

Influence des Facteurs Génétiques sur le

Risque Infectieux et la Réponse Inflammatoire

DURPI 2020-2021

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Groupe Hospitalier Paris Centre – CHU Cochin – APHP - Paris**

Disclosures

- **None**

We Are All Zebras:

How Rare Disease Is Shaping the Future of Healthcare

"When you hear hoofbeats, think of horses, not zebras," Dr. Woodward told his medical interns in the 1940s to teach them the art of diagnosis. **That was then. This is now. Now there's precision medicine**, a revolution in healthcare based on the rare disease model. Precision medicine sees the zebra in all of us and focuses not on what makes you part of the herd, but what makes you unique.





Recurrent Purpura Fulminans

15 yo girl admitted in ICU

- Temperature 40° C; HR 125; BP 74/45; RR 38
- Meningitis with purpura fulminans
- MOF (Shock, ARDS, ARF, DIC, Lactic acidosis)
- Meningococcus type N in the skin biopsy
- Survival with multiple finger amputations and skin grafting
- 6 months hospitalization

Un an plus tard:

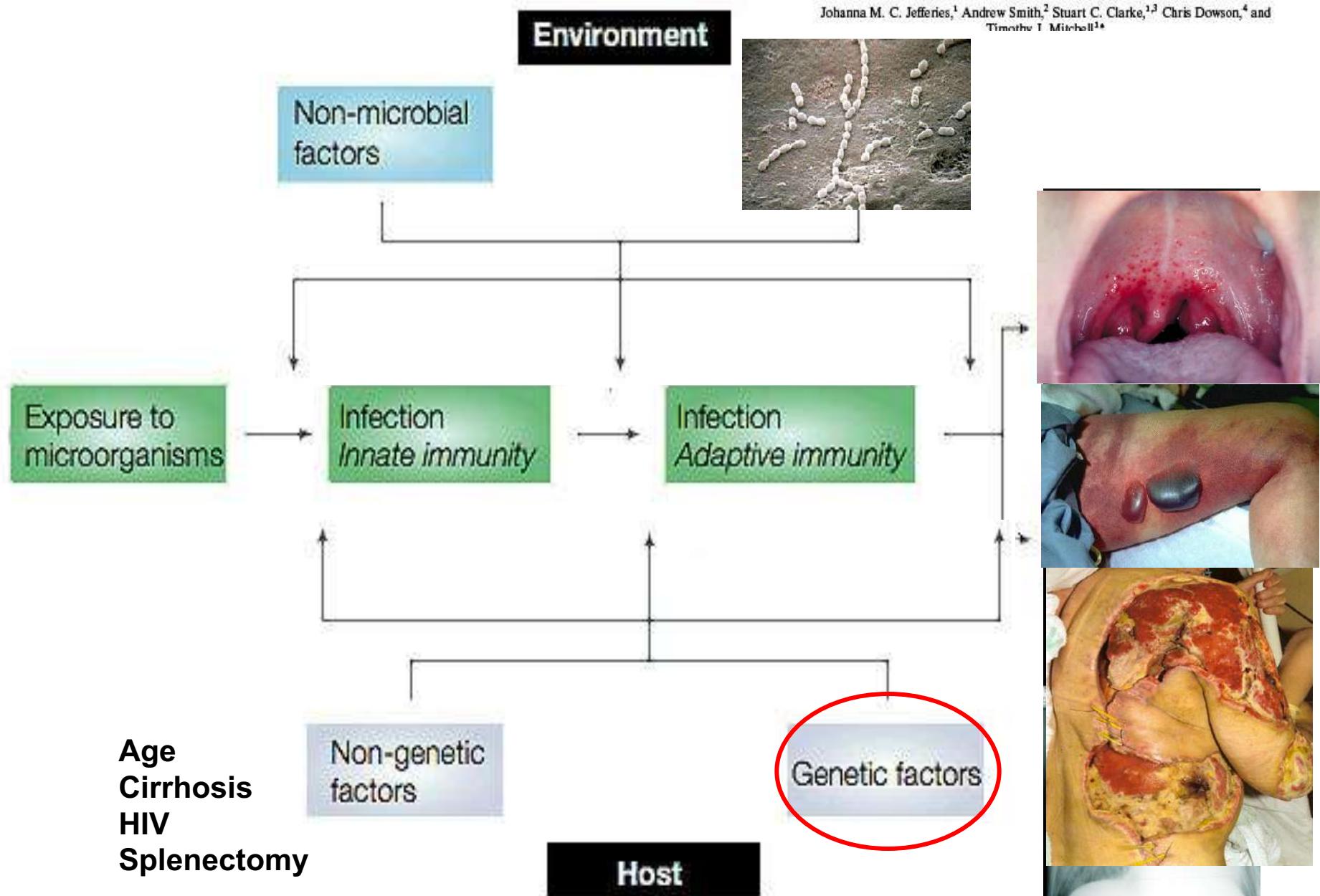
- Temperature 39° C; HR 125; BP 83/48; RR: 33
- Meningitis with purpura fulminans
- Lumbar puncture → meningococcus type Y
- Shock and DIC
- Survival with new skin grafting
- 3 months hospitalization

