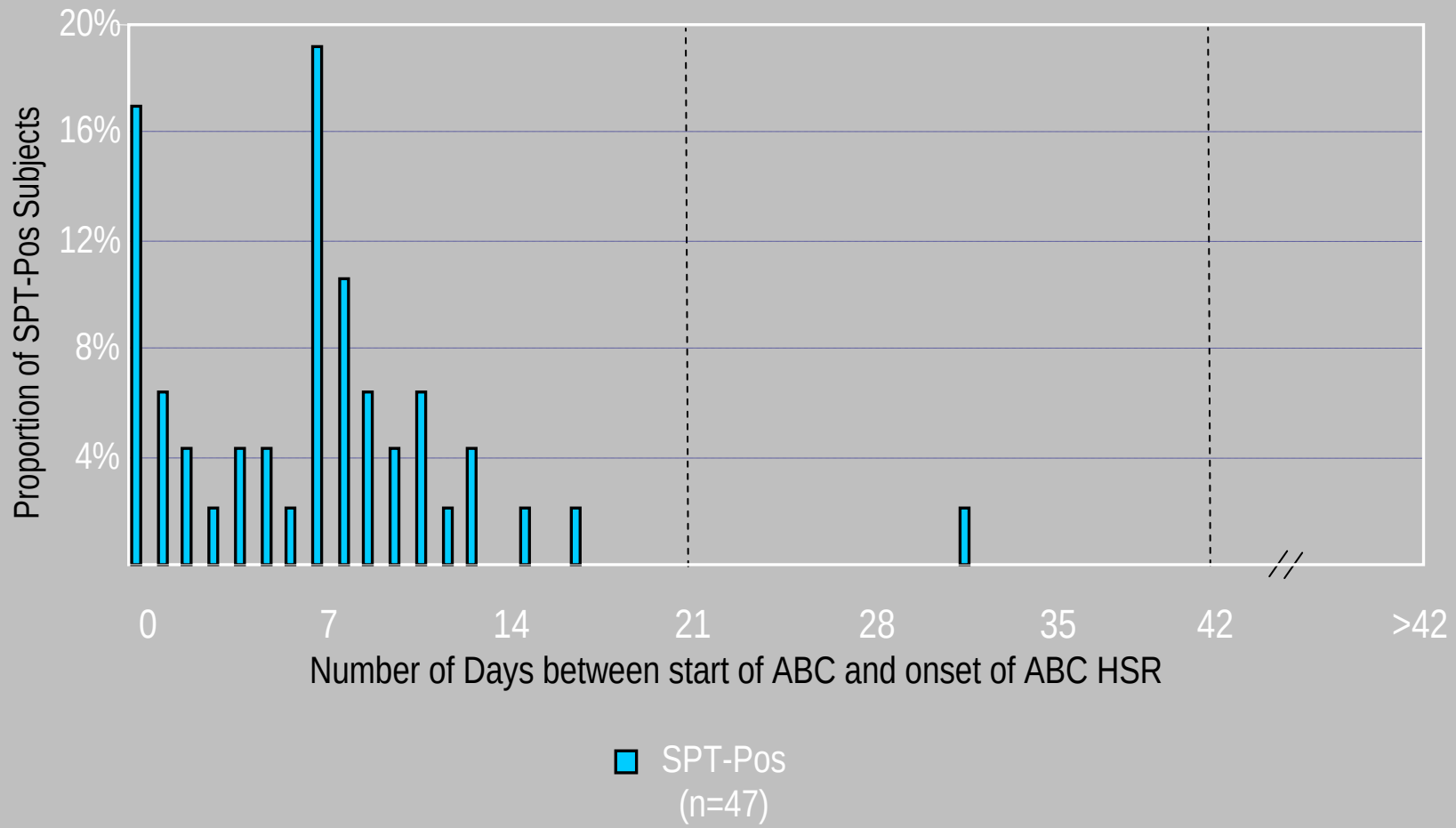
Phillips et al. AIDS 2002 and 2005

Phillips et al. IAS 2007 Abstract MOPEB001

Days to Onset of ABC HSR



Days to Onset of ABC HSR



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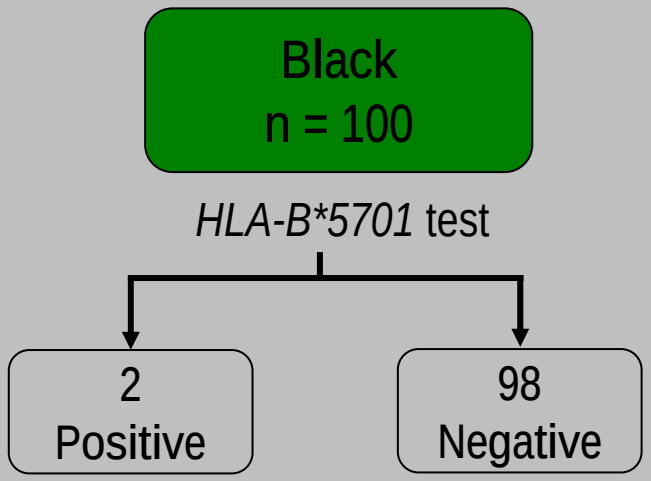
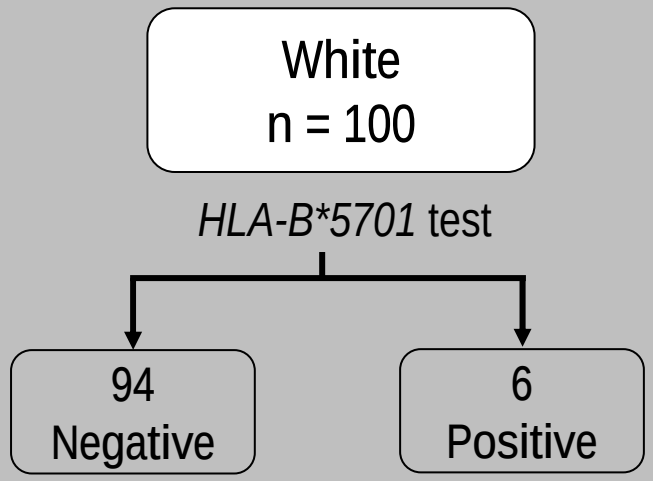
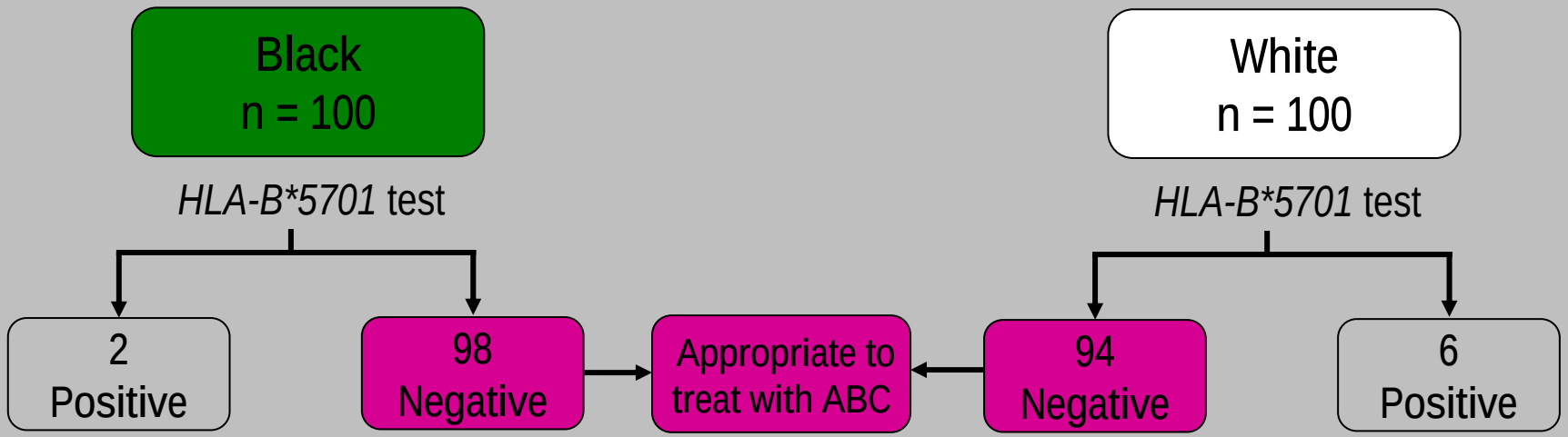
Screening Implications





