Xenética e Xenómica: o seu impacto en Medicina

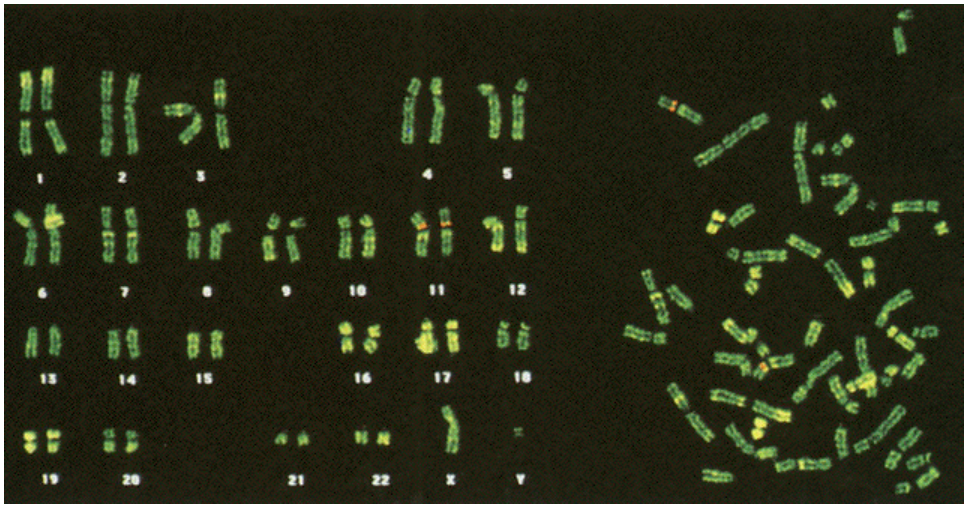
Angel Carracedo

Fundación Pública Galega de Medicina Xenómica- Consellería de Sanidade

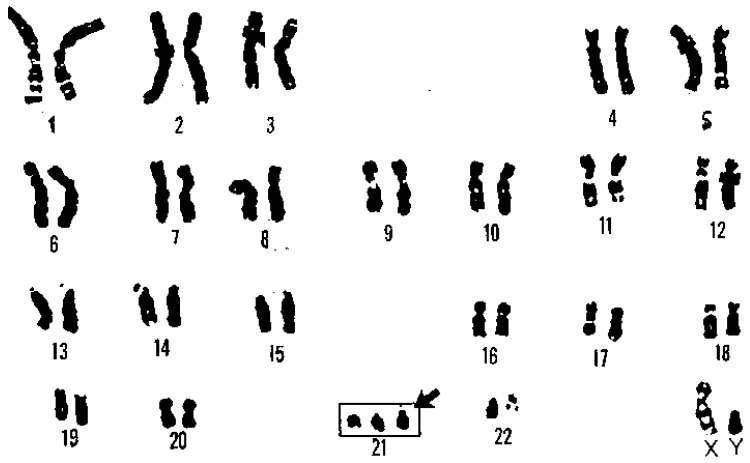
Grupo de Medicina Xenómica- IML-Universidad de Santiago de Compostela

Climántica Febreiro 2010

EL CARIOTIPO HUMANO



23 pares de cromosomas: 1956

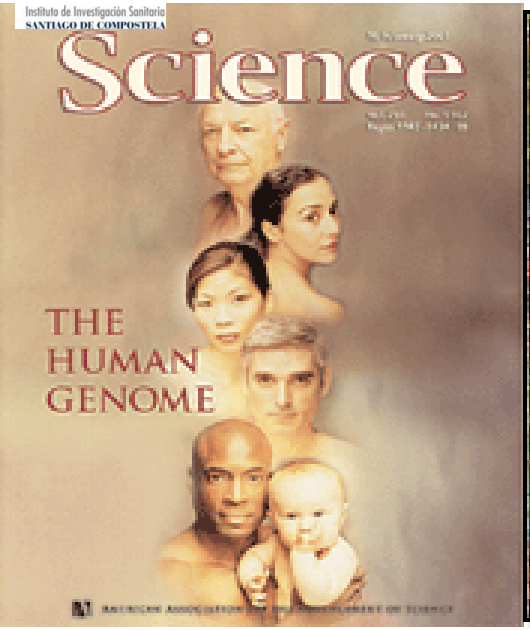


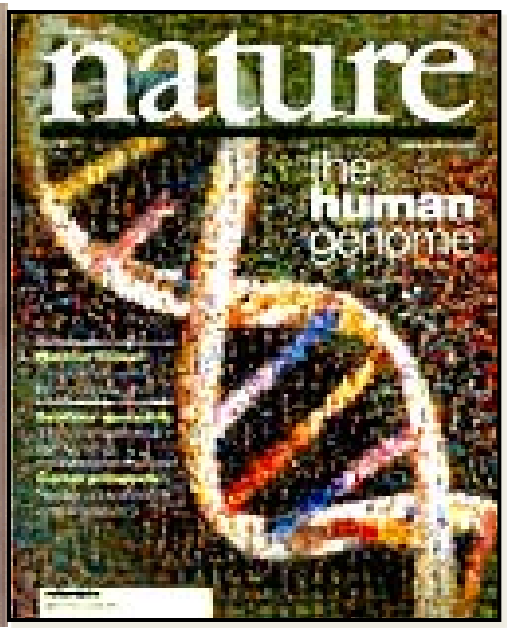
J. Lejeune (1960)

idis

Instituto de Investigación Sanitaria SANTIAGO DE COMPOSTELA

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA





EMBL Outstation
European Bioinformatics Institute

OMIM
Online Mendelian Inheritance in Man
Johns Hopkins University

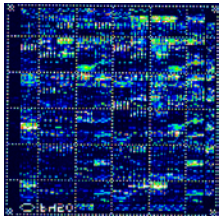
GeneTests

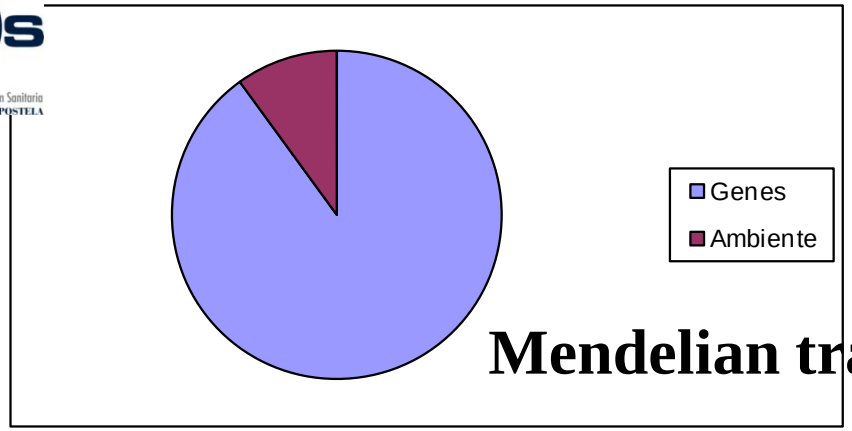
HGMD™
The Human Gene Mutation Database
Cardiff