PLEASE MAKE THIS
PRODUCTION



Genetic Analysis of Diverse Disease-Causing Pneumococci Indicates High Levels of Diversity within Serotypes and Capsule Switching

Johanna M. C. Jefferies,¹ Andrew Smith,² Stuart C. Clarke,^{1,3} Chris Dowson,⁴ and Timothy I. Mitchell^{1*}



Host Genetics and Infectious Diseases

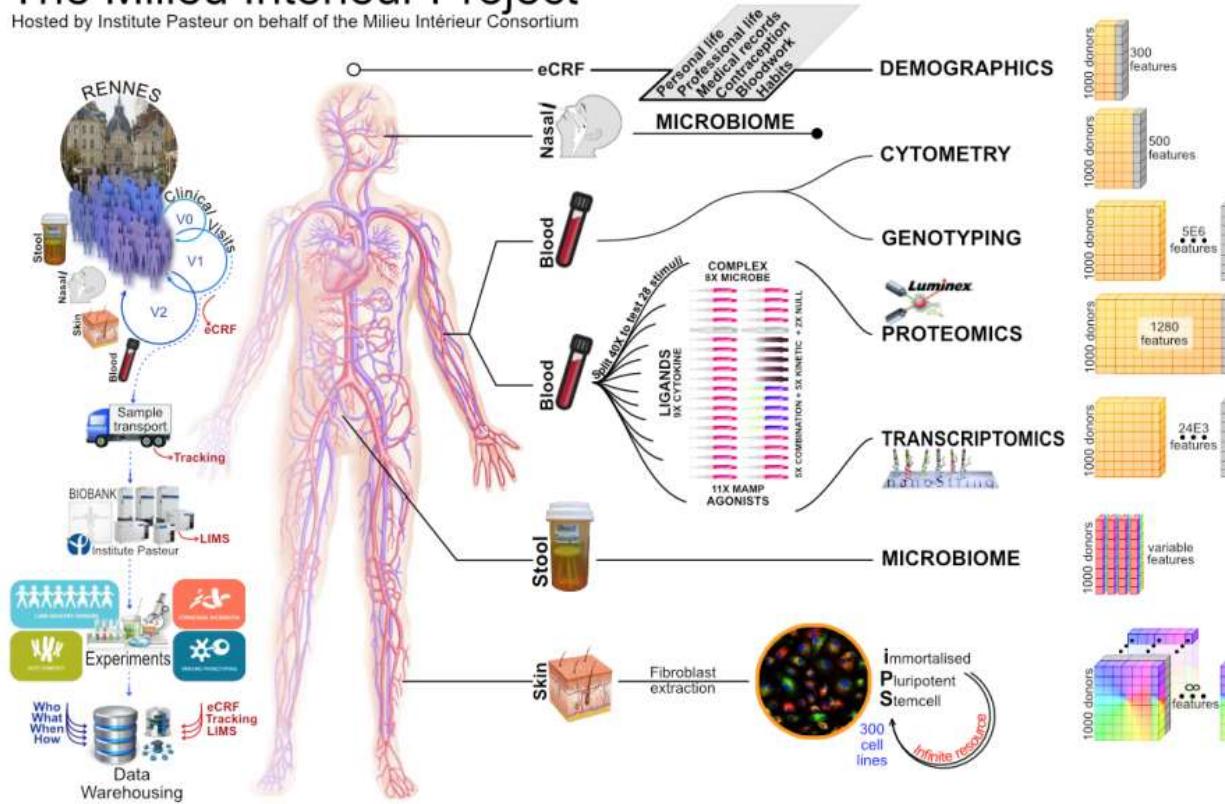
- **Infectious diseases are a major selective force in human evolution**
- **Many exposed to infection; few develop disease**
- **Host defense genes are more diverse than any other genes**
- **Human immune response genes more polymorphic than any other species**

A Functional Genomics Approach to Understand Variation in Cytokine Production in Humans