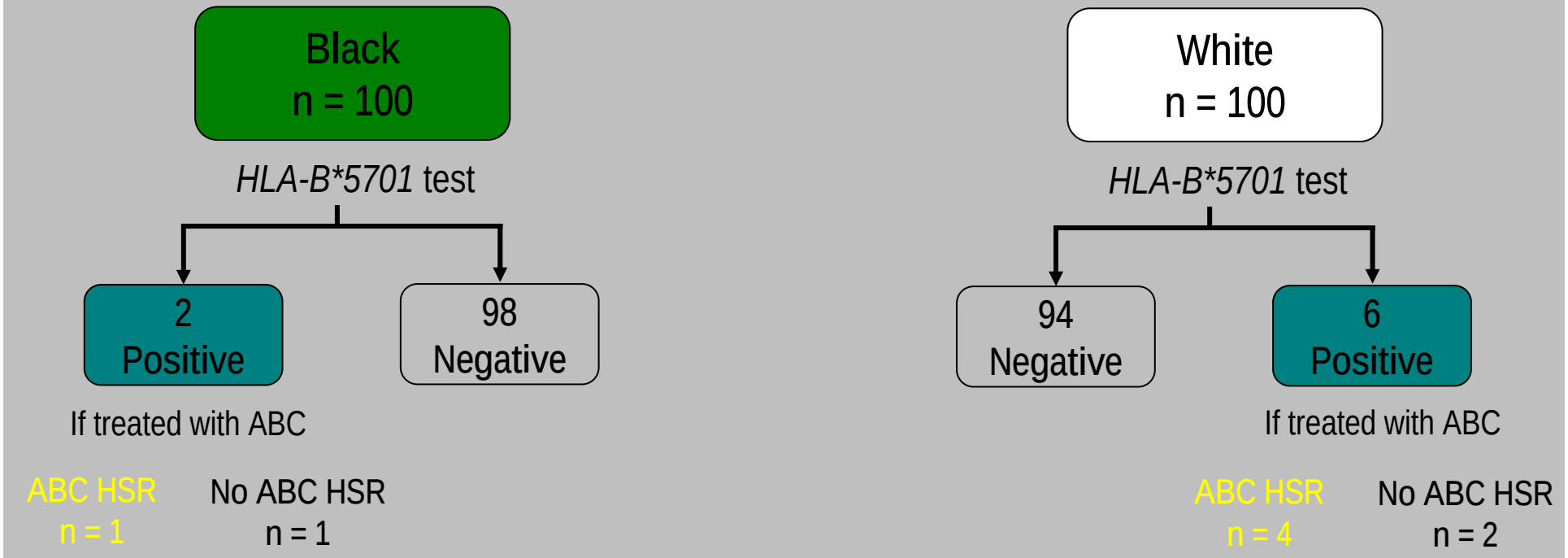
Example shown is based upon PPV derived from PREDICT-1 and SHAPE data.

Screening Implications



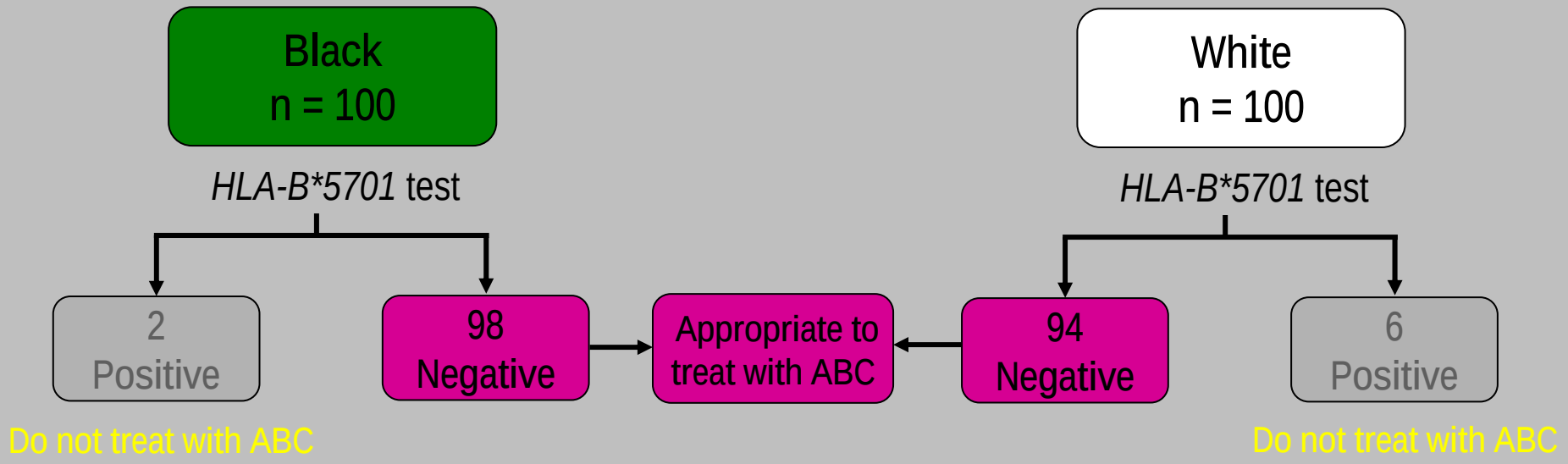
Example shown is based upon PPV derived from PREDICT-1 and SHAPE data.

Screening Implications



Example shown is based upon PPV derived from PREDICT-1 and SHAPE data.

Screening Implications



Test 100 Black patients:

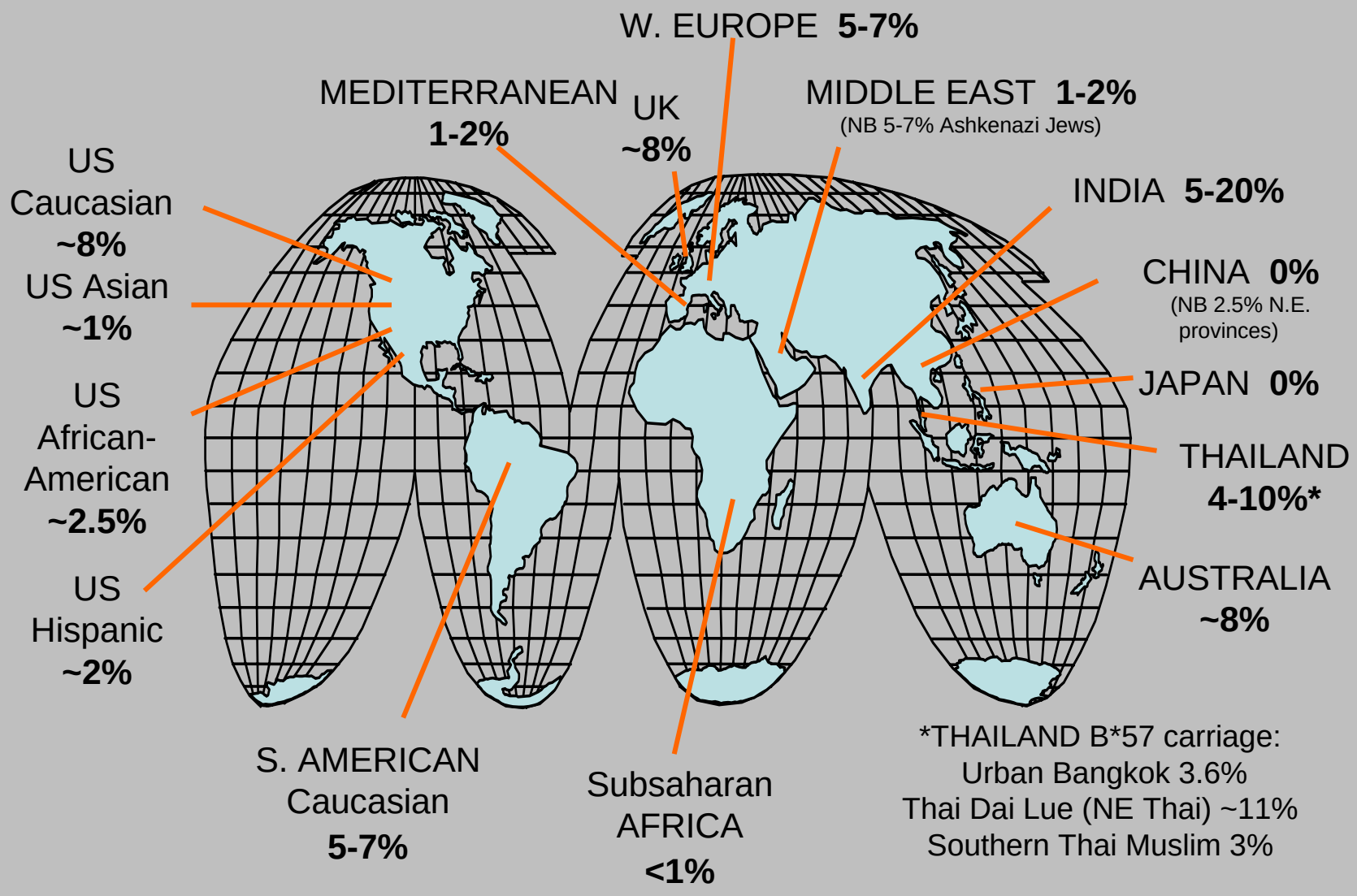
- Treat 98 patients at low risk for ABC HSR
- Prevent 1 ABC HSR event
- Exclude ABC in 1 patient

Test 100 White patients:

- Treat 94 patients at low risk for ABC HSR
- Prevent 4 ABC HSR events
- Exclude ABC in 2 patients

Example shown is based upon PPV derived from PREDICT-1 and SHAPE data.

HLA-B*5701 carriage frequency



*THAILAND B*57 carriage:
Urban Bangkok 3.6%
Thai Dai Lue (NE Thai) ~11%
Southern Thai Muslim 3%

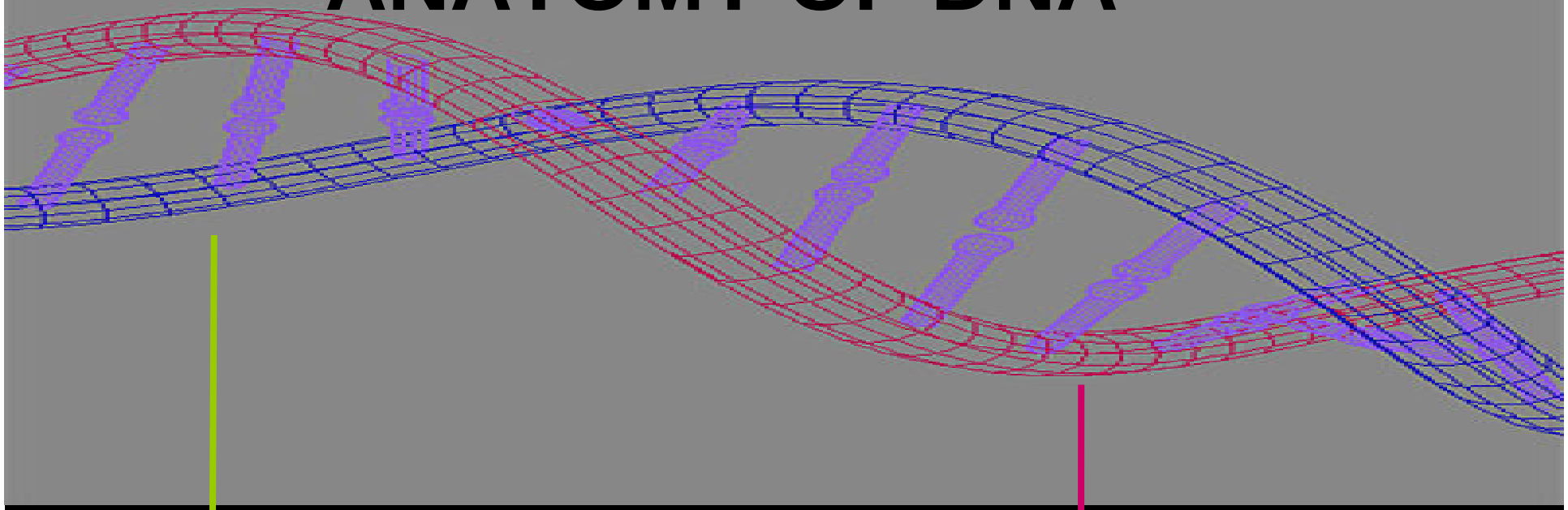
Nolan *et al*, J HIV Ther 2003; 8(2):36-41

(515-450 circa aC).

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

“Nessun uomo può bagnarsi nello stesso fiume per due volte, perché né l'uomo né le acque del fiume sono gli stessi".