PDB™
PROTEIN DATA BANK

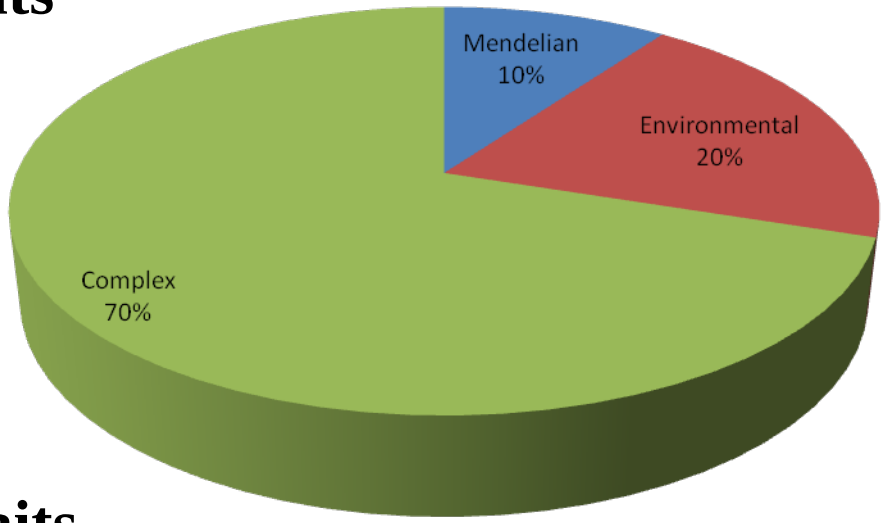
SWISS-PROT

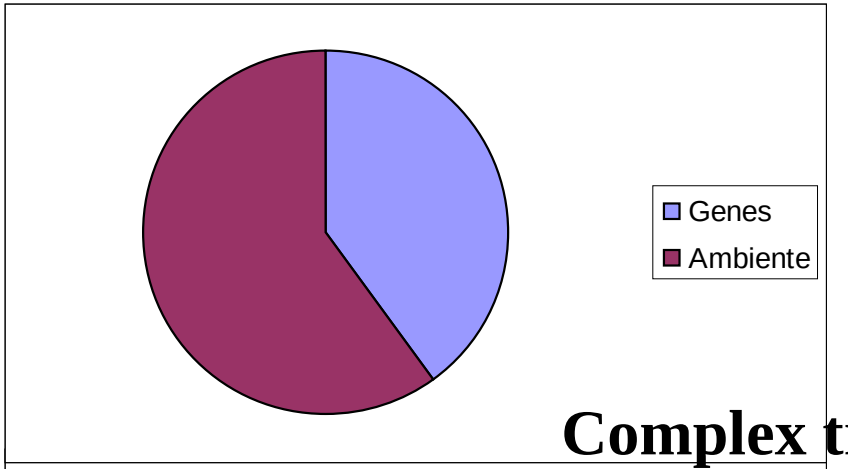
GeneCards™



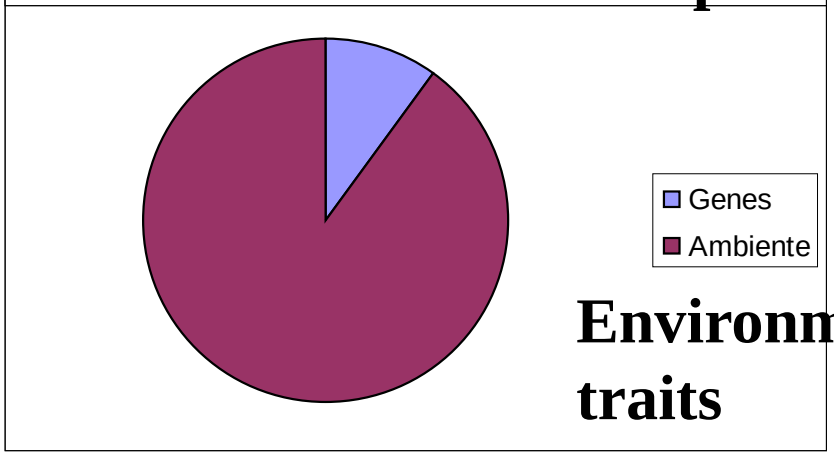


Mendelian traits





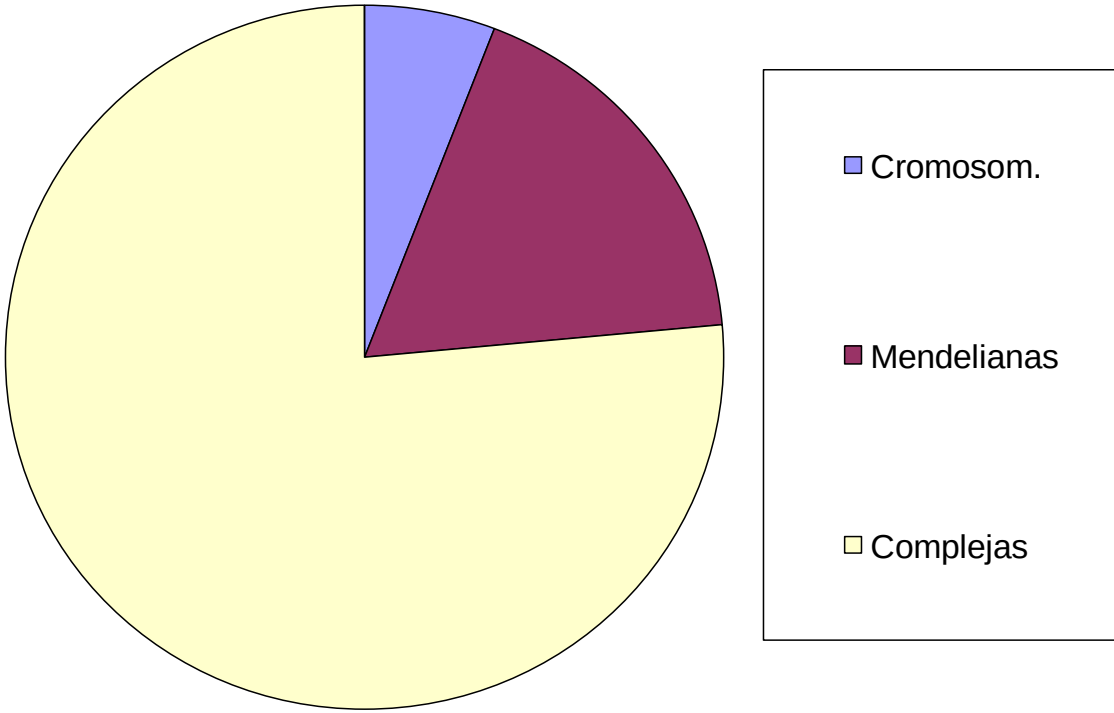
Complex traits



Environmental traits

EL CAMBIO TECNOLÓGICO:
HACER UNA PRUEBA GENÉTICA VALE MENOS QUE UN TAC Y ES MUY COSTE EFECTIVA PUES SUELE SER PREDICTIVA

EL CAMBIO EN EL ESPECTRO DE ENFERMEDAD GENÉTICA IDENTIFICABLE



FROM MEDICAL GENETICS TO GENOMIC MEDICINE

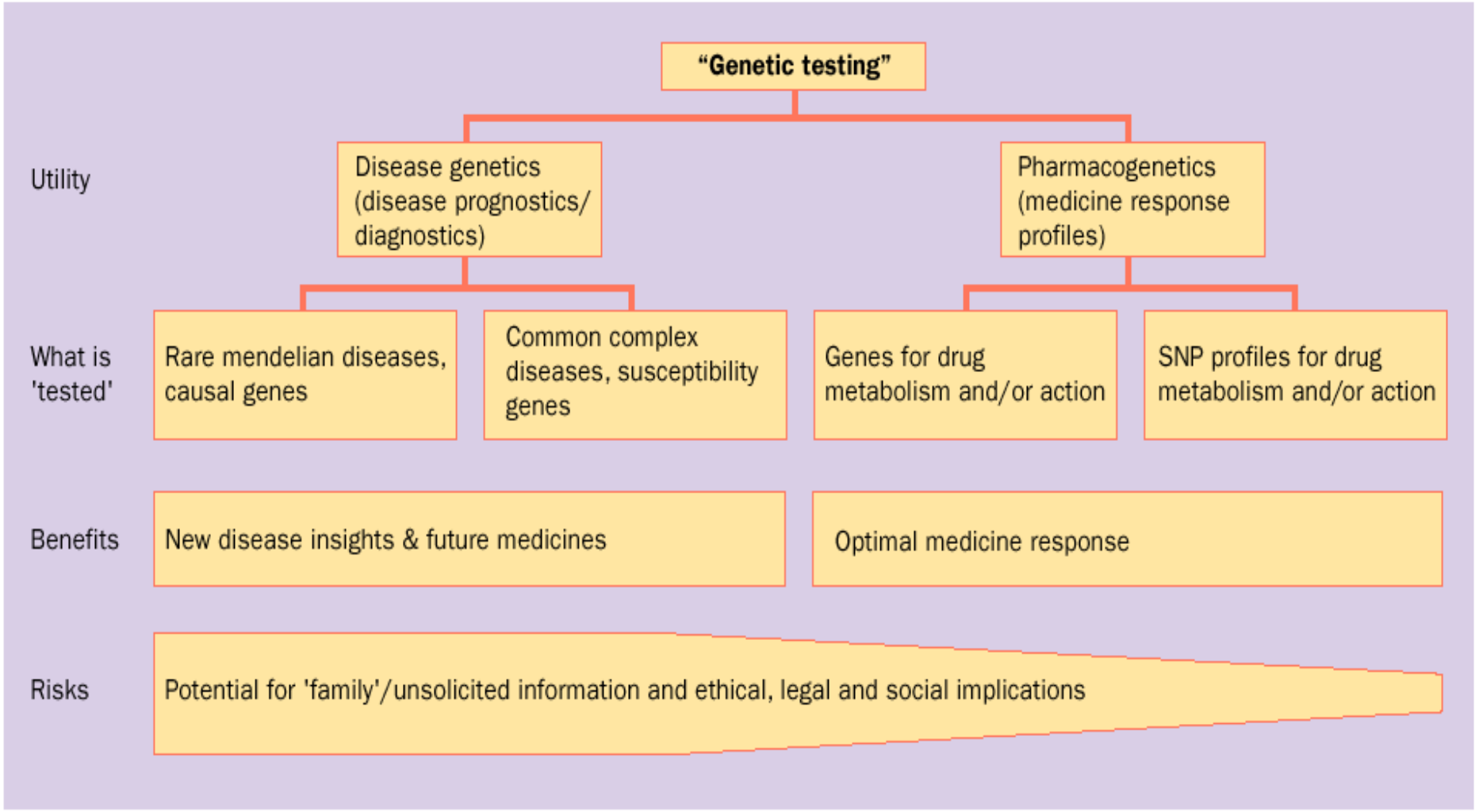


Figure 2: **"Genetic testing" needs to be defined carefully**

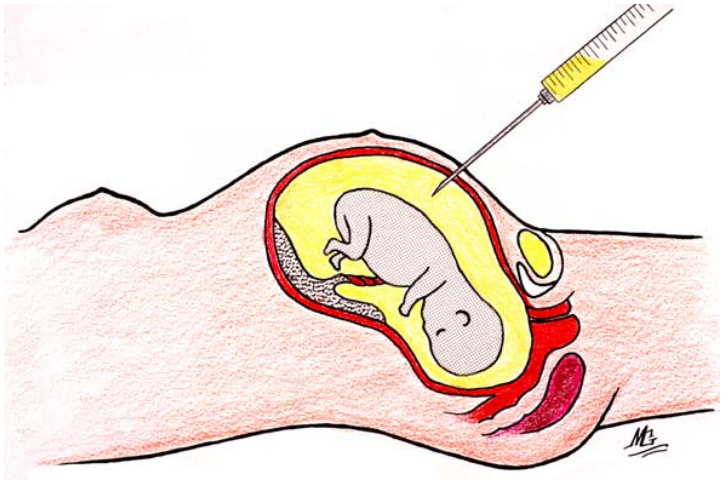
AD Roses, *Lancet* 2000; 355: 1358–61

UTILIDAD DE LOS ANÁLISIS GENÉTICOS

*DIAGNÓSTICO

*PRONÓSTICO

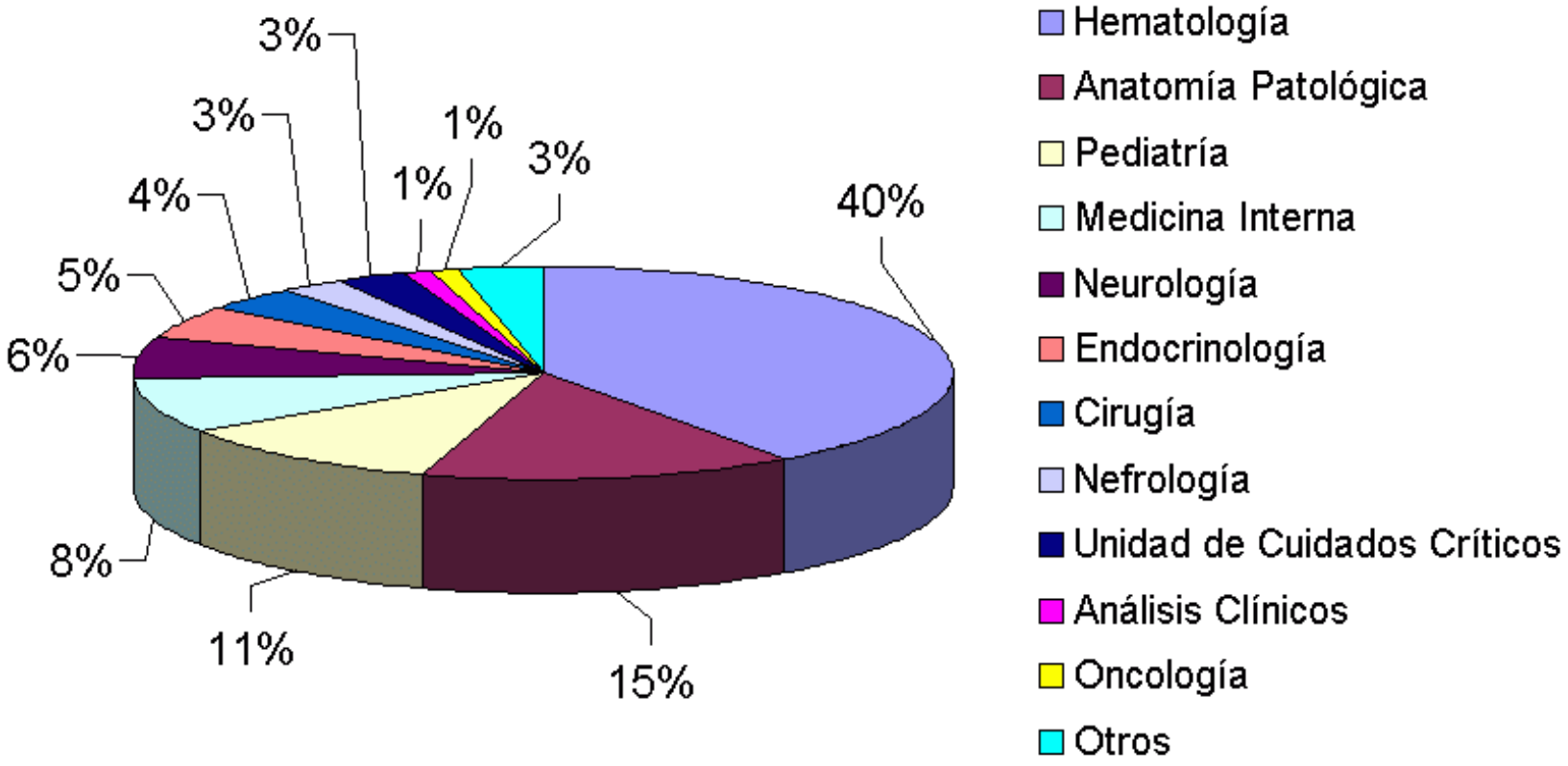
*TRATAMIENTO

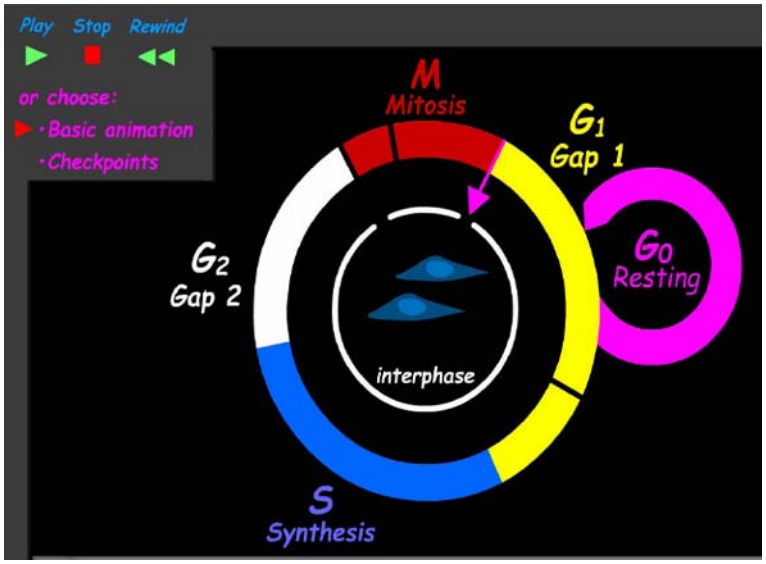


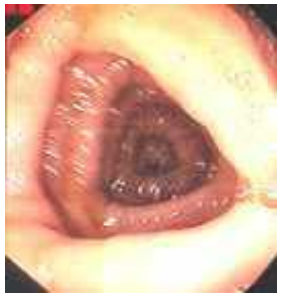
Consejo genético

Diagnóstico prenatal

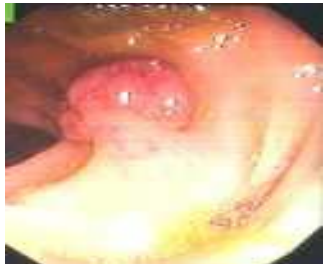
Diagnóstico preimplantacional


3%
3%
1%
1%
3%
4%
40%
5%
6%
8%
11%
15%
Hematología
Anatomía Patológica
Pediatría
Medicina Interna
Neurología
Endocrinología
Cirugía
Nefrología
Unidad de Cuidados Críticos
Análisis Clínicos
Oncología
Otros

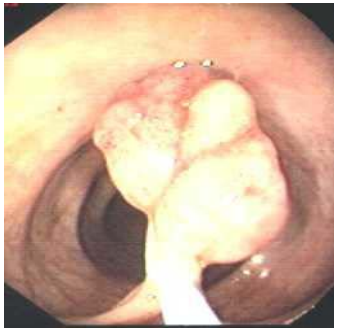




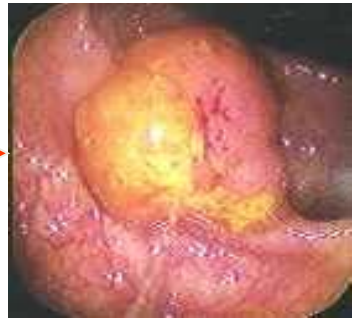
Colon normal



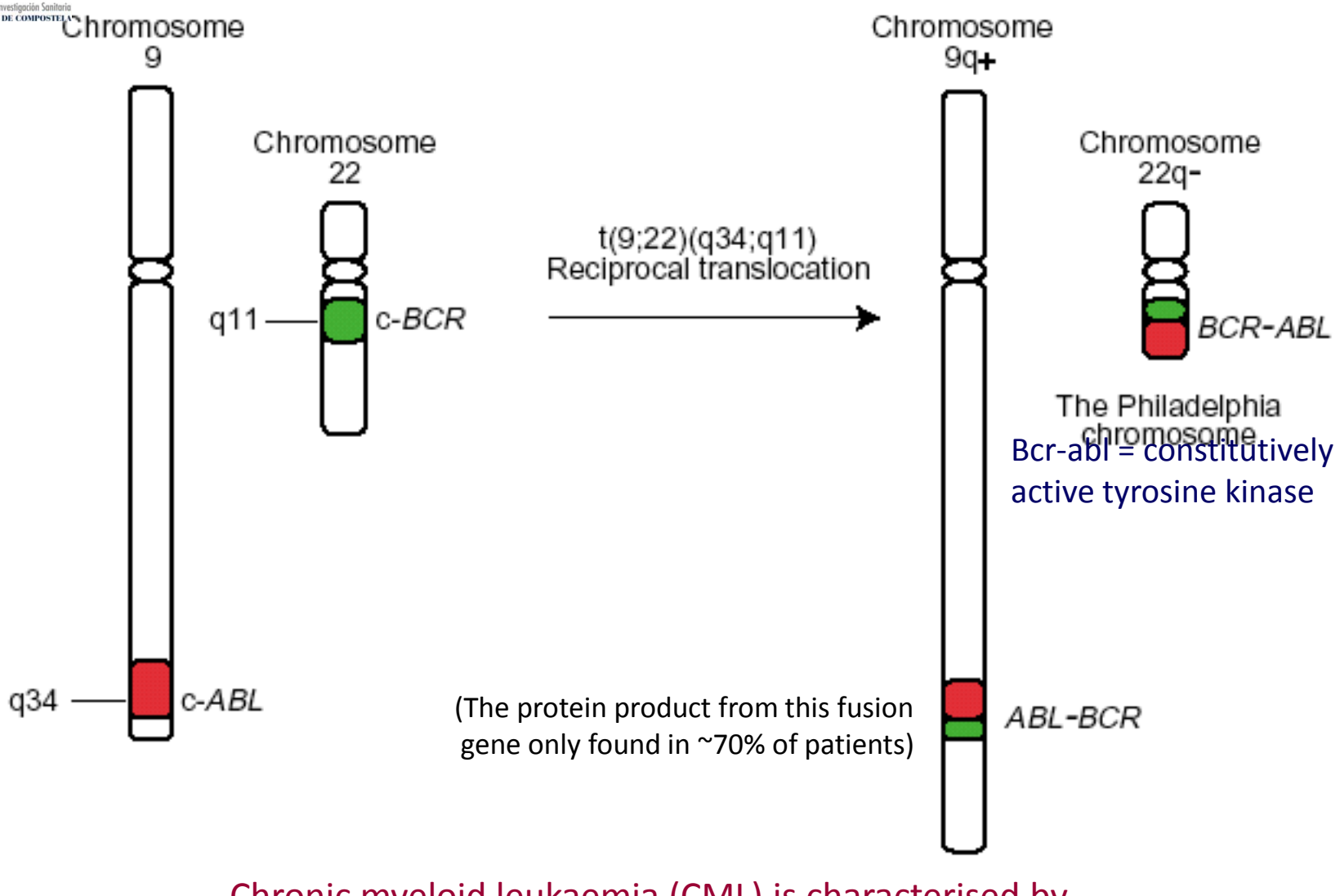
Adenoma



Adenoma avanzado

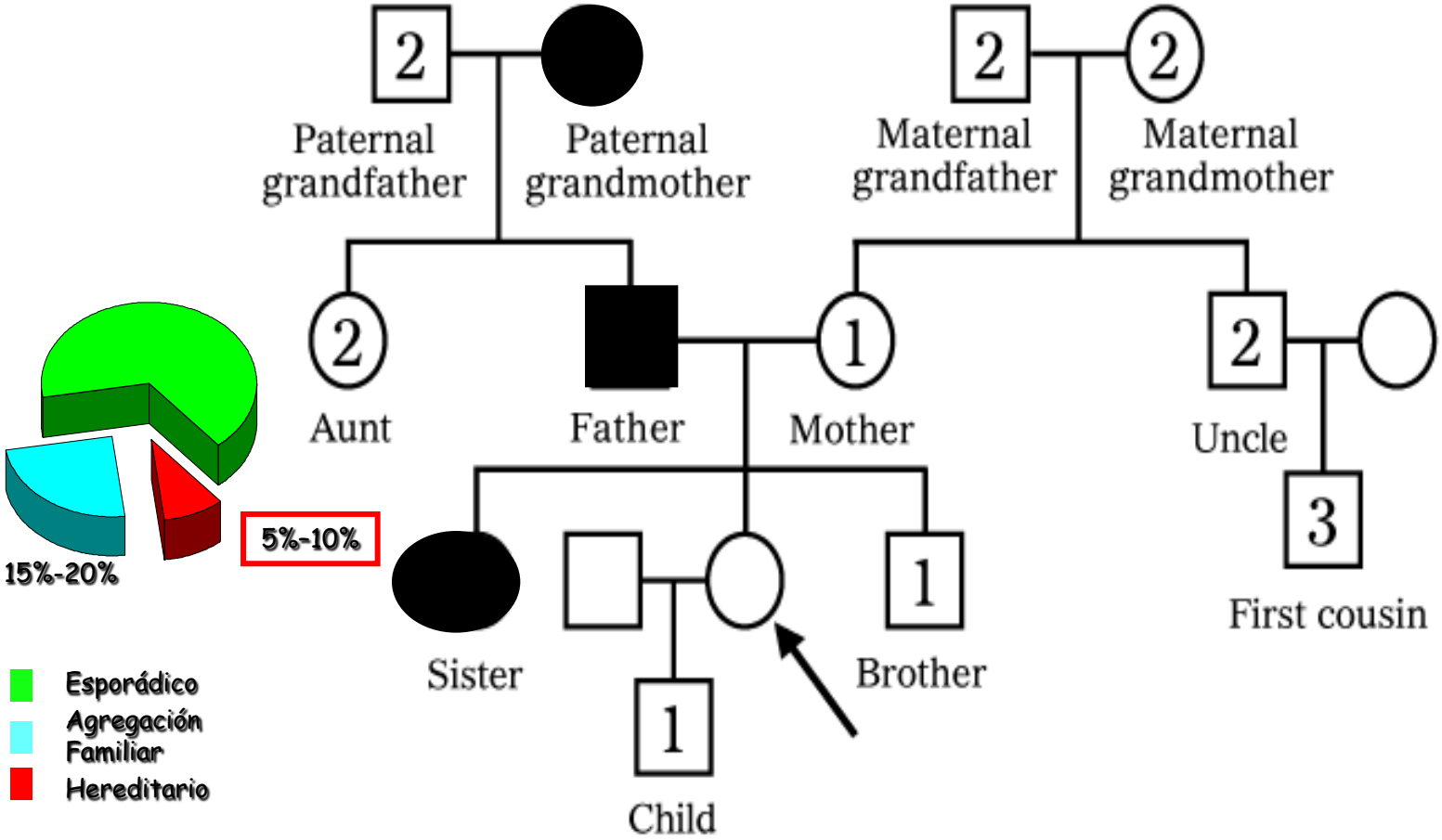


Cancer

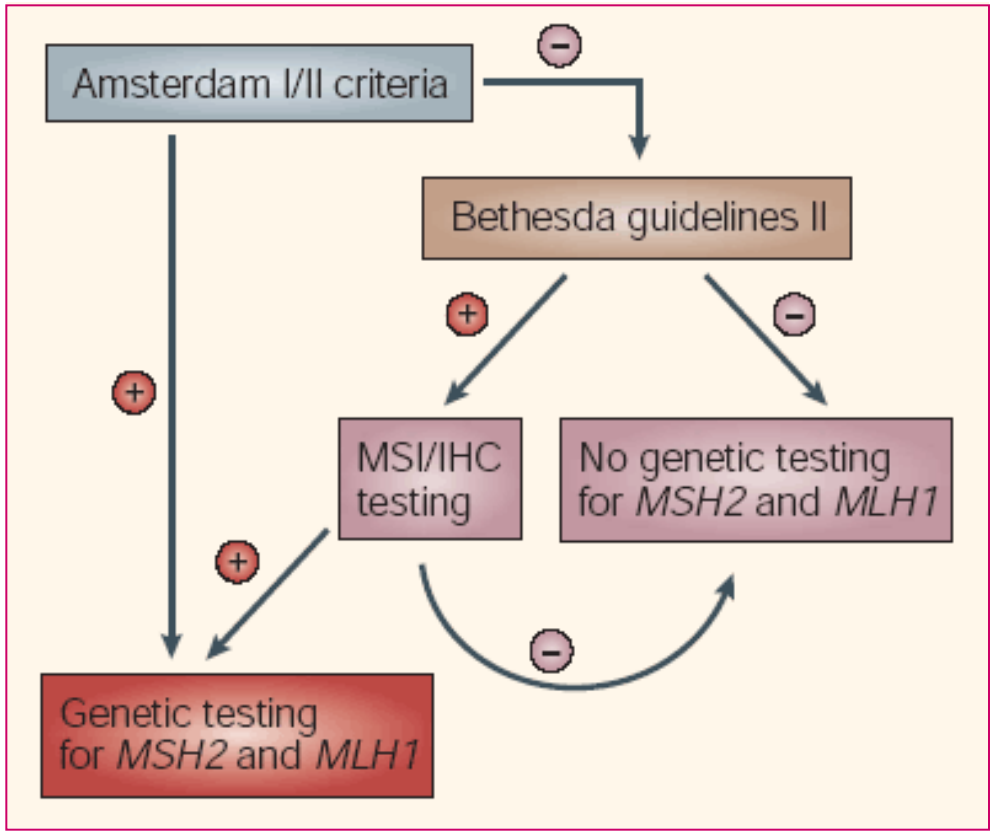


Chronic myeloid leukaemia (CML) is characterised by the t(9;22)(q34;q11) reciprocal translocation

CÁNCER HEREDITARIO



HNPCC families



Sequencing: *MLH1, MSH2, MSH6*

FAP families

Classical FAP

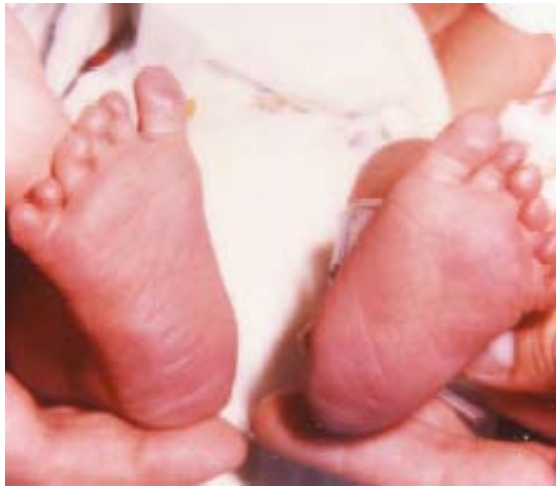
Attenuated FAP (AFAP)

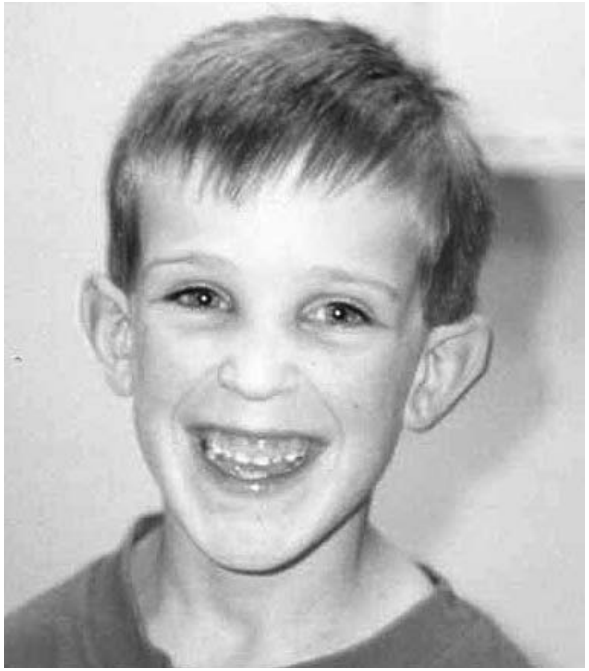
Sequencing: *APC, MYH*

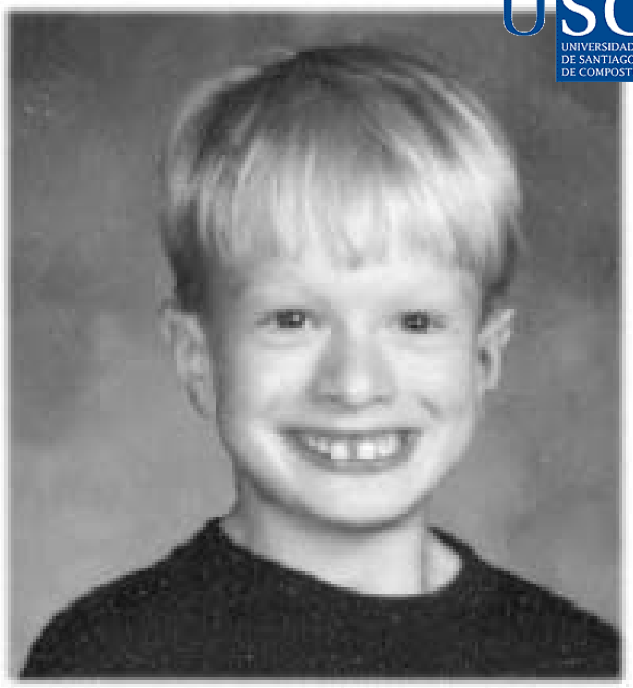
New genes: GWAs-mutation screening

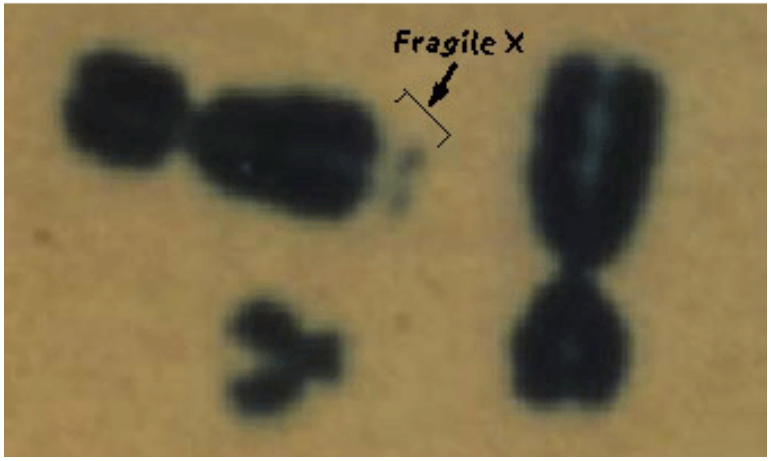
Fundación Pública Galega de Medicina Xenómica