The Milieu Intérieur Project

Hosted by Institut Pasteur on behalf of the Milieu Intérieur Consortium



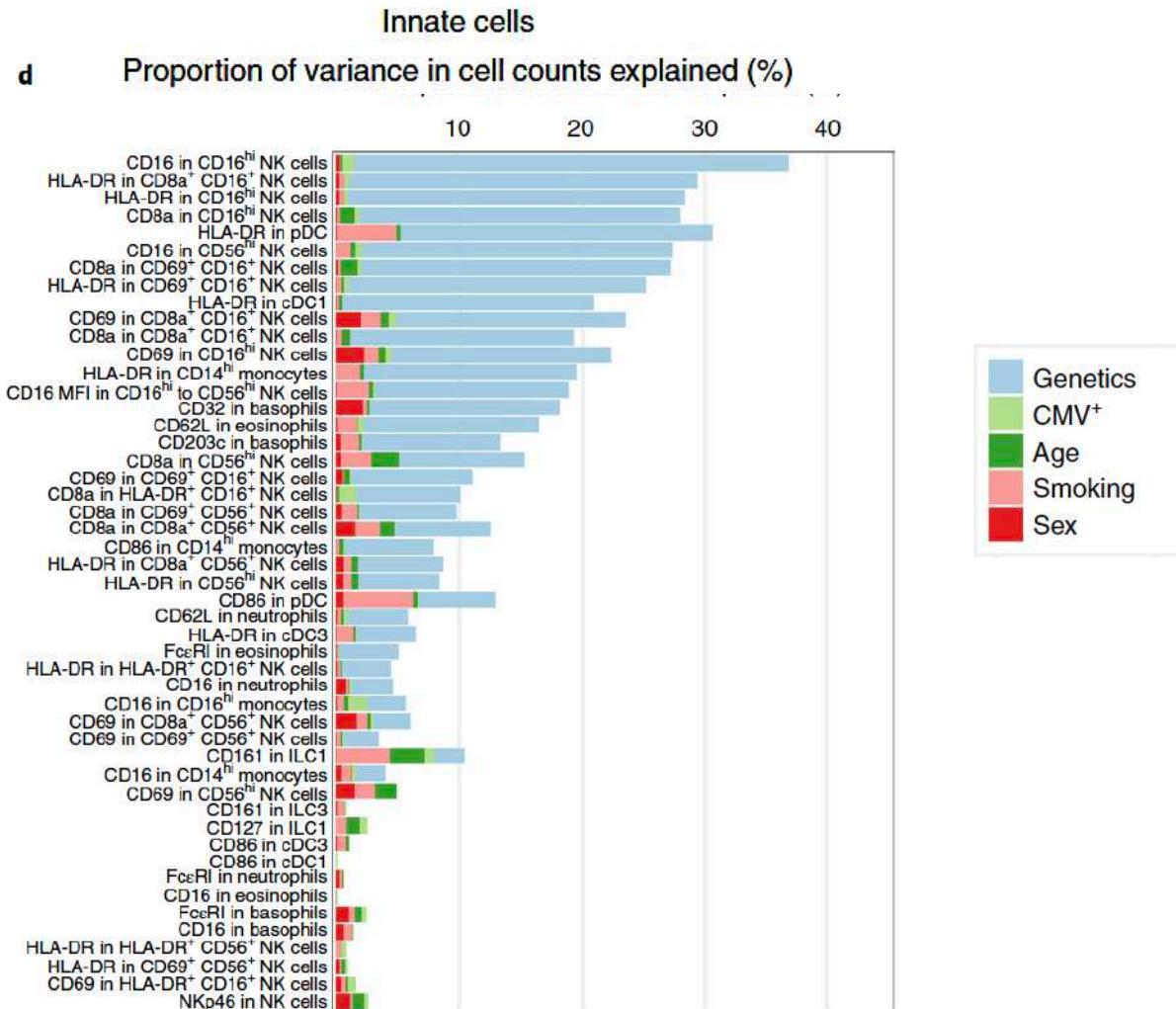
Natural variation in the parameters of innate immune cells is preferentially driven by genetic factors