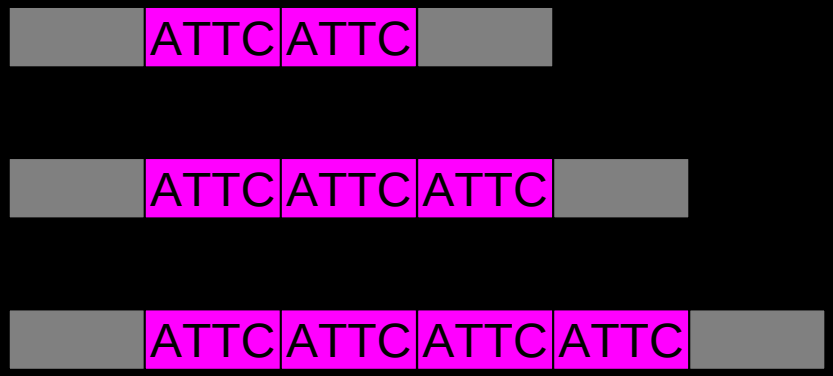
ANATOMY OF DNA



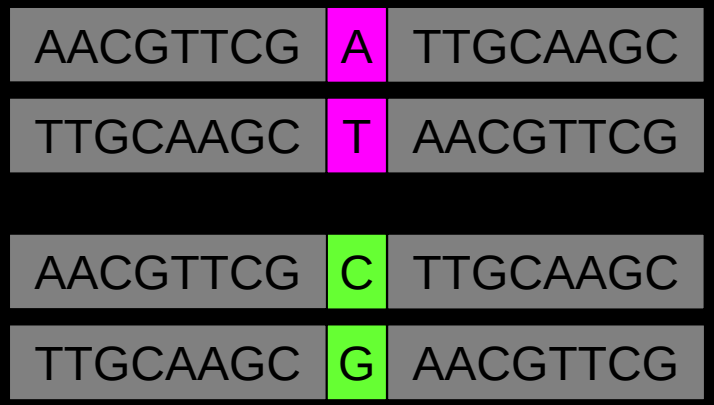
ENVIRONMENTAL/INTERACTION GENES
NEED FOR GREAT VARIABILITY
POLYMORPHIC REGIONS

CORE BIOLOGY FUNCTION GENES
NO NEED FOR GREAT VARIABILITY
BLOCKED REGIONS

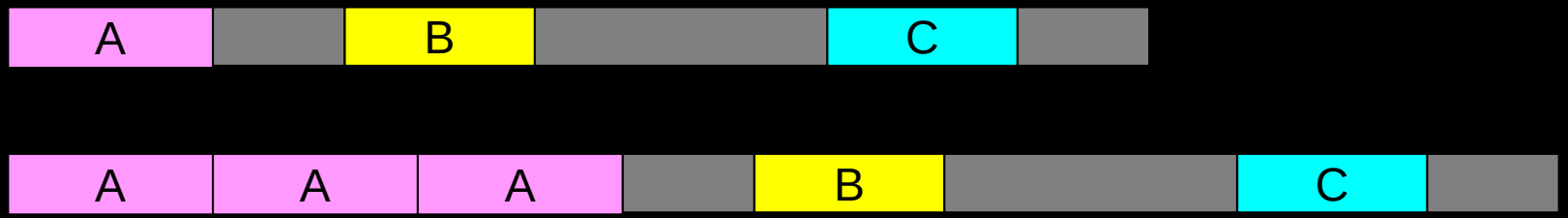
Polimorfismi di lunghezza



Polimorfismi di sequenza



Copy Number Variation



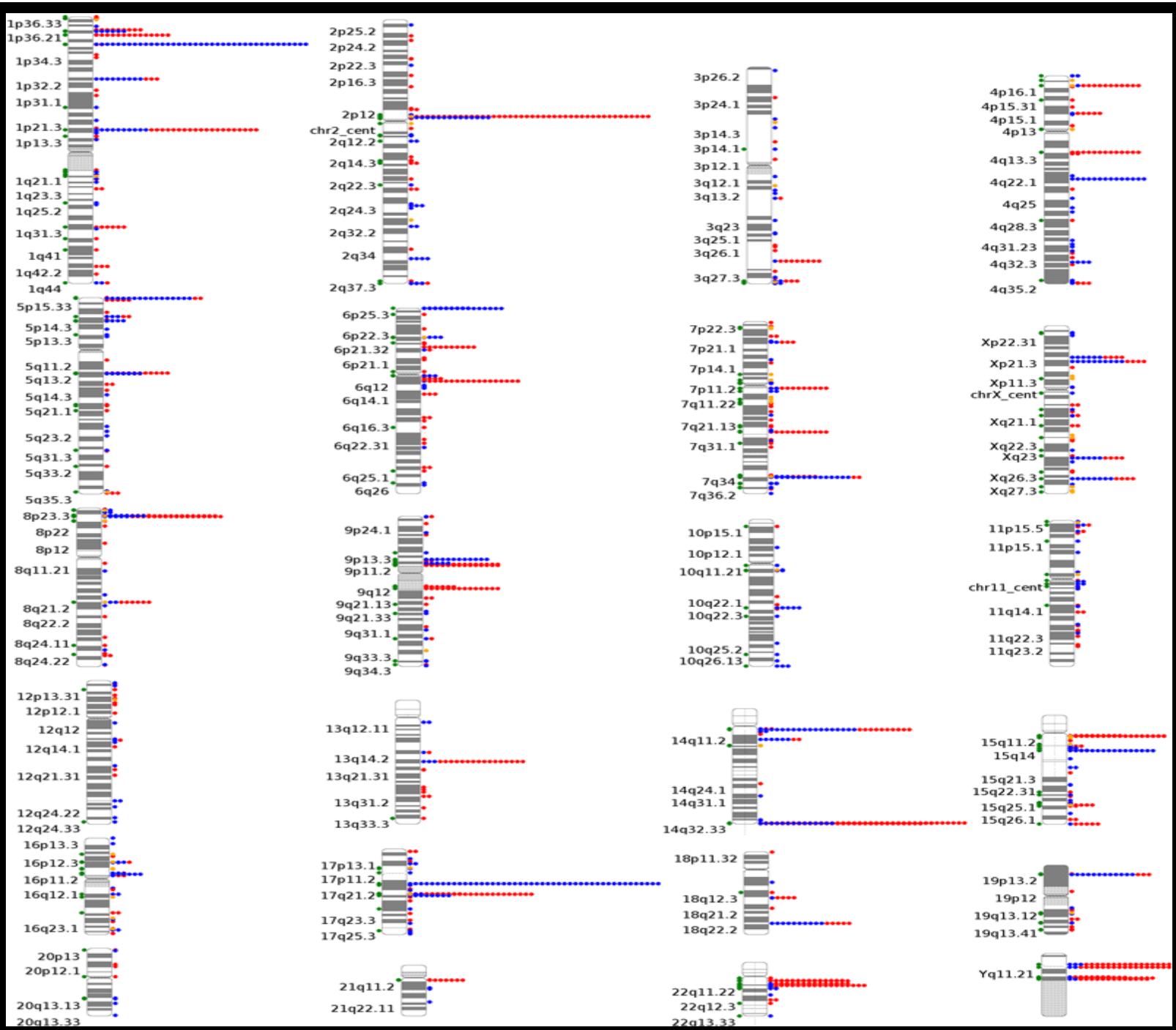
nature genetics

October, 2006

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

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

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


1p36.33
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1p34.3
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1p31.1
1p21.3
1p13.3
1q21.1
1q23.3
1q25.2
1q31.3
1q41
1q42.2
1q44
5p15.33
5p14.3
5p13.3
5q11.2
5q13.2
5q14.3
5q21.1
5q23.2
5q31.3
5q33.2
5q35.3
8p23.3
8p22
8p12
8q11.21
8q21.2
8q22.2
8q24.11
8q24.22
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12p12.1
12q12
12q14.1
12q21.31
12q24.22
12q24.33
16p13.3
16p12.3
16p11.2
16q12.1
16q23.1
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20p12.1
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20q13.33
2p25.2
2p24.2
2p22.3
2p16.3
2p12
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3p12.1
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3q13.2
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3q26.1
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4q35.2
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Xp21.3