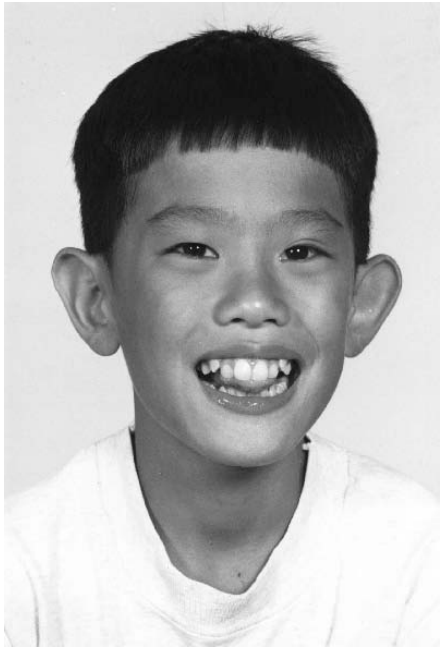
USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

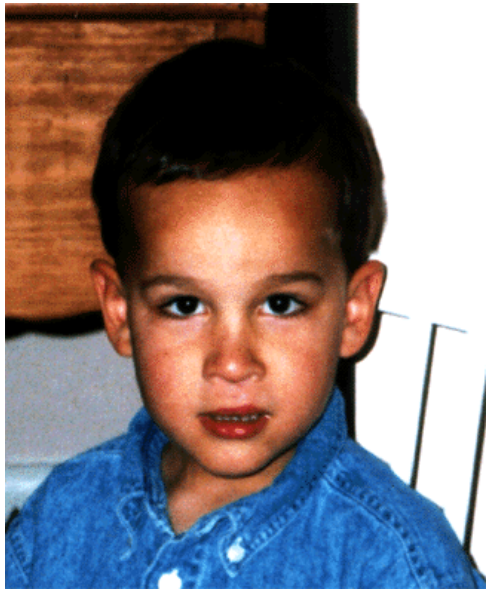


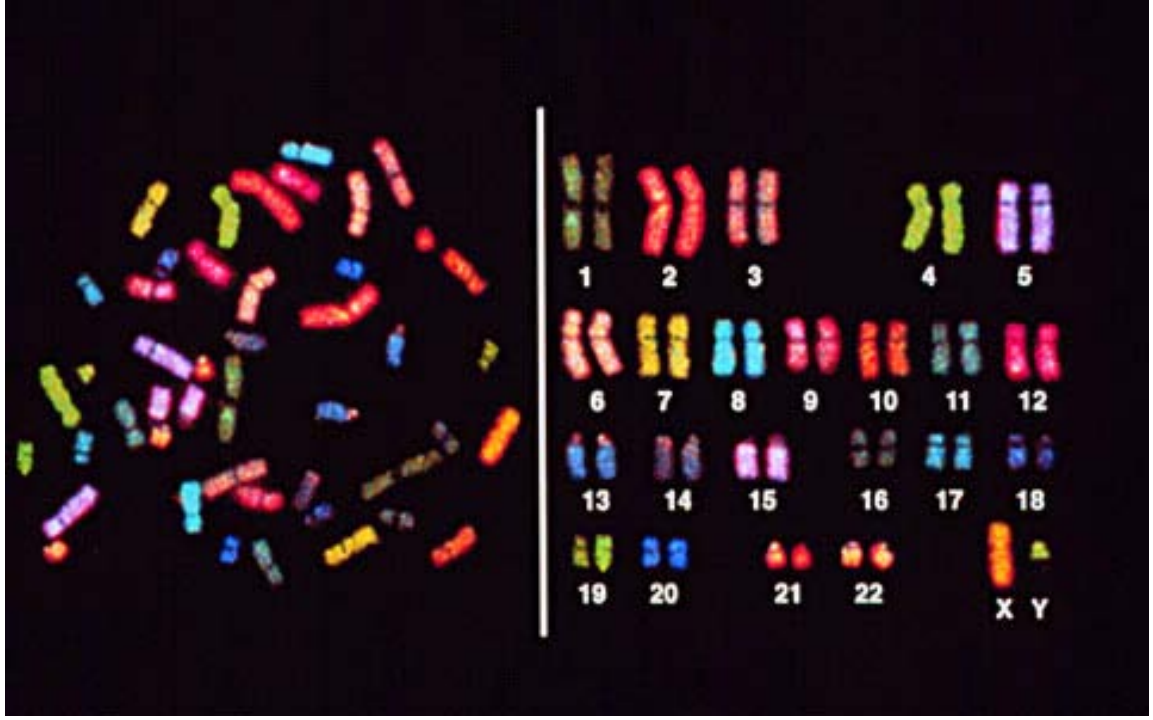


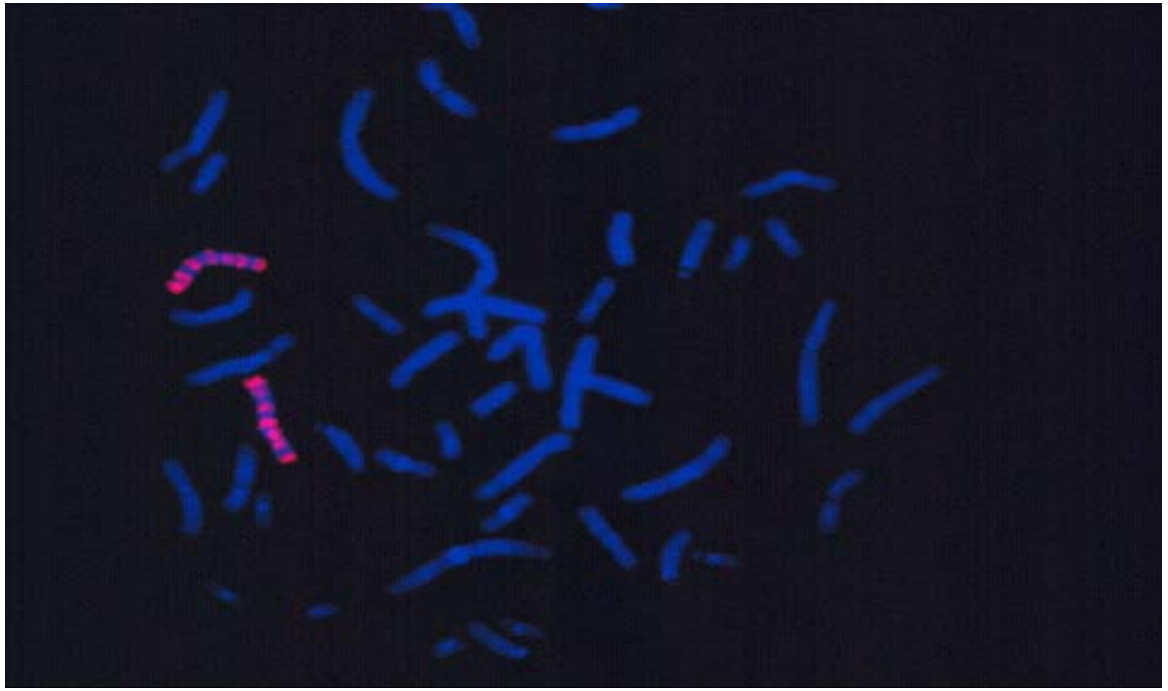




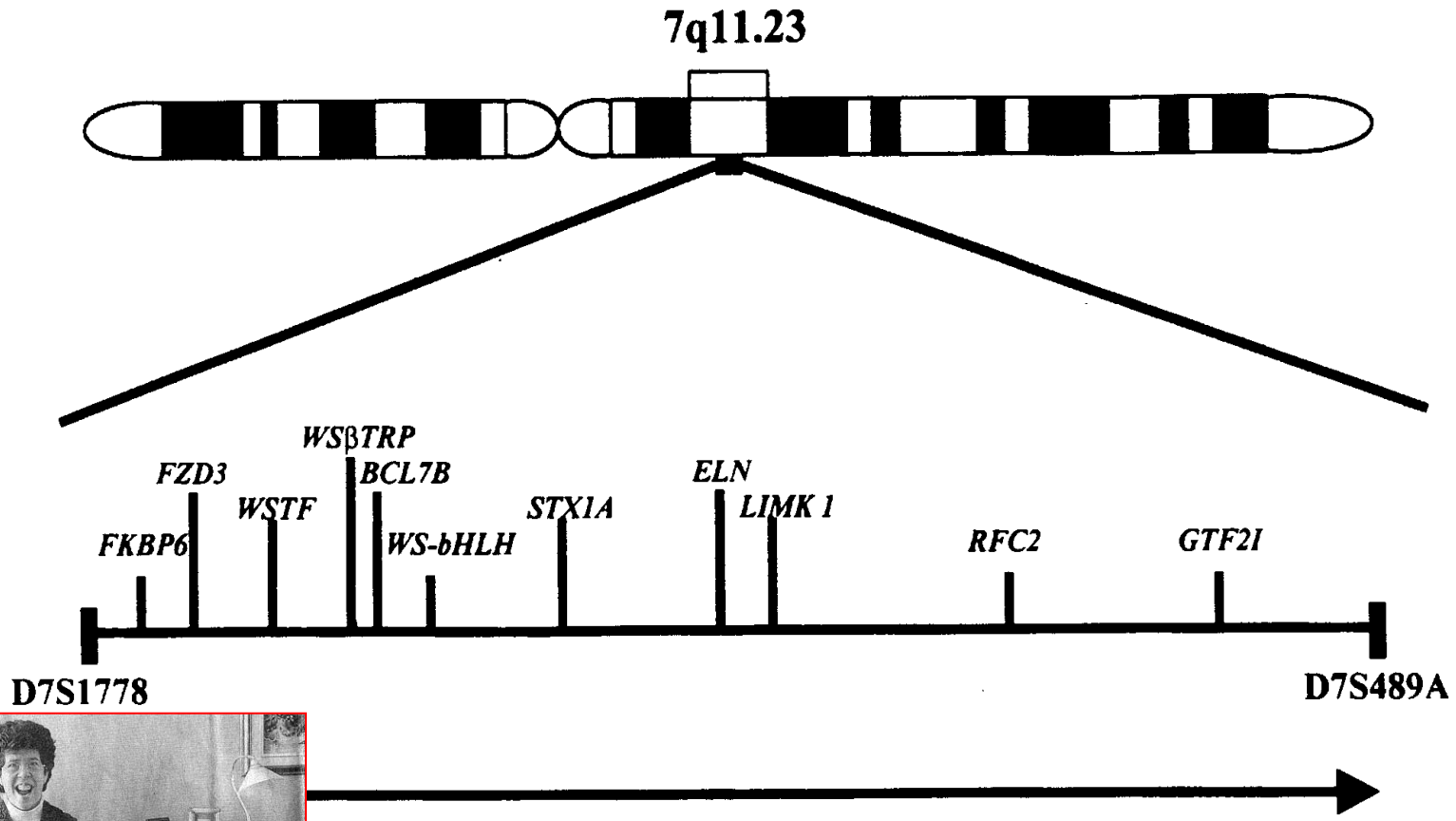




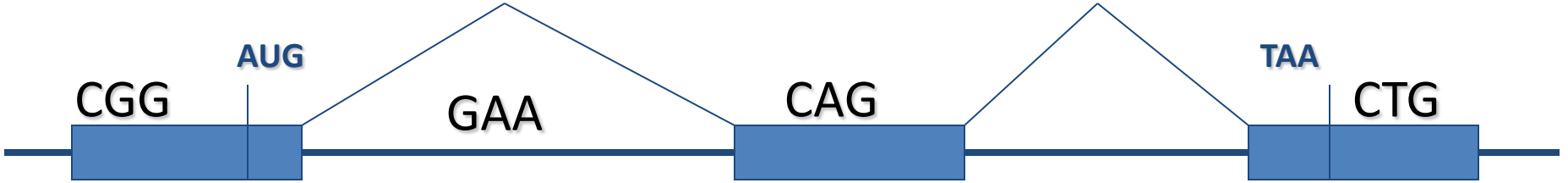

1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X Y



Williams Deletion Region



14 Unstable Trinucleotide Repeat Disorders in Humans



Fredreich's Ataxia

Myotonic Dystrophy

Fragile X Syndrome

Fragile XE MR

Spinobulbar Muscular Atrophy

Huntington's Disease

Dentatorubral-Pallidoluyslan Atropphy

Spinocerebellar Ataxia Type 1

Spinocerebellar Ataxia Type 1

Spinocerebellar Ataxia Type 2

Spinocerebellar Ataxia Type 6

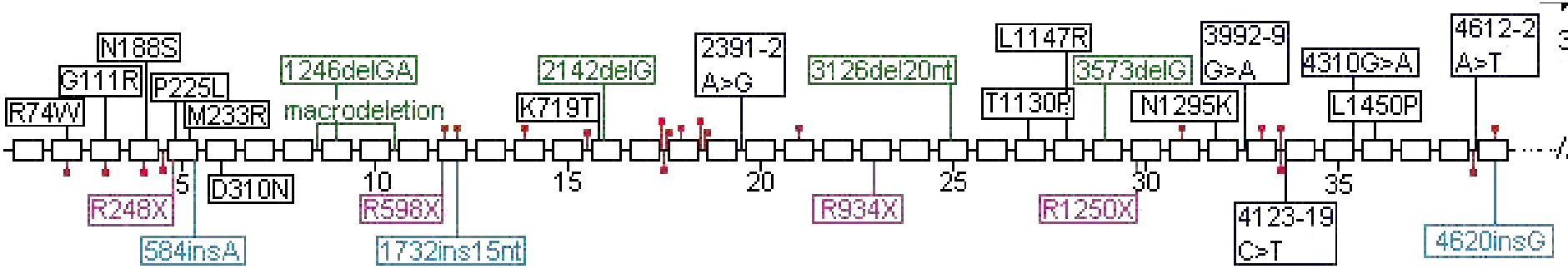
Spinocerebellar Ataxia Type 7

Spinocerebellar Ataxia Type 8

Spinocerebellar Ataxia Type 12

Machado-Joseph Disease (SCA3)

Mutaciones encontradas en los pacientes con Hiperinsulinismo Congénito españoles a lo largo del gen ABCC8



El 70% de los pacientes CHI españoles presentaban al menos 1 mutación en ABCC8

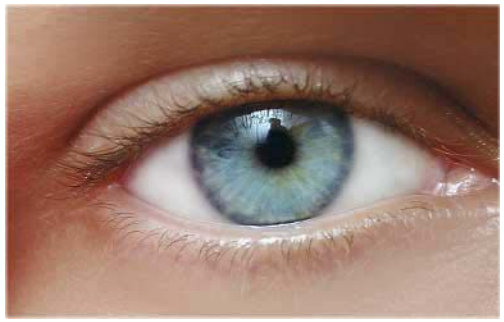
>60% mutaciones severas

8 frameshift

7 splicing

4 nonsense

RP causing genes



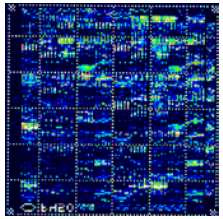
30 genes and 10 loci have been identified

arRP: *RP28* (2p11-p16), *RP26* (2q31-q32), *RP29* (4q32-q34), *RP25* (6cen-q15), *RP22* (16p12.1-p12.3)

adRP: *RP9* (7p15.1-p13), *RP17* (17q22)

X-linked RP: RP23 (Xp22), RP6 (Xp21), RP24 (Xq26-q27)

The genetic basis of more than 50% of the cases remains unknown



Genetics of sudden death in young people

Genetics of sudden death

Syndrome	Genes
HCM	MYH7, TNNT2, TPM1, MyBPC3, TNNI3, MYL2, MYL3, ACTC, TTN, PRKAG2, MYH6, GLA, MYO6, MYLK2, TNNC1, TCAP,…
DCM	MYH7, TNNT2, TPM1, ACTC, TNNC1, TTN, TCAP, ZASP, PLN, LMNA, DES, ABCC9, ACTN2, CSRP3
ARVD	PKP2, DSP, JUP, DSC2, DSG2, RYR2, TGFB3, LAMR1, PTPLA, ZASP, DES,..
LQTS	KCNQ1, KCNH2, SCN5A, ANKB, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B,…
SQTS	KCNH2, KCNQ1, KCNJ2, CACNA1C, CACNB2,…
WPW	PRKAG2
CPVT	RyR2, CASQ2
PCCD	SCN5A
Brugada	SCN5A

1

Analysis of samples

2

SEQUENOM

3

Mut (50%)

CLINICAL REPORT

APPLIES KNOWLEDGE

4

Novel mutation

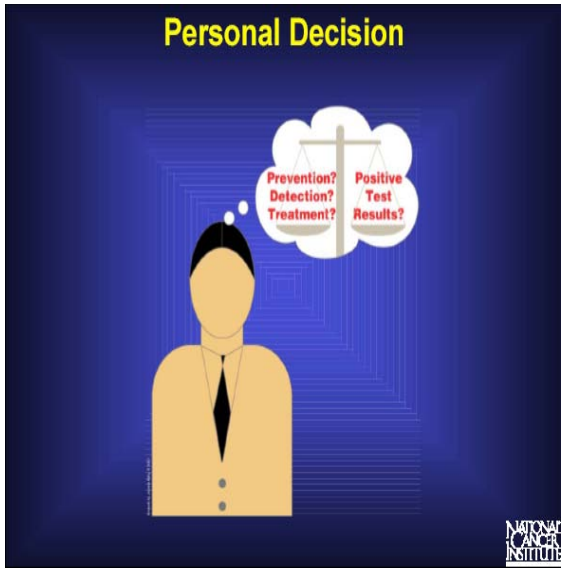
Sequencing

No mut (50%)

CREATES KNOWLEDGE

IMPROVES RESULT

Negative cases are sequenced for the sarcomeric genes, looking for new mutations



HOW TO HANDLE THE INFORMATION:

GENETIC COUNSELING

The ultimate end is genetic counseling and appropriate clinical management in relatives at risk but the knowledge of the functional significance of each mutation is variable

THE HUMAN VARIOME PROJECT

Science 7 November 2008:
Vol. 322. no. 5903, pp. 861 - 862
DOI: 10.1126/science.1167363

POLICY FORUM

GENETICS:

The Human Variome Project

Richard G. H. Cotton,[1,2,3*] Arleen D. Auerbach,[1] Myles Axton,[1] Carol Isaacson Barash,[1] Samuel F. Berkovic,[4] Anthony J. Brookes,[1] John Burn,[1] Garry Cutting,[1] Johan T. den Dunnen,[1] Paul Flicek,[1] Nelson Freimer,[5] Marc S. Greenblatt,[1] Heather J. Howard,[2] Michael Katz,[1] Finlay A. Macrae,[1] Donna Maglott,[1] Gabriela Möslein,[1] Sue Povey,[1] Rajkumar S. Ramesar,[1] Carolyn S. Richards,[1] Daniela Seminara,[1] Timothy D. Smith,[2] María-Jesús Sobrido,[6] Jan Helge Solbakk,[1] Rudolph E. Tanzi,[7] Sean V. Tavtigian,[1] Graham R. Taylor,[1] Joji Utsunomiya,[1] Michael Watson,[3]

An ambitious plan to collect, curate, and make accessible information on genetic variations affecting human health is beginning to be realized.

---

[1]Discussion leaders for the Human Variome Project Planning Meeting 2008.

[2]Genomic Disorders Research Centre, Howard Florey Institute, Melbourne, Australia.

[3]Cochair of the HVP Planning Meeting.

[4]Epilepsy Research Centre.

[4]University of Melbourne, Austin Health West Heidelberg, Australia.