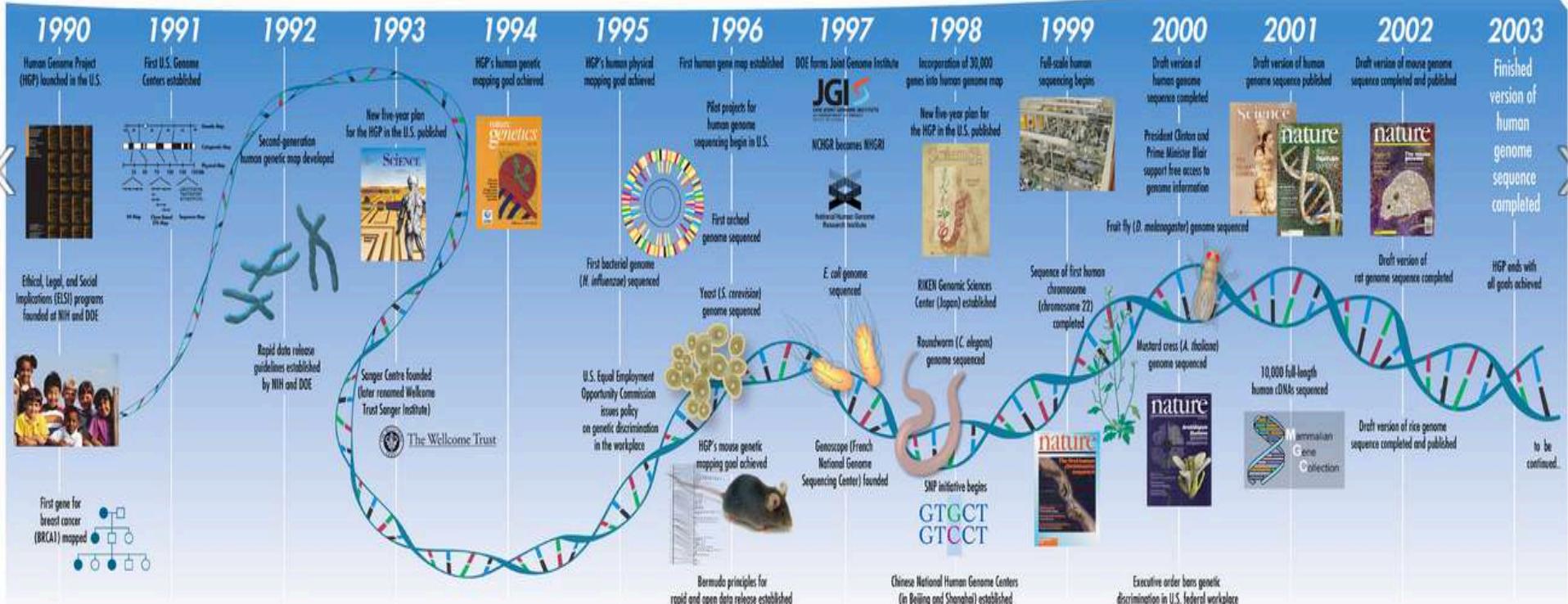
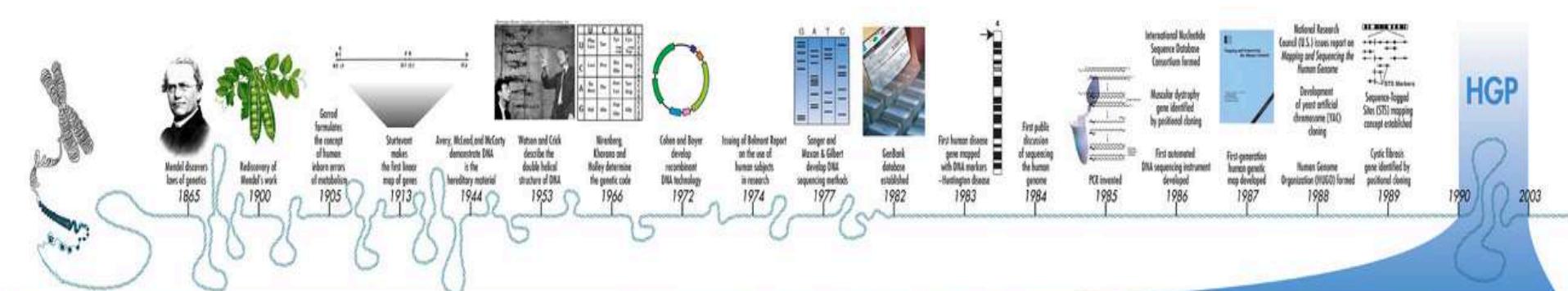
**1,000 healthy, unrelated people of Western European ancestry.
Flow cytometry of blood leukocytes and genome-wide DNA genotyping
(<http://milieu-interieur.cytogwas.pasteur.fr/>)**

