Figura 1. Imagen de un Oncochip CNIO.
El Oncochip consta de 9.300 genes humanos relacionados con el cáncer y distribuidos en 22.300 manchas (spots) impresos.

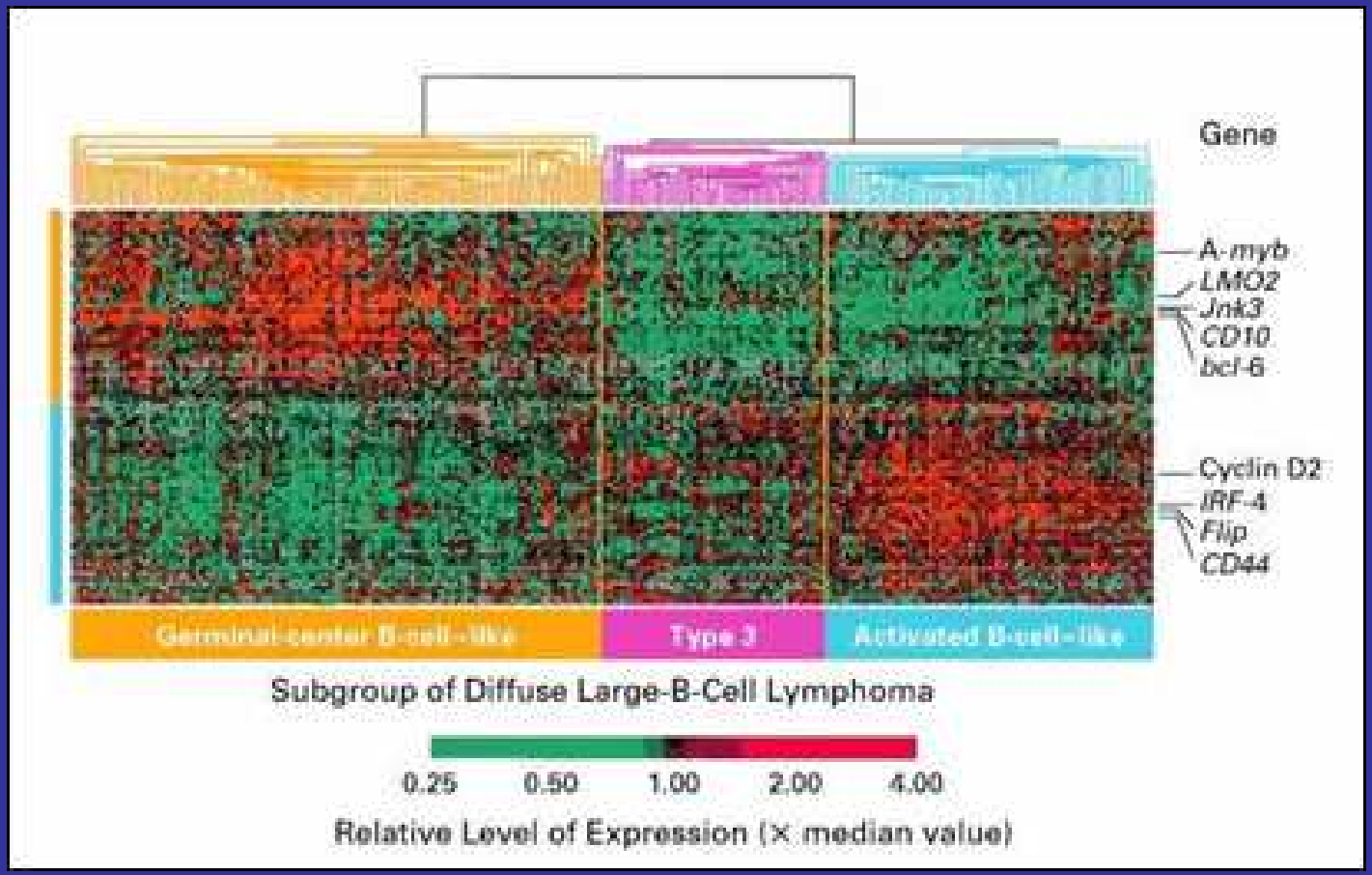
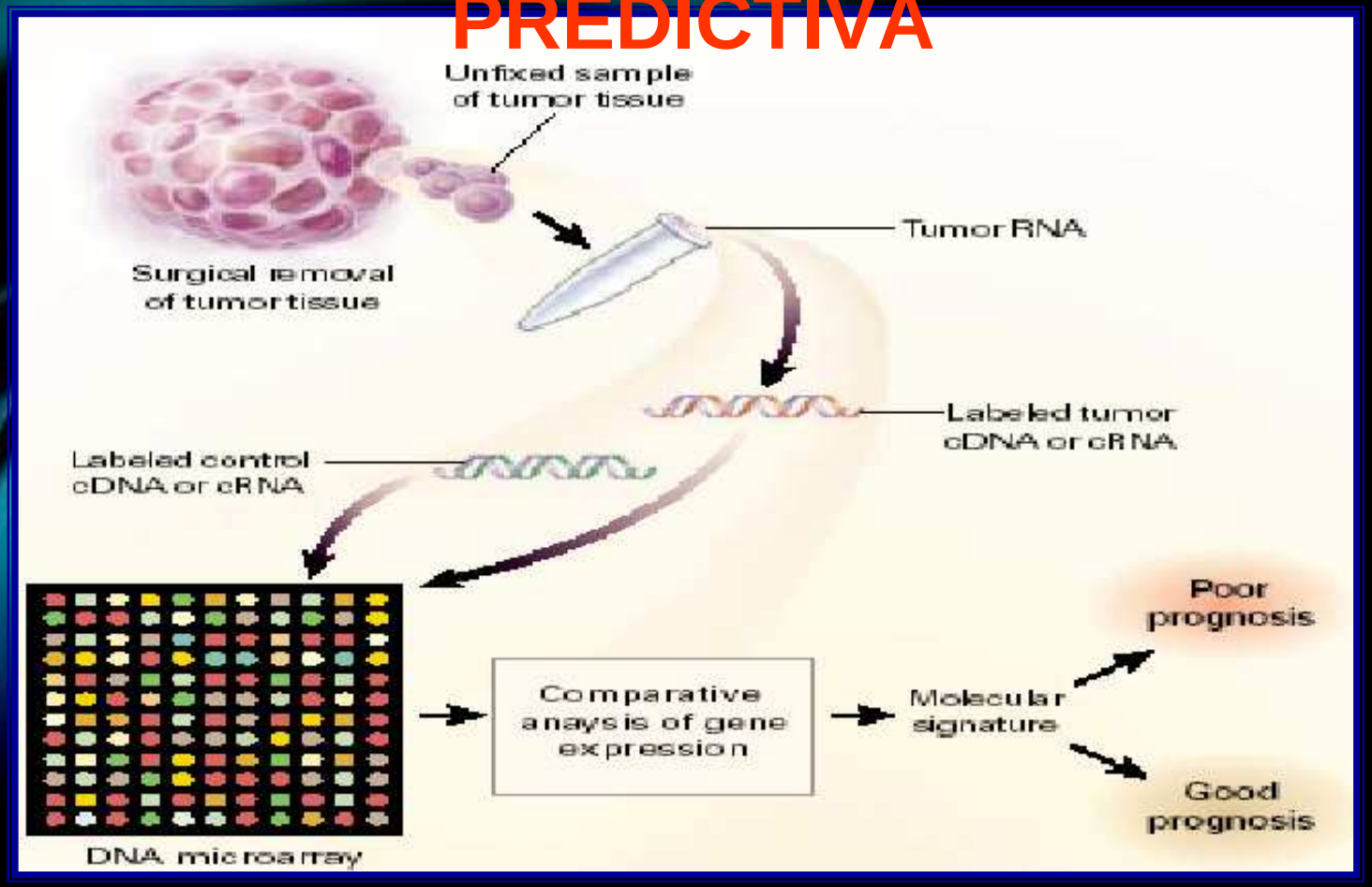


Figura 2. Estratificación de pacientes de linfoma difuso de célula B grandes. El uso de microarrays de DNA permite la separación de este tipo de linfomas en tres subgrupos distintos con distinta firma molecular y muy diferente pronóstico. Los tres subgrupos son indistinguibles por técnicas histológicas convencionales. Rosenwald et al (2003) J. Exp. Med 198, 851-862.

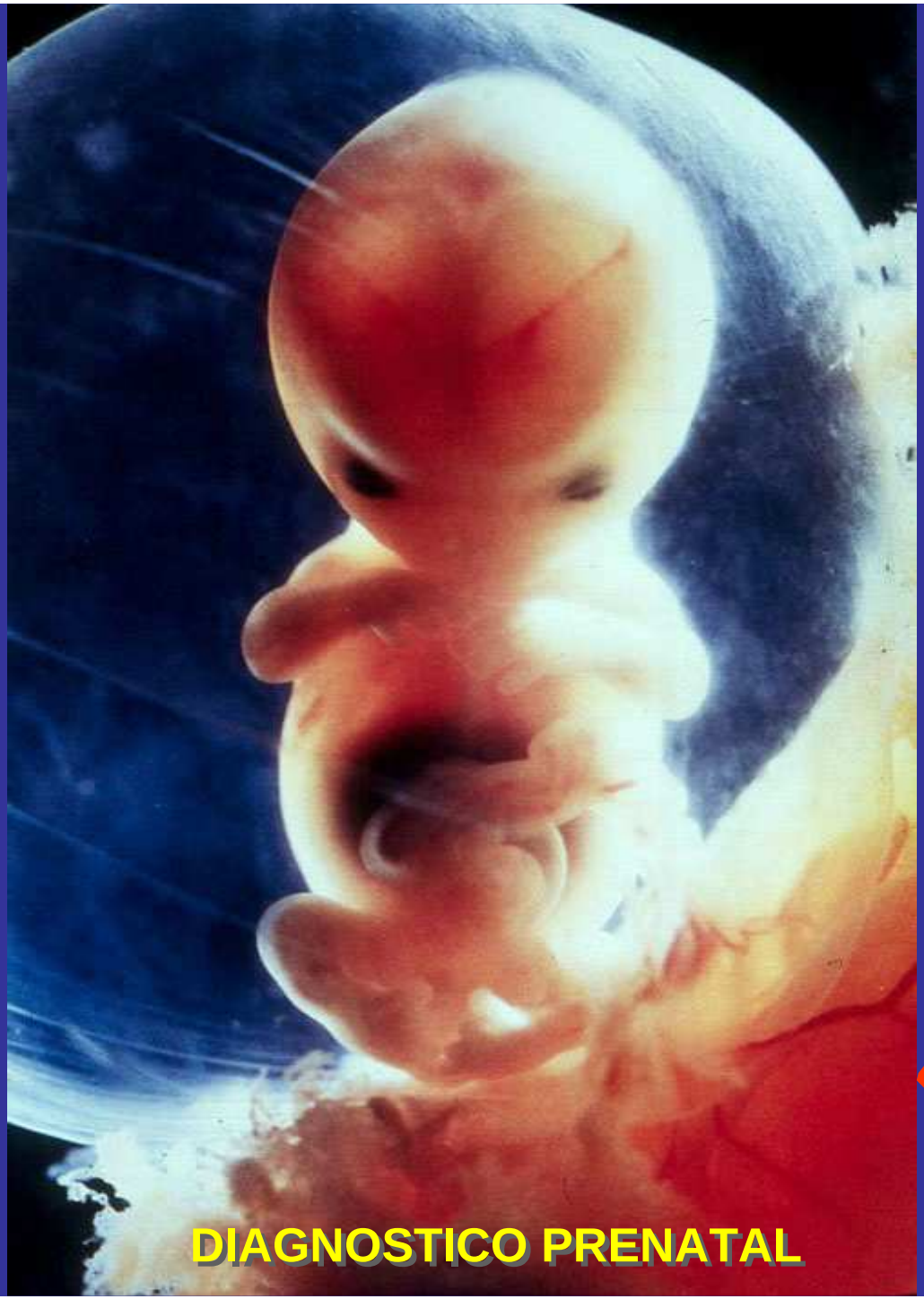
PATOLOGIA MOLECULAR PREDICTIVA



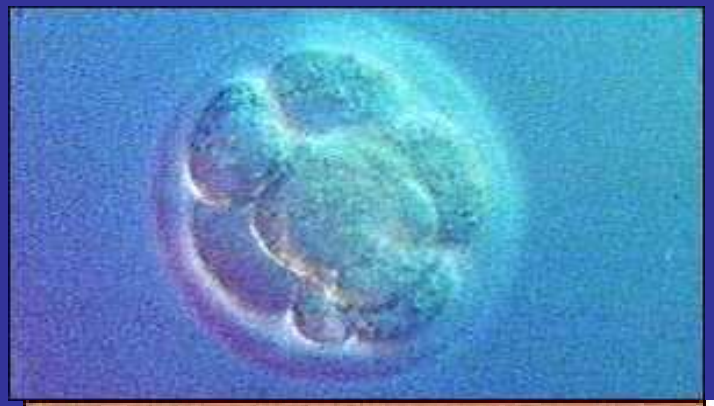
- **Muestras de tejido tumoral obtenidas durante cirugía son material para tipificación de la expresión de genes.**
- **Los niveles de expresión de genes relevantes para pronóstico son determinados por análisis en DNA Microarray.**
- **El resultado molecular permite que los pacientes sean clasificados para el pronóstico de su enfermedad, lo que facilita la decisión terapéutica.**

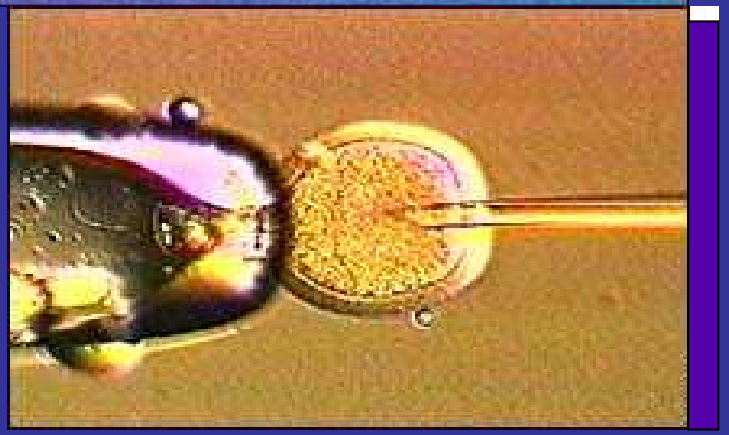
Se inició un proceso de cambio sobre la forma de entender la medicina, el desarrollo humano y la causa de muchas enfermedades .

Este conocimiento incorporado a la práctica clínica está permitiendo progresos insospechados en el diagnóstico prenatal y preimplantatorio, en el *"screening"* de diversas enfermedades en recién nacidos, en la identificación de portadores asintomáticos de enfermedades de base genética y en la comprensión de las denominadas enfermedades raras.



DIAGNOSTICO PRENATAL





DIAGNOSTICO PREIMPLANTATORIO

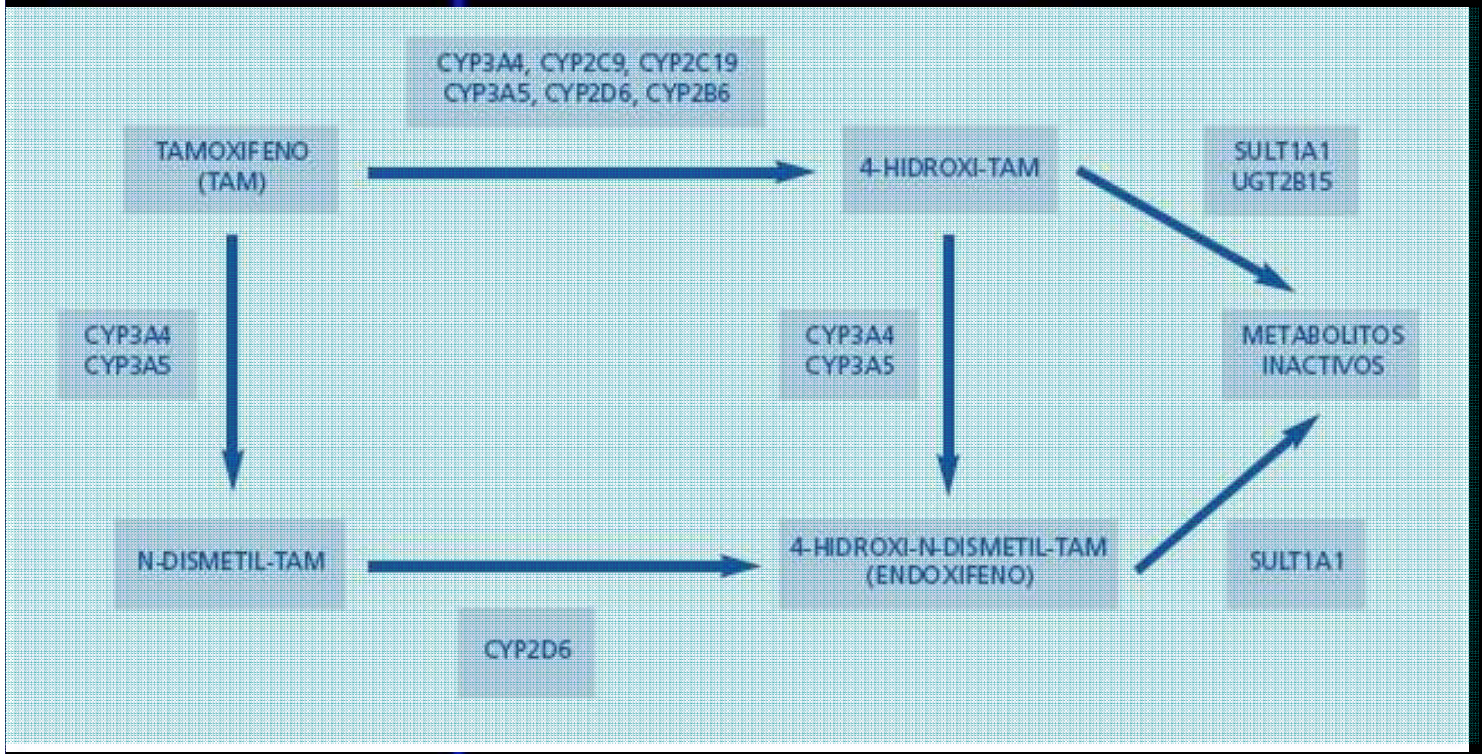
DIAGNOSTICO PRESINTOMATICO

Estos adelantos empiezan a aportar mejoras significativas en el tratamiento de determinados tipos de cáncer, en enfermedades hematológicas, neurológicas y cardiovasculares, sea desde la perspectiva del diagnóstico predictivo como de la farmacogenética y la farmacogenómica, además de la "toxigenómica", que se ocupa de la respuesta de los individuos a las sustancias tóxicas en función de su genoma y a la evaluación de riesgos para la salud en función de diferentes entornos, profesional o habitual.