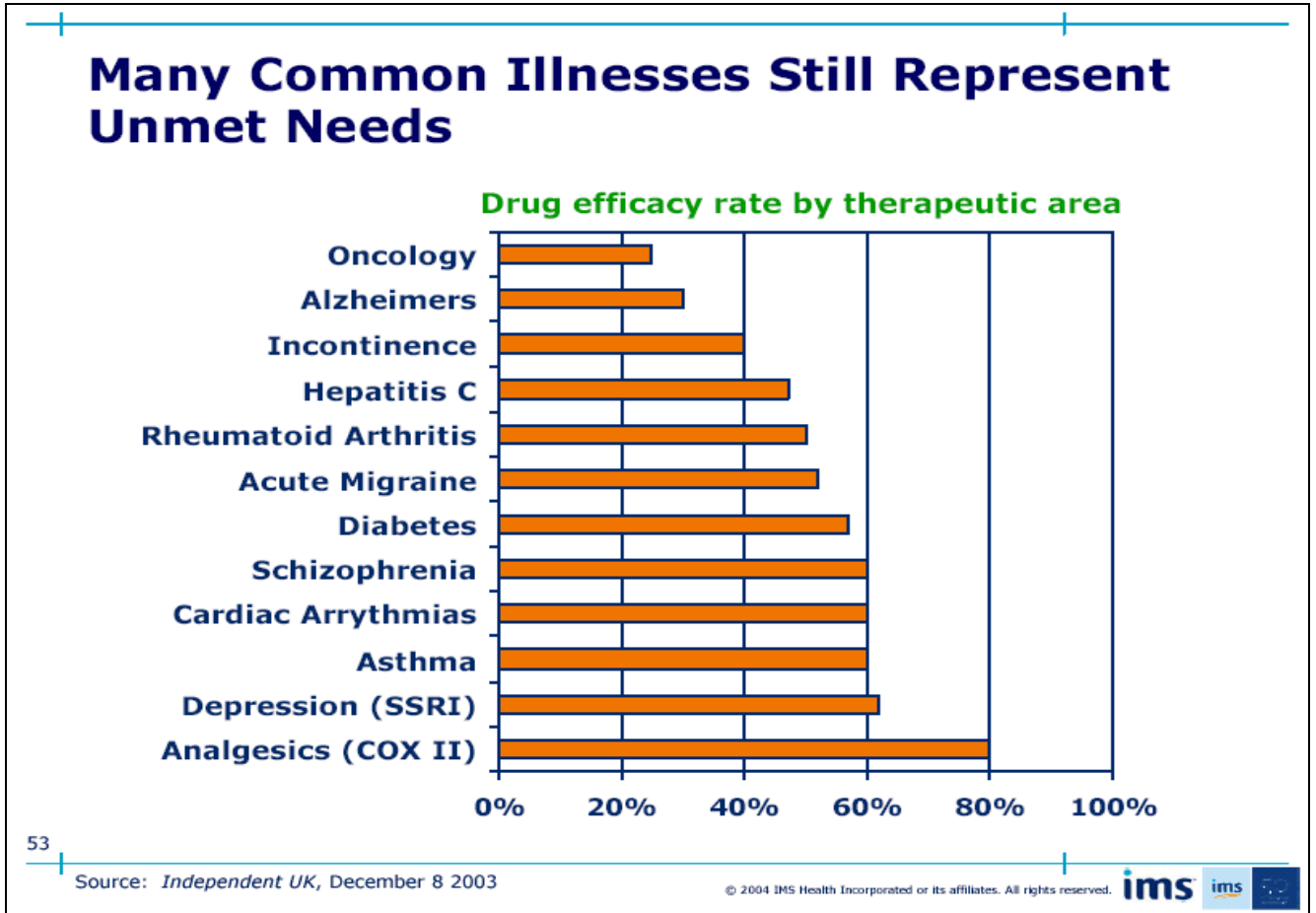
[5]UCLA Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA.

[5]Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, Spain, and Center for Network Biomedical Research on Rare Diseases (CIBERER), Institute of Health Carlos III, Madrid, Spain.

Our knowledge of the etiopathogenesis of the disease is limited

Our classification of diseases is mainly based in signs and symptoms

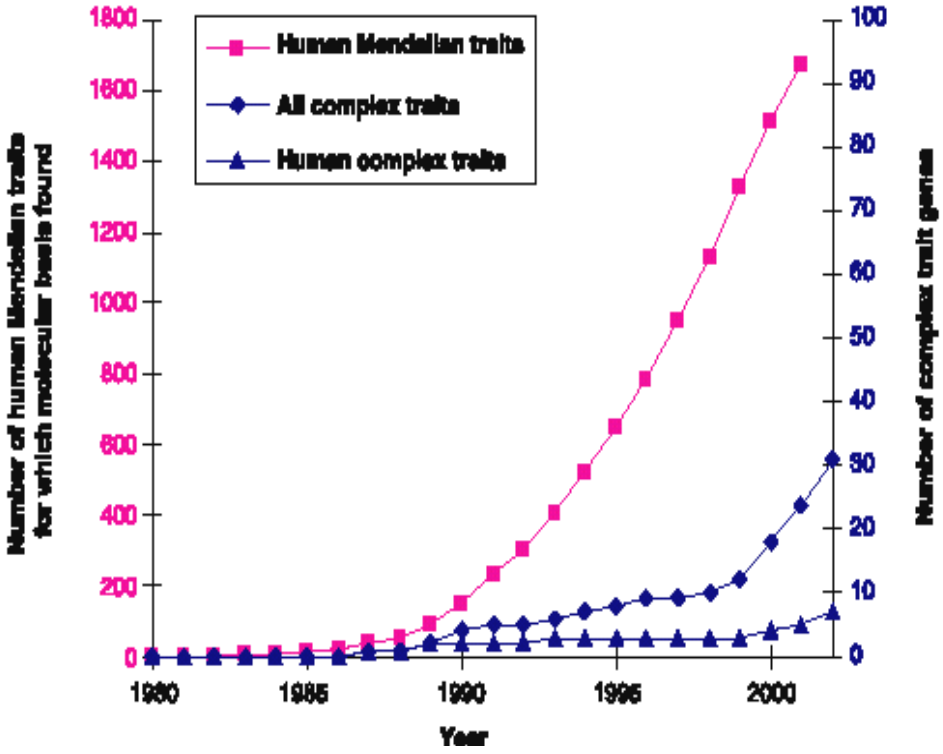
Limited therapeutic efficacy in many TAs



Fundación Pública Galega de Medicina Xenómica

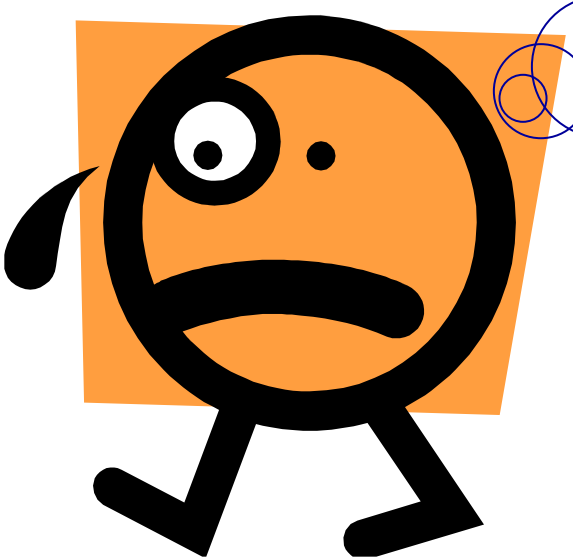
USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Using genetics to find genes that underlie complex traits is a potential useful tool for a better understanding of the disease and pharmacogenetics and pharmacogenomics



But still the advance in knowledge ir genes involved in complex traits is limited !

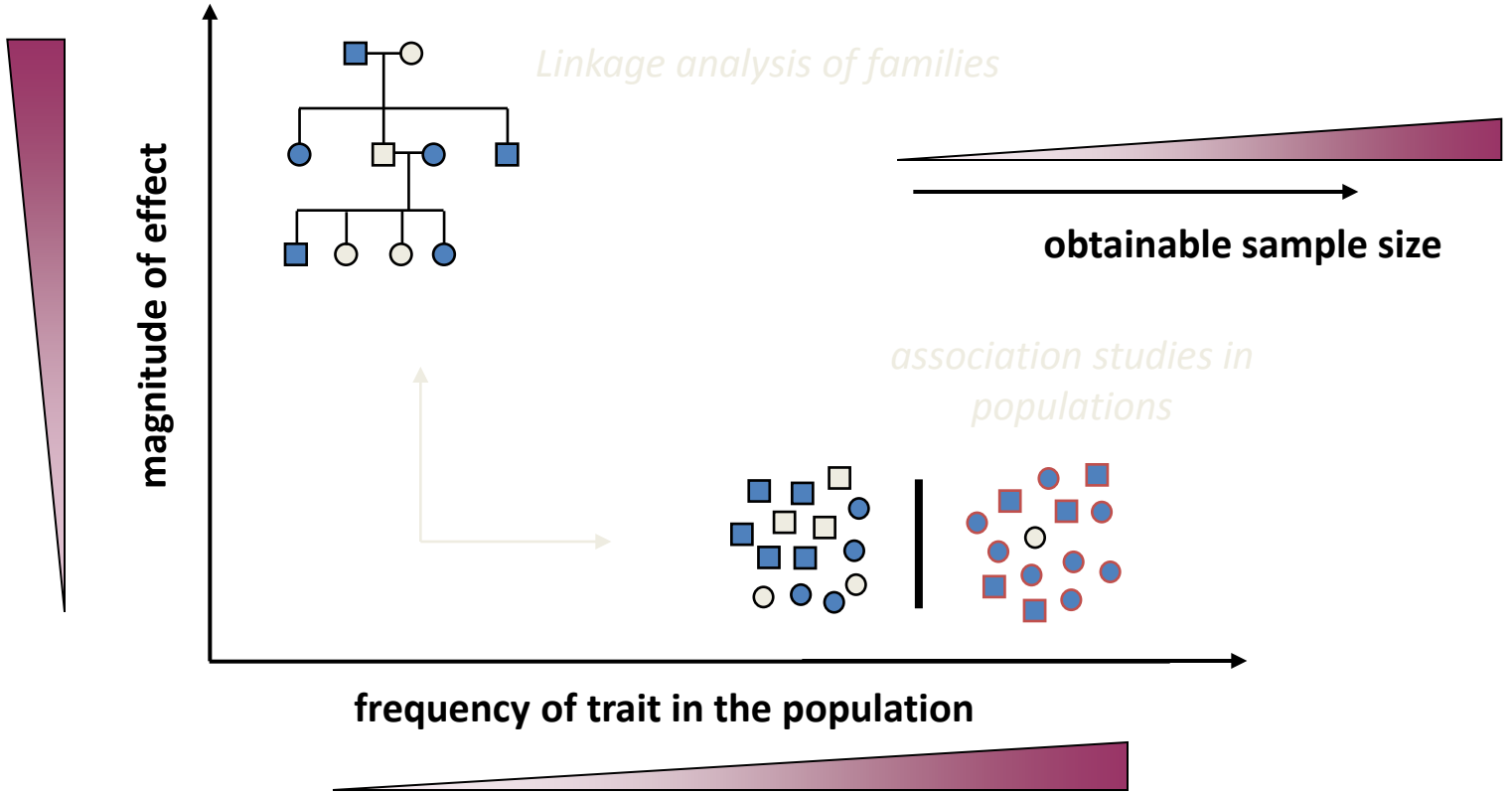
Allelic heterogenity
Locus heterogeneity
Phenocopy
Phenotypic variability
Trait heterogeneity
Gene-gene interactions
Gene-environment interactions



Linkage analysis or association studies ?

- linkage analysis is usually more robust in the identification of mendelian traits (Bergman et al. Genome-wide linkage scan for breast cancer susceptibility loci in Swedish hereditary non-BRCA1/2 families: suggestive linkage to 10q23.32-q25.3. Genes, chromosome, cancer 46, 302, 2007)

- association studies have more power to detect genes with small effects (Risch & Merikangas, *Science* 1996)

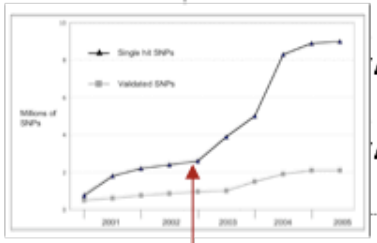


3.3 gigabases of genome>12M SNPs

ACAGTCTGAC **C** GTACTAGTTA
ACAGTCTGAC **T** GTACTAGTTA

1.42 million SNPs

1 SNP / 2,300 bp

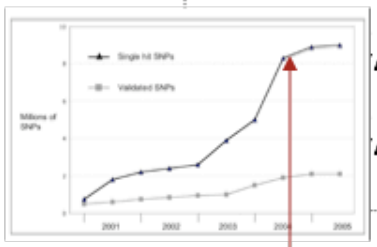


AGTCTGAC **C** GTACTAGTTA
AGTCTGAC **T** GTACTAGTTA

3 million

1 SNP / 1,000 bp

International HapMap Project



AGTCTGAC **C** GTACTAGTTA
AGTCTGAC **T** GTACTAGTTA

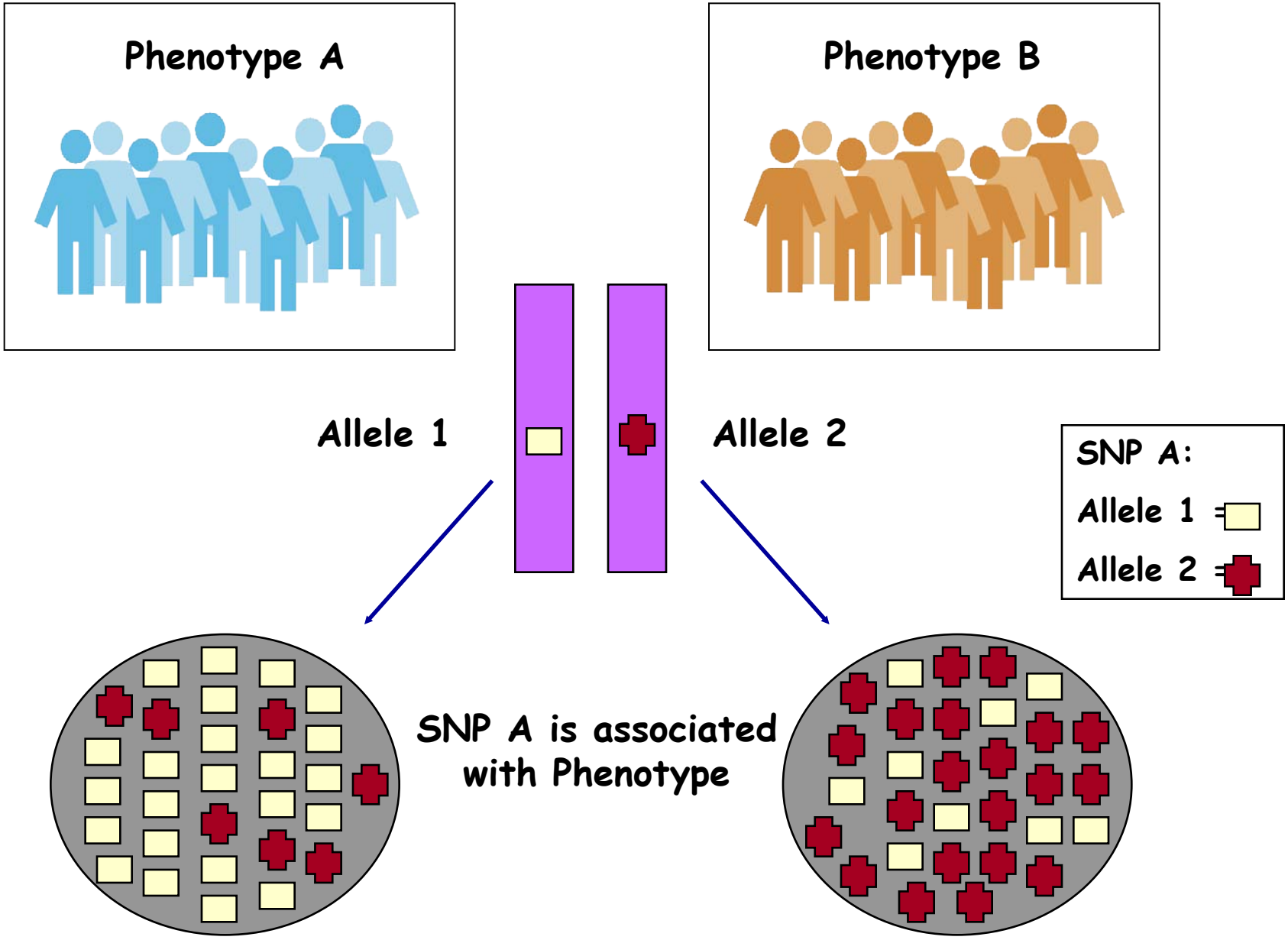
10 million

HapMap ENCODE

1 SNP / 330 bp

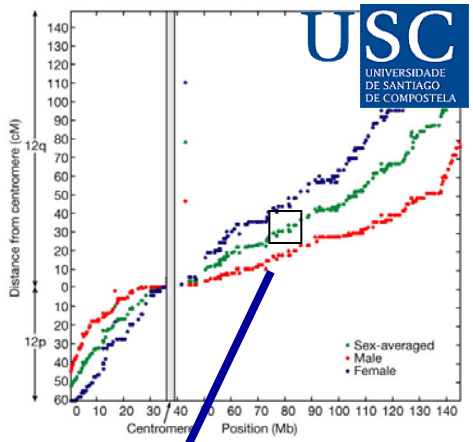
1 SNP / **279bp**

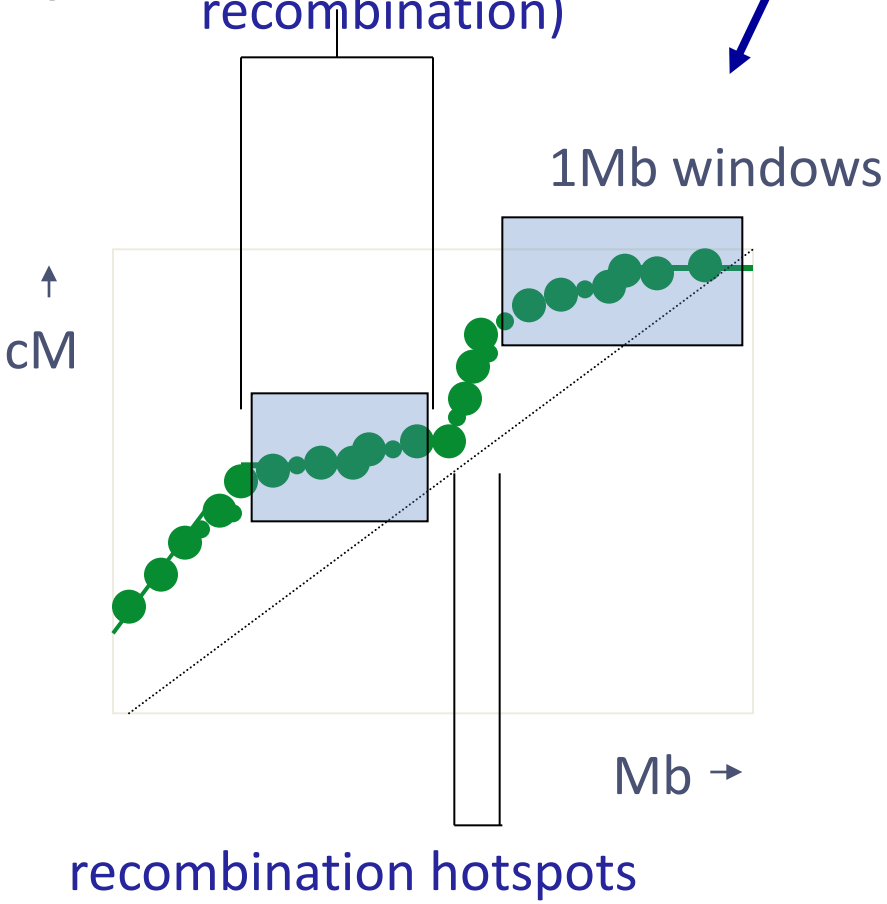
Human Genetic Association Study Design



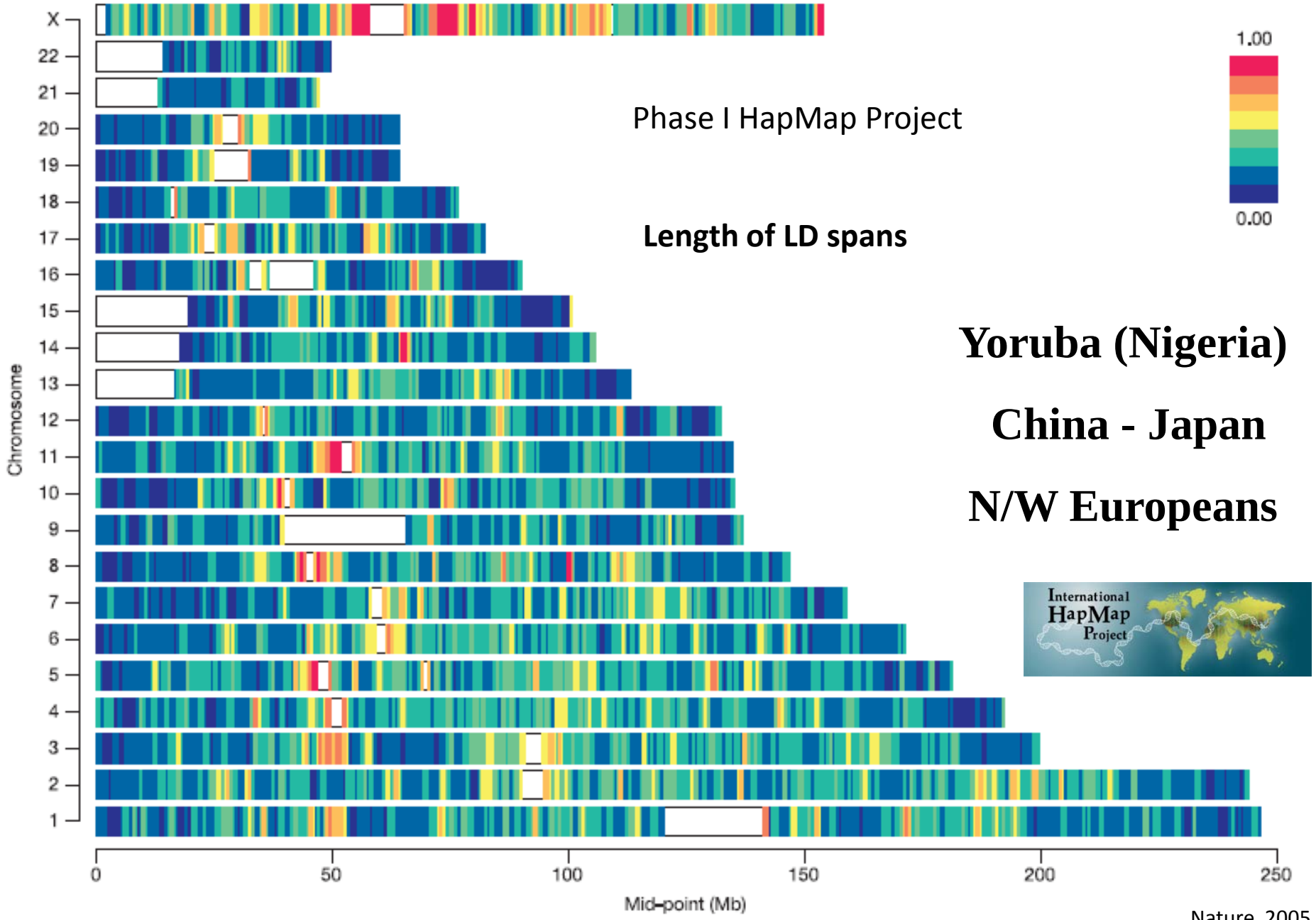
Characteristics of SNP Variation

- Clustering is observed on all the autosomes: Haplotype blocks: Blocks with little evidence of recombination
- Some clusters appear functional : MHC on chromosome 6 (with extensive replication)