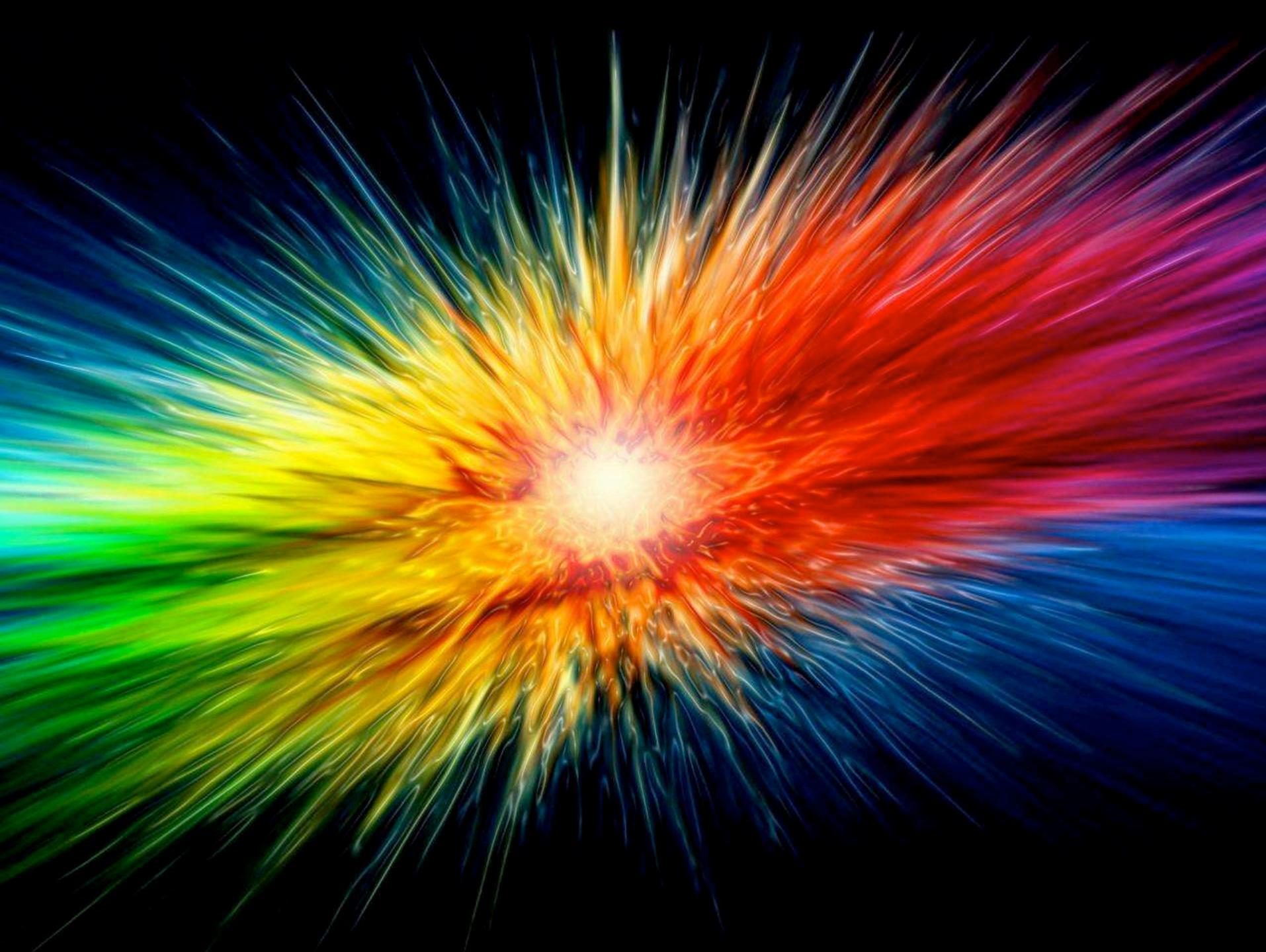
Adaptative immunity mainly influenced by

- Age**
- Sex**
- Tabacco status**
- Latent CMV infection**

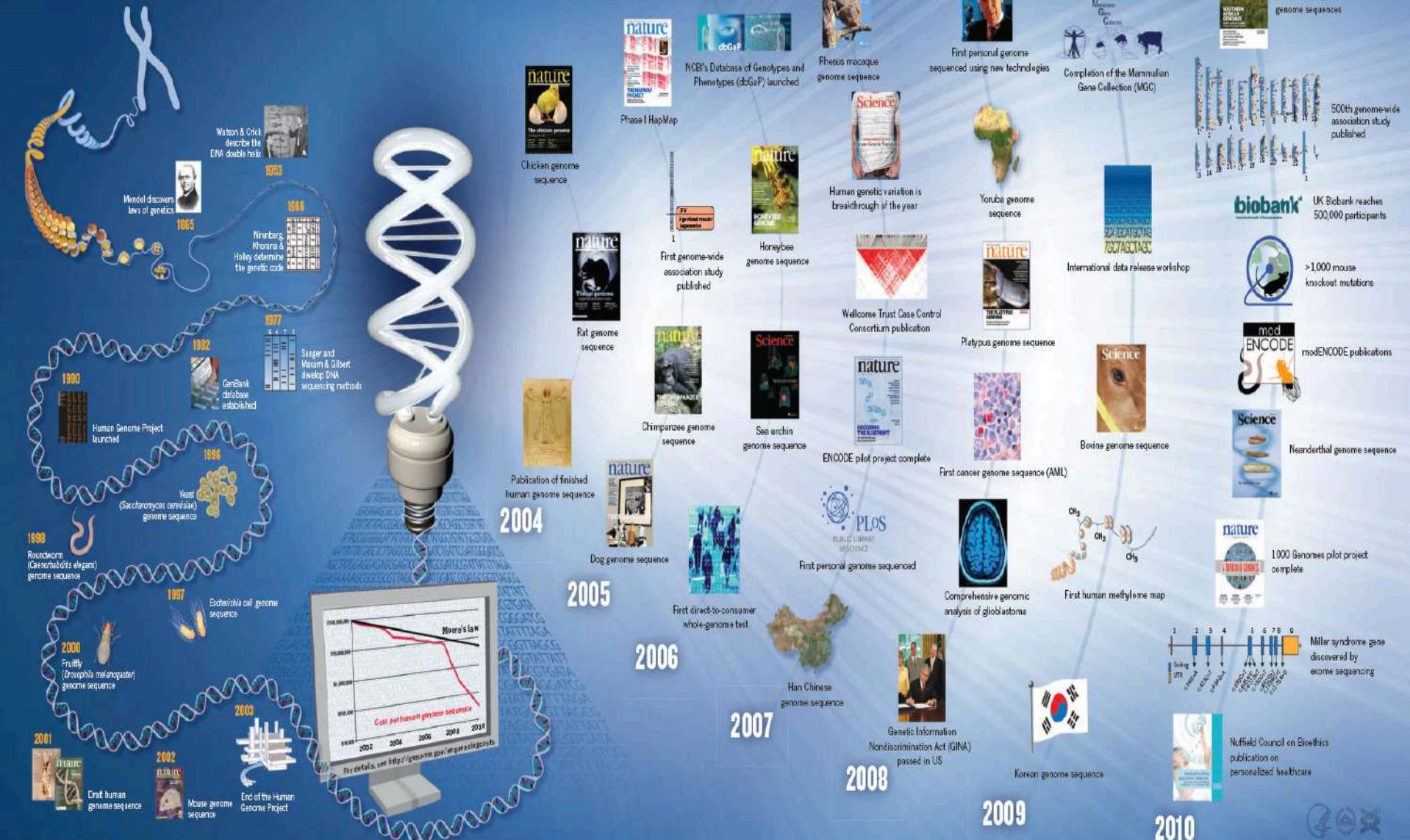
Natural variation in the parameters of innate immune cells is preferentially driven by genetic factors