La posibilidad de conocer la susceptibilidad individual para padecerlas, lograr diagnósticos en fases muy precoces, o predecir la respuesta personal de cada paciente al tratamiento, nos conducen al nuevo paradigma: *el de la medicina individualizada, predictiva y preventiva.*

Las variantes fenotípicas del metabolismo de drogas se pueden investigar basándose en las particulares variantes de SNPs que poseen los genes del citocromo P- 450.
Fuente: Caraco, Y., N

***Engl J Med,2004*.**

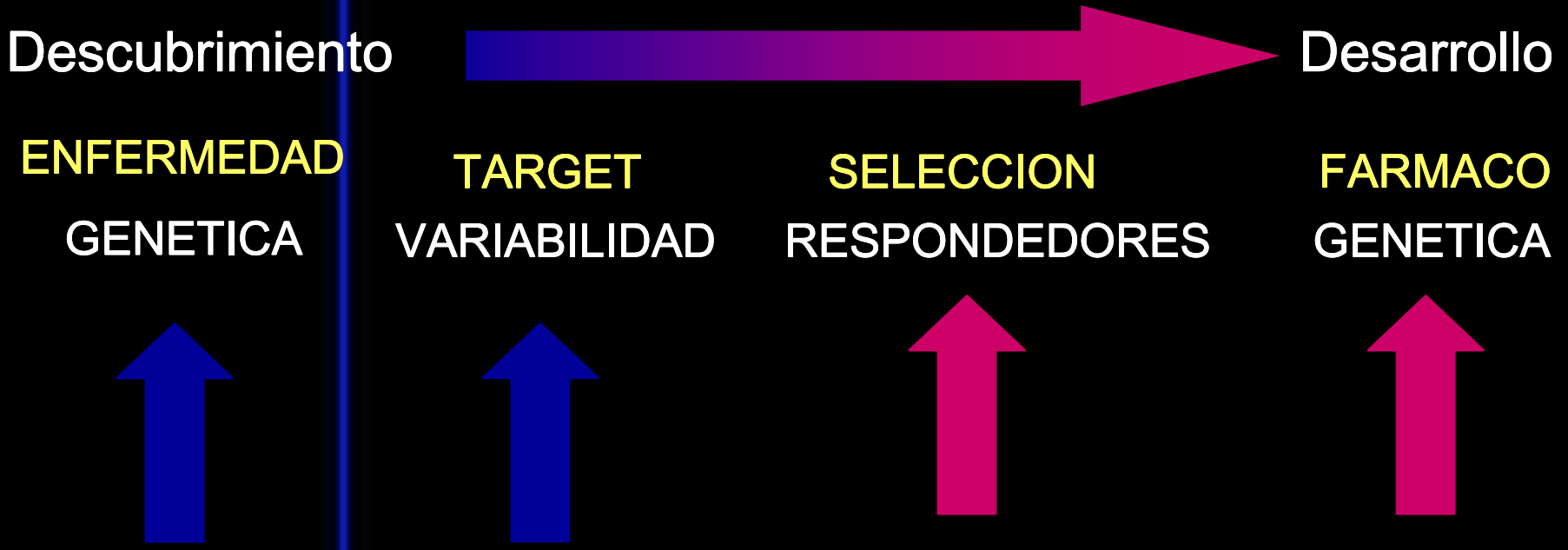


Cáncer de mama: genes implicados en el metabolismo del tamoxifeno

Farmacogenómica

- El Proyecto Genoma Humano permitió detectar en distintas personas respuestas diferentes a un mismo fármaco.
- Estas respuestas están directamente vinculadas a la estructura genómica de cada individuo.
- Nace la “medicación personalizada de acuerdo al genoma” del paciente.

Farmacogenómica aplicada



Elección del mejor target

Comprender mejor nuestro target

Toma de decisiones

Predecir eficacia y seguridad

Farmacogenomica y Medicina Personalizada.

PERMITE AL MEDICO PRESCRIBIR

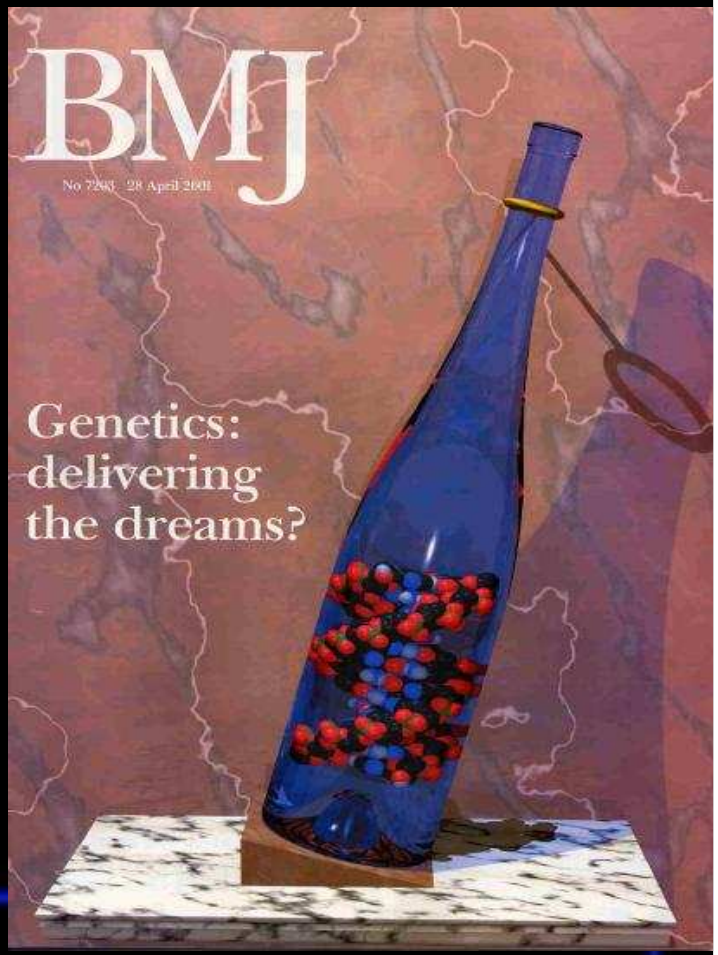
- *Droga correcta.*
- *En la correcta dosis.*
- *Para la enfermedad correcta.*
- *Para el paciente correcto.*

Conociendo todo esto previamente a que el paciente inicie el tratamiento

Farmacogenética y Farmacogenómica

Un tratamiento para cada paciente con el fármaco más adecuado, a la dosis necesaria para obtener la máxima eficacia terapéutica con el mínimo riesgo y costo.

Esto demuestra que «*la Fármacogenómica es una ruta inevitable con la cual, tarde o temprano, la Industria y la Medicina se tienen que encontrar».*



DIAGNOSTICO PREDICTIVO

SNPs

Aplicaciones de los DNA microarray

Análisis de expresión

GWAS: Genome Wide Association Study

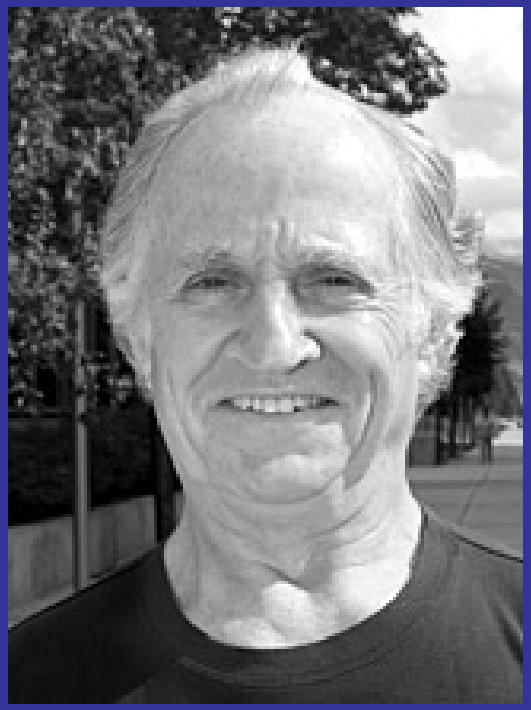
Genotipado de mutaciones y polimorfismos

NUEVAS BIOTECNOLOGIAS

INGENIERIA GENETICA

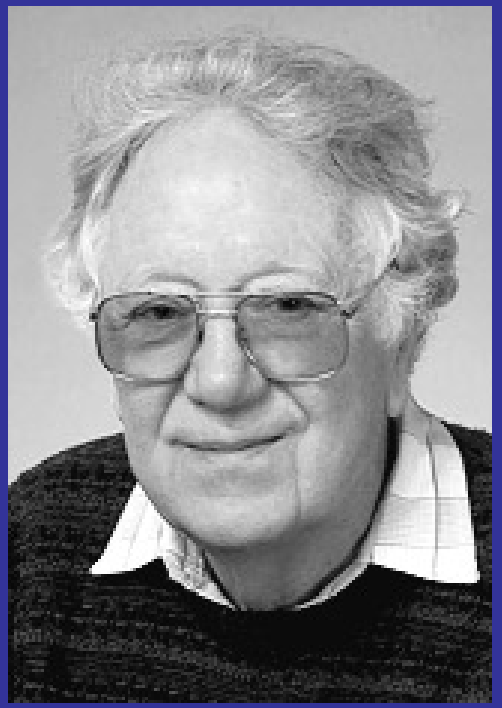
Premio Nobel en Medicina 2007

Mario R. Capecchi



Sir Martin J. Evans

Oliver Smithies



Tres científicos comparten el Premio Nobel en Medicina 2007 por sus descubrimientos en principios para introducir modificaciones genéticas en ratones utilizando células madre embrionarias El Instituto Karolinska hizo público el lunes 8 de octubre, el premio Nobel de Medicina del año 2007.

MODELOS ANIMALES

. Ratones transgénicos

. Ratones knock-out

La transgénesis se puede definir como la introducción de ADN extraño en un genoma, de modo que se mantenga estable de forma hereditaria y afecte a todas las células en los organismos multicelulares. Los tres métodos principales empleados en la creación de animales transgénicos son las microinyecciones de ADN, la transferencia o eliminación de genes mediante manipulación de células madre embrionarias y la transferencia de genes mediante vectores virales. Un transgén es el fragmento de ADN manipulado que se desea introducir en el genoma del animal. El transgén debe contener, además del gen que se desee insertar, ADN adicional por delante (secuencia promotora) y por detrás (poli-A) en las hebras constituidas por los sucesivos pares de bases. Este ADN adicional es el que garantiza el engarce de las hebras en el genoma del animal receptor. Aplicaciones de los animales transgénicos: .- estudiar desarrollo embrionario y su regulación, manipular la expresión génica *in vivo,* función de genes específicos, utilizar a mamíferos como biorreactores para producción de proteinas humanas, corrección de errores innatos de metabolismo mediante terapia génica.

Ratones Knock-Out

A los ratones en los que se elimina por completo la expresión de un gen propio se les denomina ratones knockout. La pérdida del gen puede ser de carácter Heterocigota u Homocigota. Los ratones knockout permiten estudiar el efecto que produce la eliminación de un gen de modo experimental..

Fracaso del Sistema Inmunitario

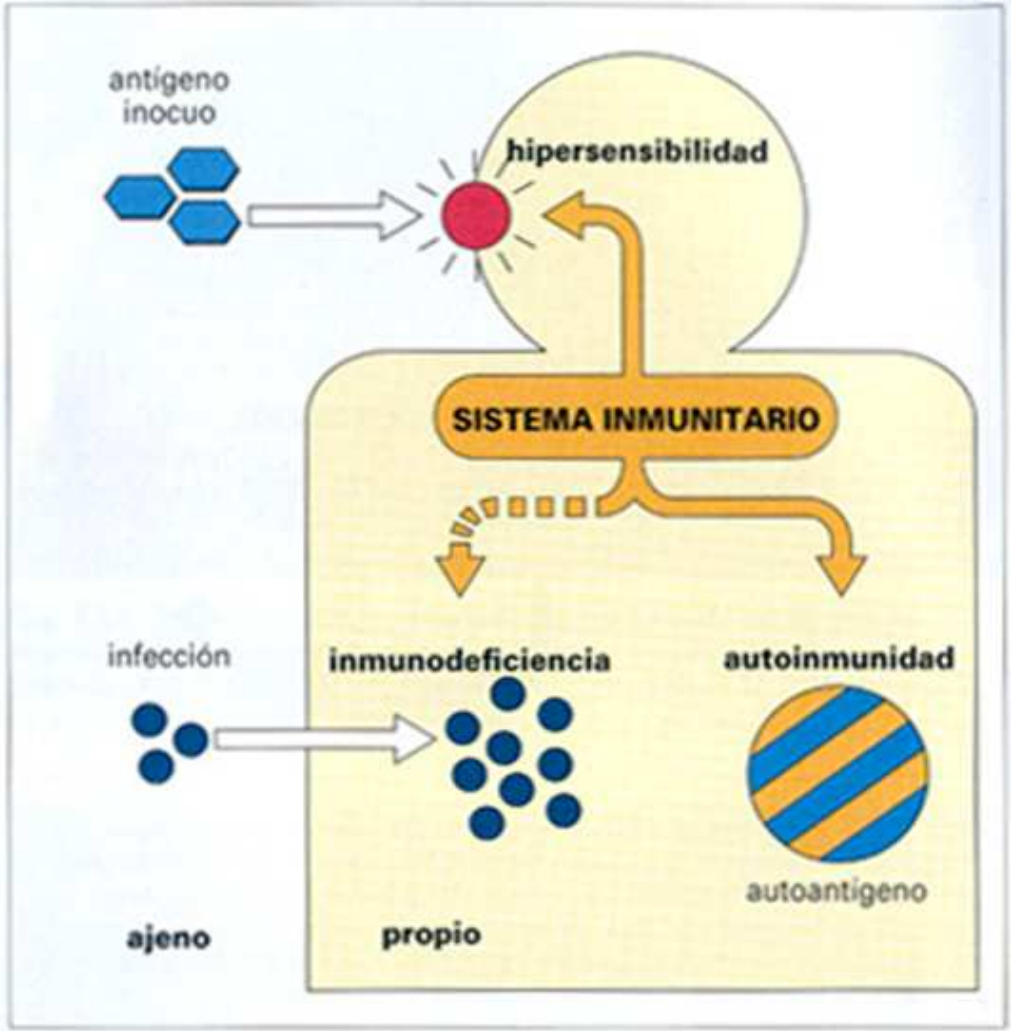


Fig. 1.20. Los defectos del sistema inmunitario pueden ser de tres tipos: hipersensibilidad, inmunodeficiencia y autoinmunidad. Los dos primeros son debidos a respuestas exageradas o insuficientes, respectivamente. La autoinmunidad es debida a un defecto en la discriminación entre lo propio y lo ajeno en el proceso de reconocimiento inmunitario.

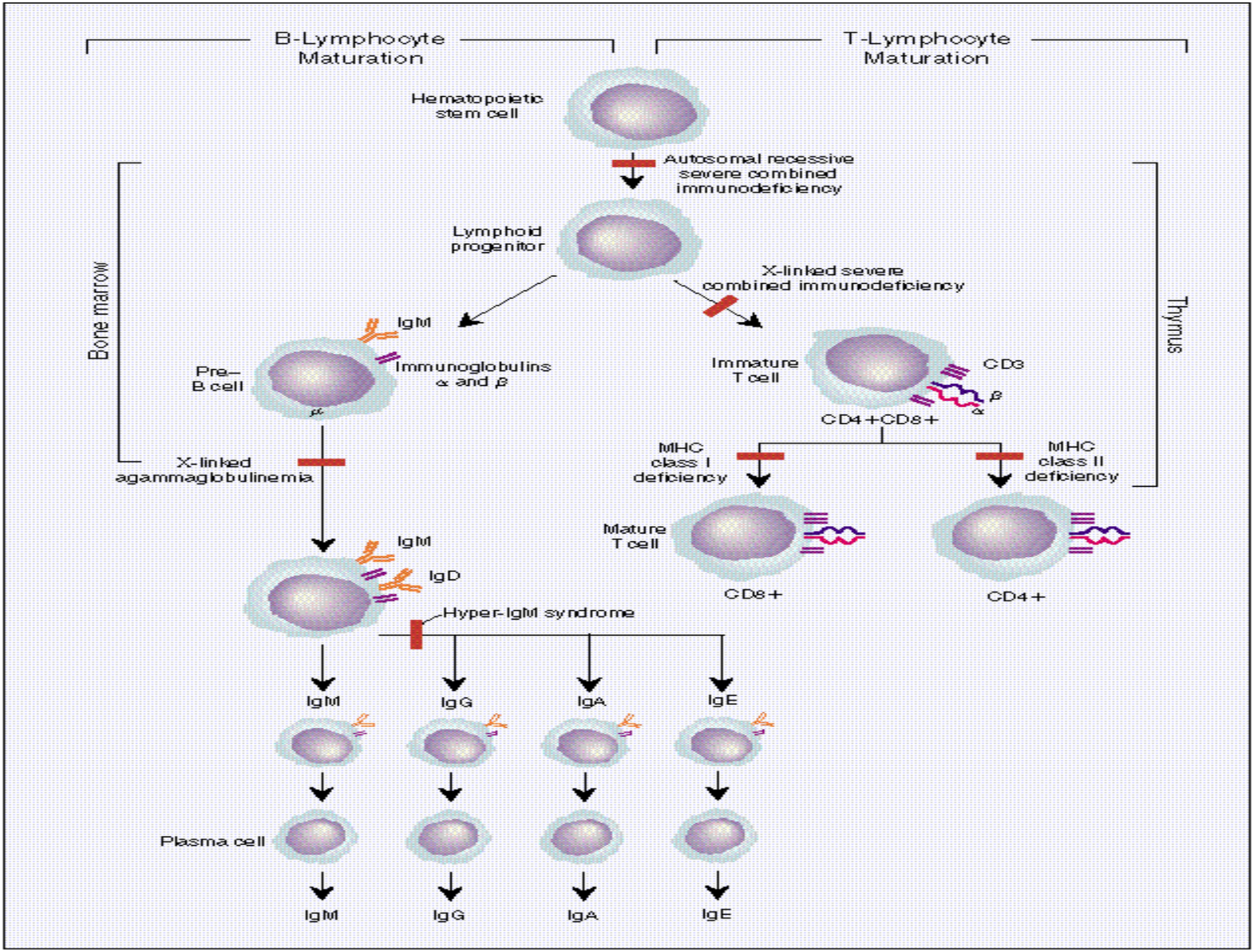
Las fallas del Sistema pueden ser de tres tipos:

1) **Reacciones inadecuadas frente a autoantígenos: *Autoinmunidad*, no reconocimiento de lo propio.**

2) **Respuesta inmunitaria ineficaz: *Inmunodeficiencias*. Defecto de cualquiera de los elementos del Sistema Inmune congénito o adquirido.**

3) **Respuesta inmunitaria exagerada: *Hipersensibilidad*. Reacciones desproporcionadas en relación al daño que puede provocar el agente patógeno en la mayoría de los individuos de la población general.**

INMUNOLOGIA MOLECULAR

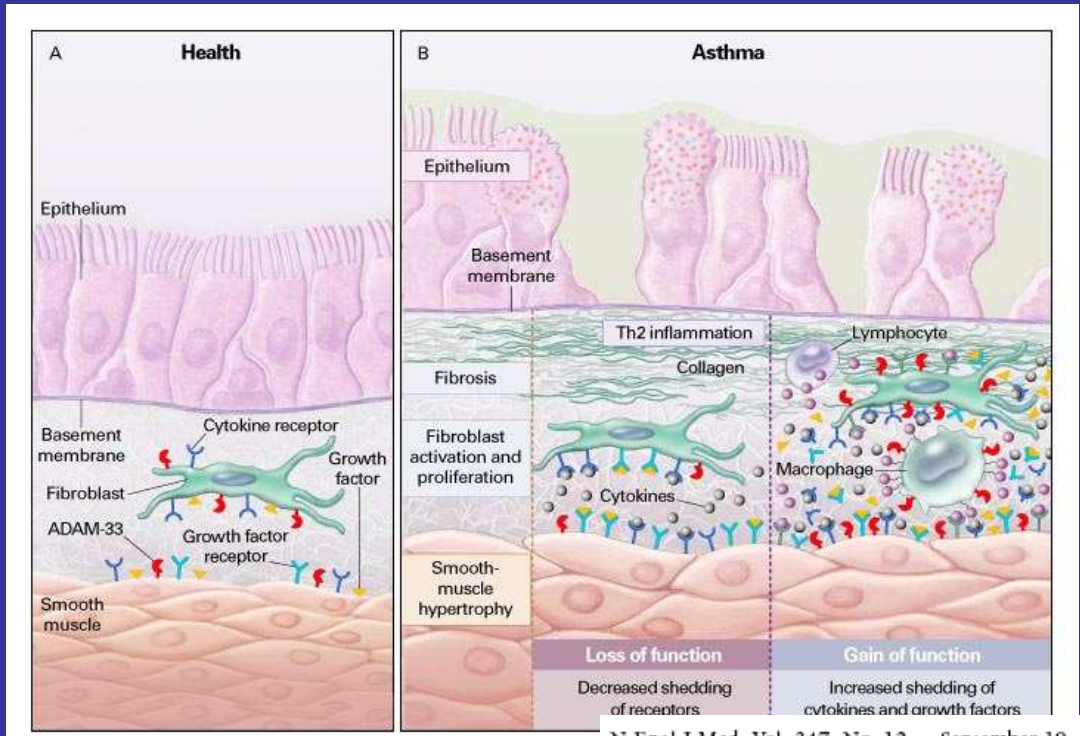

B-Lymphocyte Maturation
T-Lymphocyte Maturation
Hematopoietic stem cell
Autosomal recessive severe combined immunodeficiency
Lymphoid progenitor
X-linked severe combined immunodeficiency
Bone marrow
Thymus
IgM
Pre–B cell
Immunoglobulins α and β
μ
Immature T cell
CD3
β
α
CD4+CD8+
MHC class I deficiency
MHC class II deficiency
X-linked agammaglobulinemia
Mature T cell
CD8+
CD4+
IgM
IgD
Hyper-IgM syndrome
IgM
IgG
IgA
IgE
Plasma cell
IgM
IgG
IgA
IgE

GENES DEL ASMA IDENTIFICADOS

ADAM 33

- Ligamiento en 460 familias de UK y USA: cromosoma 20p
- Confirmado en múltiples poblaciones de distintos grupos étnicos
- Desintegrina y metaloproteasa de expresión restringida a células mesenquimáticas como fibroblastos pulmonares y músculo liso bronquial
- FUNCIONES: Fusión celular – Proteólisis – Adhesión celular – Señalización celular.