Gabriel et al. Science, 296,2002


Phase I HapMap Project
Length of LD spans
1.00
0.00
Yoruba (Nigeria)
China - Japan
N/W Europeans
International HapMap Project
Chromosome
X
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
50
100
150
200
250
Mid-point (Mb)

Nature, 2005

Spanish National Genotyping Center

GeGen

CEGEN

Scientific International Committee

Ethical International Committeel

Coordination

NODE 1 Barcelona (CRG)

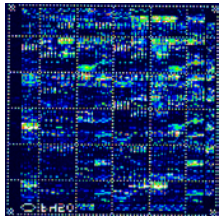
SNPlex / Illumina

NODE 2 Santiago de Compostela (USC)

Sequenom / SNPlex/ Affymetrix

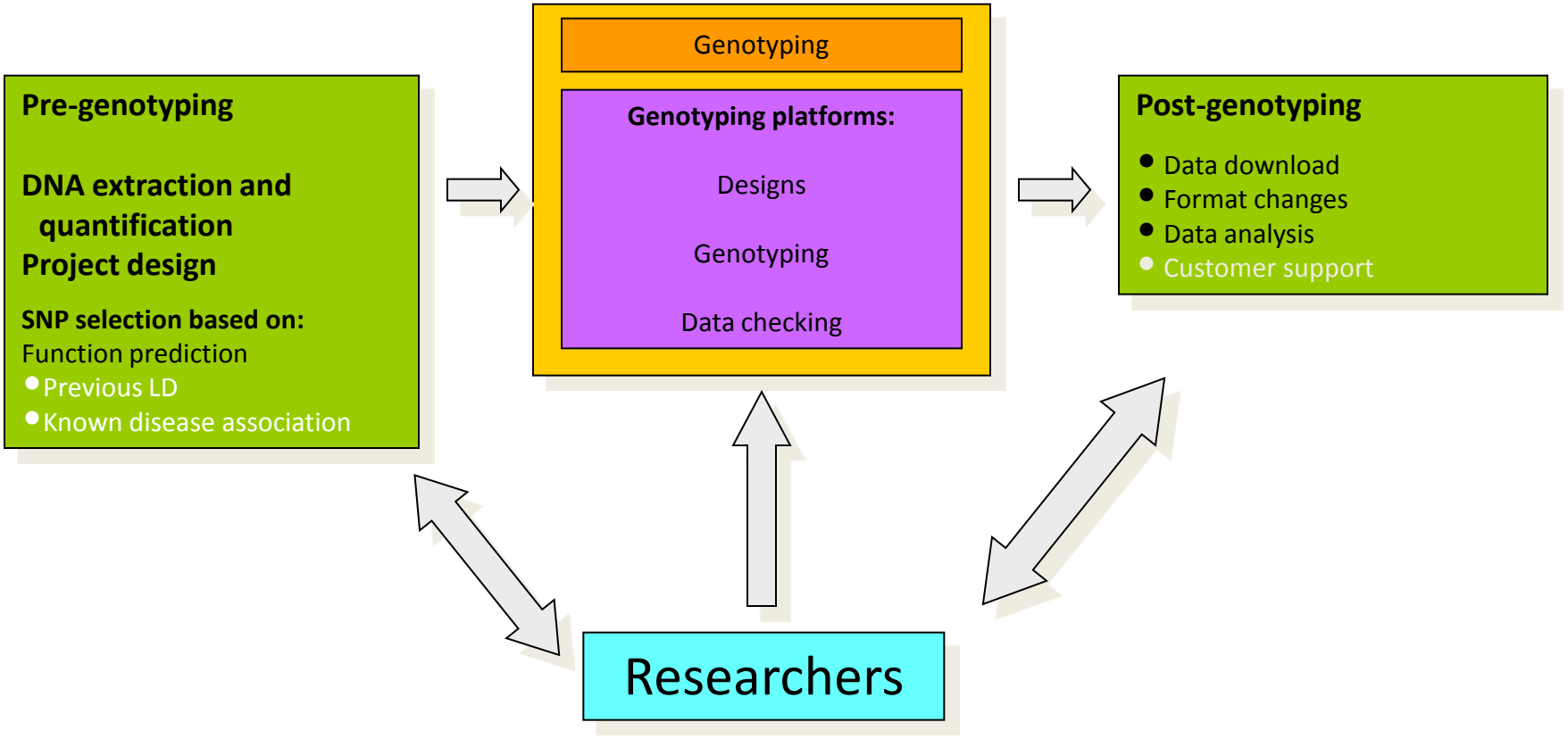
NODE 3 Madrid (CNIO)

Illumina




CeGen
TECAN
eedom evo
TECAN
te-mo

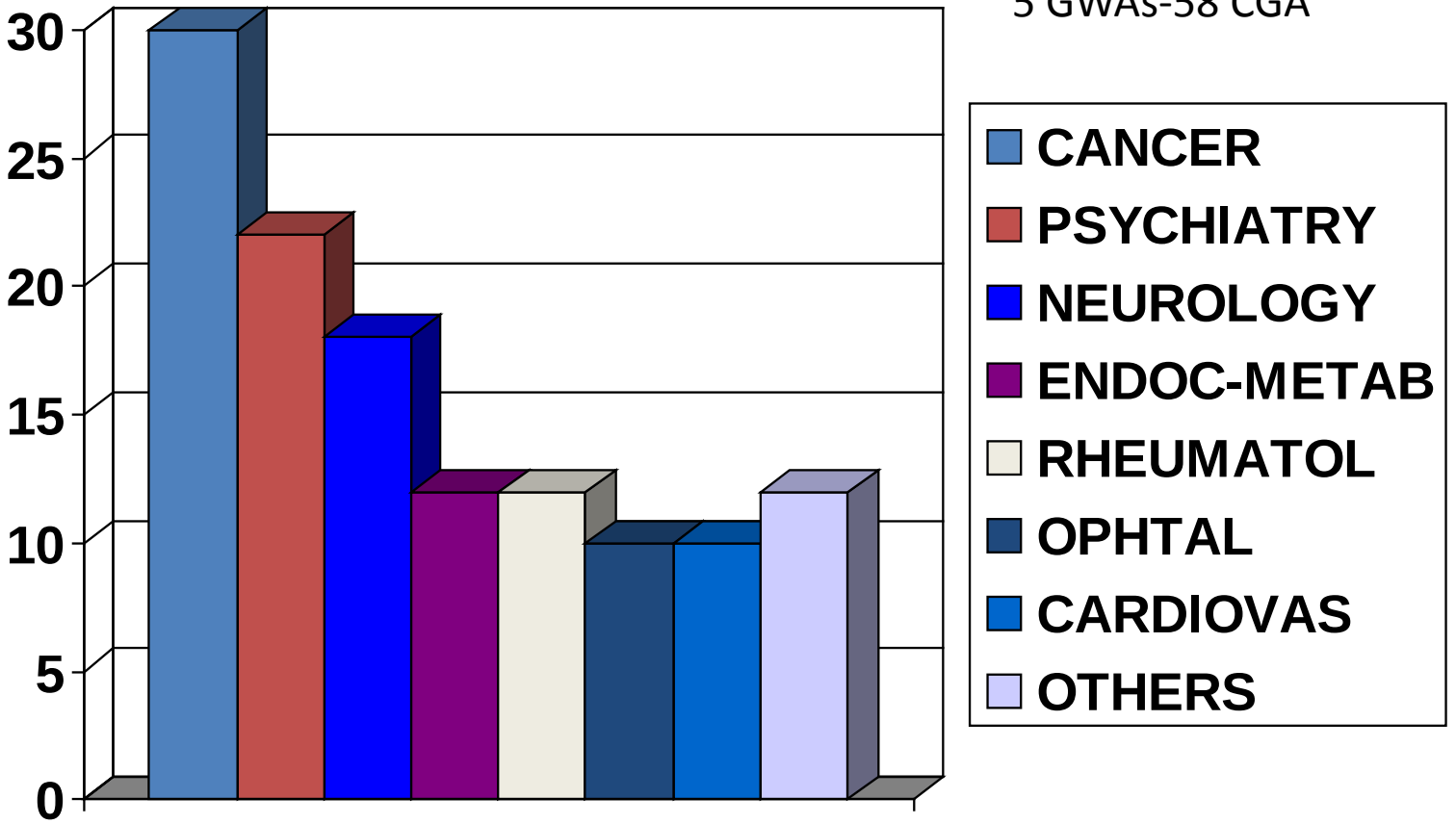
Spanish National Genotyping Center



Plataform of genotyping services for research groups in Spain

ASSOCIATION STUDIES CARRIED OUT IN OUR CENTER

Scheduled 2008-2009
5 GWAs-58 CGA



TOTAL 2005: 55 PROJECTS

TOTAL 2006: 95 PROJECTS

TOTAL 2007: 124 PROJECTS

Association studies

Candidate gene approach

-Causative hypothesis or candidate genes

Genome wide analysis (GWAs)

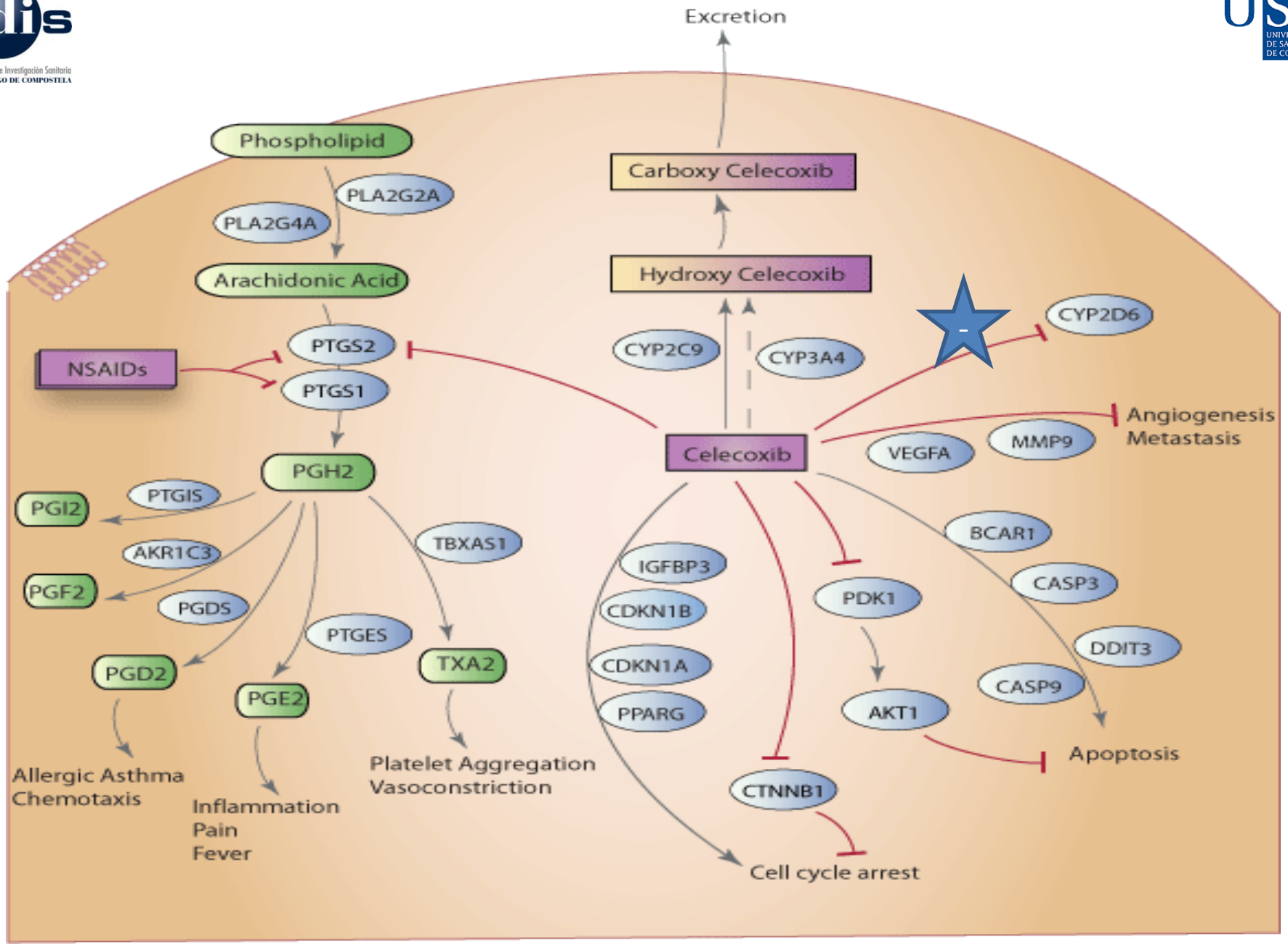
-No need of gene selection

-Lack of bias towards specific genes

Both approaches are complementary

Candidate gene approach

- If candidate gene approach selected:
  - Look for candidate genes using pathways, functional studies, comparative genomics, functional data, markers informative for ancestry: selection signatures can provide clues for genes involved in complex traits
  - 1st step: Possible causative SNPs (mis-sense, non-sense, splicing sites, factor transcription sites, AIMs...) (Frec>5%).
  - 2nd step: Additional SNPs in regulating regions at frequencies $\geq$ 5% for haplotype analysis (minimum of 3 SNPs/gen)


Excretion
Phospholipid
PLA2G2A
PLA2G4A
Arachidonic Acid
Carboxy Celecoxib
Hydroxy Celecoxib
CYP2C9
CYP3A4
CYP2D6
NSAIDs
PTGS2
PTGS1
Celecoxib
Angiogenesis
Metastasis
VEGFA
MMP9
PGH2
PTGIS
PGI2
AKR1C3
PGF2
PGDS
PGD2
PTGES
PGE2
TBXAS1
TXA2
IGFBP3
CDKN1B
CDKN1A
PPARG
PDK1
AKT1
BCAR1
CASP3
DDIT3
CASP9
Apoptosis
CTNNB1
Cell cycle arrest
Allergic Asthma
Chemotaxis
Inflammation
Pain
Fever
Platelet Aggregation
Vasoconstriction

Genetic polymorphisms and risk of CRC with candidate gene approaches

Gene	Name	Polymorphism
ABCB1	Glicoproteína-P	1236C>T
ABCC2	Transportador de aniones orgánicos canalicular	3972C>T
ABCG2	Proteína de resistencia al cáncer de mama	19572–19569delCTCA
ADH3	Alcohol deshidrogenasa	Codón 350
APC	*Adenomatous polyposis coli*	E1317Q
APOE	Apolipoproteína E	ε2/3
BLM	Síndrome de Bloom	BLM^{Ash}
CBS	Cistationina β-síntasa	ins68bp x8
CCDN1	Ciclina D1	A870G
CDH1	E-caderina	-347insA (promotor)
CHEK2	*Checkpoint* quinasa 2	del1100C
COX1	Prostaglandina H sintasa 1	R8W, L15Δ, P17L, L237M
COX2	Prostaglandina H sintasa 2	V511A
CYP1A1	Citocrom P450 1A1	I462V, nt 6235T>C
EPHX	Epóxido hidrolasa microsomal	Y113H, H139R
GCPII	Glutamato carboxipeptidasa	H475Y
GSTM1	Glutatión S-transferasa mu1	Alelos nulos
GSTP1	Glutatión S-transferasa pi1	I101V, A114V
GSTT1	Glutatión S-transferasa theta1	Alelos nulos
HRAS1	*Harvey rat sarcoma virus 1*	Alelos VNTR raros
HFE	Hemocromatosis	H63D, C282Y
IGF1	*Insulin-like growth factor 1*	Repetición CA
IGFBP3	*IGF binding protein*	-202A>C
IL6	Interleucina 6	-174G>C
IL8	Interleucina 8	-251T>A
IRS1	Receptor insulina substrato 1	G972R
IRS2	Receptor insulina substrato 2	G1057D
MLH1	MutL homólogo	D132H
MLH3	MutL homólogo	P844L, S845G
MMP1	Matrix metaloproteínasa 1	2G
MMP3	Matrix metaloproteínasa 3	6A
MSH2	MutS homólogo 2	nt 2006C>T
MTHFD1	MTHF deshidrogenasa	R653Q
MTHFR	MTHF reductasa	C677T, A1298C
MTR	Metionina sintasa	D919G, A2756G
MTRR	Metionina sintasa reductasa	A66G
NAT1	N-Acetiltransferasa 1	Alelos múltiples, ej.*10
NAT2	N-Acetiltransferasa 2	Alelos acetiladores rápidos
PAI1	*Plasminogen activator inhibitor 1*	Ins G promotor
PLA2G2A	Fosfolipasa secretora A2	nt 964 C>G, nt 1073 G>C
PPARG	*Peroxisome proliferator activated receptor*	P10A
SHMT	Serina hidroximetiltransferasa	L474F
TGFB1	*Transforming growth factor beta1*	L10P
TGFBR1	TGF beta receptor 1	del(Ala)3
TNFA	Factor de necrosis tumoral alfa	-308 G>A
TNFB	Factor de necrosis tumoral beta	-238 G>A
TP53	p53	R72P
TS	Timidilato sintasa	2R/3R promotor, 1494del6
UGT1A1	Uridina difosfatoglucuronosiltransferasa 1ª	*28, -3156G>A
UGT1A9	Uridina difosfatoglucuronosiltransferasa 9A	*22
VDR	Receptor vitamina D	M1T, intrón 8 BsmI, I352I C>T 3'-UTR poliA corto/largo

Meta-analysis of candidate CRC genes

• Xenobiotic metabolism	?N
• Iron absoprtion/metabolism	?
• Ha-ras VNTR rare alleles	?Y
• APC I1307K (Ashkenazi)	Y
• MTHFR	?
• p53	N
• TGFBR1	N
• BLM*Ash	?
• CHEK2	?N