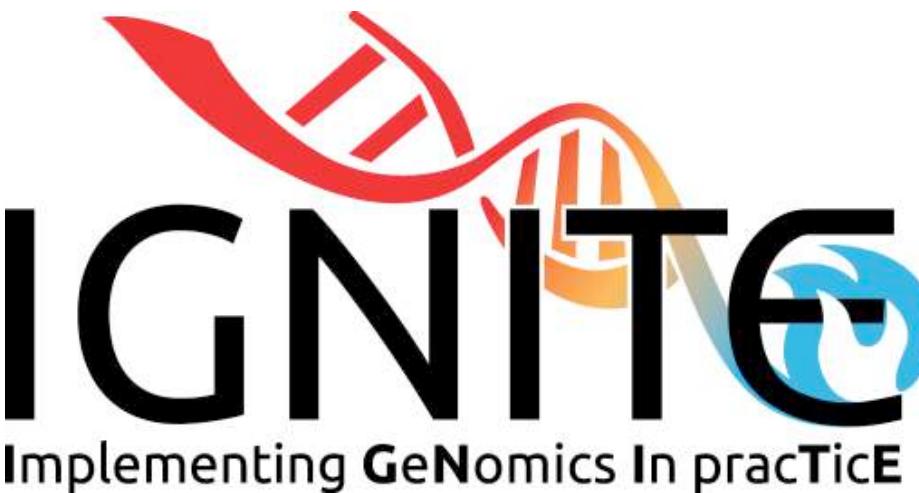
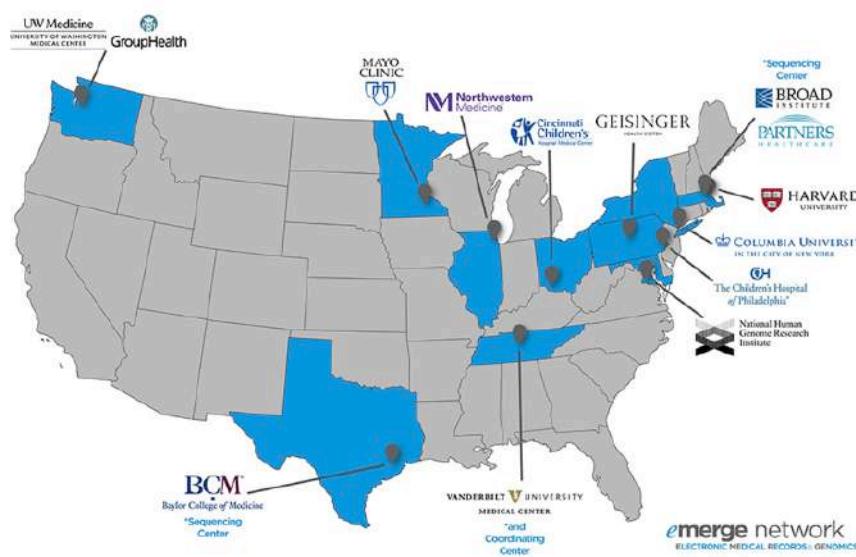






Genomic achievements since the Human Genome Project





The NIH site will continue to enroll about 150 patients per year, each of the clinical sites will ultimately enroll about 50 patients per year.