ADAM 33:



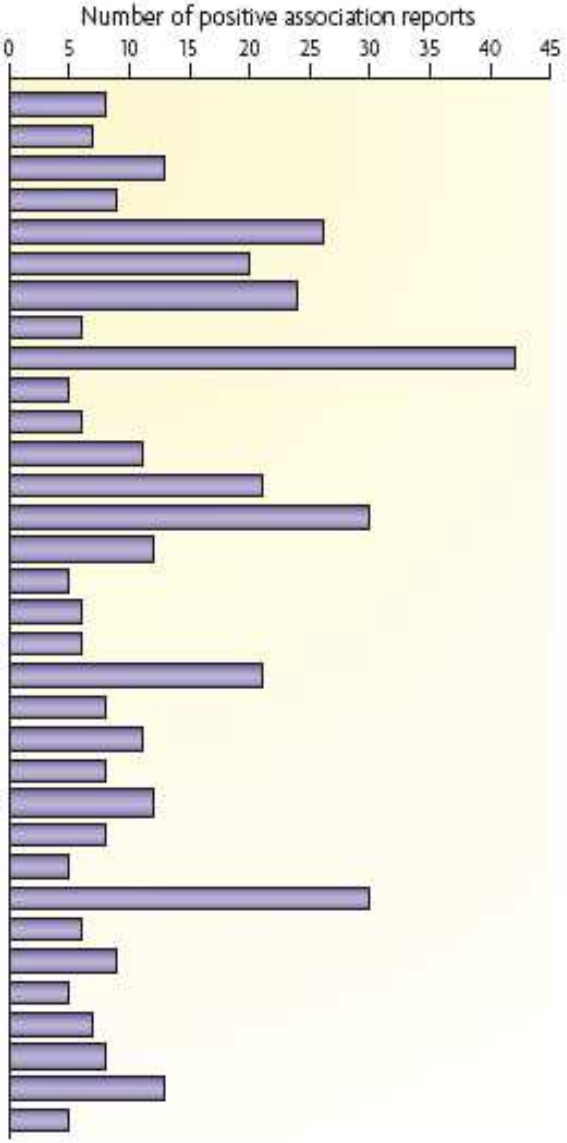
N Engl J Med, Vol. 347, No. 12 · September 19, 2002

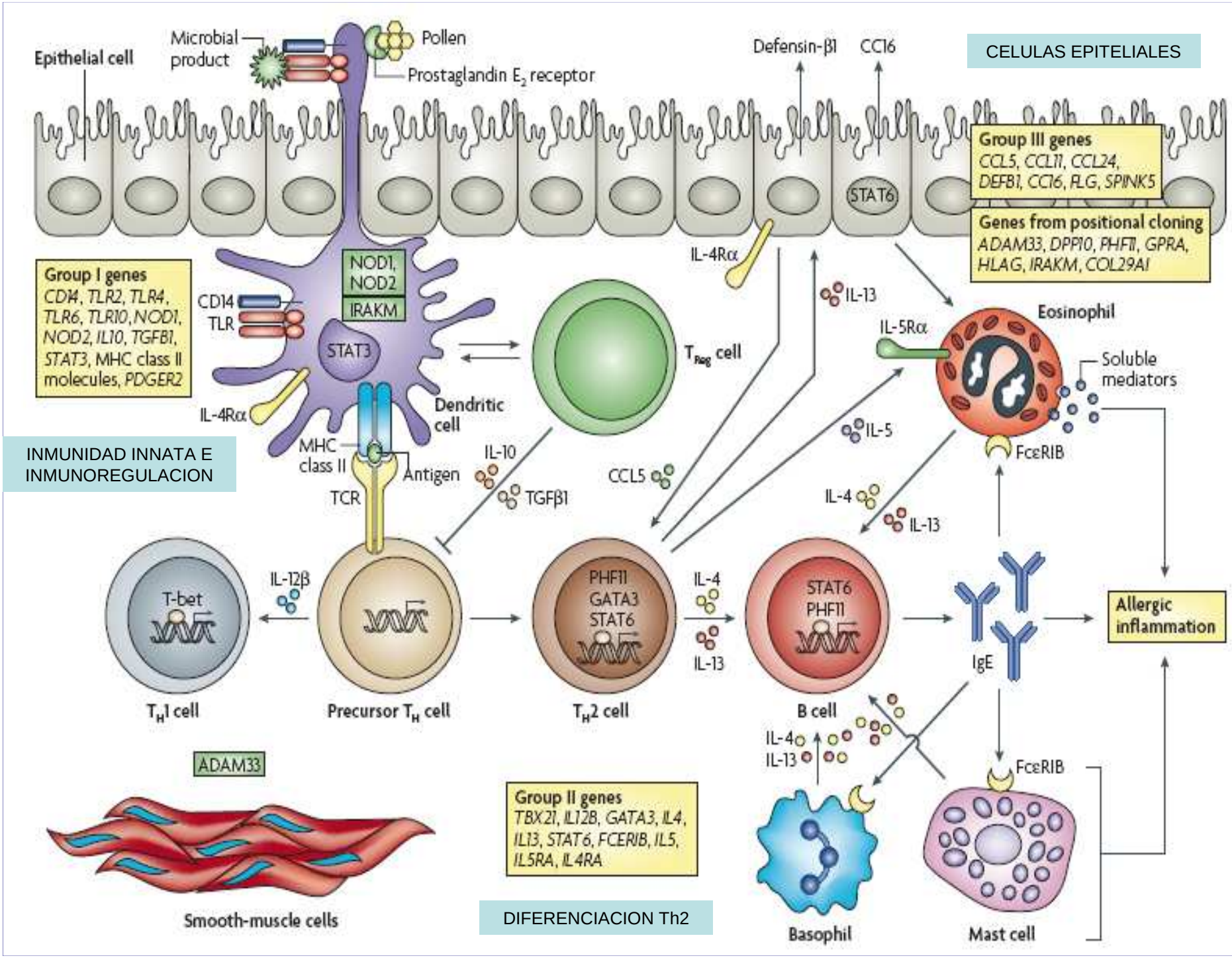
Eerdewegh et al. 2002

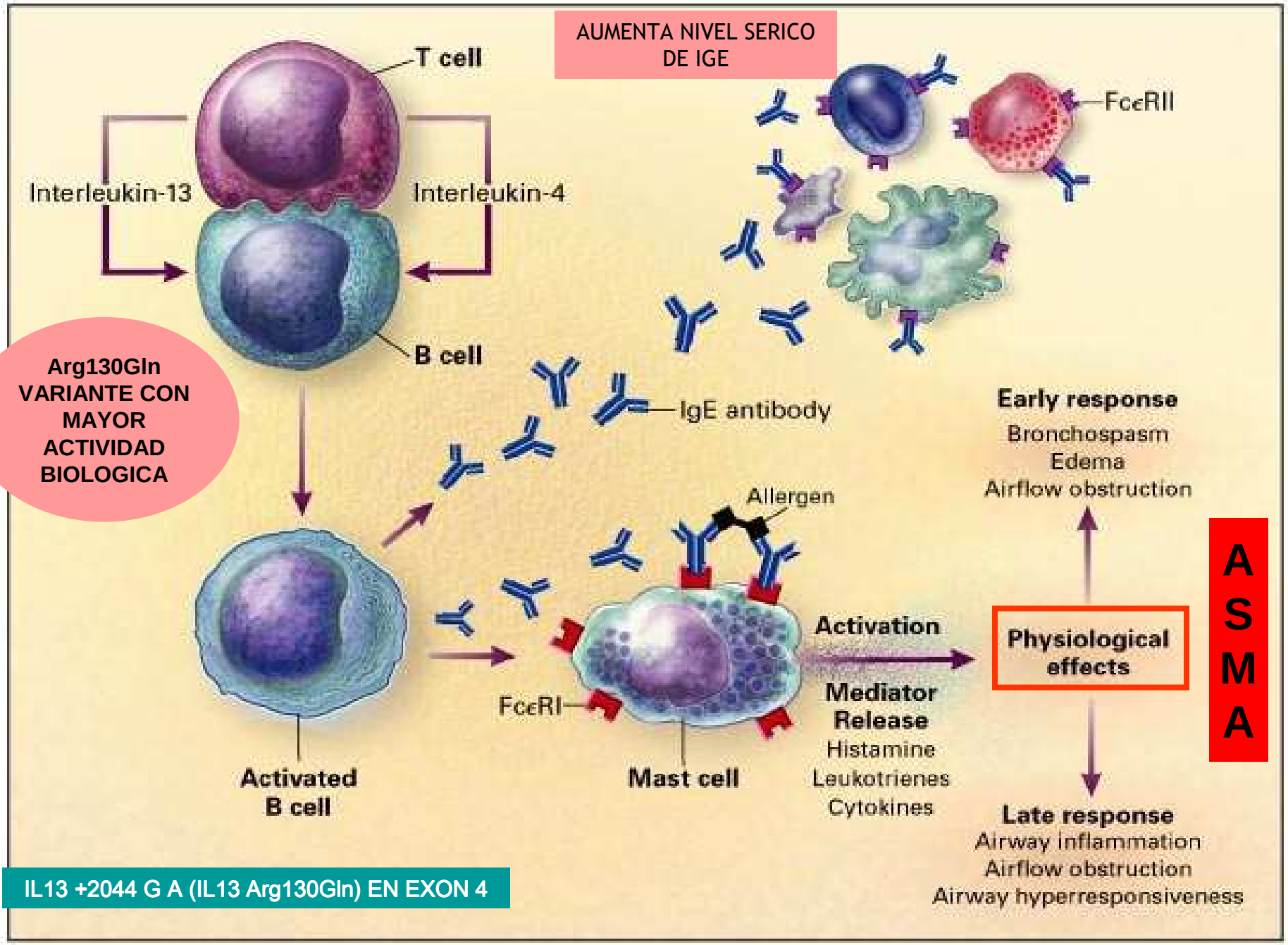
GENES DE SUSCEPTIBILIDAD AL ASMA

1. GENES ASOCIADOS CON LA INMUNIDAD INNATA Y LA INMUNOREGULACION
2. GENES ASOCIADOS CON LA DIFERENCIACION DE CELULAS Th2
3. GENES ASOCIADOS CON LA BIOLOGIA EPITELIAL Y LA INMUNIDAD DE MUCOSAS
4. GENES ASOCIADOS CON LA FUNCION PULMONAR, LAS MODIFICACIONES DE LA VIA AEREA Y LA SEVERIDAD DE LA LESION

Gene	Chromosome	Function and pathway	Common variants
GSTM1	1p13.3	Environmental and oxidative stress — detoxification	+/null
FLG	1q21.3	Epithelial barrier integrity	Arg510X, 2282del4
IL10	1q31-q32	Immunoregulation	–1082A/G, –571C/A
CTLA4	2q33	T-cell-response inhibition and immunoregulation	–318C/T, 49A/G
IL13	5q31	T_H2 effector functions	–1112C/T, Arg130Gln
IL4	5q31.1	T_H2 differentiation and IgE induction	–589C/T, +33C/T
CD14	5q31.1	Innate immunity — microbial recognition	–1721G/A, –260C/T
SPINK5	5q32	Epithelial serine protease inhibitor	Glu420Lys
ADRB2	5q31-q32	Bronchial smooth-muscle relaxation	Arg16Gly, Gln27Glu
HAVCR1	5q33.2	T-cell-response regulation — HAV receptor	5383_5397del
LTC4S	5q35	Cysteinyl leukotriene biosynthesis — inflammation	–444A/C
LTA	6p21.3	Inflammation	*Nco*I (intron 1)
TNF	6p21.3	Inflammation	–308G/A, –857C/T
HLA-DRB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DQB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DPB1	6p21	Antigen presentation	Multi-SNP alleles
GPRA	7p14.3	Regulation of cell growth and neural mechanisms	Haplotypes
NAT2	8p22	Detoxification of drugs and carcinogens	Slow acetylation SNPs
FCERIB	11q13	High-affinity Fc receptor for IgE	Ile181Leu, Gly237Glu
CC16	11q12.3-q13.1	Epithelium-derived anti-inflammatory protein	38A/G
GSTP1	11q13	Environmental and oxidative stress — detoxification	Ile105Val
IL18	11q22.2-q22.3	Induction of IFNγ and TNF	–656T/G, –137G/C
STAT6	12q13	IL-4 and IL-13 signalling	2964G/A, (GT)n exon 1
NOS1	12q24.2-q24.31	Nitric oxide synthesis — cell–cell communication	3391C/T, 5266C/T
CMA1	14q11.2	Mast-cell chymotryptic serine protease	*Bst*X1, –1903G/A
IL4R	16p12.1-p12.2	α-chain of the IL-4 and IL-13 receptors	Ile50Val, Glu551Arg
CCL11	17q21.1-q21.2	Epithelium-derived eosinophil chemoattractant	Ala23Thr, –1328G/A
CCL5	17q11.2-q12	Monocyte, T-cell and eosinophil chemoattractant	–403A/G, –28C/G
ACE	17q23.3	Inactivation of inflammatory mediators	In/del
TBXA2R	19p13.3	Smooth-muscle contraction, inflammation	924T/C, 795T/C
TGFB1	19q13.1	Immunoregulation, cell proliferation	–509C/T
ADAM33	20p13	Cell–cell and cell–matrix interactions	Multiple SNPs
GSTT1	22q11.23	Environmental and oxidative stress — detoxification	A/null




Epithelial cell
Microbial product
Pollen
Prostaglandin E_2 receptor
Defensin-β1
CC16
CELULAS EPITELIALES
Group III genes
CCL5, CCL11, CCL24, DEFB1, CC16, FLG, SPINK5
Genes from positional cloning
ADAM33, DPP10, PHF11, GPRA, HLAG, IRAKM, COL29A1
STAT6
IL-4Rα
IL-13
Eosinophil
IL-5Rα
Soluble mediators
FcεRIB
Group I genes
CD14, TLR2, TLR4, TLR6, TLR10, NOD1, NOD2, IL10, TGFB1, STAT3, MHC class II molecules, PDGER2
NOD1, NOD2
IRAKM
CD14
TLR
STAT3
Dendritic cell
T_{Reg} cell
IL-4Rα
MHC class II
Antigen
TCR
IL-10
TGFβ1
CCL5
IL-5
IL-4
IL-13
INMUNIDAD INNATA E INMUNOREGULACION
T-bet
IL-12β
PHF11
GATA3
STAT6
IL-4
IL-13
STAT6
PHF11
IgE
Allergic inflammation
T_H1 cell
Precursor T_H cell
T_H2 cell
B cell
IL-4
IL-13
FcεRIB
ADAM33
Group II genes
TBX21, IL12B, GATA3, IL4, IL13, STAT6, FCERIB, IL5, IL5RA, IL4RA
Smooth-muscle cells
DIFERENCIACION Th2
Basophil
Mast cell

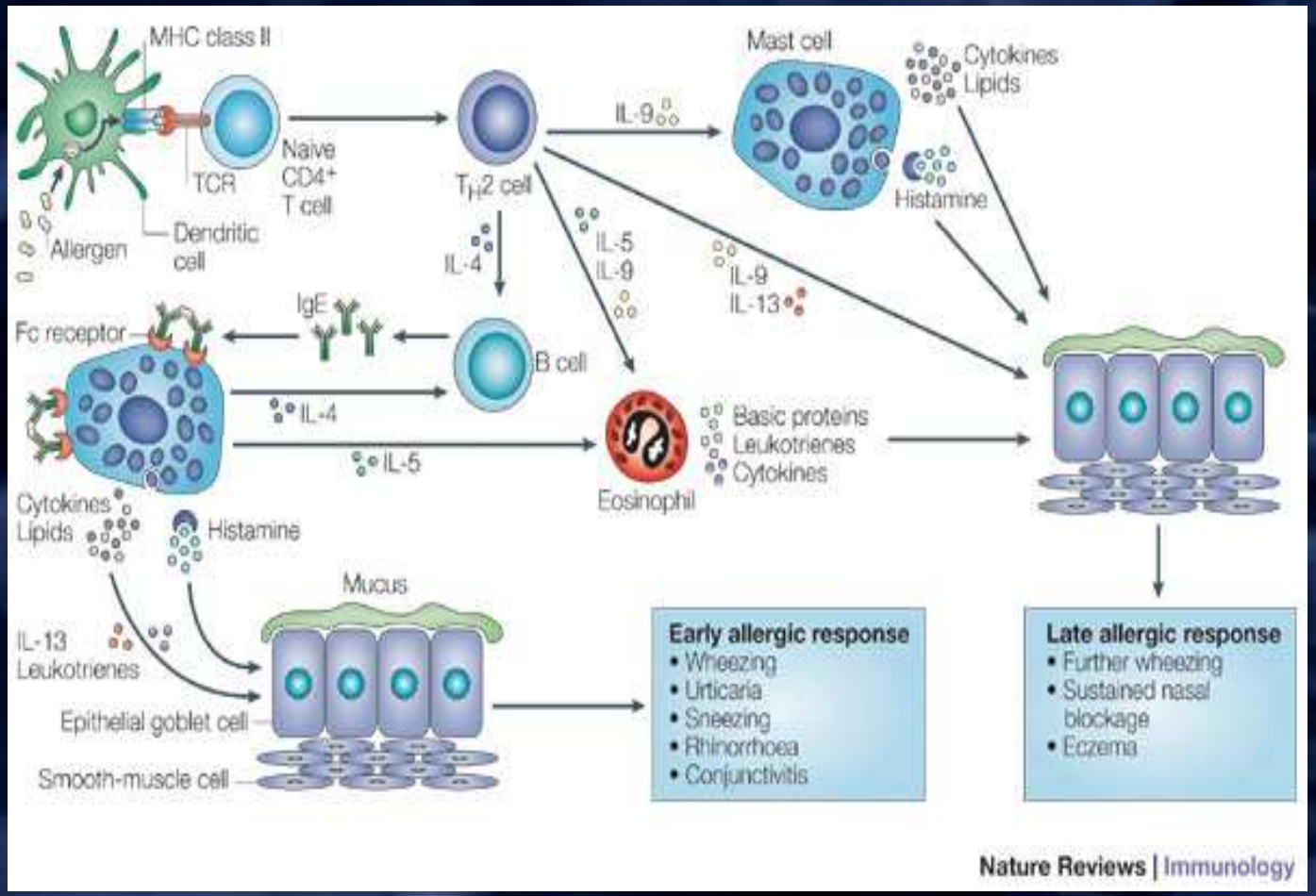

AUMENTA NIVEL SERICO DE IGE
T cell
Interleukin-13
Interleukin-4
B cell
FcεRII
IgE antibody
Arg130Gln VARIANTE CON MAYOR ACTIVIDAD BIOLOGICA
Allergen
Early response
Bronchospasm
Edema
Airflow obstruction
Activated B cell
FcεRI
Mast cell
Activation
Mediator Release
Histamine
Leukotrienes
Cytokines
Physiological effects
Late response
Airway inflammation
Airflow obstruction
Airway hyperresponsiveness
ASMA
IL13 +2044 G A (IL13 Arg130Gln) EN EXON 4