Previous case-control (association) studies to identify common, low-penetrance cancer genes

- Many small-scale studies in past, candidate genes
- Many positive reports
- *A priori* p(false+) >>> p(true+)
- Publication bias, failure to match cases and controls/population stratification, lack of correction for multiple comparisons, lack of replication

Numero estimado de pacientes para el estudio de asociación con la enfermedad

NECESIDAD DE REDES-DEFINICIÓN DEL FENOTIPO

Proyecto EPICOLON

Sebastián)

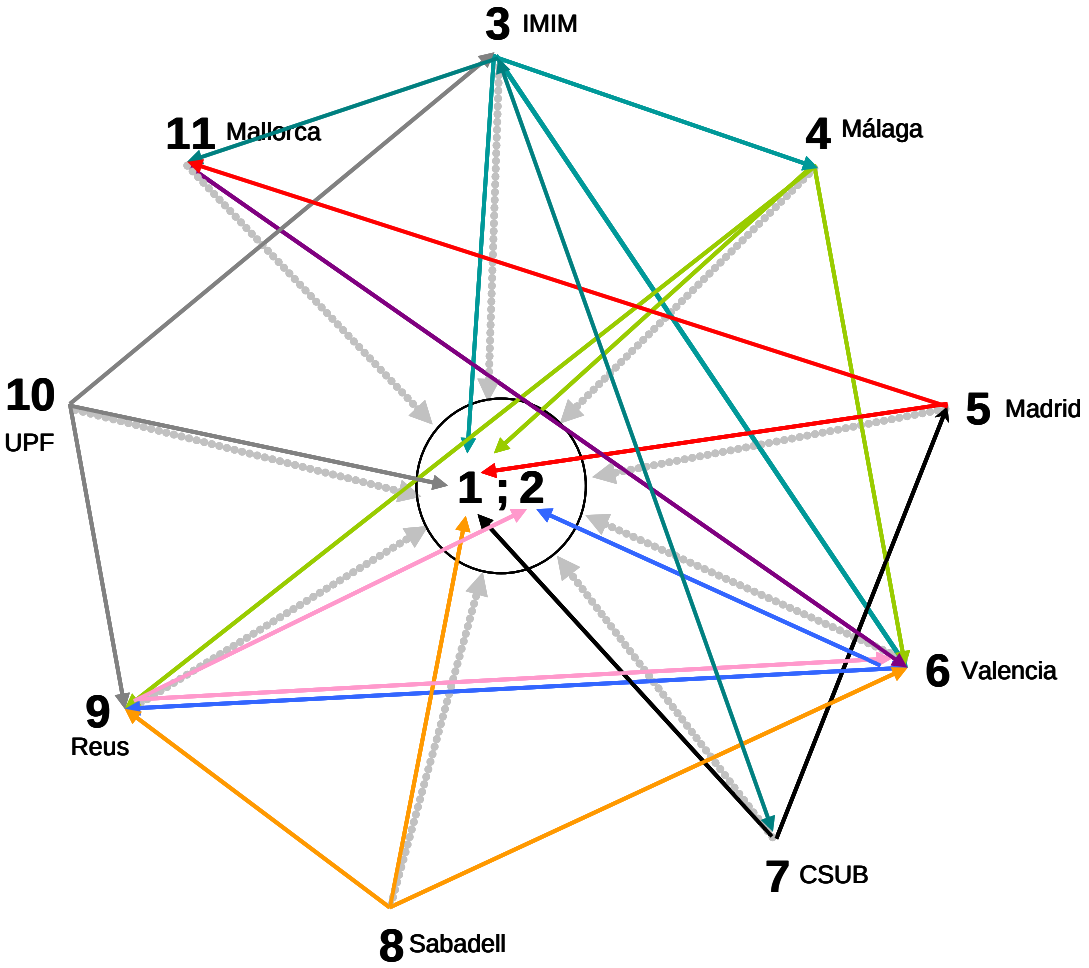
- H. San Eloy (Barakaldo)
- H. San Agustín (Avilés)
- H. Clínico (Zaragoza)
- H. Gral. Huesca
- H. Cristal Piñor (Ourense)
- H. Meixoeiro (Pontevedra)
- H. 12 octubre (Madrid)
- H. Gral. Guadalajara
- H. Reina Sofía (Córdoba)
- H. Virgen del Rocio (Sevilla)
- H. Univ. Canarias (Tenerife)

EPICOLON I (2000-2001): 515 cases and 515 controls

EPICOLON II (2006-2008): 900 cases/600 controls

- H. Clínic (Barcelona)
- H. Mar (Barcelona)
- H. Arnau de Vilanova (Lleida)
- H. Gral. Vic
- H. Esperit Sant (Sta. Coloma Gramenet)
- H. Germans Trias i Pujol (Badalona)
- H. Alt Penedès (Vilafranca del P.)
- Institut Dexeus (Barcelona)
- H. Mútua de Terrassa
- H. Gral. Granollers
- H. Gral. Palma (Palma de Mallorca)
- H. Gral. València
- H. Gral. Alacant
- H. La Fe (València)

Interaction between nodes (5)

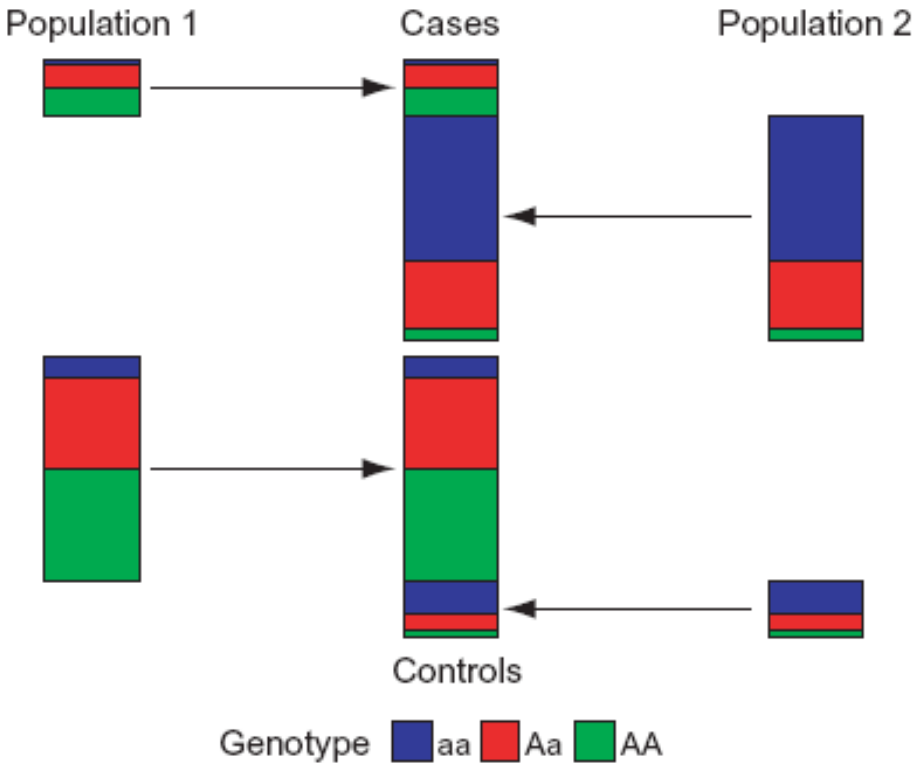


(1) Santiago

(2) Barcelona

Each color corresponding to one project- 10 projects

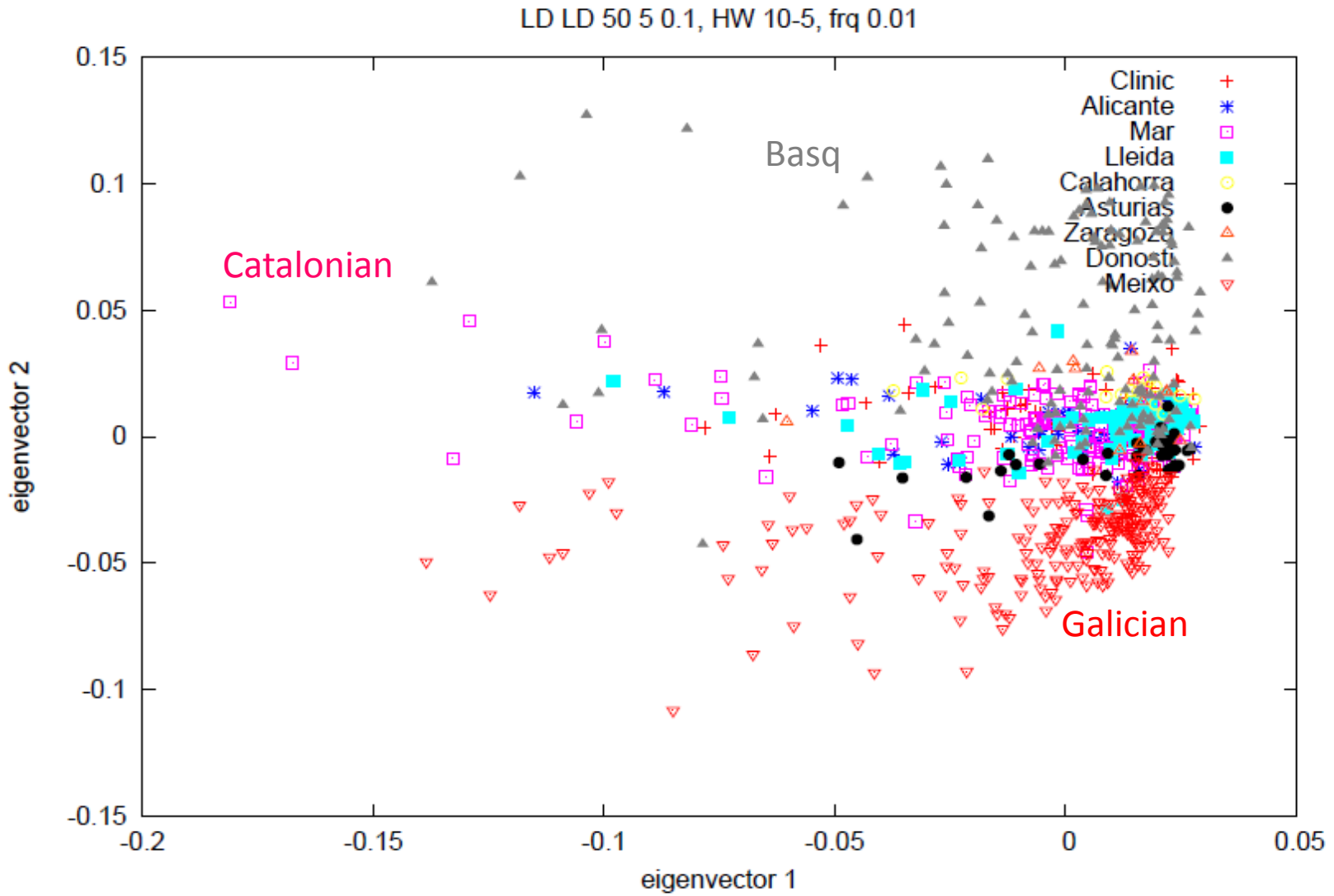
TYPE I ERRORS: Population stratification



CRC GWAS Affy 6.0

923 Spanish cases and 276 controls (detailed phenotypic information, follow-up, pharmacogenetic data-ADRs)

PCA for QC showed significant differences amongst Spanish populations



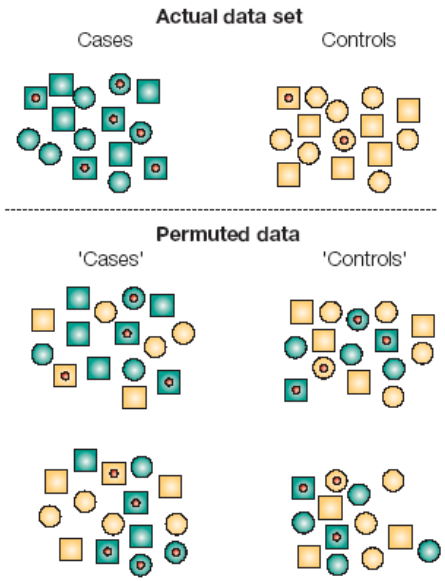
Type I errors: random

Corrections for multiple comparisons (p= 0.01
1 false positive every 100 comparisons)

- Bonferroni method

$P_{cor} = 1-(1-P_{noncor})^n \Rightarrow$ new signif = alfa/n. comparisons

-Very conservative-Assumption of independence



- Permutations (the most commonly used method-computational intensive!)
- Other methods:

-False discovery rate (FDR)

-Sum Statistics

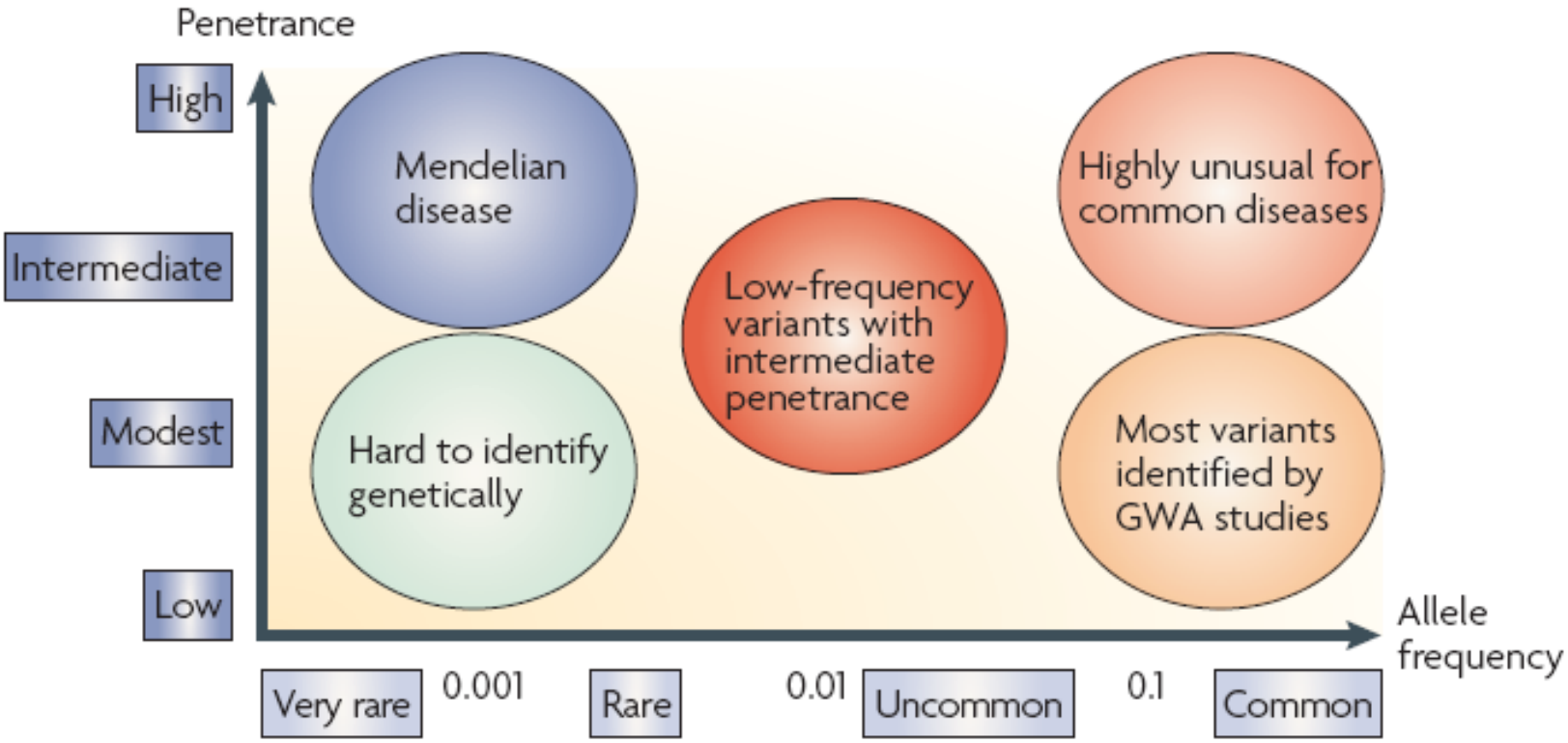
-Single Nucleotide Polymorphism Spectral Decomposition

-Others

Genes candidatos vs GWAs

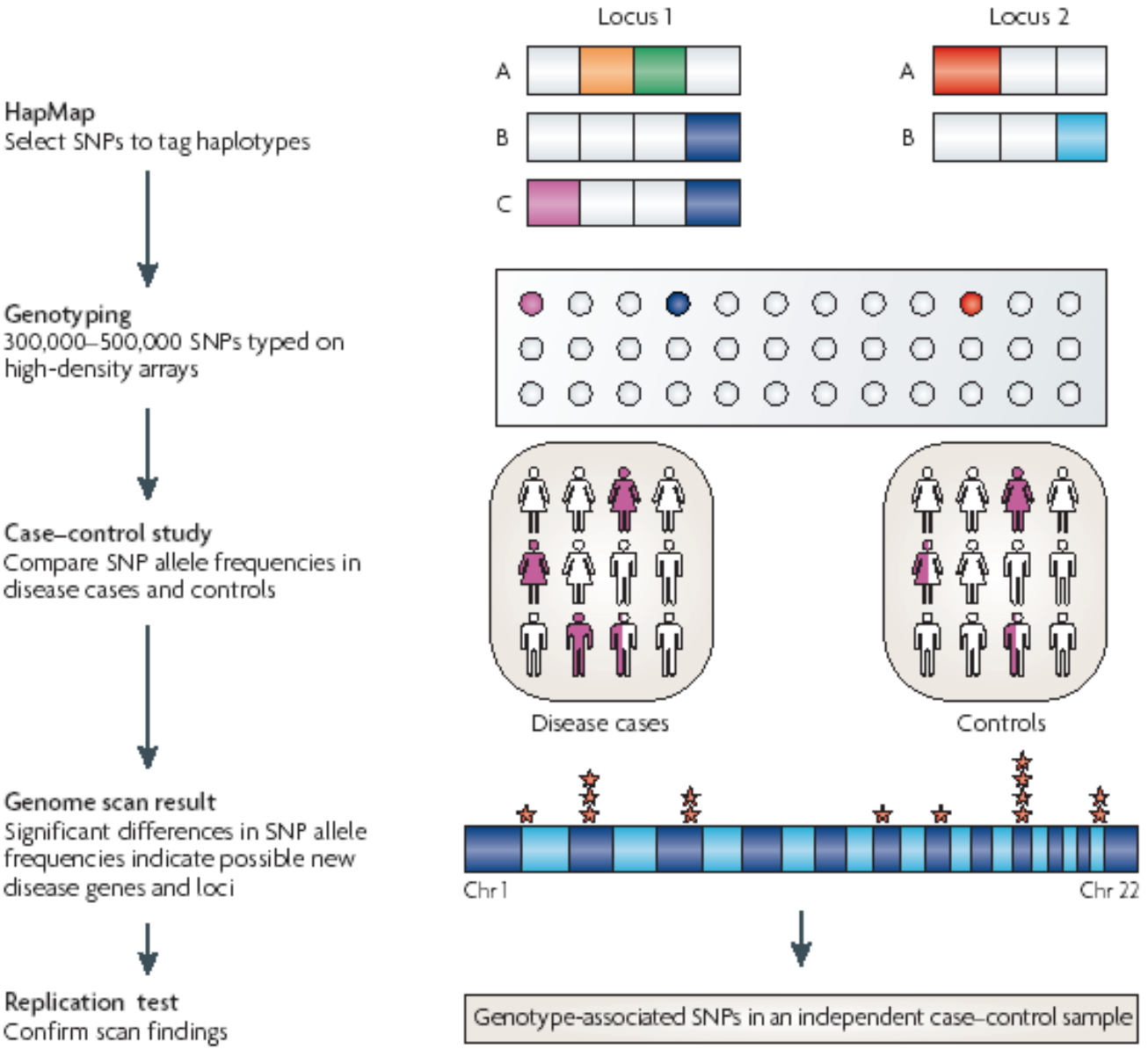
Common diseases&Rare alleles -Candidate genes- GWAs of functional SNPs

Common disease&Common alleles-GWAs



McCarthy, *Nature Rev Genet* 2008

Whole-genome association analysis



GWAS

Two systems for whole genome SNP analysis are available each with varying densities, SNP selection and cost :

Illumina 1K

Affy 20K functional SNPs

Cost 200€-300€/chip

Affymetrix 6.0 2 M genotypes

nature genetics

Integrated detection and population-genetic analysis of SNPs and copy number variation