Xp11.3
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Xq22.3
Xq23
Xq26.3
Xq27.3
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15q14
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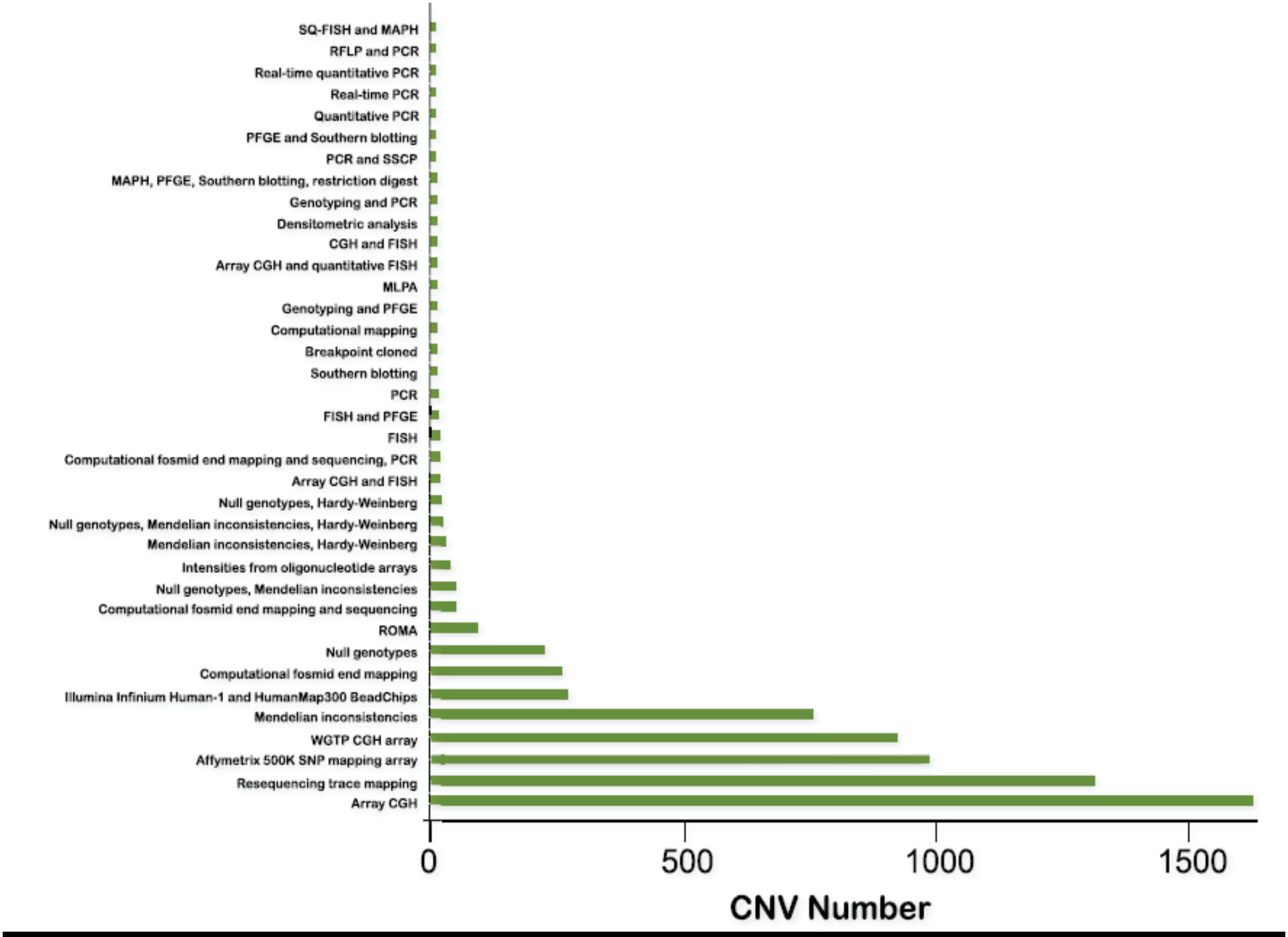
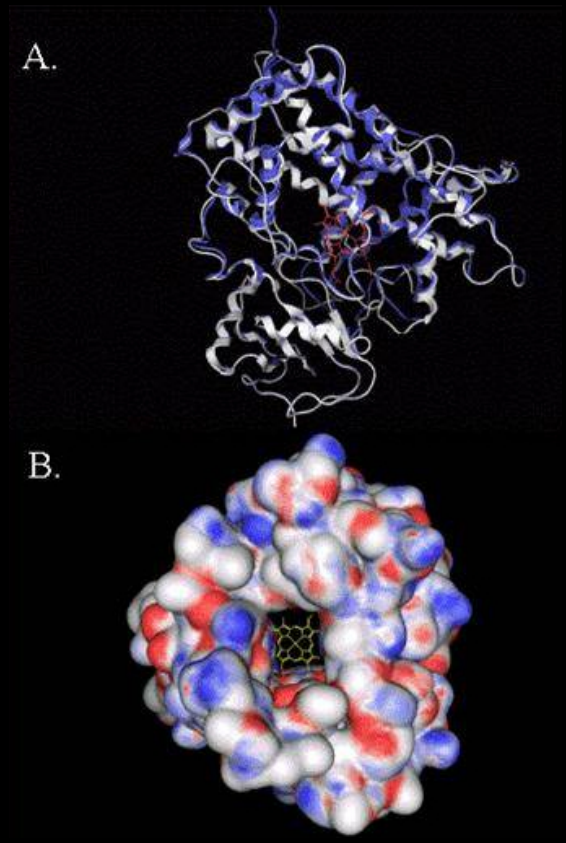
Yq11.21


SQ-FISH and MAPH
RFLP and PCR
Real-time quantitative PCR
Real-time PCR
Quantitative PCR
PFGE and Southern blotting
PCR and SSCP
MAPH, PFGE, Southern blotting, restriction digest
Genotyping and PCR
Densitometric analysis
CGH and FISH
Array CGH and quantitative FISH
MLPA
Genotyping and PFGE
Computational mapping
Breakpoint cloned
Southern blotting
PCR
FISH and PFGE
FISH
Computational fosmid end mapping and sequencing, PCR
Array CGH and FISH
Null genotypes, Hardy-Weinberg
Null genotypes, Mendelian inconsistencies, Hardy-Weinberg
Mendelian inconsistencies, Hardy-Weinberg
Intensities from oligonucleotide arrays
Null genotypes, Mendelian inconsistencies
Computational fosmid end mapping and sequencing
ROMA
Null genotypes
Computational fosmid end mapping
Illumina Infinium Human-1 and HumanMap300 BeadChips
Mendelian inconsistencies
WGTP CGH array
Affymetrix 500K SNP mapping array
Resequencing trace mapping
Array CGH
0
500
1000
1500
CNV Number

CNVs in CYP2D6

- ✓ process more than 30 drugs (antiarrhytmics, antihypertensives, beta-blockers)
- ✓ 737 caucasian individuals
- ✓5.1% with deletion [*CYP2D6*5*]
- ✓7.2% with duplication [*CYP2D6* 2×]

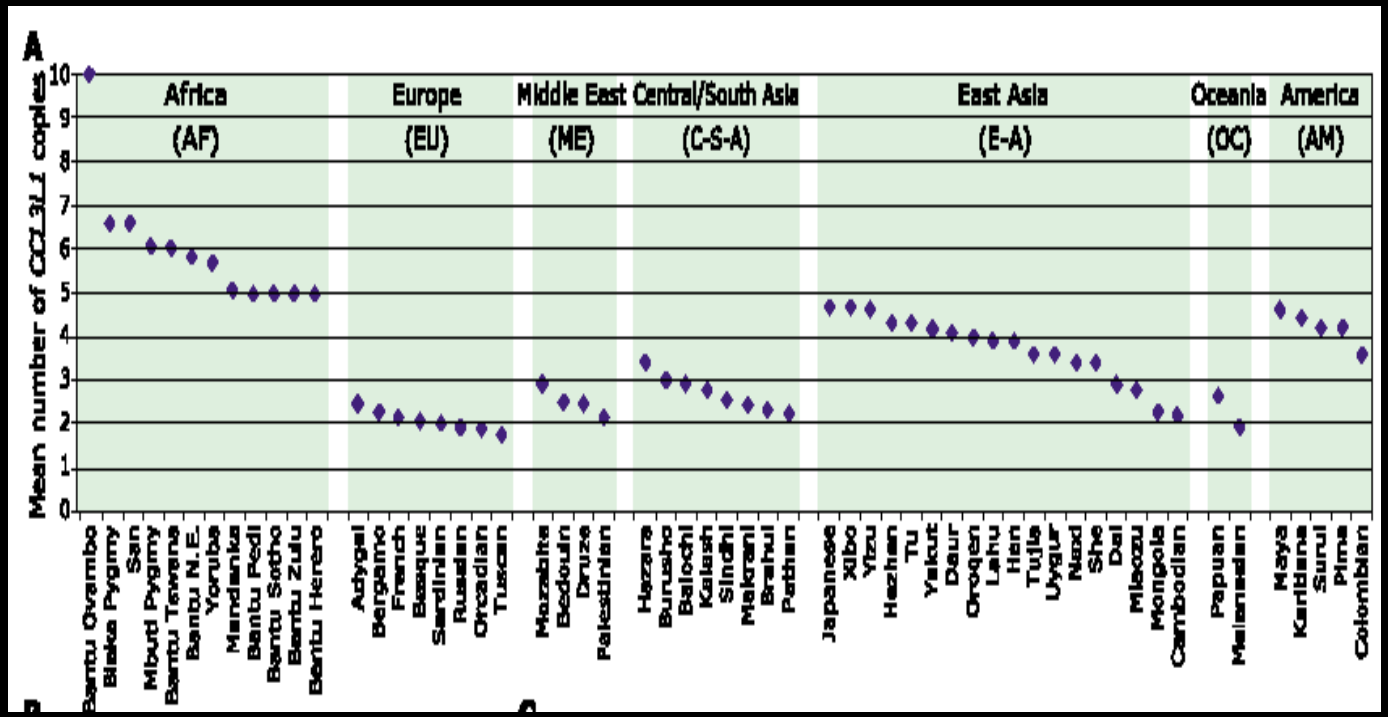


[Ledesma et al.,2005]