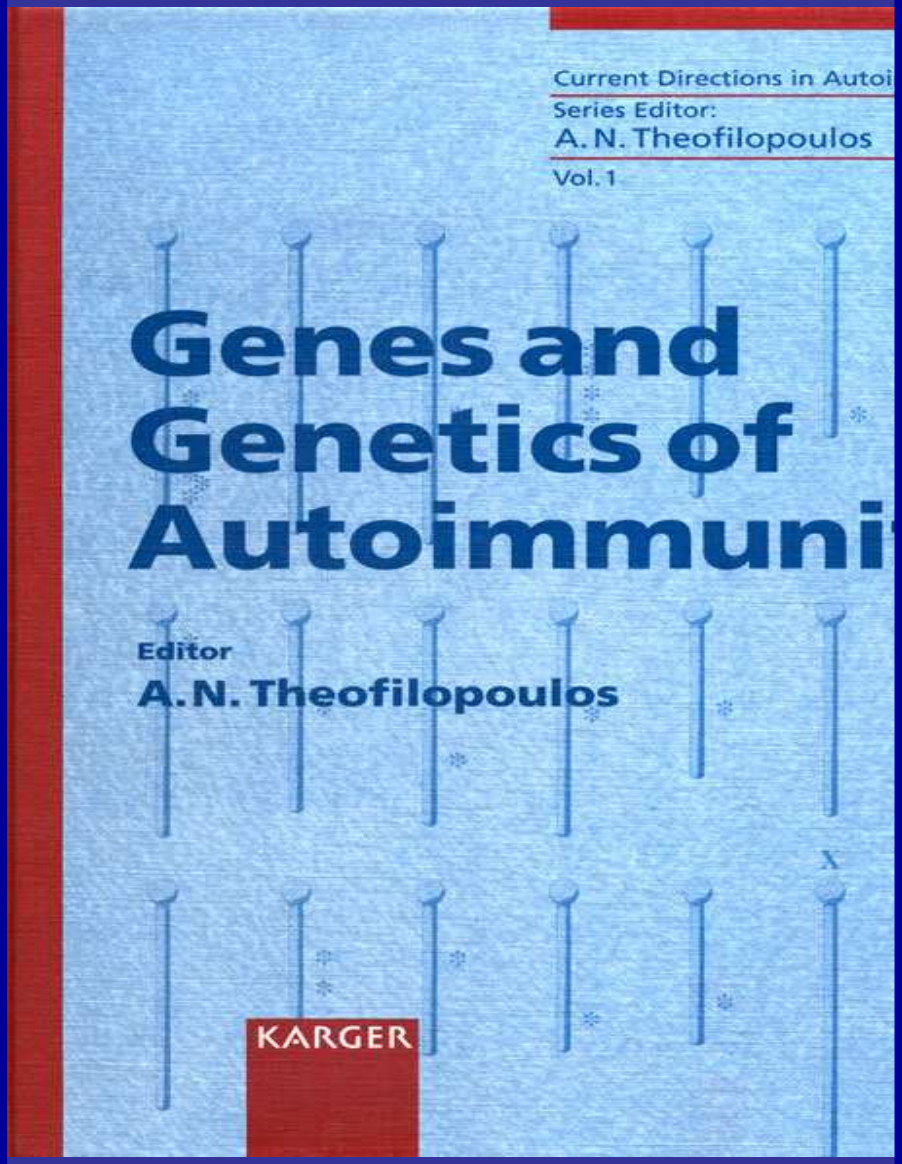
DEPENDIENTE DE LA SINTESIS DE IgE, SINO TAMBIEN LA

AMPLIFICACION DE LA REACCION DEPENDIENTE DE CITOQUINAS Th2 LIBERADAS POR BASOFILOS Y MASTOCITOS EN ASMA

POLIMORFISMO SNP EN CADENA β DE RECEPTOR FcεR1

POLIMORFISMO MAS FRECUENTEMENTE REPLICADO




Current Directions in Autoi
Series Editor:
A. N. Theofilopoulos
Vol. 1
Genes and
Genetics of
Autoimmuni
Editor
A. N. Theofilopoulos
KARGER

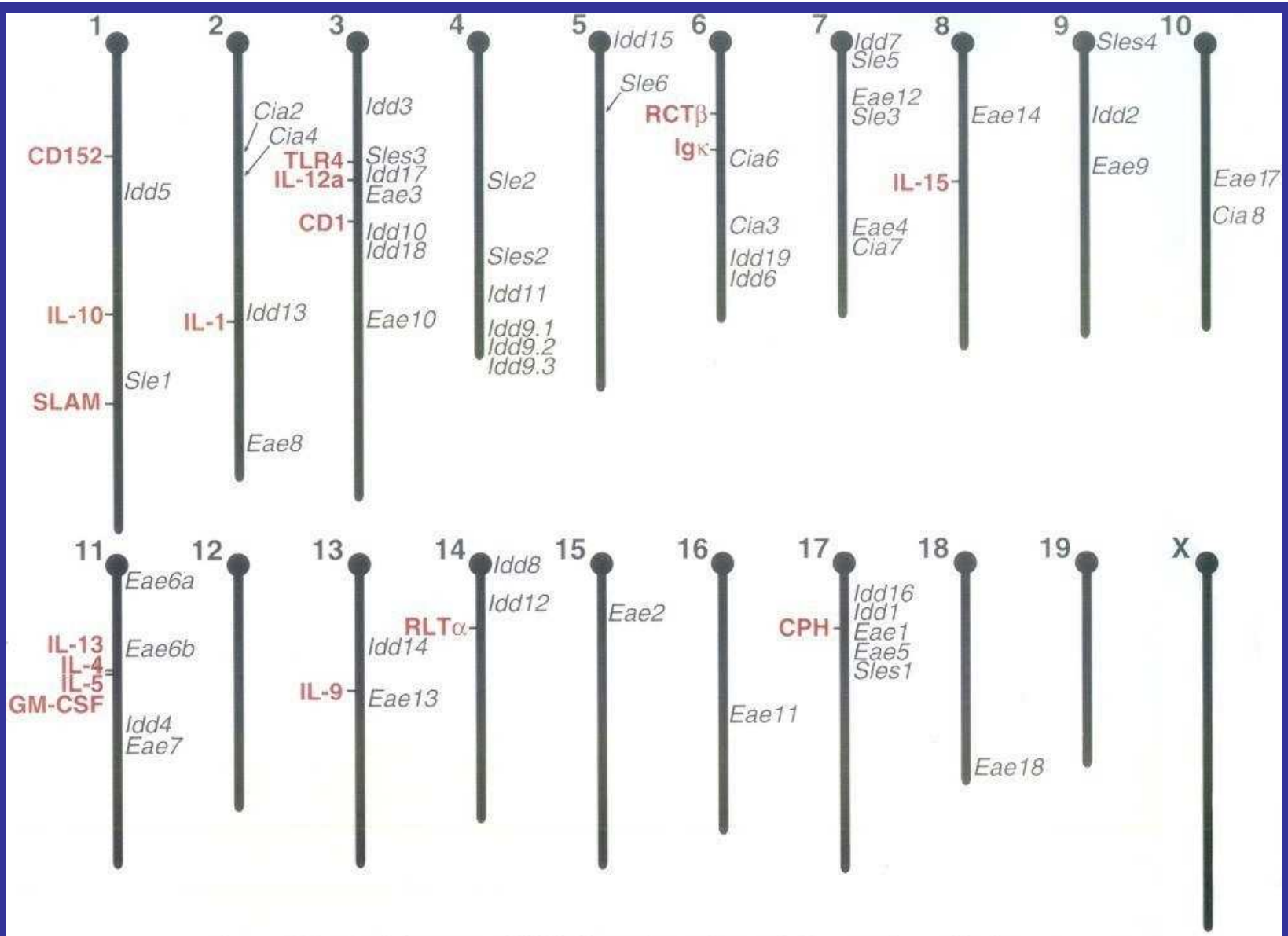
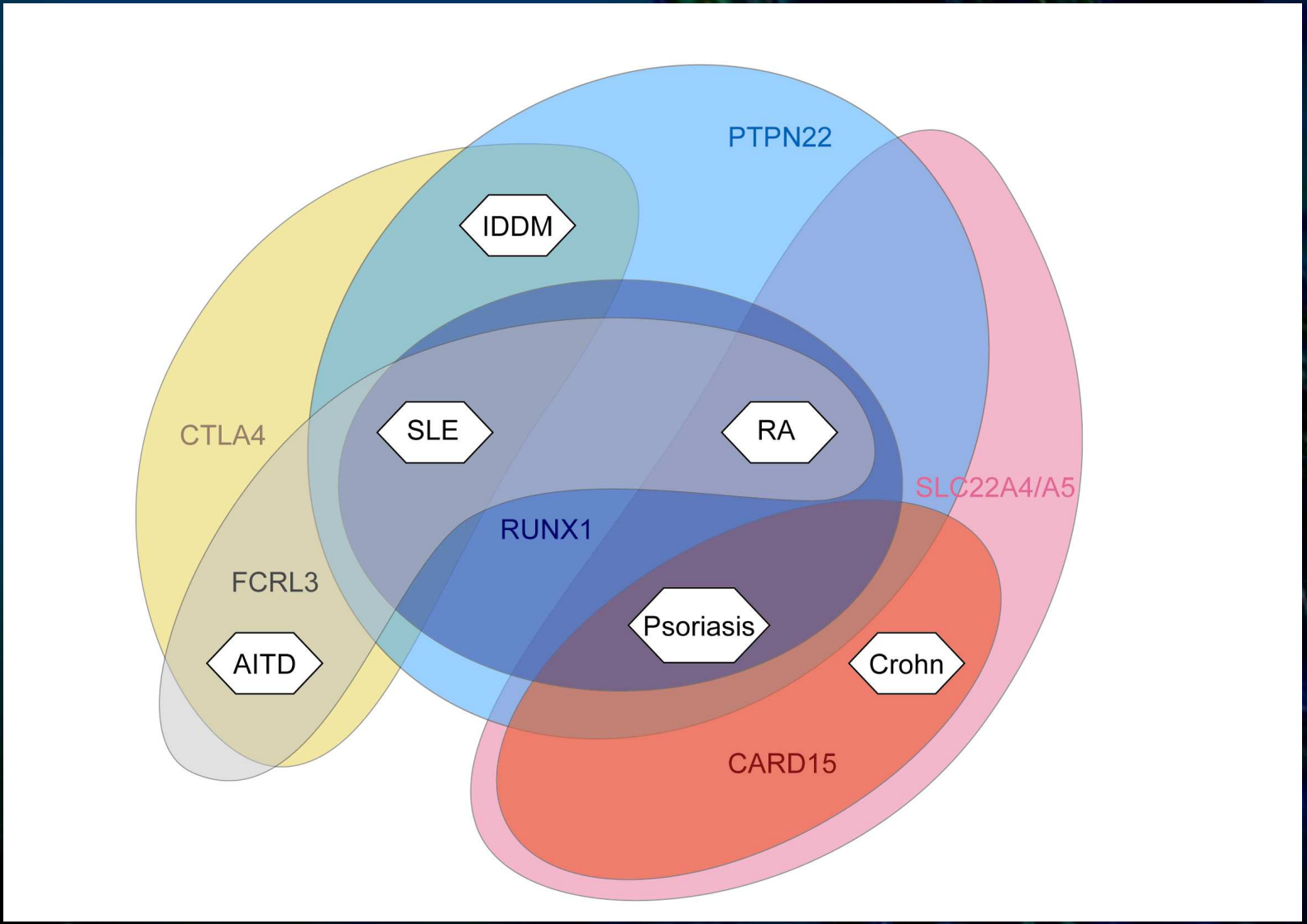
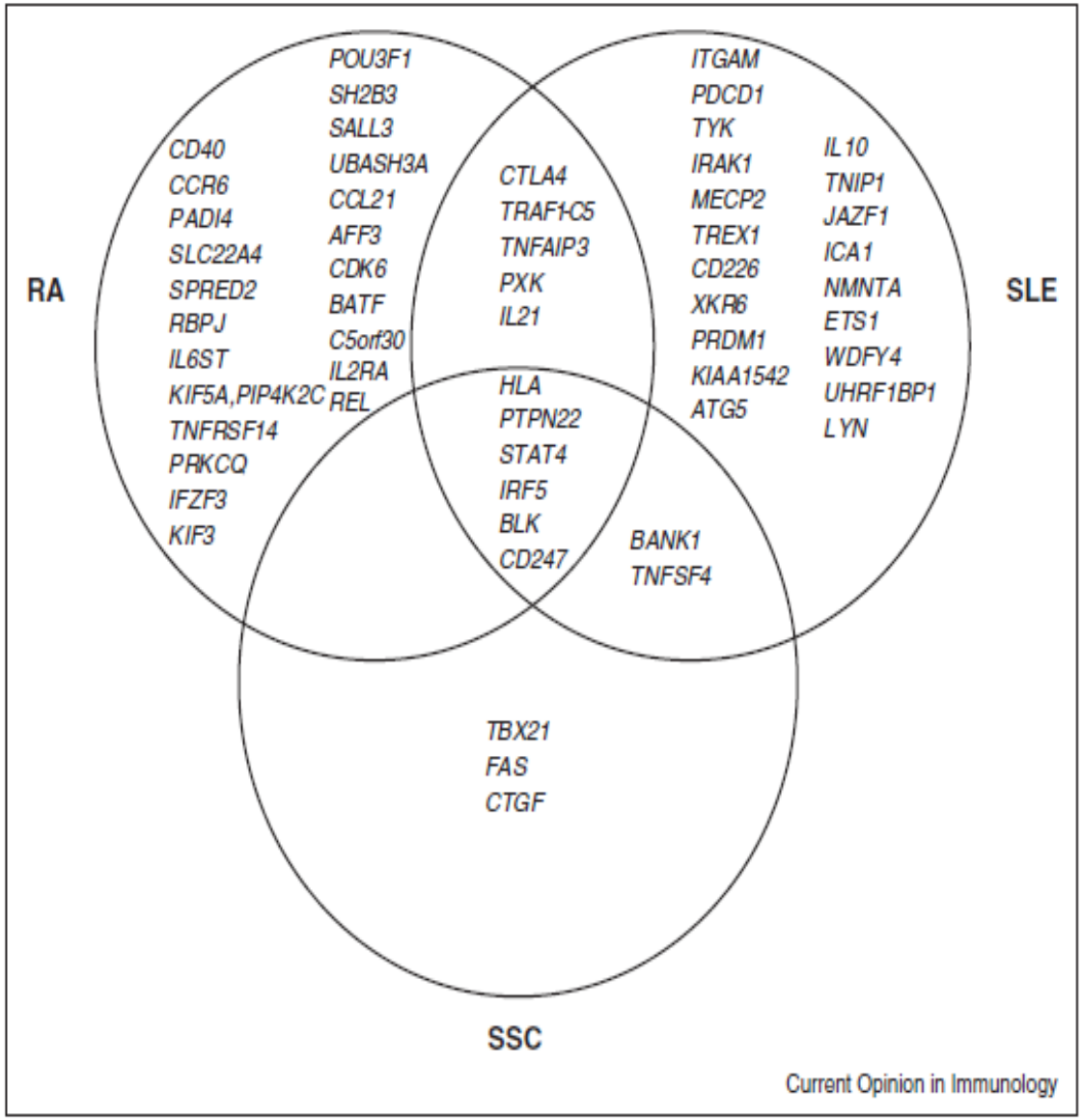


Figura 18-7 Loci de susceptibilidad para las enfermedades autoinmunitarias.

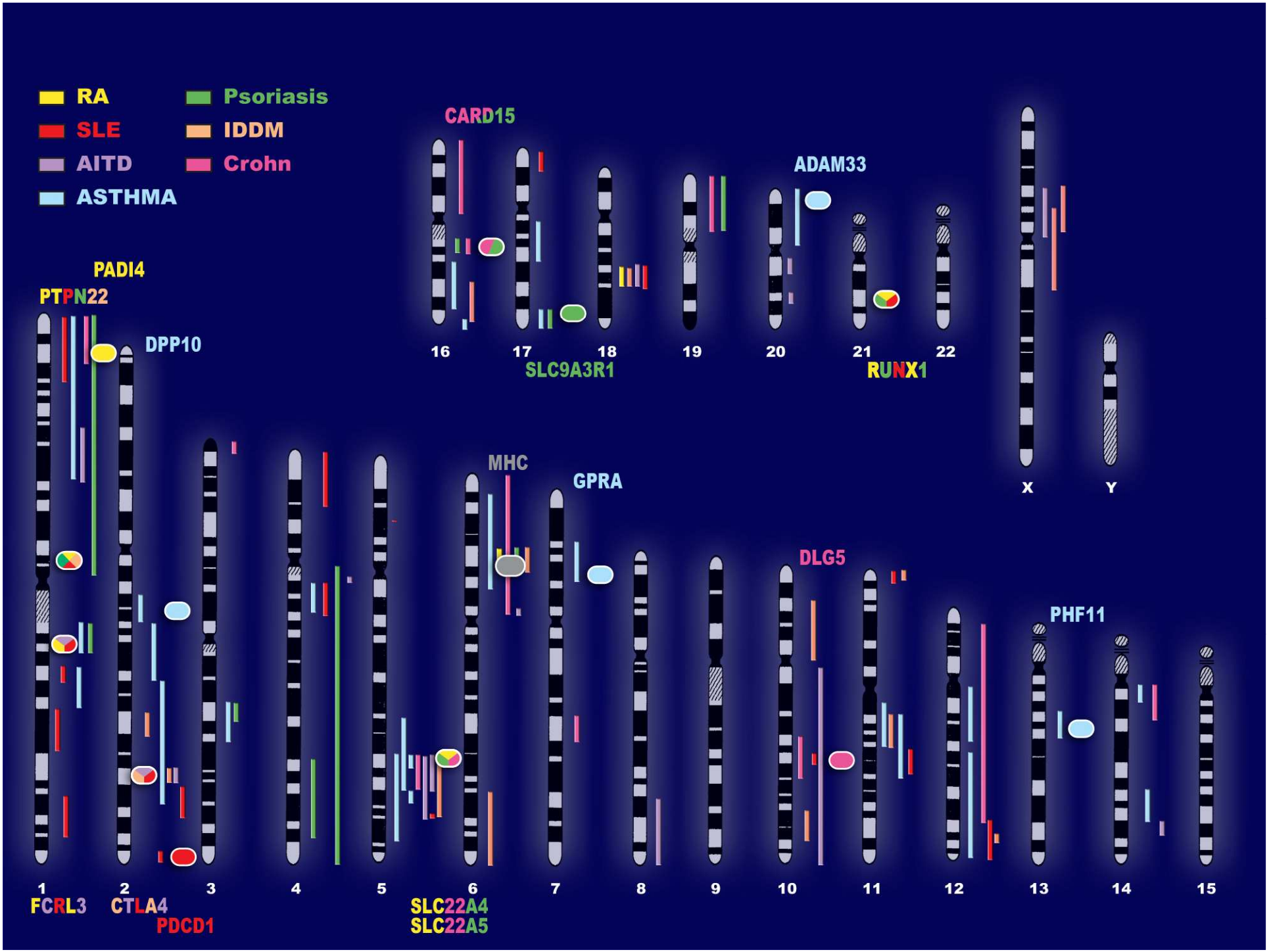
Se muestran las localizaciones cromosómicas de los loci de susceptibilidad de varias enfermedades autoinmunitarias en ratones endogámicos: *Cia*, artritis inducida por colágeno; *Eae*, encefalomielitis autoinmunitaria experimental; *Idd*, diabetes insulinodependiente (tipo I); *Sle*, lupus eritematoso sistémico (*Sles* se refiere a los locus que suprimen el LES). También se muestran en rojo las localizaciones de otros genes de interés inmunológico tales como CPH, citocinas (interleucinas, IL) y algunas moléculas CD. (Cortesía del Dr. Vijay Kuchroo, Department of Neurology, Harvard Medical School, y del Dr. Jeffrey Encinas, Bayer.)

Múltiples Genes y Múltiples Enfermedades





Unique and shared genes between SLE, RA and SSc.