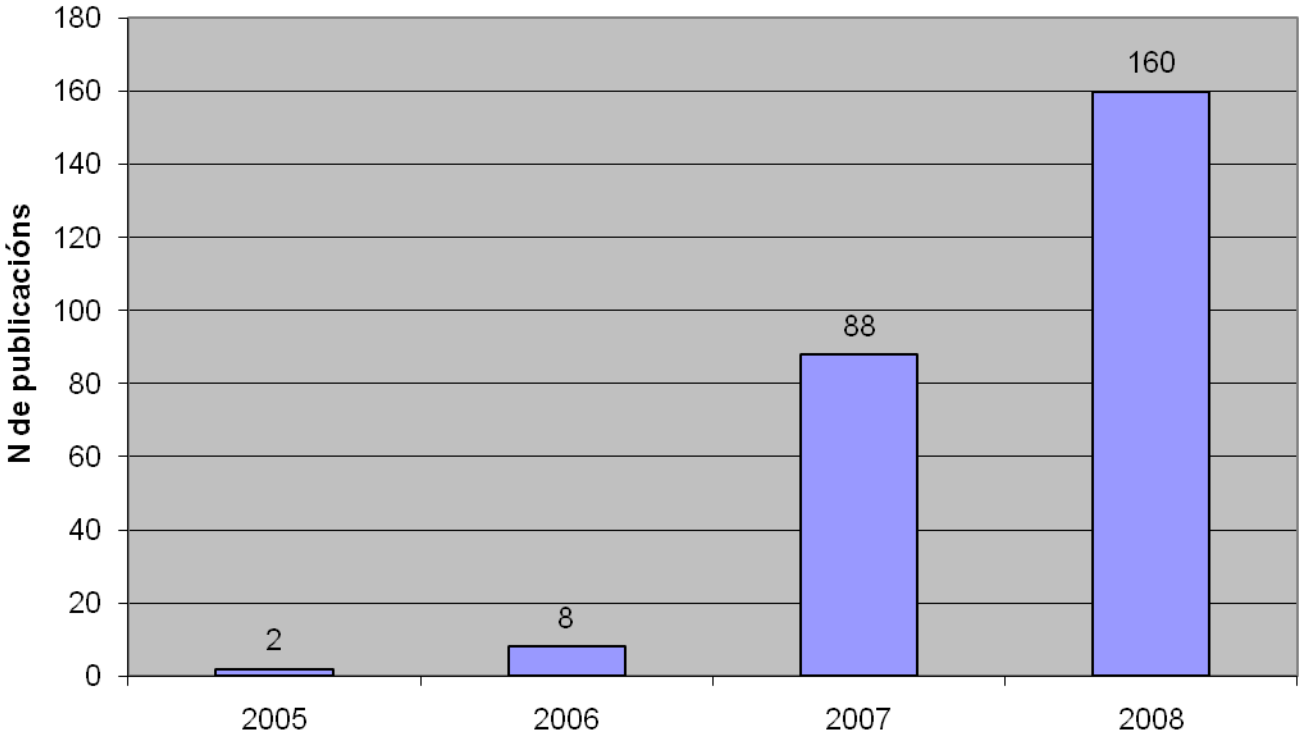
Steven A McCarroll[1–4,10], Finny G Kuruvilla[1–4,10], Joshua M Korn[1–6], Simon Cawley[7], James Nemesh[1], Alec Wysoker[1], Michael H Shapero[7], Paul I W de Bakker[1,4,8], Julian B Maller[3], Andrew Kirby[3], Amanda L Elliott[1], Melissa Parkin[1], Earl Hubbell[7], Teresa Webster[7], Rui Mei[7], James Veitch[7], Patrick J Collins[7], Robert Handsaker[1], Steve Lincoln[7], Marcia Nizzari[1], John Blume[7], Keith W Jones[7], Rich Rava[7], Mark J Daly[1,3,4,9], Stacey B Gabriel[1] & David Altshuler[1–4,9]

Principal difficulties are data management and statistical analysis of data generated

genome.gov
National Human Genome Research Institute
National Institutes of Health

A Catalog of Published Genome-Wide Association Studies

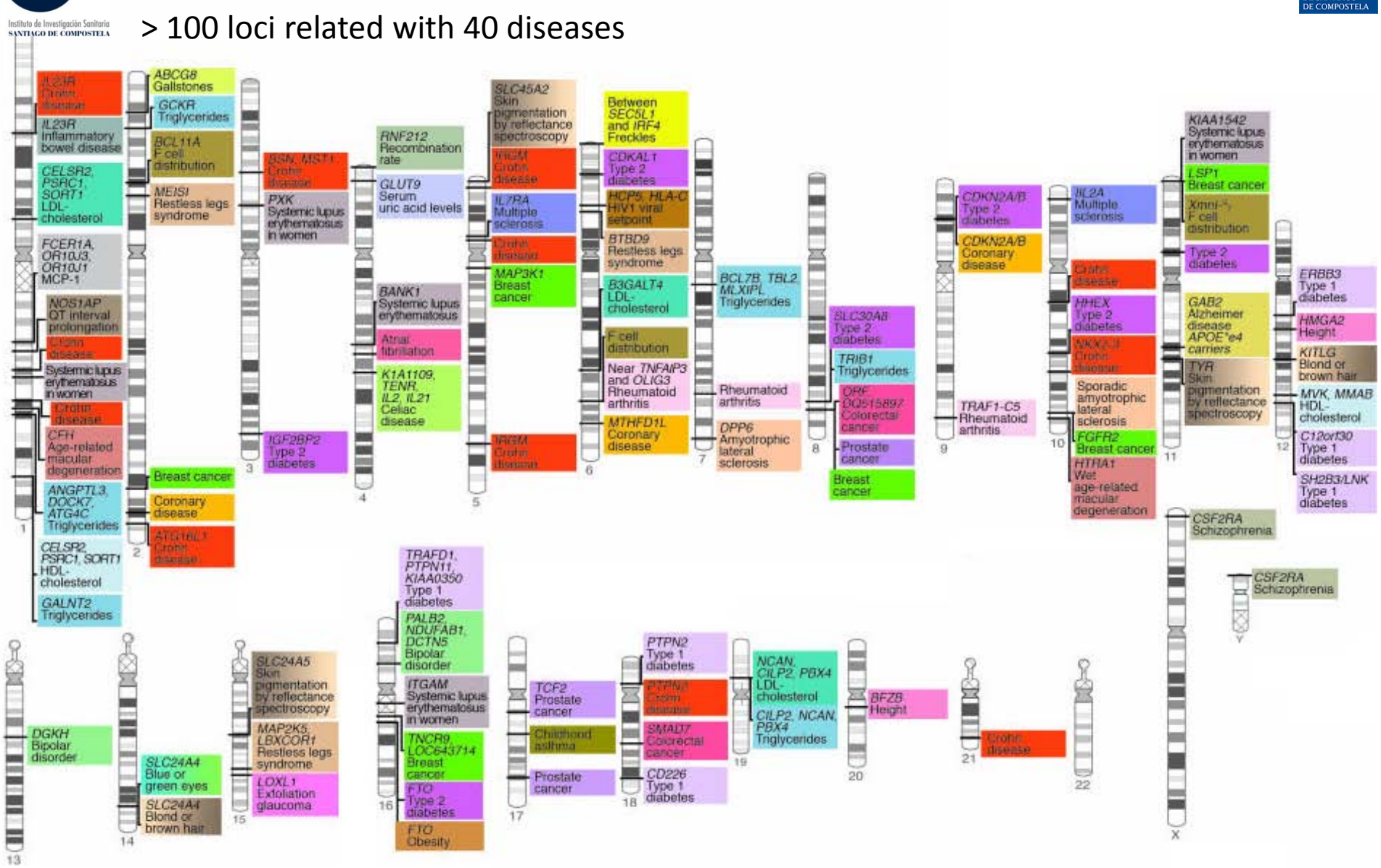
(>100.000 SNPs)



http://www.genome.gov/GWAstudies/

GWAs preliminary results

> 100 loci related with 40 diseases

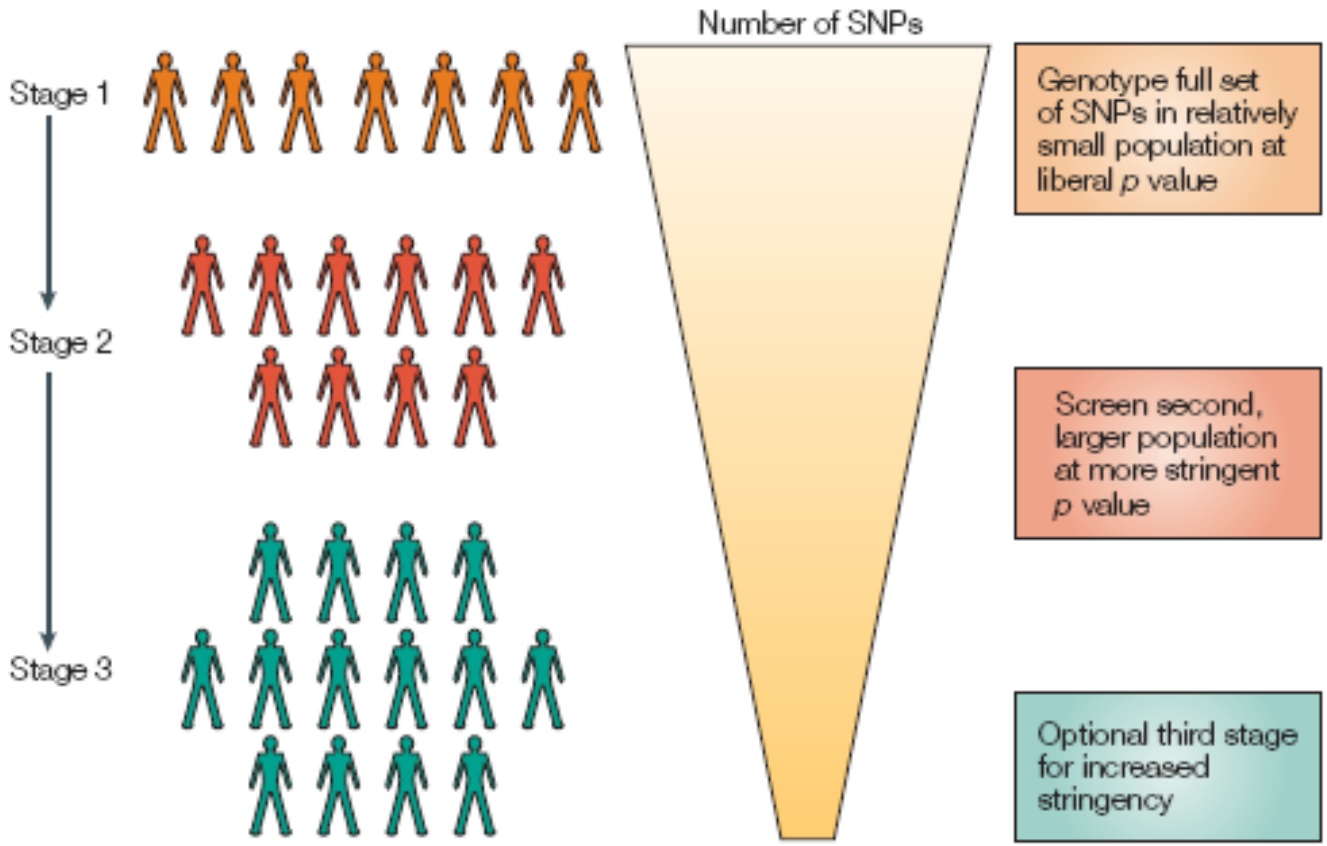


J. Clin. Invest. **118**:1590–1605 (2008)

Genome-wide association study (GWAS) to identify low-penetrance genes

- Require 1000s of cases and controls (but not always)
- Can improve power by selecting cases (early-onset, familial) and controls (cancer-free)
- Search for alleles or genotypes over-represented in cases
- Verify in other sample sets

GWAs in stages



A multi-stage GWAS to identify common colorectal cancer genes

Tomlinson et al. Nat Genet. 2008 May;40(5):623-30

Stage 1: 550K tagging SNPs
1,000 familial cases + 1,000 controls (CORGI2)

Stage 2: ~40,000 SNPs brought forward from Stage 1
3,000 cases + 3,000 controls (NSCCG)

Stage 3: 3,000 cases + 3,000 controls (NSCCG2+VCQ)

Stage 4: Multiple replication sets (6000 cases/controls)

Stage 5: Meta-analysis with Edinburgh (14000 cases/control)

RESULTS GWAS CRC
Tomlinson et al. 2008 Nature Genetics

Locus	gen	MAF	OR alelico	P-val
8q24	Ninguno/MYC/ POU5F1p1	0.48	1.35 (1.20-1.53)	$1.3*10^{-14}$
18q21	SMAD7	0.47	0.84 (0.75-0.94)	$1.0*10^{-12}$
15q	GREM1	0.19	1.17 (1.06-1.30)	$4.4*10^{-14}$
8q23	EIF3H	0.07	1.27 (1.20-1.34)	$3.3*10^{-18}$
10p	Ninguno	0.33	0.87 (0.83-0.91)	$2.5*10^{-12}$
11q23	POU52AF1		1.11 (1.08-1.15)	$7.7*10^{-28}$

LETTERS

nature genetics

A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3

Ian PM Tomlinson[*1,38], Emily Webb[2], Luis Carvajal-Carmona[1], Peter Broderick[2], Kimberley Howarth[1], Alan M Pittman[2], Sarah Spain[1], Steven Lubbe[2], Axel Walther[1], Kate Sullivan[2], Emma Jaeger[1], Sarah Fielding[2], Andrew Rowan[1], Jayaram Vijayakrishnan[2], Enric Domingo[1], Ian Chandler[2], Zoe Kemp[1], Mobshra Qureshi[2], Susan M Farrington[3], Albert Tenesa[3], James GD Prendergast[3], Rebecca A Barnetson[3], Steven Penegar[2], Ella Barclay[1], Wendy Wood[2], Lynn Martin[1,4,5], Maggie Gorman[1], Huw Thomas[6], Julian Peto[7,8], D Timothy Bishop[9], Richard Gray[10], Eamonn R Maher[5], Anneke Lucassen[11], David Kerr[12], D Gareth R Evans[4], The CORGI Consortium[37], Clemens Schafmayer[13,14], Stephan Buch[16,17], Henry Völzke[15], Jochen Hampe[16], Stefan Schreiber[14,17], Ulrich John[15], Thibaud Koessler[18], Paul Pharoah[18], Tom van Wezel[19], Hans Morreau[19], Juul T Wijnen[20], John L Hopper[21], Melissa C Southey[22], Graham G Giles[21,23], Gianluca Severi[23], Sergi Castellví-Bel[24], Clara Ruiz-Ponte[25], Angel Carracedo[25], Antoni Castells[24], The EPICOLON Consortium[37], Asta Försti[26,27], Kari Hemminki[26,27], Pavel Vodicka[28], Alessio Naccarati[28], Lara Lipton[29], Judy WC Ho[30], KK Cheng[30], Pak C Sham[30], J Luk[30], Jose AG Agúndez[31], Jose M Ladero[32], Miguel de la Hoya[33], Trinidad Caldés[33], Iina Niittymäki[34], Sari Tuupanene[34], Auli Karhu[34], Lauri Aaltonen[34], Jean-Baptiste Cazier[35], Harry Campbell[36,38], Malcolm G Dunlop[3,38] & Richard S Houlston[2,38]

From tagSNP to causal variation ….. Why is this important?

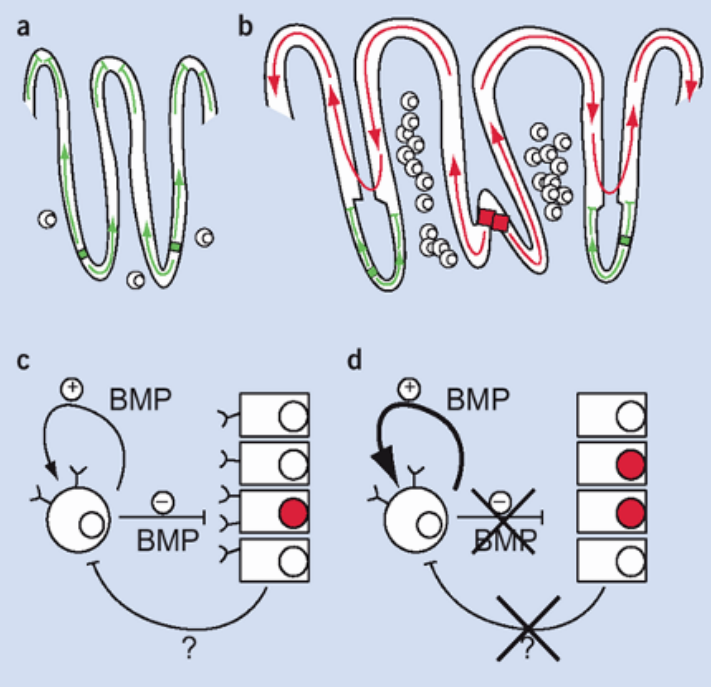
- Population portability
- Targeted interventions
- Learn more about how cancer develops
- Plan (?): re-sequence each region and/or type every SNP in databases in a small panel
- In full sample set, genotype all SNPs in reasonable LD with primary association
- Maximum support regions (LD blocks) for first 5 CRC regions are 470kb, 160kb, 100kb, 210kb, 250kb
- For 11q, only 70kb after imputation

And now what?