CNVs in CCL3L1

(Chemokine ligand 3-like 1)

- ✓ HIV-1 suppressive chemokine and ligand for HIV coreceptor (CCR5);
- ✓ low copy number and HIV susceptibility



[Gonzalez et al.,2005]

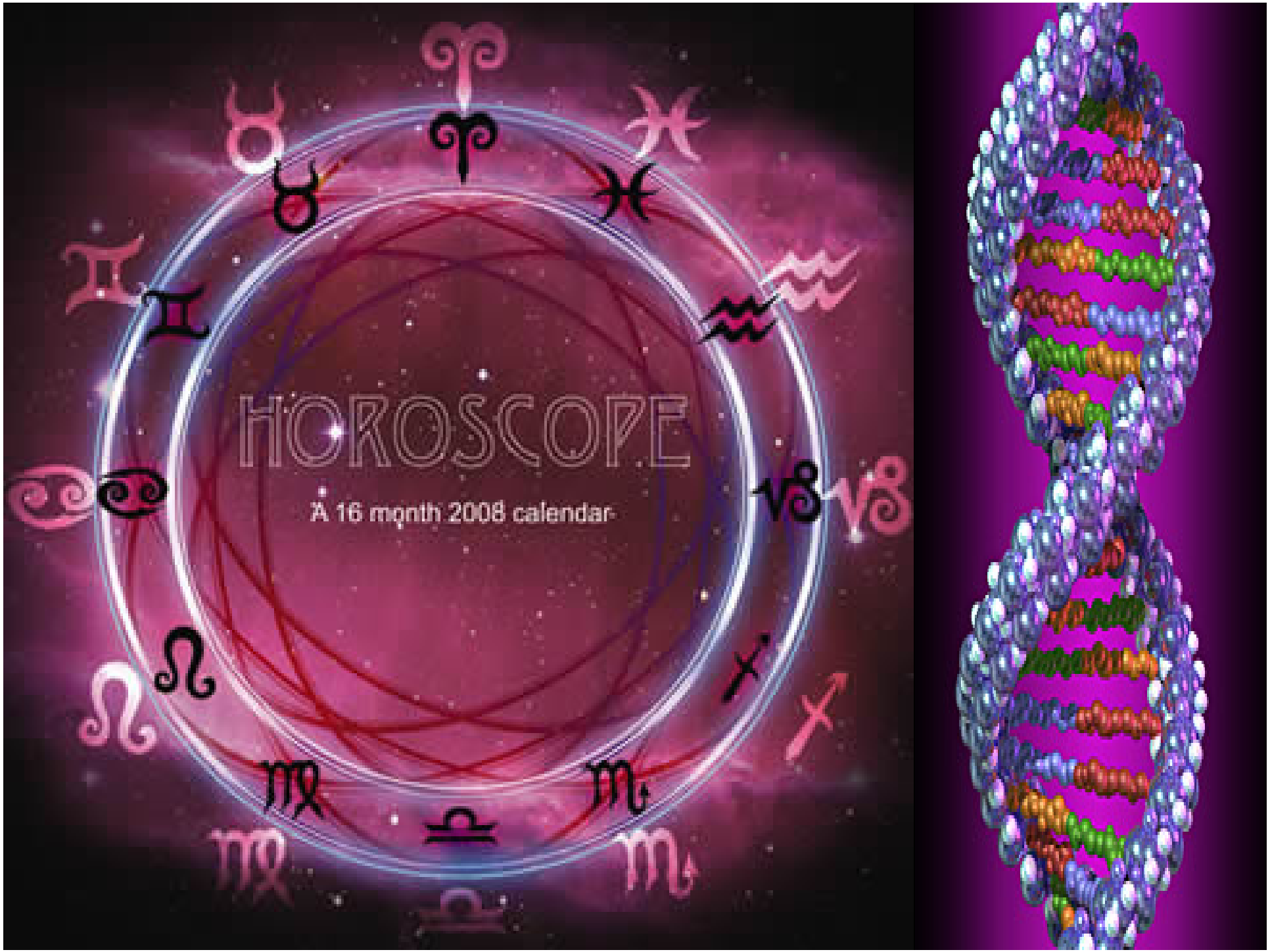
Esempi di biomarker validi:

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

Probabilmente Validi :