RA
SLE
AITD
ASTHMA
Psoriasis
IDDM
Crohn
CARD15
ADAM33
PADI4
PTPN22
DPP10
MHC
GPRA
DLG5
PHF11
SLC9A3R1
RUNX1
FCRL3
CTLA4
PDCD1
SLC22A4
SLC22A5
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y

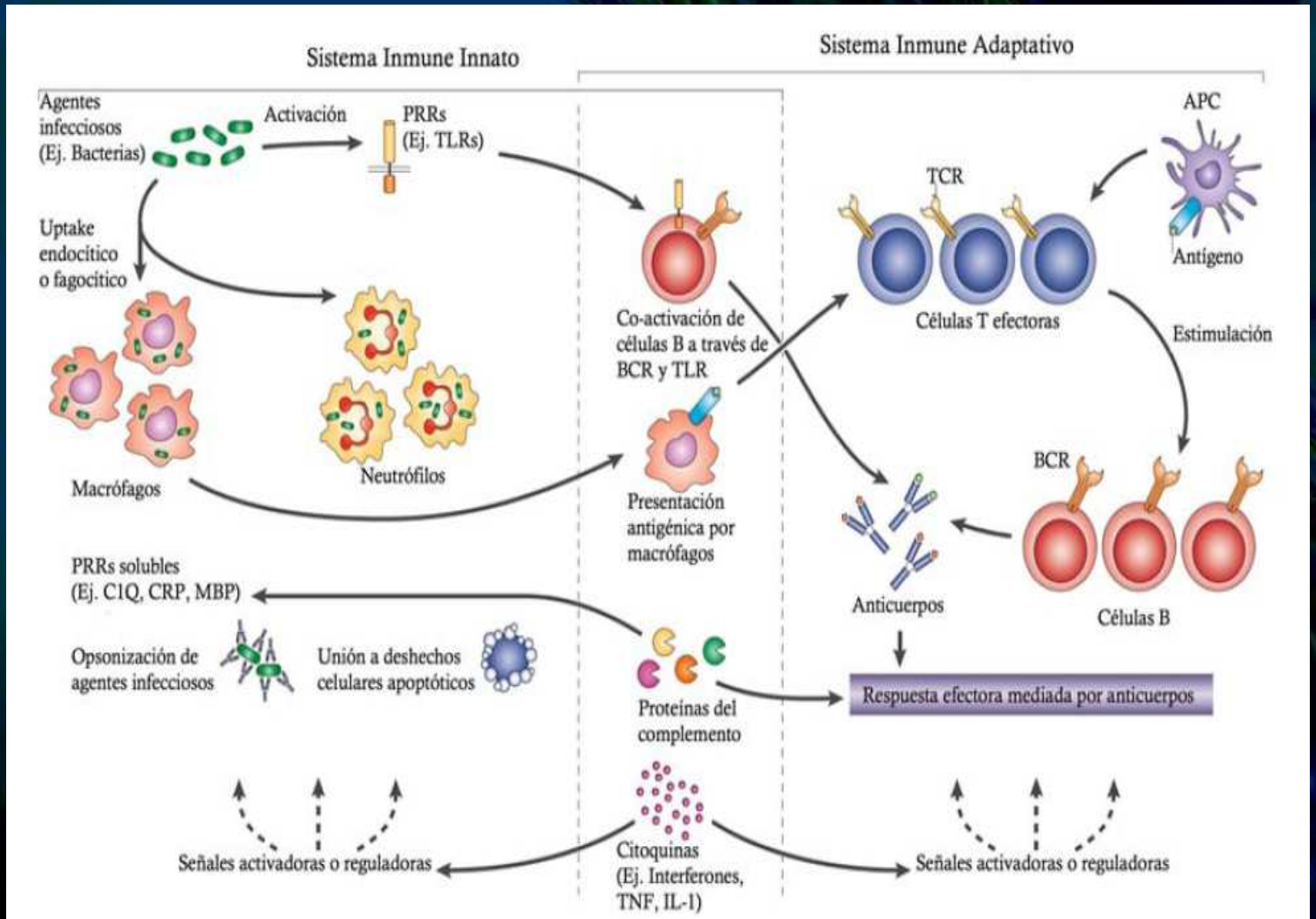
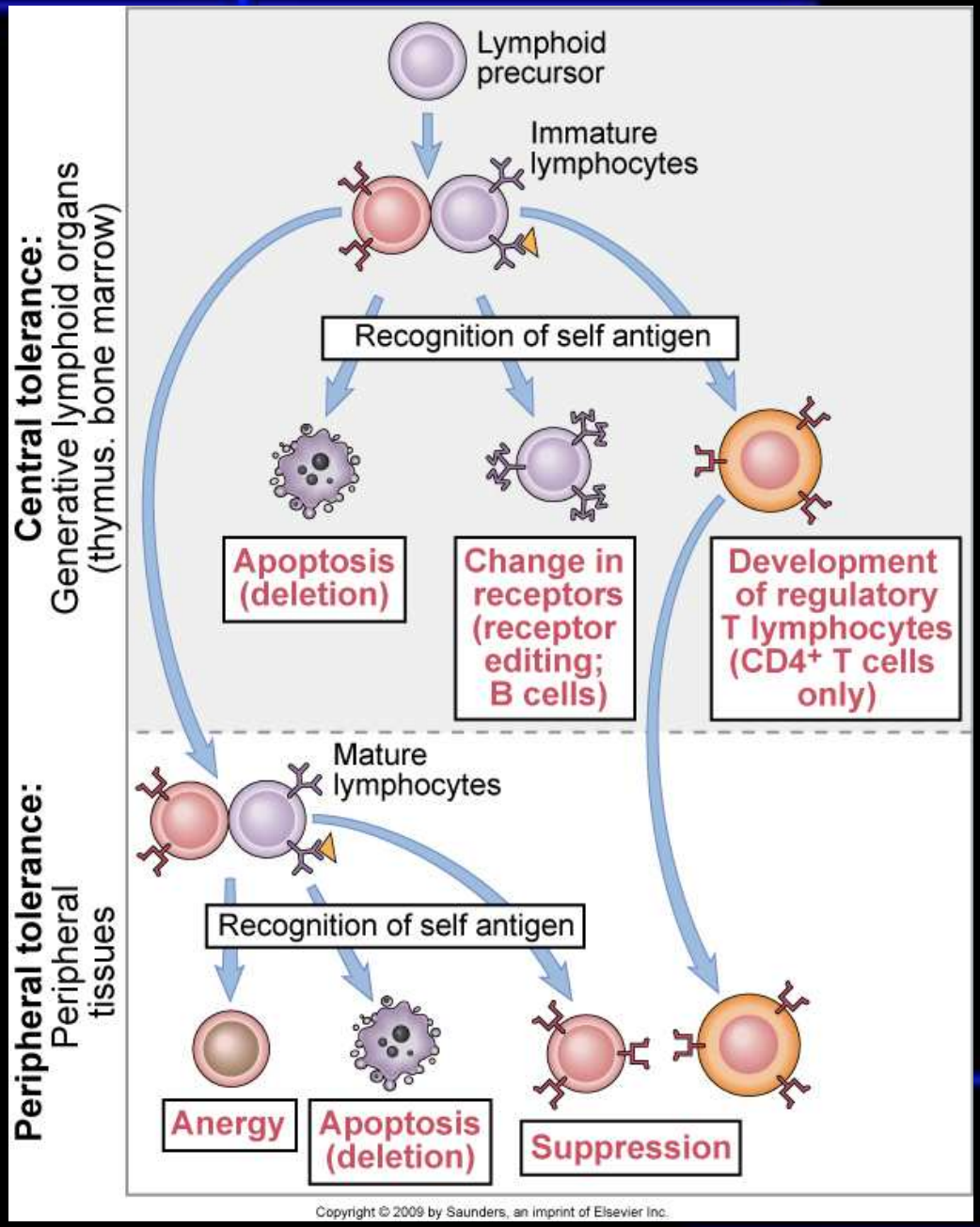
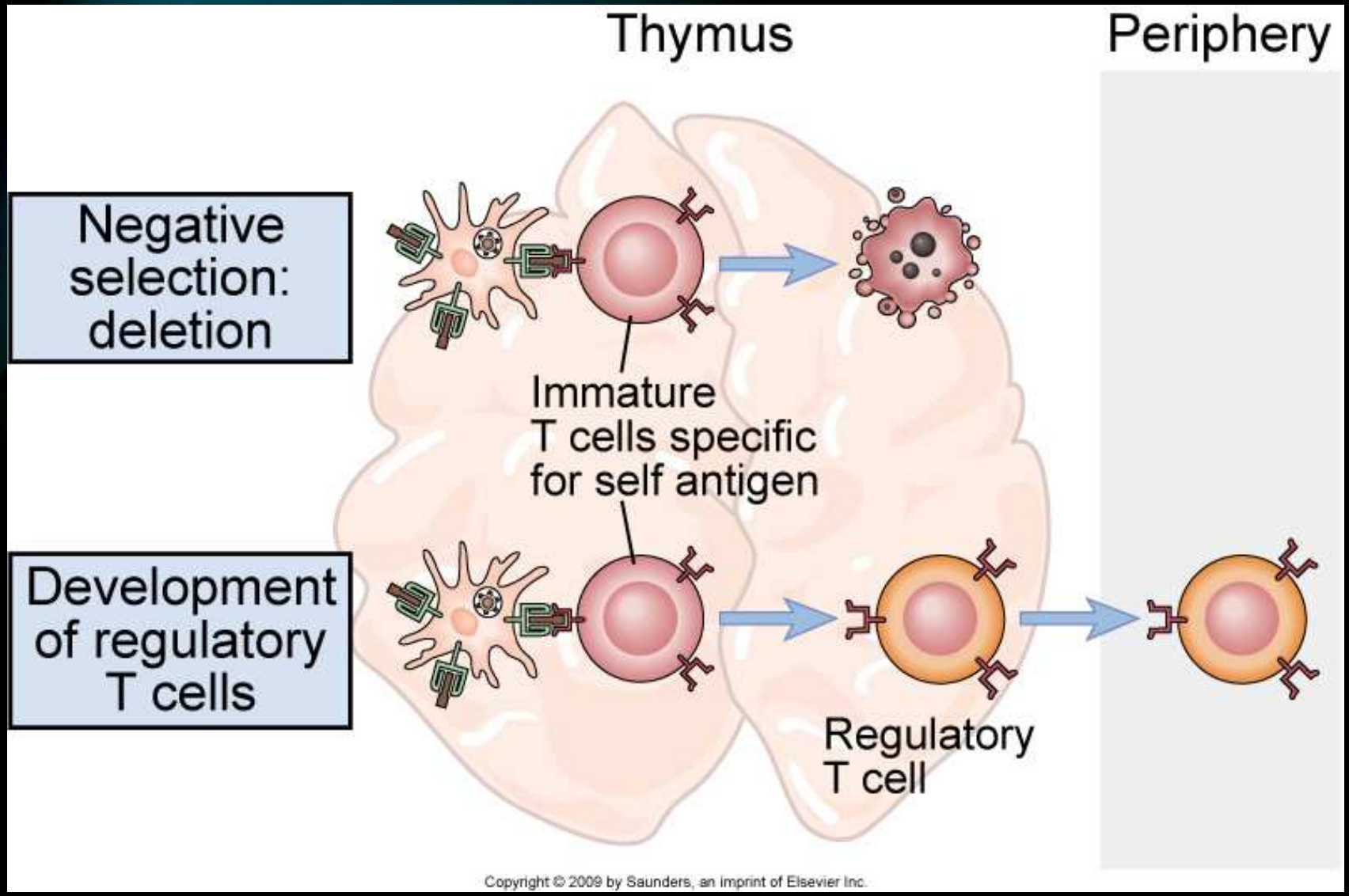


Figura 2.4. Representación esquemática de los sistemas inmunes innato y adaptativo y el solapamiento entre ambos.

Tolerancia Inmunológica





Autoinmunidad: factores genéticos

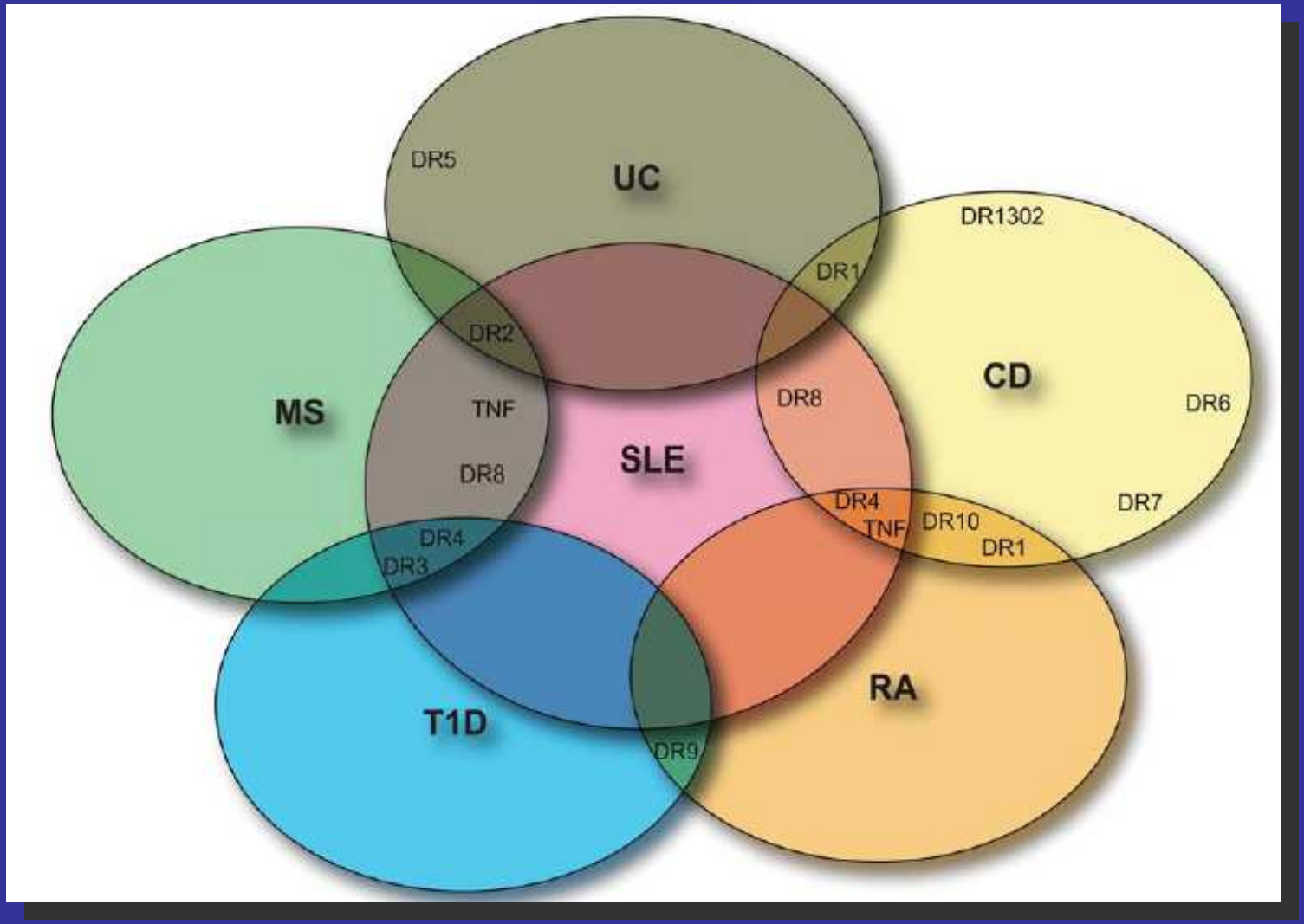
- La mayoría de las enfermedades autoinmunes tiene un fuerte componente genético, ejemplos de alteraciones genéticas:
  - Alteración genética del sistema HLA
  - Deficiencia congénitas de proteínas del complemento
  - Gen de IL-2
  - Mutación del gen Fas
  - Alteraciones en la génesis de las inmunoglobulinas
  - Gen del CTLA-4

Associations of HLA serotype with susceptibility to autoimmune disease

Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	< 0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~ 25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Figure 13-20 Immunobiology, 6/e. (© Garland Science 2005)

Haplotipos compartidos y distintivos en las enfermedades AI más conocidas.



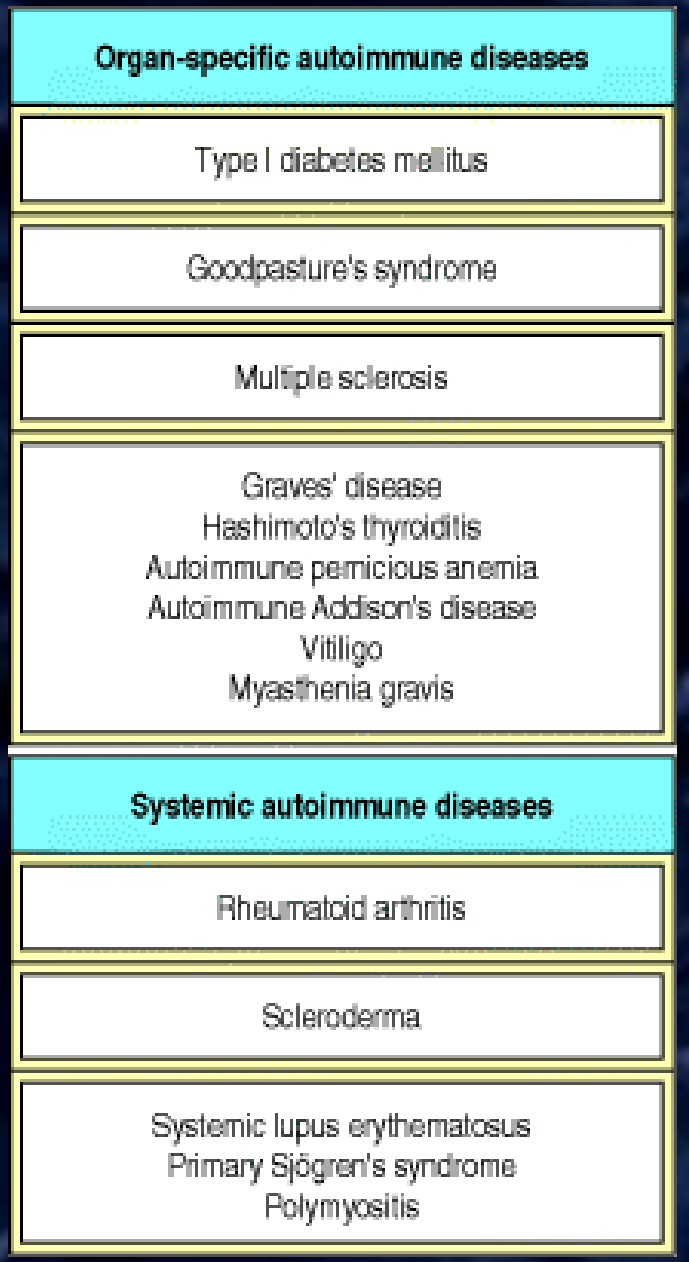
Some common autoimmune diseases classified by immunopathogenic mechanism

Syndrome	Autoantigen	Consequence
Type II antibody to cell-surface or matrix antigens		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and FcR^+ phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Noncollagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Type III immune-complex disease		
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis
Type IV T cell-mediated disease		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-Cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness

ENFERMEDADES AUTOINMUNES

Dependiendo si la respuesta está dirigida principalmente a:

- Antígenos localizados en un tejido específico (ÓRGANO-ESPECÍFICAS).
- Antígenos sistémicos (NO ÓRGANO-ESPECÍFICAS).