FINE SEQUENCING-IMPUTING

FUNCTIONAL STUDIES

In some cases we could have idead... BMP pathway and colorectal tumorigenesis



- SMAD4 and BMPR1A mutations cause juvenile polyposis
- Inhibition of BMP signalling proposed to increase stem cell numbers in crypt
- Is tumorigenesis affected by subtle differences in stem cell numbers?
- Problem: identifying the stem cell

Common variants conferring risk of schizophrenia

Nature 1 de julio

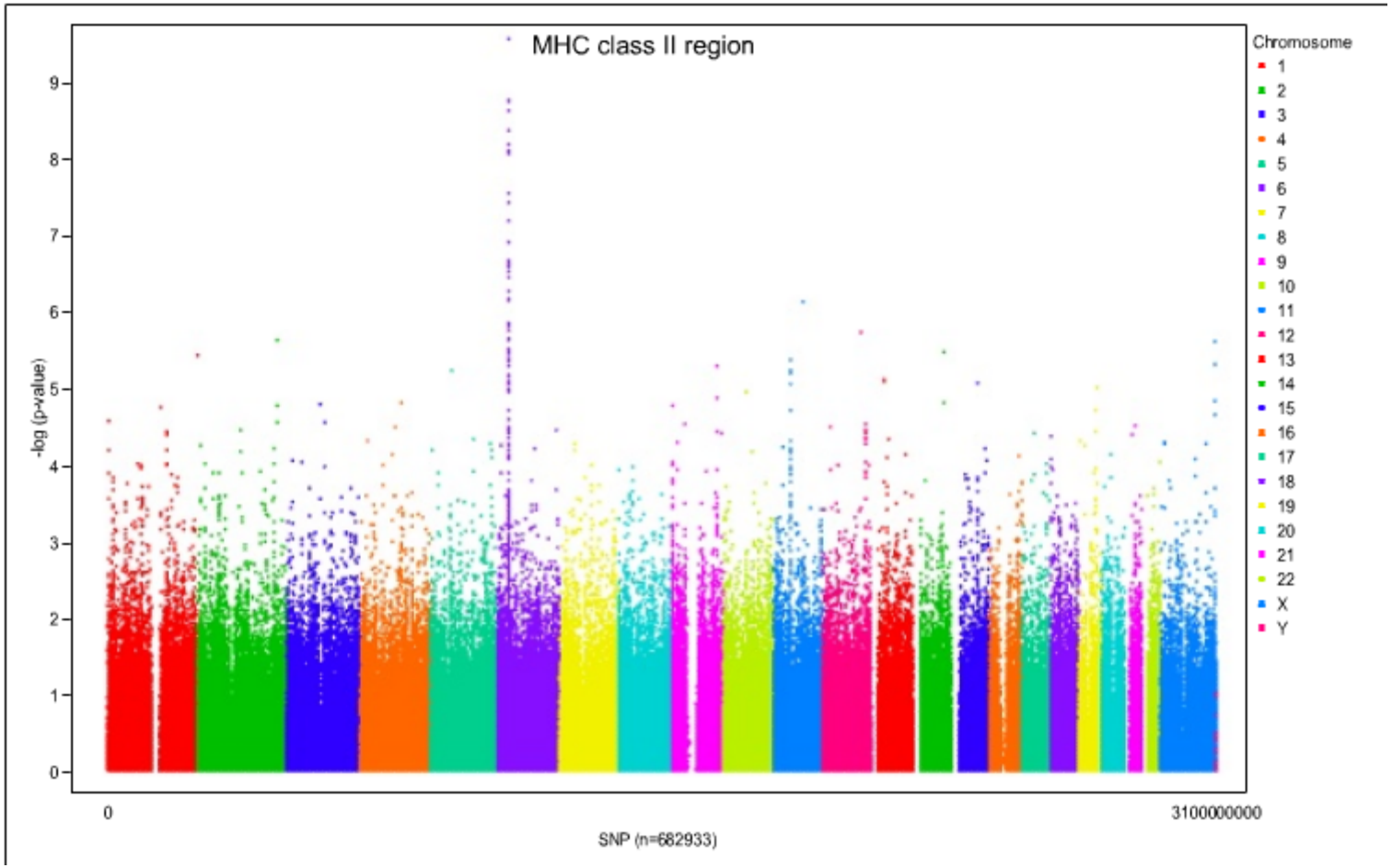
Genome-wide significant association of seven markers with schizophrenia

ne/ SNP[allele]	Frequency	SGENE-plus* (2,663 cases; 13,498 controls)		Follow-up (4,999 cases; 15,555 controls)		SGENE-plus + follow-up (7,662 cases; 29,053 controls)		SGENE-plus + follow-up + ISC + MGS (12,951 cases; 34,594 controls)		Region/ neighbouring gene
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
rs6913660[C]†☆	0.85	1.22 (1.10, 1.36)	0.00023	1.11 (1.04, 1.19)	0.0021	1.14 (1.08, 1.21)	4.7×10^{-6}	1.15 (1.10, 1.21)	1.1×10^{-9}	MHC/ *HIST1H2BJ*
rs13219354[T]‡☆	0.90	1.25 (1.11, 1.42)	0.00043	1.19 (1.08, 1.30)	0.00022	1.21 (1.12, 1.30)	4.4×10^{-7}	1.20 (1.14, 1.27)	1.3×10^{-10}	MHC/ *PRSS16*
rs6932590[T]§☆	0.78	1.15 (1.05, 1.26)	0.0024	1.17 (1.10, 1.25)	4.9×10^{-7}	1.17 (1.11, 1.23)	4.4×10^{-9}	1.16 (1.11, 1.21)	1.4×10^{-12}	MHC/ *PRSS16*
rs13211507[T]‖☆	0.92	1.24 (1.08, 1.42)	0.0027	1.27 (1.15, 1.40)	3.1×10^{-6}	1.26 (1.16, 1.36)	3.1×10^{-8}	1.24 (1.16, 1.32)	8.3×10^{-11}	MHC/ *PGBD1*
rs3131296[G]¶☆	0.87	1.21 (1.08, 1.36)	0.0011	1.20 (1.11, 1.30)	5.3×10^{-6}	1.21 (1.13, 1.29)	2.1×10^{-8}	1.19 (1.13, 1.25)	2.3×10^{-10}	MHC/ *NOTCH4*
rs12807809[T]	0.83	1.19 (1.08, 1.32)	0.00045	1.13 (1.06, 1.21)	0.00022	1.15 (1.09, 1.22)	5.0×10^{-7}	1.15 (1.10, 1.20)	2.4×10^{-9}	*NRGN*
rs9960767[C]#☆	0.056	1.30 (1.11, 1.51)	0.0011	1.20 (1.08, 1.33)	0.00044	1.23 (1.13, 1.34)	2.2×10^{-6}	1.23 (1.15, 1.32)	4.1×10^{-9}	*TCF4*

4999 cases and 15,555 controls from Denmark (Aarhus), Denmark (Copenhagen), Germany (Bonn), Germany (Munich), Hungary, the Netherlands, Norway, Russia, Sweden Finland; Spain (Santiago) and Spain (Valencia))

41 cases/170 controls

Genome-wide association results for all SNPs (p-values graphed by genomic location; >5xULN ALT/AST)

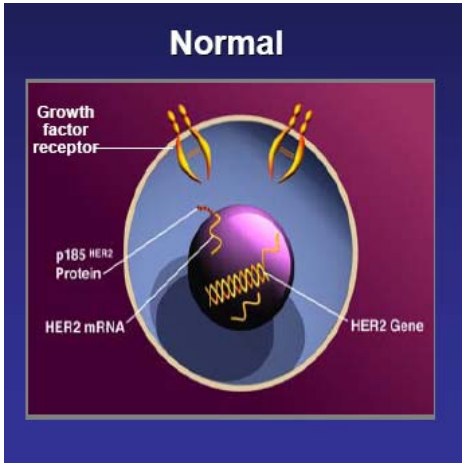


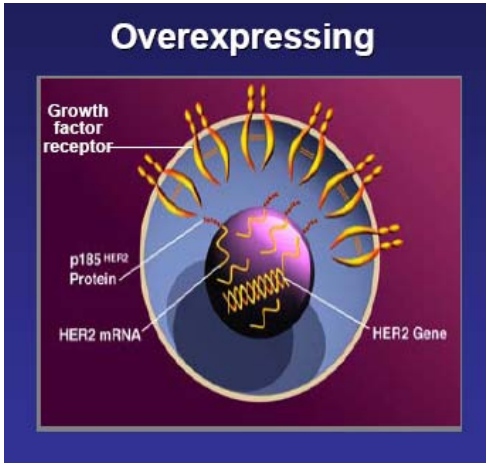
Genome-wide results >5xULN ALT/AST patients

- Significant findings from the exploratory genome-wide association study after multiple testing corrections

rs number	Chromosome	Region	Position	Nominal p-value	Study-wide p-value
rs9270986	6	MHC	32682038	2.8×10^{-10}	0.0075
rs3129900	6	MHC	32413957	1.8×10^{-9}	0.022
rs3132943	6	MHC	32416443	1.9×10^{-9}	0.023
rs3129934	6	MHC	32444165	2.5×10^{-9}	0.026
rs3135365	6	MHC	32497233	4.5×10^{-9}	0.038
rs3129932	6	MHC	32444105	6.5×10^{-9}	0.047
rs910049	6	MHC	32423705	6.6×10^{-9}	0.047

Farmacogenética



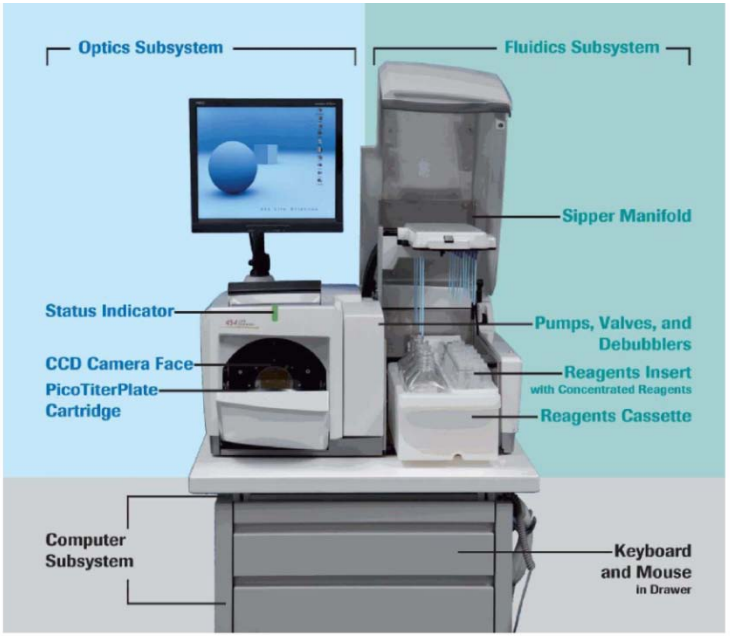


- ***Safety***
  - **• TPMT (6-MP, azathioprine)**
  - **• UGT1A1 (irinotecan)**
  - **• CYP2C9/VKORC1 (warfarin)**
  - **• CYP2D6 (Strattera)**
  - **• HLAB*5701 (Abacavir)**
- ***Efficacy***
  - **• EGFR status (Erbitux, Tarceva)**
  - **• Her2/neu status (Herceptin)**
  - **• Philadelphia chromosome ~ Bcr-abl (Gleevec)**
  - **• C-kit (Gleevec)**
  - **• K ras mutation (Cetuximab)**

High-throughput sequencing

2001	**€ 200 M**	**Sanger/ABI**
2008	**€1.4 M**	**Roche/454**
2009	**€0.17 M**	**Illumina**
2010	**€ 6,000**	**Solid-AB**

SOLID



454

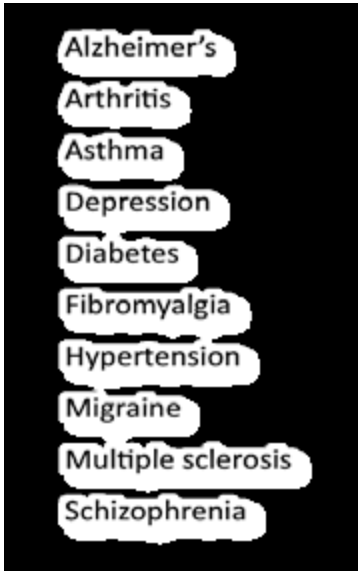
454 LIFE SCIENCES

gEUVADIS Promotors
– ES: Xavier Estivill
– UK: Leena Peltonen and Richard Durbin
– NL: Joris Veltman and Han Brunner
– CH: Stylianos Antonarakis
Members
– FR: Mark Lathrop and Arnold Munich
– DE: Stefan Schreiber and Thomas Meitinger
– SE: Ann-Christine Syvänen
– UK: Ewan Birney and Peter Donnelly
– ES: Roderic Guigó, Cedric Notredame and Angel Carracedo
– NL: Gert Jan van Ommen
– AU: Kurt Zatloukal
– European Commission: Manuel Hallen and Jacques Remacle

gEUVADIS

- **Phase I (2009-2011):**
  - **Sequence 1,000 genomes for each of 10 common disorders**
  - **Research teams as core of the analysis of each disorder**
  - **Research funds for each disorder could come from several sources**

- **Phase II (2012-2014):**
  - **Sequence 1,000 genomes for each of 50 disorders**
  - **Deep sequencing (single molecule sequencing)**
  - **Digital molecular analysis of DNA and RNA**
  - **Phenotype Capture**



Fundación Pública Galega de Medicina Xenómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

International Cancer Genome Consortium

Home | Members | News | Documents | Contact

ICGC

ICGC Goal: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.

The International Cancer Genome Consortium (ICGC) has been organized to launch and coordinate a large number of research projects that have the common aim of elucidating comprehensively the genomic changes present in many forms of cancers that contribute to the burden of disease in people throughout the world.

The primary goals of the ICGC are to generate comprehensive catalogues of genomic abnormalities (somatic mutations, abnormal expression of genes, epigenetic modifications) in tumors from 50 different cancer types and/or subtypes which are of clinical and societal importance across the globe and make the data available to the entire research community as rapidly as possible, and with minimal restrictions, to accelerate research into the causes and control of cancer. The ICGC will facilitate communication among the members and provide a forum for coordination with the objective of maximizing efficiency among the scientists working to understand, treat, and prevent these diseases.

International Cancer Genome Consortium (ICGC) Goals, Structure, Policies and Guidelines : HTML | PDF

ICGC Presentation April 29, 2008 : PPT

Fundación Pública Galega de Medicina Xenómica

USC Universidade de Santiago de Compostela

SabioBBi

Área Clientes

Área Reservac

Home | Compañía | Salud | Servicios | Solicitar prueba | FAQ's | Contacto | English

Conoce ya tu perfil genético

Cómo vivir más y mejor

Todos nacemos con unas características genéticas determinadas que no cambiarán a lo largo de nuestra vida. **Es nuestro perfil genético**. Si quieres, ahora puedes conocer tus fortalezas y debilidades desde el punto de vista genético. Sólo tienes que realizar uno de los test que Sabiobbi facilita, y así, **podrás actuar como más convenga para mejorar tu calidad de vida**.

Muestra el potencial global de un deportista, identifica los puntos vulnerables donde se ha de actuar para lograr un mejor rendimiento y evalua el riesgo de padecer muerte súbita y otras enfermedades cardiovasculares.

Leer más | Solicitar información

Identifica la posibilidad de sufrir enfermedades asociadas con el envejecimiento, la capacidad metabólica y los mecanismos de defensa.

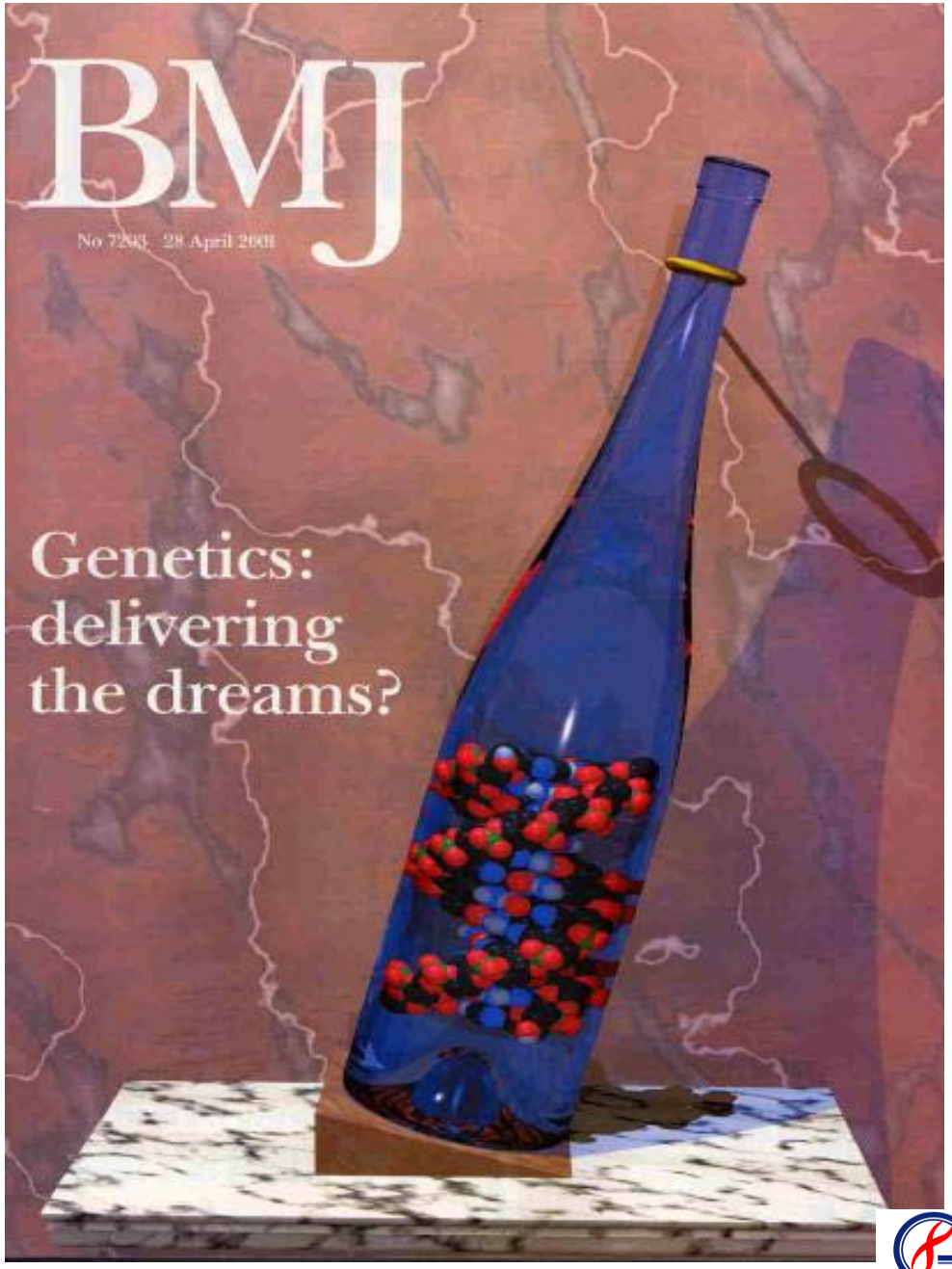
Leer más | Solicitar información

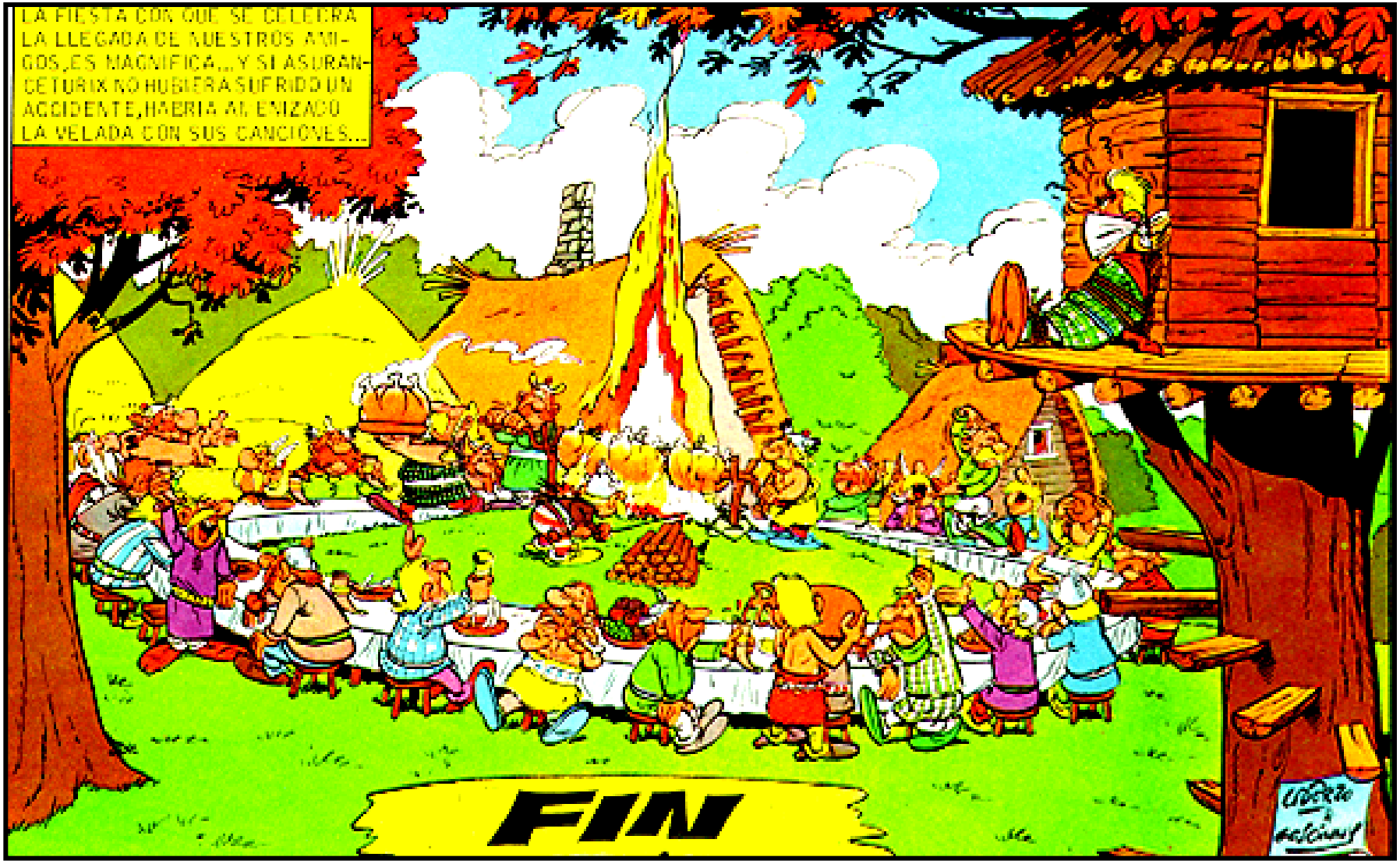
ExecutiveChip®
Mejore su calidad de vida

QualityChip®
Mejore su calidad de vida

ObesityChip®
Pierda peso, gane en salud

Seminarios
Talleres de Genética


BMJ
No 7283 28 April 2001
Genetics:
delivering
the dreams?


LA FIESTA CON QUE SE CELEBRA LA LLEGADA DE NUESTROS AMIGOS, ES MAGNIFICA... Y SI ASURANCETURIX NO HUBIERA SUFRIDO UN ACCIDENTE, HABRIA AMENIZADO LA VELADA CON SUS CANCIONES...
FIN