1000 Genomes

Mapping Human Genetic Variation



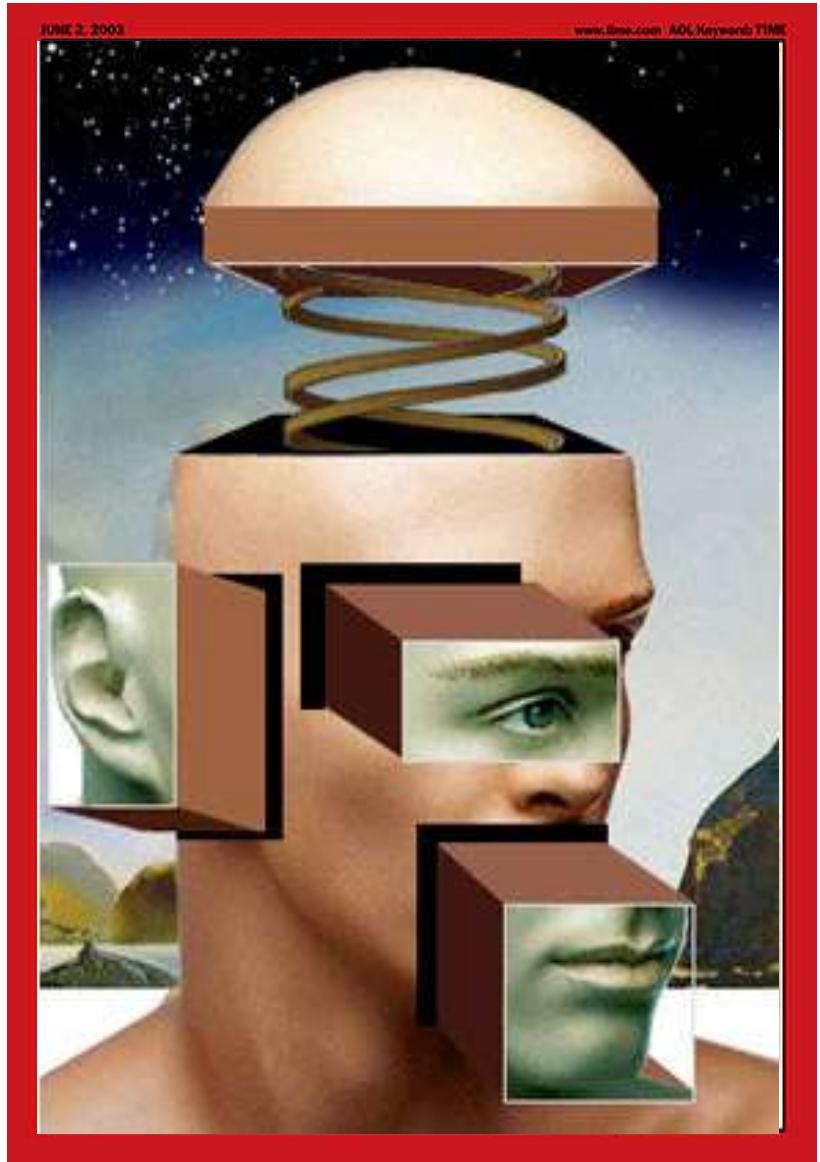
Differences Between Two Humans = 4MB



Basic features of the Human genome

Basic features of the Human genome

Nucleotides in the genome	3.2×10^9
Protein-coding genes in the genome	23,500
DSVs	4×10^6
SNPs	3.5×10^6
nsSNPs	10,000
SV/CNVs	$10^3\text{--}10^5$
Variants known to be associated with inherited diseases	50–100
De novo variants	30



Biodiversity: 0,1% of whole genome

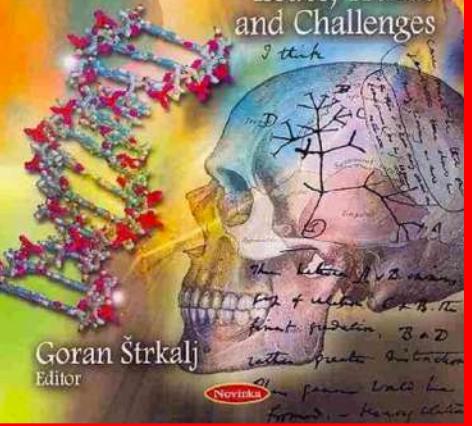
HUMAN BIOLOGICAL VARIATION

- James H. Mielke • Lyle W. Konigsberg • John H. Relethford -



TEACHING HUMAN VARIATION

Issues, Trends
and Challenges



Goran Štrkalj
Editor

Human Biological Variation

JAMES H. MIELKE • LYLE W. KONIGSBERG • JOHN H. RELETHFORD



OXFORD
UNIVERSITY PRESS

Second Edition

INVESTIGATING THE HUMAN GENOME

INSIGHTS INTO HUMAN VARIATION
AND DISEASE SUSCEPTIBILITY

MOYRA SMITH

INVESTIGATING THE HUMAN GENOME

INSIGHTS INTO HUMAN VARIATION
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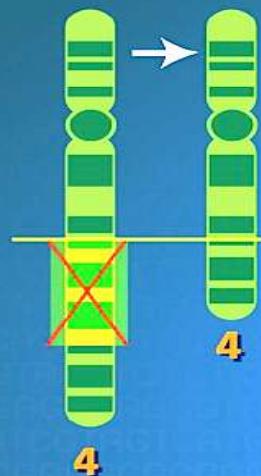
MOYRA SMITH