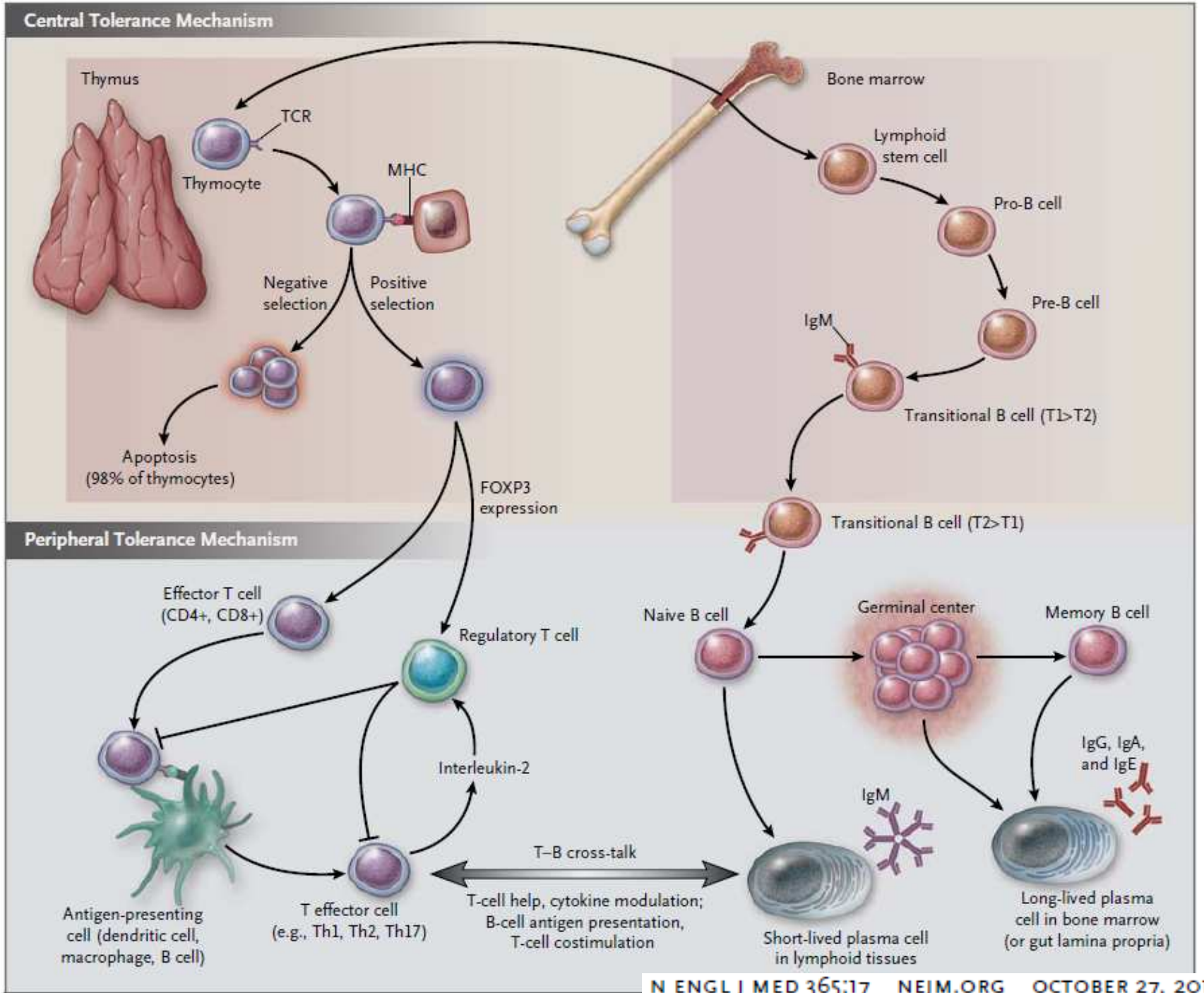
Janeway, et. al, 2001

Table 1. **Selected Major Association Signals in Autoimmune Diseases.***

Candidate Gene	Chromosome Location	Possible Functions and Mechanisms of Action	Major Associated Diseases
Lymphocyte activation and intracellular signaling			
Major histocompatibility complex (HLA)	6p21	Antigen presentation; complex, often disease-specific association signals that finely modulate antigen presentation	Most autoimmune disorders
Protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*)	1p13	Modulation of lymphocyte receptor activation; a polymorphism resulting in an Arg620Trp substitution drives the association	Type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, Graves' disease,† Crohn's disease
Cytotoxic lymphocyte-associated protein (*CTLA4*)	2q33	Transmission of inhibitory signals in T cells	Type 1 diabetes mellitus, rheumatoid arthritis, celiac disease, alopecia areata
T-cell activation, Rho-GTPase-activating protein (*TAGAP*)	6q25	Expression in activated T cells	Rheumatoid arthritis, Crohn's disease, celiac disease, type 1 diabetes mellitus
Protein tyrosine phosphatase nonreceptor type 2 (*PTPN2*)	18p11	Expression in T cells; role in cell growth and differentiation	Type 1 diabetes mellitus, Crohn's disease, celiac disease
Tyrosine protein kinase 2 (*TYK2*)	19p13	Janus kinase downstream of cytokine receptors	Psoriasis, type 1 diabetes mellitus, systemic lupus erythematosus, Crohn's disease, multiple sclerosis
Tumor necrosis factor α–induced protein 3 (*TNFAIP3*)	6q23	Regulation of ubiquitination; down-regulation of nuclear factor κB activation	Rheumatoid arthritis, systemic lupus erythematosus
TNFAIP3-interacting protein (*TNIP1*)	5q33	Down-regulation of nuclear factor κB activation; function of TNIP is dependent on ubiquitin-binding domain	Systemic lupus erythematosus, psoriasis
Tumor necrosis factor receptor superfamily member 5 (*CD40*)	20q13	Costimulatory molecule for B-cell activation; interaction with T cells through CD40 ligand (CD154); broadly expressed	Rheumatoid arthritis
Protein kinase C theta (*PRKCQ*)	10p15	T-cell activation and signaling through c-Rel	Type 1 diabetes mellitus, rheumatoid arthritis
Cytokines and cytokine receptors			
Interleukin-23 receptor gene (*IL23R*) region	1p31	Enhancement of select cell subsets, including Th17 cells; multiple association signals (e.g., Arg381Gln polymorphism)	Crohn's disease, ulcerative colitis, psoriasis, ankylosing spondylitis, primary biliary cirrhosis†
Interleukin-2 receptor, subunit alpha (*IL2RA*)	10p15	One component of interleukin-2 receptor signaling; linkage of disease-associated genotypes with decreased IL2RA expression	Type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, Crohn's disease, vitiligo, alopecia areata
Interleukin-2/21 gene region	4q26	T-cell trophic growth factors; multiple associations flanking both cytokines	Celiac disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, type 1 diabetes mellitus
Interleukin-7 receptor (*IL7R*)	5p13	Differentiation and activation of T cells affected by interleukin-7 signaling	Multiple sclerosis, primary biliary cirrhosis, alopecia areata
Interleukin-12B, p40 (*IL12B*)	5q33	Cytokine subunit common to interleukin-12 and interleukin-23	Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, systemic lupus erythematosus
Interleukin-10 gene (*IL10*) region	1q32	Down-regulation of cytokines, MHC class II and costimulatory molecules	Systemic lupus erythematosus, type 1 diabetes mellitus, Crohn's disease, ulcerative colitis

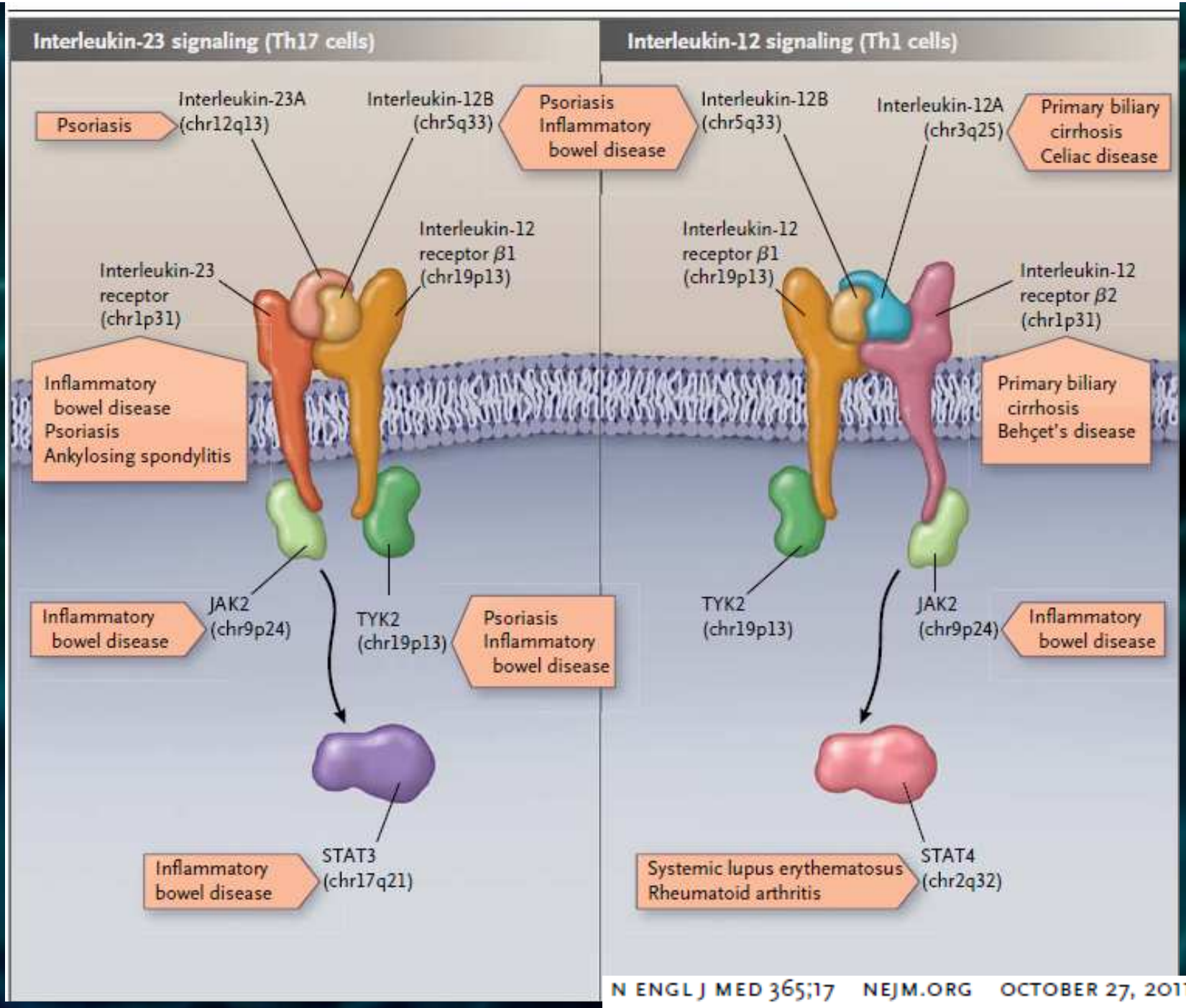
Innate immunity and microbial recognition			
Nucleotide oligomerization domain 2 (*NOD2*)	16q12	Sensing of bacterial peptidoglycan in nuclear factor κB activation; loss-of-function, uncommon missense polymorphisms	Crohn's disease
Interferon regulatory factor 5 (*IRF5*)	7q32	Inducement of interferons, regulation of activation of pattern-recognition receptor; multiple associated polymorphisms affecting splicing and messenger RNA levels	Systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, systemic sclerosis
Interferon-induced helicase C domain–containing protein 1 (*IFIH1*)	2q24	Recognition of single-stranded RNA from picornaviruses; protection against disease conferred by extremely rare missense mutations	Type 1 diabetes mellitus, psoriasis, selective IgA deficiency
Autophagy-like 16L1 (*ATG16L1*)	2q37	Targeting of intracellular components to lysosomes	Crohn's disease
PR domain zinc finger protein 1 (*PRDM1*); autophagy protein 5 (*ATG5*)	6q21	Expression of genes encoding beta-interferons repressed by PRDM1 (also known as *BLIMP1*), which is a key regulator of B-cell differentiation; ATG5 part of autophagy complex, with major association between PRDM1 and ATG5	Systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease
Transcription factors			
Signal transducer and activator of transcription 4 (*STAT4*)	2q32	Mediation of multiple cytokine signals, including interleukin-12	Systemic lupus erythematosus,‡ rheumatoid arthritis,‡ primary biliary cirrhosis, systemic sclerosis
Signal transducer and activator of transcription 3 (*STAT3*)	17q21	Mediation of multiple cytokine signals (e.g., interleukins 6, 10, 22, and 23); gene-rich region of association	Crohn's disease, multiple sclerosis
c-Rel (*REL*)	2p16	Transcription factor, a component of nuclear factor κB	Rheumatoid arthritis, Crohn's disease, ulcerative colitis, celiac disease, psoriasis
Other pathways or mechanisms			
Endoplasmic reticulum aminopeptidase 1 (*ERAP1*)	5q15	Trimming of peptides for HLA class I presentation; interactive associations with class I alleles observed in MHC class I–predominant diseases	Psoriasis,‡ ankylosing spondylitis
Fc fragment of IgG, low affinity IIa, receptor (*FCGR2A*)	1p23	Cell-surface receptor on phagocytic cells; associations including His131Arg polymorphism	Systemic lupus erythematosus, rheumatoid arthritis; ulcerative colitis‡
Chemokine (C-C motif) receptor 6 (*CCR6*)	6q27	Expression on immature dendritic cells and memory T cells; involvement in lymphocyte trafficking	Crohn's disease,‡ rheumatoid arthritis,‡ Graves' disease,‡ vitiligo‡
Integrin alpha M precursor (*ITGAM*)	16p11	Immune complex clearance and leukocyte adhesion; amino acid change implicated as one causal allele	Systemic lupus erythematosus
Ubiquitin-associated and SH3 domain-containing protein A (*UBASH3A*)	21q22	Association with ubiquitin and SH3 domain-containing protein	Type 1 diabetes mellitus, rheumatoid arthritis, celiac disease
Ubiquitin-conjugating enzyme E2L 3 (*UBE2L3*)	22q11	Ubiquitin-conjugating enzyme	Rheumatoid arthritis, celiac disease, systemic lupus erythematosus
Insulin locus (*INS*)	11p15	Targeting autoantigen; expression polymorphism; possible role in thymic selection	Type 1 diabetes mellitus

* MHC denotes major histocompatibility complex.
† A potentially distinct association within this implicated genetic region has been shown for this disease.
‡ Genetic associations with this disease have been observed in patients of Asian or European ancestry.


Central Tolerance Mechanism
Thymus
TCR
Thymocyte
MHC
Negative selection
Positive selection
Apoptosis (98% of thymocytes)
FOXP3 expression
Bone marrow
Lymphoid stem cell
Pro-B cell
Pre-B cell
IgM
Transitional B cell (T1>T2)
Transitional B cell (T2>T1)
Peripheral Tolerance Mechanism
Effector T cell (CD4+, CD8+)
Regulatory T cell
Naive B cell
Germinal center
Memory B cell
IgG, IgA, and IgE
IgM
Interleukin-2
T–B cross-talk
Antigen-presenting cell (dendritic cell, macrophage, B cell)
T effector cell (e.g., Th1, Th2, Th17)
T-cell help, cytokine modulation; B-cell antigen presentation, T-cell costimulation
Short-lived plasma cell in lymphoid tissues
Long-lived plasma cell in bone marrow (or gut lamina propria)

Interleukina-12 y la interleukina-23

- **Se observó que varios componentes JAK- STAT han sido implicados en la señalización de interleukina-12 y de interleukina-23, cada componente JAK-STAT es capaz de la señalización corriente abajo de múltiples citokinas.**
- **En enfermedad intestinal inflamatoria, psoriasis, y espondilitis anquilosante, las señales de asociación en el cromosoma 1p31 en la región que codifica el extremo C terminal de receptor de interleukina-23 (IL23R) y se extienden en la región intergénica entre el IL23R y IL12RB2.**
- **Por el contrario, las asociaciones con cirrosis biliar primaria y enfermedad de Behçet predominan más en la región intergénica IL12RB2.**
- **Las asociaciones genéticas particularmente fuertes**


Interleukin-23 signaling (Th17 cells)
Interleukin-12 signaling (Th1 cells)
Psoriasis
Interleukin-23A (chr12q13)
Interleukin-12B (chr5q33)
Psoriasis Inflammatory bowel disease
Interleukin-12B (chr5q33)
Interleukin-12A (chr3q25)
Primary biliary cirrhosis Celiac disease
Interleukin-12 receptor β1 (chr19p13)
Interleukin-23 receptor (chr1p31)
Interleukin-12 receptor β1 (chr19p13)
Interleukin-12 receptor β2 (chr1p31)
Inflammatory bowel disease Psoriasis Ankylosing spondylitis
Primary biliary cirrhosis Behçet's disease
Inflammatory bowel disease
JAK2 (chr9p24)
TYK2 (chr19p13)
Psoriasis Inflammatory bowel disease
TYK2 (chr19p13)
JAK2 (chr9p24)
Inflammatory bowel disease
Inflammatory bowel disease
STAT3 (chr17q21)
Systemic lupus erythematosus Rheumatoid arthritis
STAT4 (chr2q32)

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 14875–14879, December 1998
Genetics

A genome-wide search for susceptibility genes in human systemic lupus erythematosus sib-pair families

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Communicated by Arno G. Motulsky, University of Washington, Seattle, WA, October 16, 1998 (received for review September 14, 1998)

Estudios de ligamiento con marcadores microsatélites se encontró asociación en pacientes con LES con varias regiones cromosómicas : 1q, 4p, 4q, 6, 7p, 16, 20.

No-HLA y Autoinmunida

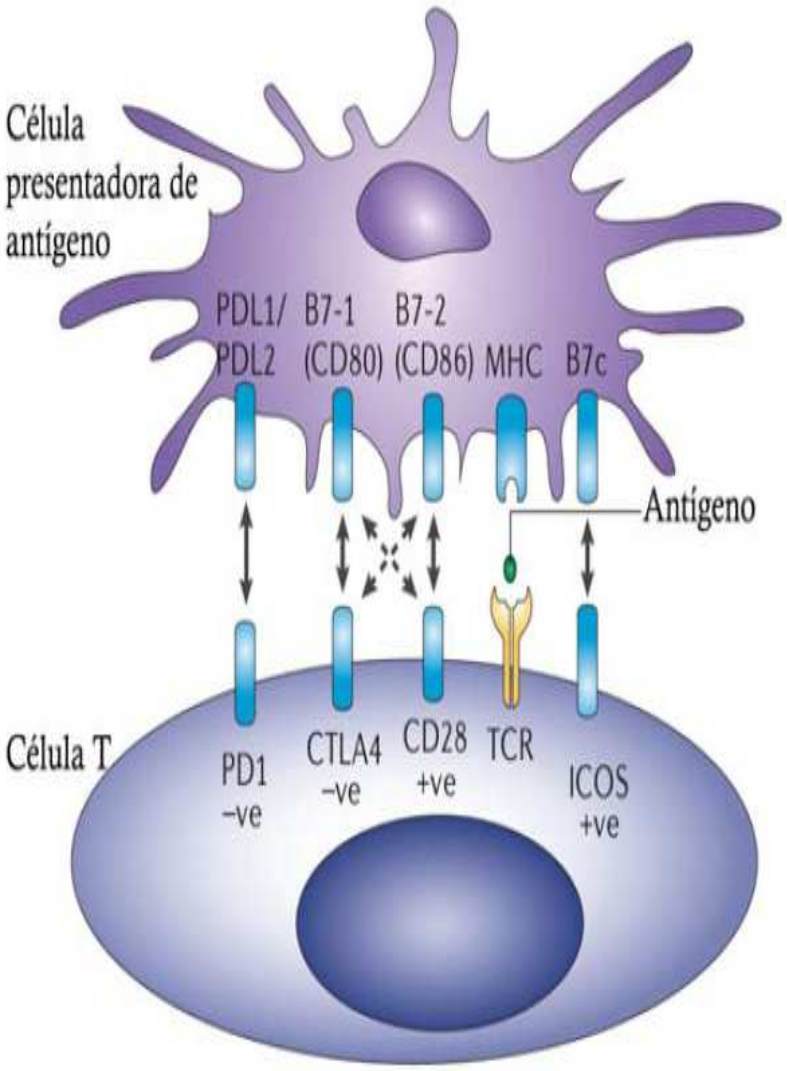
Gene(s)	Disease association	Mechanism
AIRE	Autoimmune polyendocrine syndrome	Defective expression of tissue antigens and elimination of self-reactive T cells in the thymus
Complement proteins (C2, C4)	Lupus-like disease	Defective clearance of immune complexes? Defects in B cell tolerance?
Fas, FasL	Lpr, gld mouse strains; human ALPS	Defective elimination of self-reactive lymphocytes
FcγRIIb	Lupus-like diseases	Defective feedback inhibition of B cell activation
Foxp3 *	X-linked polyendocrinopathy and enteropathy (IPEX)	Deficiency of regulatory T cells
IL-2; IL-2Rα/β	Several autoimmune diseases (increased risk with polymorphisms)	Deficiency of regulatory T cells
NOD-2 *	Crohn's disease (inflammatory bowel disease)	Defective resistance or abnormal responses to intestinal microbes?
PTPN22 *	Several autoimmune diseases	Abnormal tyrosine phosphatase regulation of lymphocyte activation?