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


68
DNA
DOCTOR
Genome Medical Futures


HOROSCOPE
A 16 month 2008 calendar

The year of sequencing

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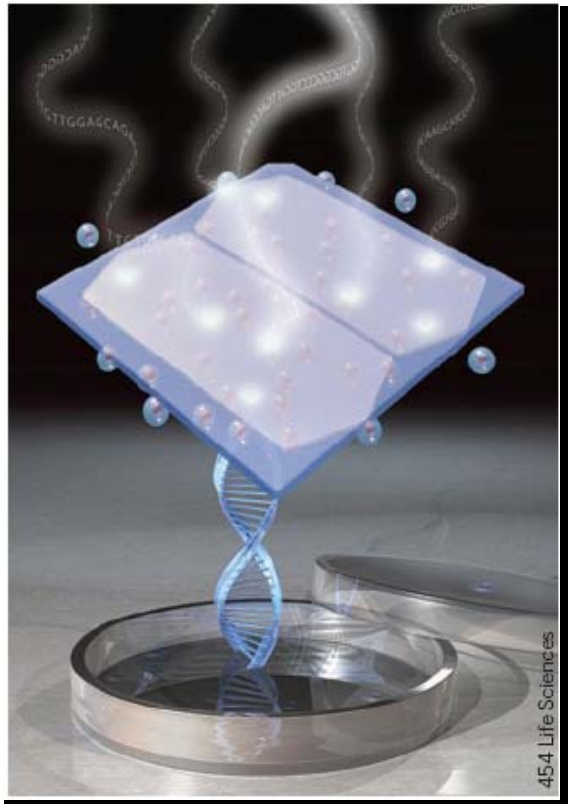
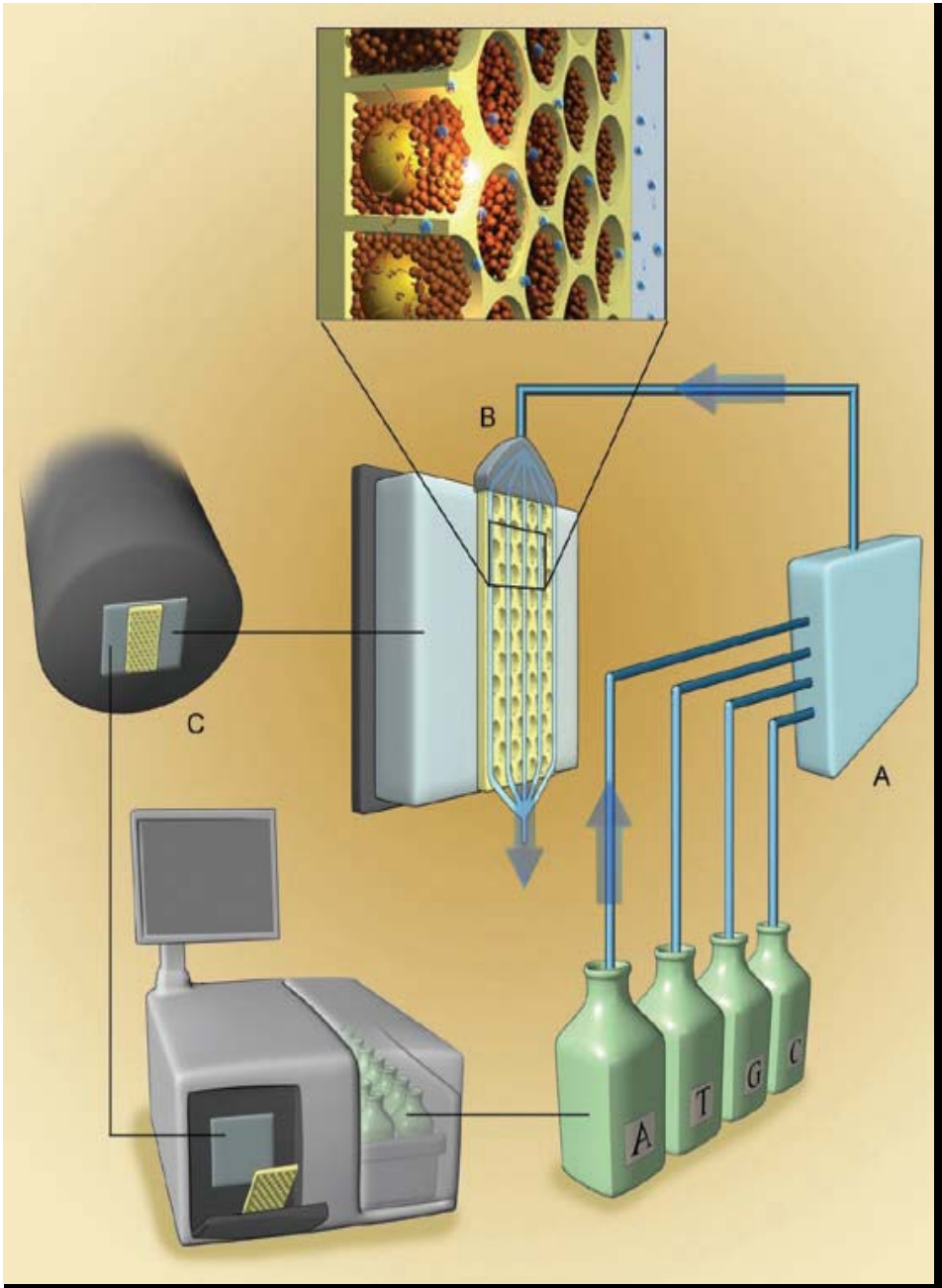
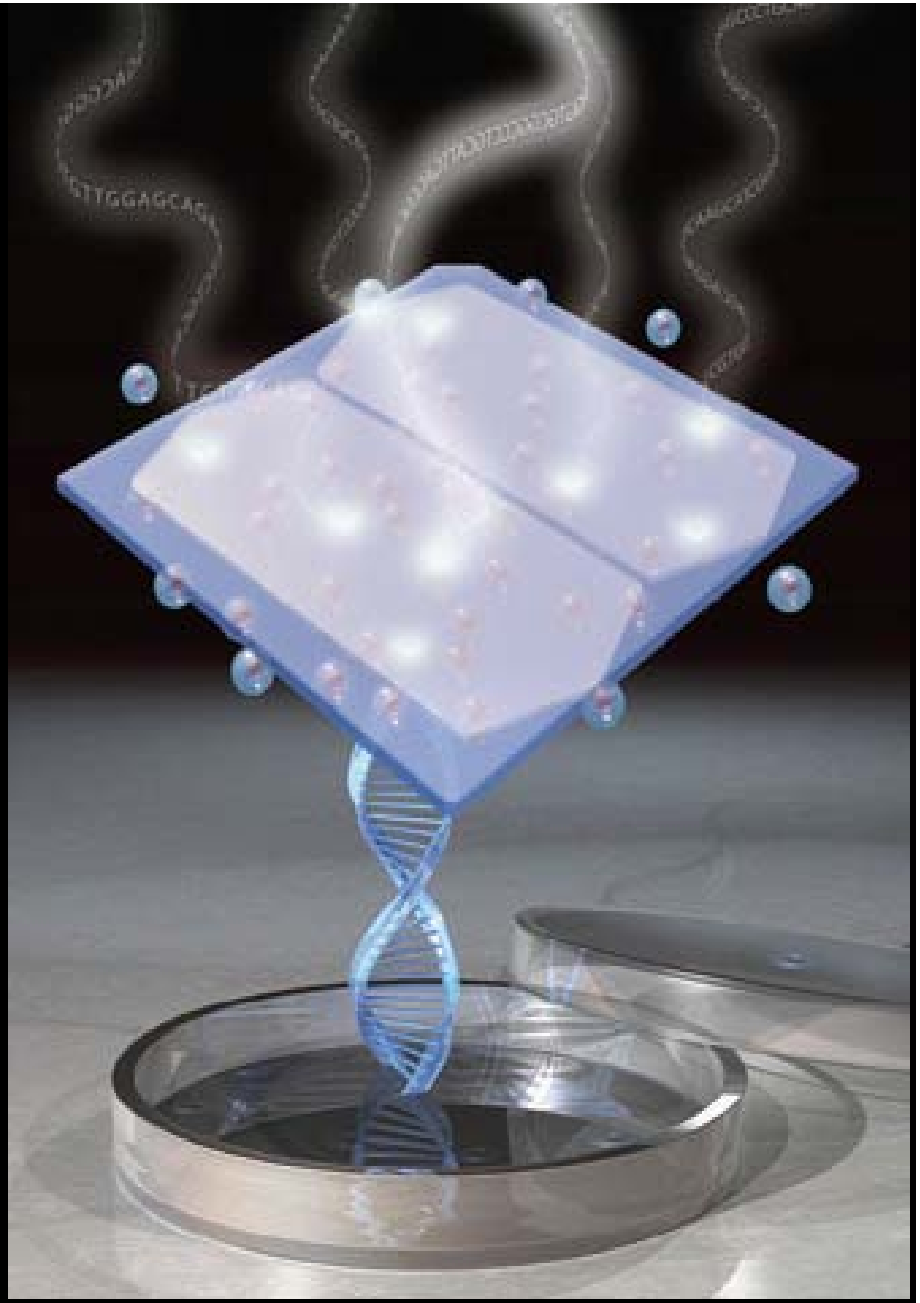
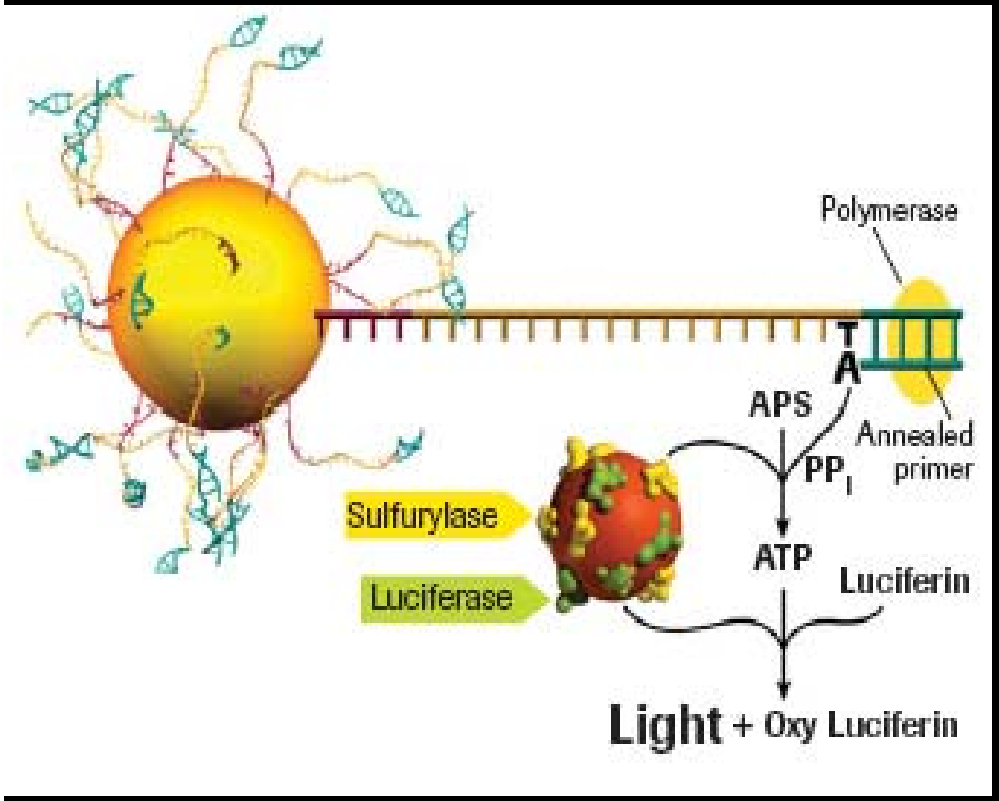