CTLA 4

- **Una de las señales coestimulatorias más importante en la cél. T es mediada por CD28-CD80/86, que regula la producción de IL2 y la expresión de moléculas antiapoptóticas como Bcl-xL .**

- **CD28 está presente en muchas céls. T y se une a CD80 (B7-1) y a CD86 (B7-2), las cuales estan en las CPA , cels dendríticas, cels. B, y macrófagos.**

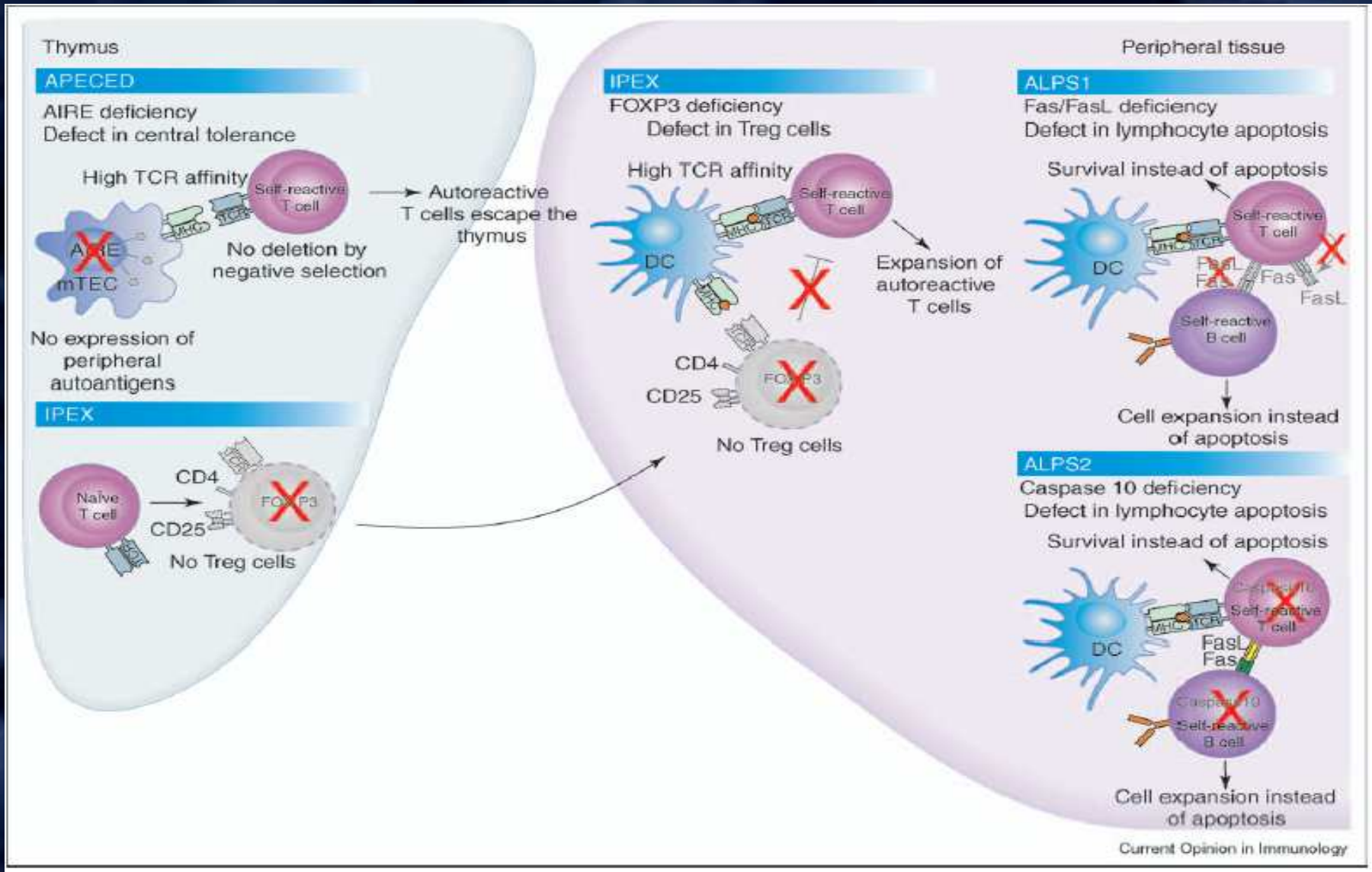
- **El antígeno asociado a LT citotóxicos (CTLA)4 (CD152), que está sobreexpresado en las céls. T luego de su activación, también interactúa con CD80 y CD86, *resultando en un importante mecanismo inhibitorio de la función T.***



Moléculas coestimuladoras y coinhibidoras que intervienen en la activación de la célula T.

CTLA4 se expresa constitutivamente en las céls Treg y es activadora.

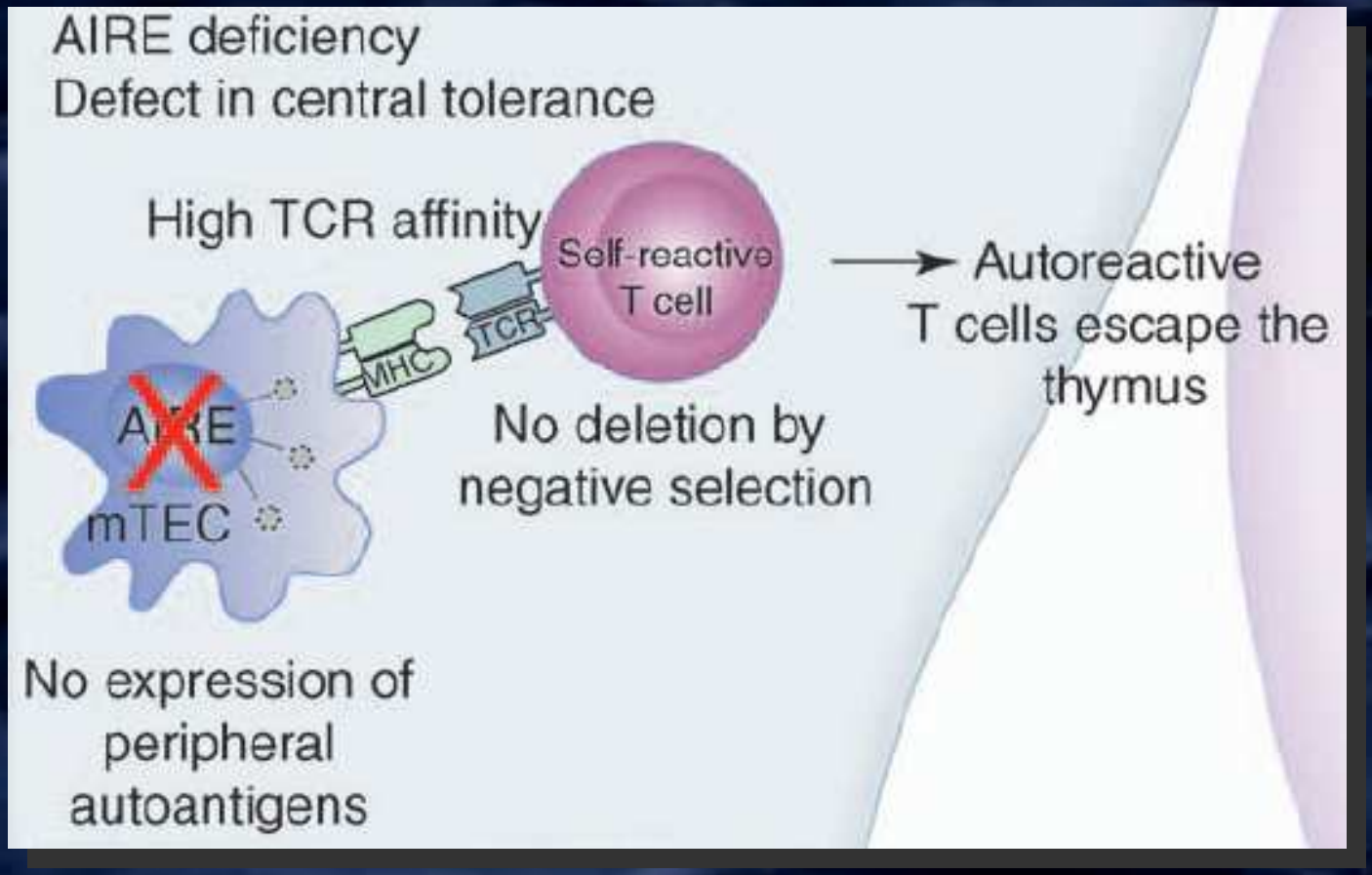
Por lo tanto una alteración en CTLA4 podría suponer una disminución de la actividad Treg , propiciando autoinmunidad



A schematic model of the pathways targeted by the monogenic AIDs APS1, ALPS and IPEX in the central (thymus) and peripheral immunological organs. The red crosses pinpoint the molecules or functions hit by the disease mutations. In APECED, defects in AIRE lead to impaired expression of ectopic antigens in mTECs, causing inefficient negative selection of T cells. In IPEX, the mutations in Foxp3 prevent the normal development of regulatory T cells (Treg), and in ALPS 1 and 2 Fas/Fas ligand mutations result in the defective apoptotic elimination of autoreactive T cells. Abbreviations: DC, dendritic cell; mTEC, medullary thymic epithelial cell; TCR, T-cell receptor; Treg cell, regulatory T cell.

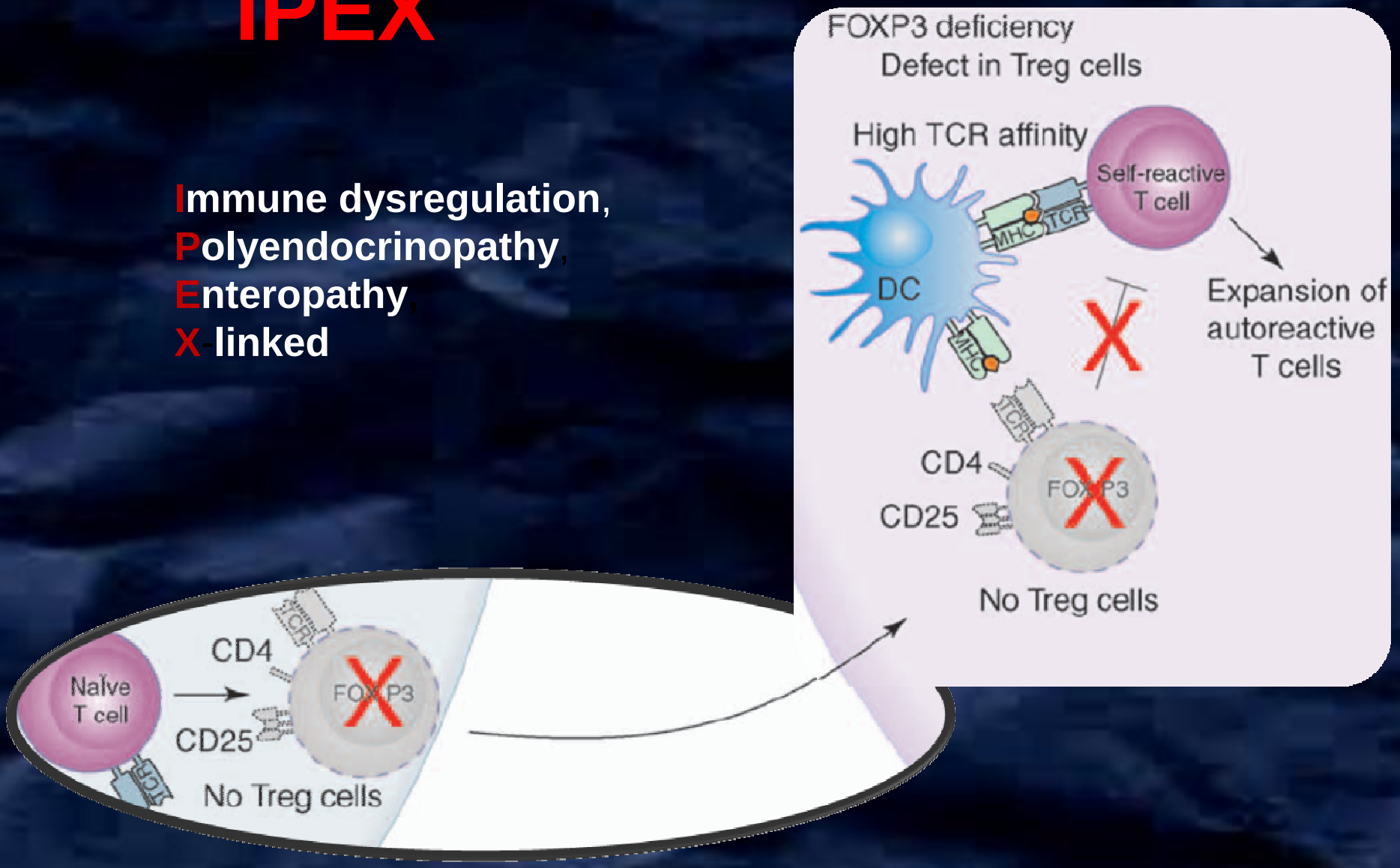
APECED

Autoimmune **P**olyendocrinopathy
Candidiasis
Ectodermal **D**ystrophy



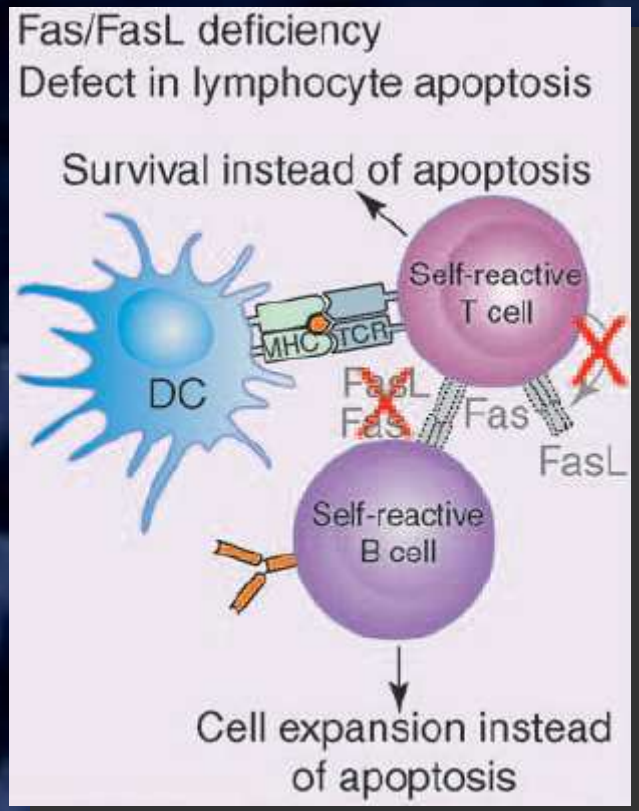
IPEX

Immune dysregulation,
Polyendocrinopathy,
Enteropathy,
X-linked

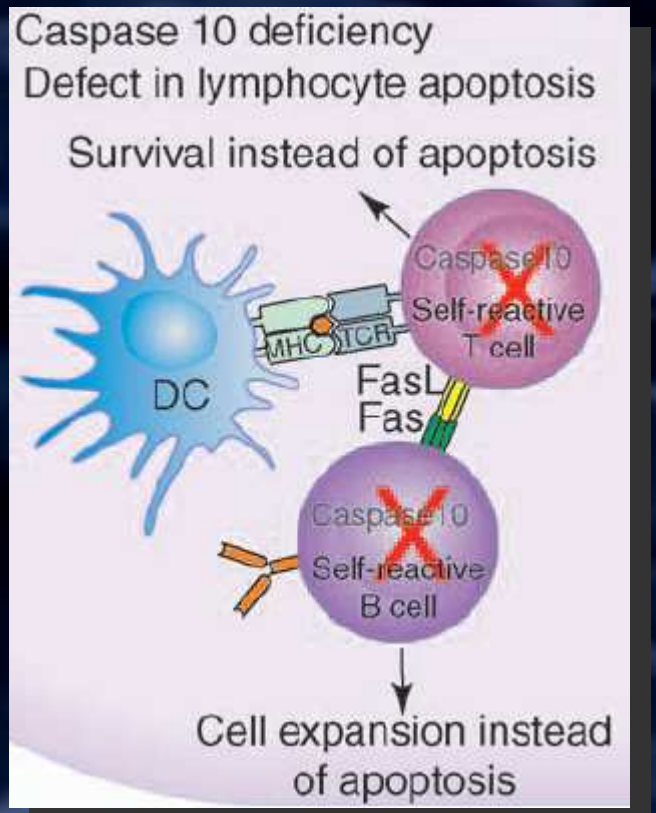


ALPS (Autoimmune Lymphoproliferative Syndrome)

ALPS1



ALPS2



ELSEVIER

Monogenic autoimmune diseases — lessons of self-tolerance

Ismo Ulmanen[1], Maria Halonen[1,2], Tanja Ilmarinen[1] and Leena Peltonen[1,2]

Table 1

Major features of monogenic autoimmune diseases.

Disease	Affected gene and function	Number of mutations	Main clinical features	Affected pathway	Mouse model
APS1	*AIRE* transactivator	>50	Hypoparathyroidism, Addison's disease, Candida, diabetes, ovarian failure	Self-antigen presentation and negative selection in thymus	KO
ALPS 1a	*TNFRSF6* membrane receptor	>40	Splenomegaly, lymphadenopathy, hypergammaglobulinemia, autoimmune diseases	Fas-mediated apoptosis	lpr/lpr-mouse KO
ALPS 1b	*TNFSF6* membrane-bound ligand	1	Systemic lupus erythematosus, lymphadenopathy	Fas-mediated apoptosis	gld/gld-mouse
ALPS 2	*Caspase 10* cysteine protease	2	Adenopathy, hepatosplenomegaly, haemolytic anaemia	Lymphocyte apoptosis cascade	None presently available
IPEX	*Foxp3* transcription factor	10	Polyendocrinopathy, haemolytic anaemia, chronic diarrhoea, eczema	$CD4^+CD25^+$ regulatory T cell development	Scurfy-mouse
IL-2Rα deficiency	*IL-2Rα* cytokine receptor	1	Lymphadenopathy, chronic diarrhoea, hepato-splenomegaly, chronic lung disease, recurrent infections	$CD4^+CD25^+$ regulatory T cell development	KO

KO, knockout.

SLEGEN - Windows Internet Explorer

http://www.lupusresearch.org/research/slegen/

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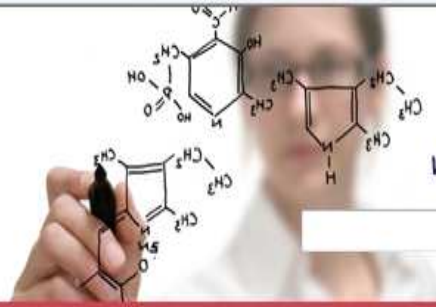
SLEGEN

Page

Alliance for Lupus Research

PREVENT. TREAT. CURE.



Leading the way to a cure

About Lupus | Lupus Research | News, Media & More | Events | Ways to Give | About The ALR

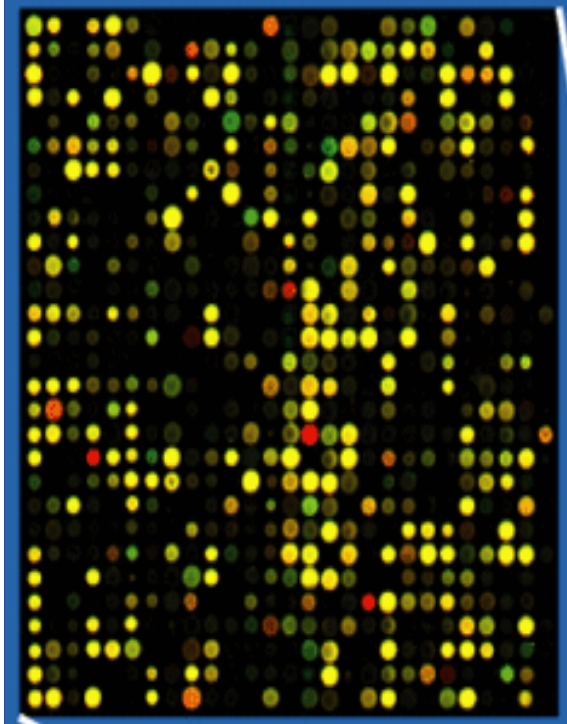
Research with results: SLEGEN

- SLEGEN HOME
- MEET THE RESEARCHERS
- ALR RESEARCH MODEL
- SLEGEN PROCESS
- PRESS ROOM

The ALR-funded International SLE Genetics (SLEGEN) Consortium research project has identified multiple genes linked to women with lupus. These findings set the stage for more studies that will eventually lead to earlier diagnosis and new treatments for this debilitating illness.

SLEGEN AT A GLANCE

- The Alliance for Lupus Research (ALR) founded the international research consortium in 2005.



Estudios de Asociación Genómica : GWAS

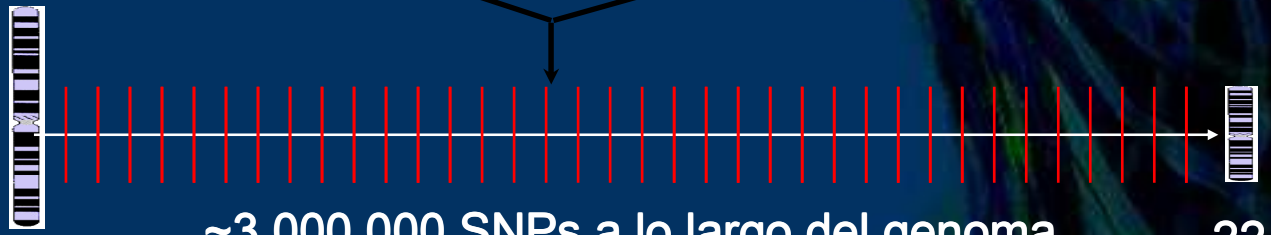
Genome Wide Association Studies

- Se basa en el análisis de gran cantidad de SNPs dispersos en todo el genoma, para determinar las variantes más frecuentes asociadas a enfermedad y/o aquellas consideradas factores de riesgo para la misma.

GWAS Asociación a todo el genoma

Población de pacientes
N=500

Población control
N=500

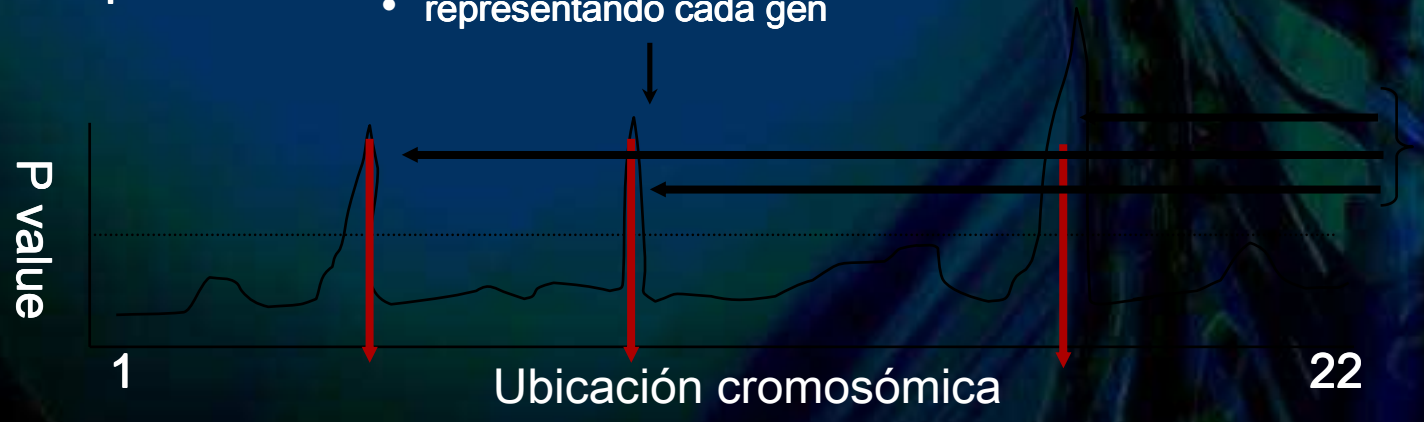


1

~3,000,000 SNPs a lo largo del genoma

- representando cada gen

22



Informática para ID genes mapeados y asociados al SNP

Estudios de asociación genómica en enfermedades

Descubrir y catalogar SNPs; construcción de haplotipos

Haplotypo# 1 2 3 4 5 ….

...100,000

Testear SNPs y haplotipos en asociación con enfermedad / condición

Diabetes

Hipertensión

Hipertrofia

Obesidad

Rta a drogas

Arterioesclerosis

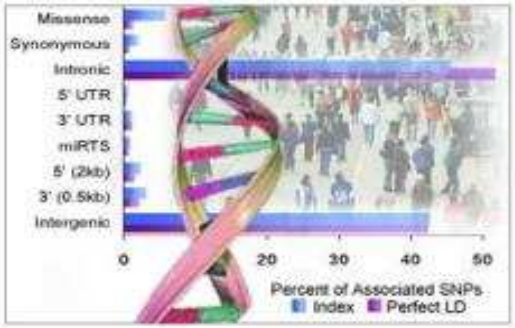
Falla cardíaca

Trombosis

Catálogo de Estudios GWAS

http://www.genome.gov/26525384

Online GWAS Catalog Helps Guide Disease Research



Researchers who want to sift through the biomedical literature to find genome-wide association results relevant to their research pursuits face an enormous challenge. But, thanks to the efforts of a dedicated team of National Human Genome Research Institute (NHGRI) scientists, they now have an online resource that can make the task a bit less daunting.

Genome-wide association studies, commonly called GWAS, efficiently scan markers across the DNA, or genomes, of large groups of people looking for variations between individuals with and without a health condition. Over the past few years, this approach has successfully plucked from our DNA code hundreds of the pesky one-letter genetic variations that contribute to the risk of common health conditions, such as obesity and Type 2 diabetes.

The recent deluge of GWAS results coming from these studies is exactly why NHGRI created a resource called A Catalog of Published Genome-Wide Association Studies. The catalog, which has been frequently cited in scientific publications, contains descriptive and association data on hundreds of published common genetic variations and their relationship with nearly 100 complex diseases and traits.

On a weekly basis, epidemiologists from NHGRI's Office of Population Genomics manually curate information from published GWAS and add them to the catalog. Researchers can search the catalog by journal name, first author, disease/trait, statistical significance of association and other categories. Data from the entire catalog can also be directly downloaded as an Excel spreadsheet.

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See Also:

Potential etiologic and functional implications of genome-wide association loci for human diseases and traits PDF
PNAS, May 18, 2009

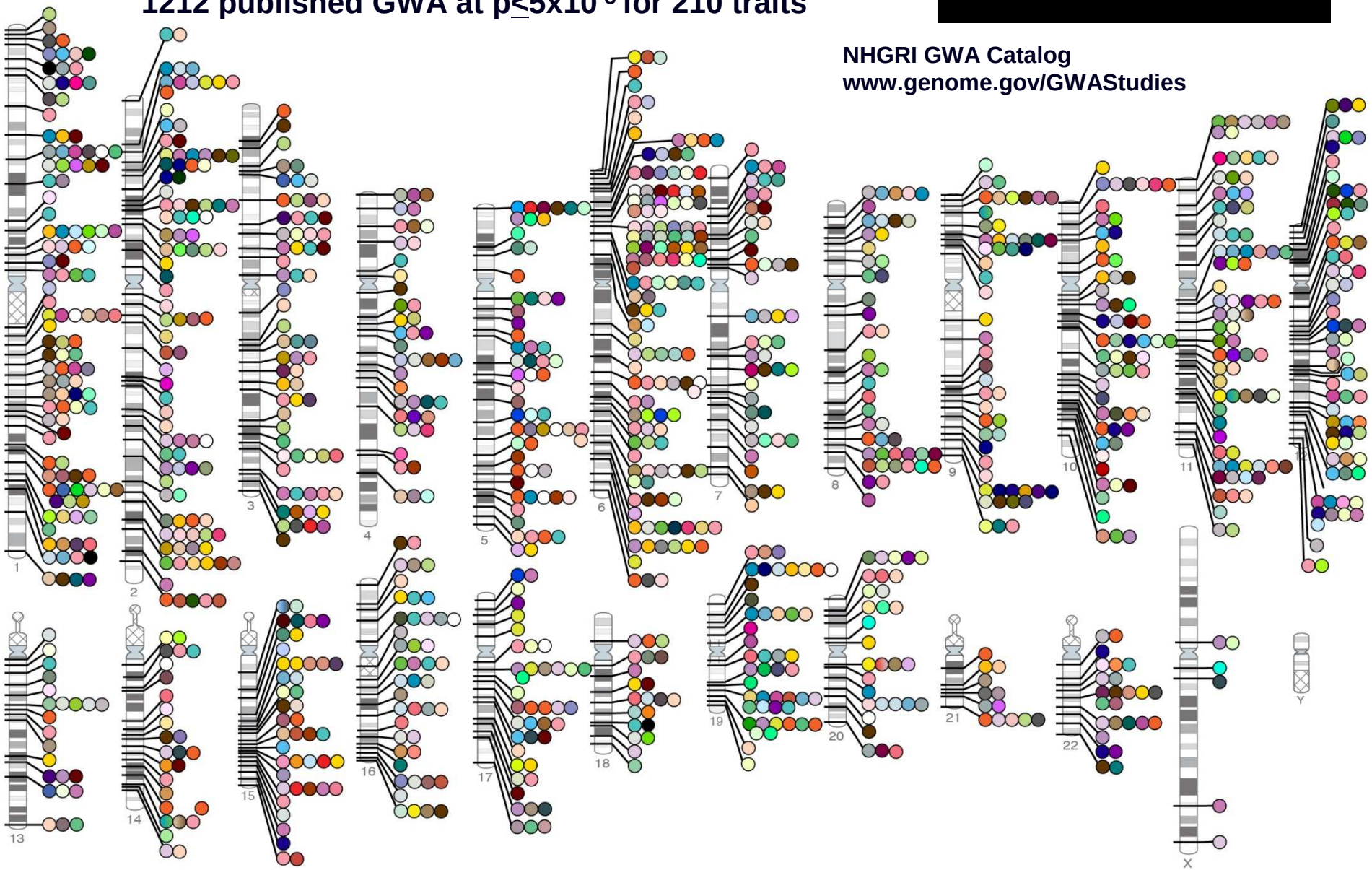
Keywords: what's this?

- GWAS
- catalog
- markers
- DNA
- genomes
- Office of Population Genomics
- OD News Features

Published Genome-Wide Associations through 12/2010, 1212 published GWA at $p \leq 5 \times 10^{-8}$ for 210 traits

[redacted]

NHGRI GWA Catalog
www.genome.gov/GWAStudies



En cada par cromosómico se indica la asociación con cada patología


Abdominal aortic aneurysm
Acute lymphoblastic leukemia
Adhesion molecules
Adverse response to carbamapezine
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alopecia areata
Alzheimer disease
Amyloid A levels
Amyotrophic lateral sclerosis
Angiotensin-converting enzyme activity
Ankylosing spondylitis
Arterial stiffness
Asparagus anosmia
Asthma
Atherosclerosis in HIV
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Behcet's disease
Bipolar disorder
Biliary atresia
Bilirubin
Bitter taste response
Birth weight
Bladder cancer
Bleomycin sensitivity
Blond or brown hair
Blood pressure
Blue or green eyes
BMI, waist circumference
Bone density
Breast cancer
C-reactive protein
Calcium levels
Cardiac structure/function
Carnitine levels
Carotenoid/tocopherol levels
Celiac disease
Cerebral atrophy measures
Chronic lymphocytic leukemia
Cleft lip/palate
Cognitive function
Conduct disorder
Colorectal cancer
Corneal thickness
Coronary disease
Creutzfeldt-Jakob disease
Crohn's disease
Cutaneous nevi
Dermatitis
Drug-induced liver injury
Endometriosis
Eosinophil count
Eosinophilic esophagitis
Erectile dysfunction and prostate cancer treatment
Erythrocyte parameters
Esophageal cancer
Essential tremor
Exfoliation glaucoma
Eye color traits
F cell distribution
Fibrinogen levels
Folate pathway vitamins
Follicular lymphoma
Fuch's corneal dystrophy
Freckles and burning
Gallstones
Gastric cancer
Glioma
Glycemic traits
Hair color
Hair morphology
Handedness in dyslexia
HDL cholesterol
Heart failure
Heart rate
Height
Hemostasis parameters
Hepatic steatosis
Hepatitis
Hepatocellular carcinoma
Hirschsprung's disease
HIV-1 control
Hodgkin's lymphoma
Homocysteine levels
Hypospadias
Idiopathic pulmonary fibrosis
IgA levels
IgE levels
Inflammatory bowel disease
Intracranial aneurysm
Iris color
Iron status markers
Ischemic stroke
Juvenile idiopathic arthritis
Keloid
Kidney stones
LDL cholesterol
Leprosy
Leptin receptor levels
Liver enzymes
Longevity
LP (a) levels
LpPLA(2) activity and mass
Lung cancer
Magnesium levels
Major mood disorders
Malaria
Male pattern baldness
Matrix metalloproteinase levels
MCP-1
Melanoma
Menarche & menopause
Meningococcal disease
Metabolic syndrome
Migraine
Moyamoya disease
Multiple sclerosis
Myeloproliferative neoplasms
N-glycan levels
Narcolepsy
Nasopharyngeal cancer
Neuroblastoma
Nicotine dependence
Obesity
Open angle glaucoma
Open personality
Optic disc parameters
Osteoarthritis
Osteoporosis
Otosclerosis
Other metabolic traits
Ovarian cancer
Pancreatic cancer
Pain
Paget's disease
Panic disorder
Parkinson's disease
Periodontitis
Peripheral arterial disease
Phosphatidylcholine levels
Phosphorus levels
Photic sneeze
Phytosterol levels
Platelet count
Polycystic ovary syndrome
Primary biliary cirrhosis
Primary sclerosing cholangitis
PR interval
Progranulin levels
Prostate cancer
Protein levels
PSA levels
Psoriasis
Psoriatic arthritis
Pulmonary funct. COPD
QRS interval
QT interval
Quantitative traits
Recombination rate
Red vs.non-red hair
Refractive error
Renal cell carcinoma
Renal function
Response to antidepressants
Response to antipsychotic therapy
Response to hepatitis C treat
Response to metaformin
Response to statin therapy
Restless legs syndrome
Retinal vascular caliber
Rheumatoid arthritis
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Ribavirin-induced anemia
Schizophrenia
Serum metabolites
Skin pigmentation
Smoking behavior
Speech perception
Sphingolipid levels
Statin-induced myopathy
Stroke
Systemic lupus erythematosus
Systemic sclerosis
T-tau levels
Tau AB1-42 levels
Telomere length
Testicular germ cell tumor
Thyroid cancer
Tooth development
Total cholesterol
Triglycerides
Tuberculosis
Type 1 diabetes
Type 2 diabetes
Ulcerative colitis
Urate
Venous thromboembolism
Ventricular conduction
Vertical cup-disc ratio
Vitamin B12 levels
Vitamin D insuffiency
Vitiligo
Warfarin dose
Weight
White cell count
YKL-40 levels

GWAS: enfermedades complejas

- Identificar un set óptimo de 300.000 SNPs
- 1.000 casos y 1.000 controles
- Genotipar todos los ADNs para esos SNPs
- 600 millones de genotipos
- En 2008, cada genotipo costaba $0.0010, con un monto de $600.000 para cada enfermedad.

ImmunoChip Home Page - Windows Internet Explorer

http://www.immunochip.nih.gov/

immunochip

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ImmunoChip Info

Home

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Presentations

Links

NCI Microarray Facility

Microarray Org

NCBI Mus Musculus UniGene

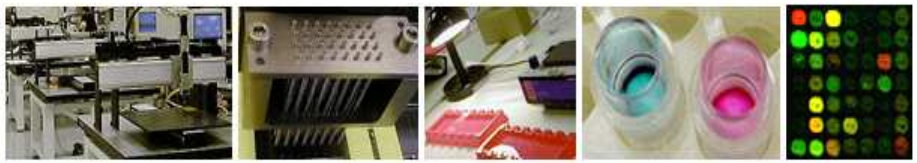
NCBI LocusLink

PubMed

NATIONAL CANCER INSTITUTE

ImmunoChip Homepage

- The Microarray for Mouse Immunology Research -



WELCOME to the ImmunoChip Homepage of the National Institutes of Health. The ImmunoChip was developed by Matthias Lorenz, Ph.D. (NCI) at the Advanced Technology Center of the National Cancer Institute. The project was initially sponsored by Edison Liu, MD and is now sponsored by Dinah Singer, Ph.D. (NCI). The ImmunoChip is a unique cDNA microarray specifically designed for **mouse immunology** research. The chip was constructed by developing and using a bioinformatics algorithm to select the best available clones representing more than 13000 different immunological gene clusters. The ImmunoChip allows the analysis of differential RNA expression between cells derived from mice or cell lines. The ImmunoChip is suitable for immunological experiments addressing questions in innate and adaptive basic immunology, tumor immunology, cancer biology of immune cells, aging, infection immunology, autoimmune diseases, allergy, and drug development against these diseases.

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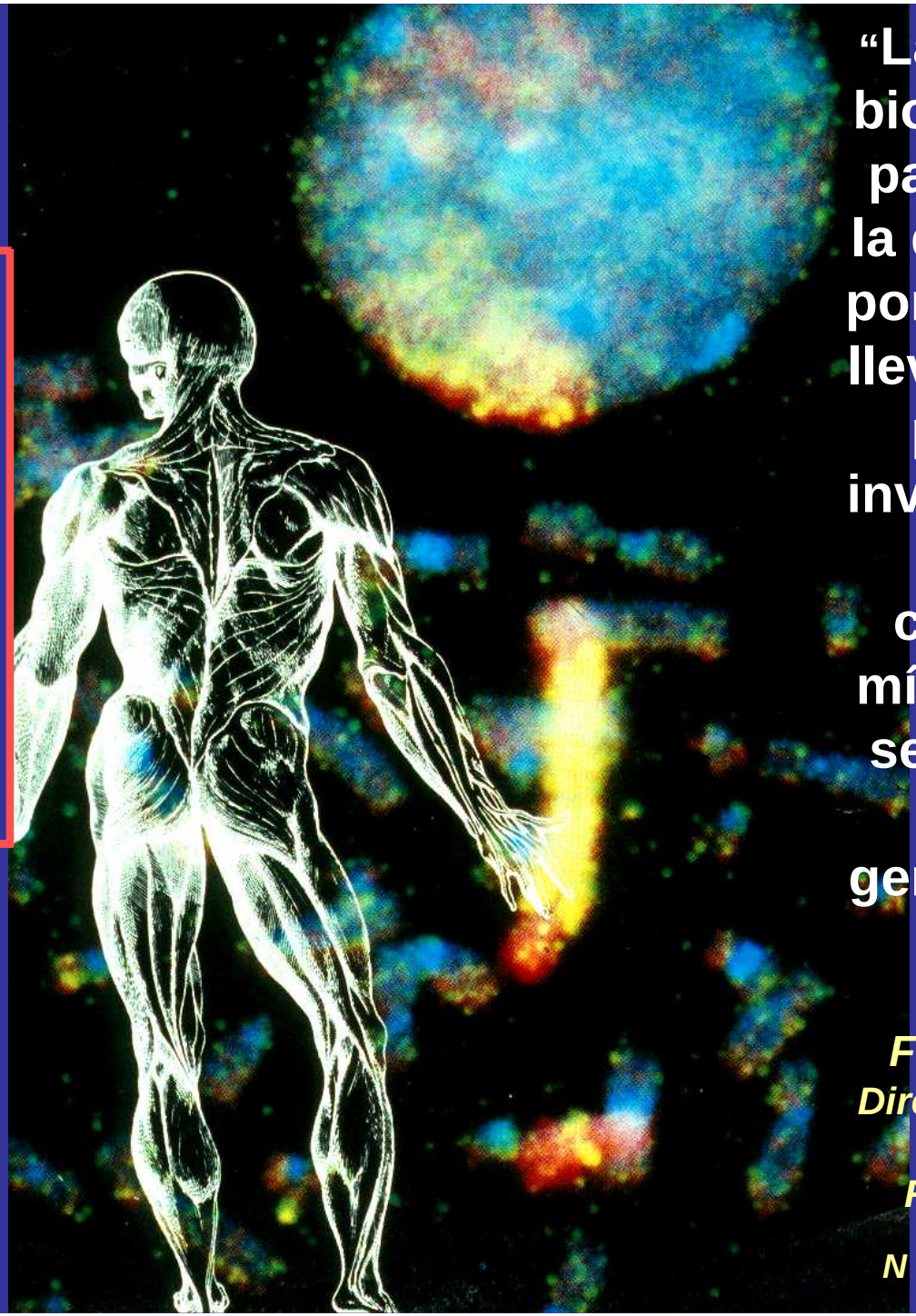
PROYECTO GENOMA HUMANO



“La historia de la biología se alteró para siempre en la década pasada por la decisión de llevar adelante un programa de investigación que permitió caracterizar al mínimo detalle el set completo de intrucciones genéticas del ser humano.”

Francis S. Collins
Director of the National Human Genome Research Institute

N EJ M 1999, 882:42-65


Milagros de la
ingeniería genética