«Tutti sanno che una cosa è impossibile da realizzare finchè arriva uno sprovveduto che non lo sa e la inventa»


B
C
A
A
T
G
C

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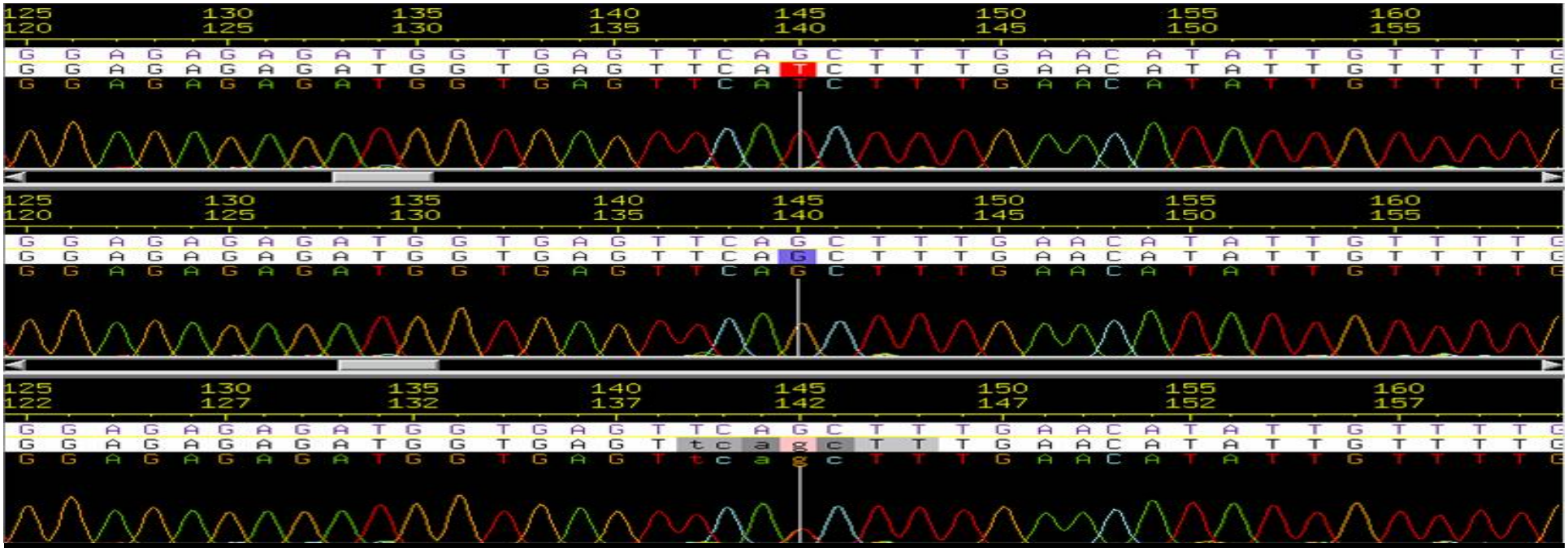
T
A
APS
PP$_i$
Annealed primer
Sulfurylase
Luciferase
ATP
Luciferin
Light + Oxy Luciferin



3.000.000.000 $
10 anni

2.000.000 $
2 mesi

[Richard Westall,1812]

- 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
Clock	rs1801260(3111C/T)	T/T	C/C	Evening preference		1.00
Per2	S662G	S662S	S662G	Advanced sleep phase syndrome (ASPA)		0.01
LCT	rs4988235(C/T_{-13910})	T/T	C/C	Adult-type hypolactasia		0.00
	rs182549(G/A_{-22018})	A/A	G/G	Adult-type hypolactasia		0.07
OCA2	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	+	0.63
	rs6497268(rs4778241)	G/G			+	0.13
	rs11855019 (rs4778138)	T/T				0.38
ABCC11	rs17822931(538G –> A)	G/G	AA:dry type; G/A&G/G: wet type.	Human earwax type(AA,Dry; G/A&G/G are wet type)	+	0.07
SLC6A3	40-bp VNTR in 3'UTR	10/10 allele	9/9 allele	Substance abuse		0.38
DRD4	DRD4 III Exon 3 VNTR polymorphism	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
	rs1800955 (DRD4,-521C/T, promoter)	C/C	C/C genotype exhibited the highest novelty seeking scores	Novelty seeking		0.38
DRD3	rs6280 (DRD3 BalI polymorphism)	A/A(allele 1)	Allele 1(aGC:S) showed significantly lower Novelty Seeking scores compared to patients without this allele. Allele 2(gGC:G) was associated with increased rates of obsessive personality disorder symptomatology	Novelty seeking		0.07
DRD2	rs1800497(DRD2TaqIA 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
CHRNA4	rs2273504	G/G	G	Tobacco addiction protection	+	0.63
	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
CHRNA5	rs16969968	G/G	A	Tobacco addiction		1.00
	rs684513	C/C	C			0.38
	rs637137	T/T	T		+	0.22
CHRNA3	rs3743078	G/G	G	Tobacco addiction		0.02
	rs1051730	G/G	A			0.13
	rs578776	A/A	G		+	0.38
CHRNB4	rs3813567	A/A	A	Tobacco addiction	+	1.00
CHRNA6	rs2304297	G/G	G	Tobacco addiction		0.22
CHRNB3	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
CHRND	rs3791729	A/G	A	Tobacco addiction	+	
	rs2767	A/G	G		+	
	rs2276560	T/T	T			0.04
	rs6749955	T/T	T		+	0.01
GABABR2	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	Hemizygosity 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	rs1330281	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
	rs1234312	C/C	N		+	0.22
CYBA	rs4673	C/T	T/T	Coronary artery disease and hypertension	+	
	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	5A/5A	5A/5A	Acute myocardial infarction	+	0.04
CD36		Germline mutation not found	Missense mutation, small or gross indels	Lipoprotein lipase deficiency, hypertriglyceridaemia,		
LPL		Germline 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
	rs2070744	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