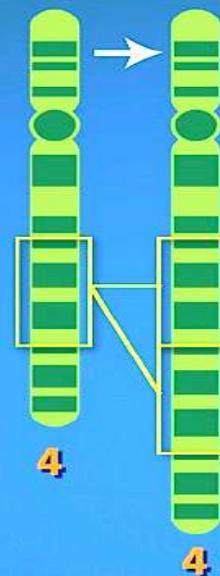
CHROMOSOME ABNORMALITIES

NHGRI FACT SHEETS
genome.gov

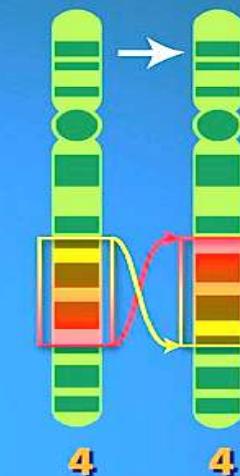
Deletion



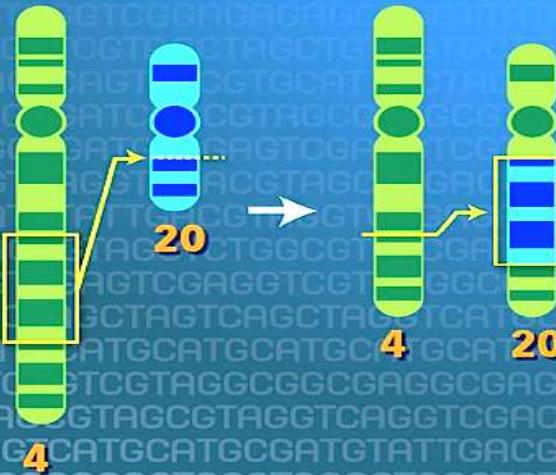
Duplication



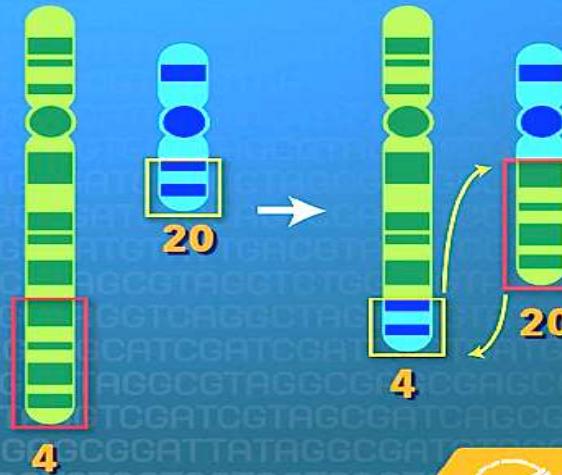
Inversion



Substitution



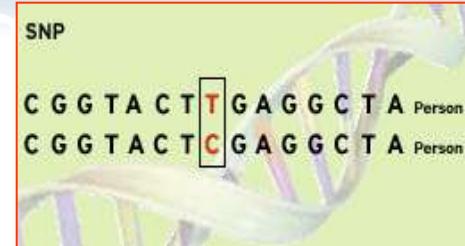
Translocation



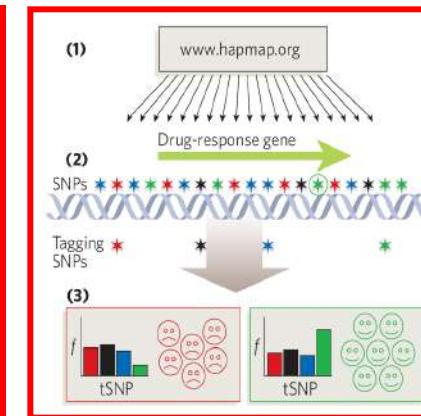
National Human Genome Research Institute

Genetic Variants

- Genetic Polymorphisms
Mars 2003



- Haplotypes
Oct 2005



- Insertion-deletion
Juin 2006

Resource

An initial map of insertion and deletion (INDEL) variation in the human genome

Ryan E. Mills,^{1,2} Christopher T. Lutting,¹ Christine E. Larkins,³ Adam Beauchamp,⁴ Circe Tsui,^{1,2} W. Stephen Pittard,^{2,5} and Scott E. Devine^{1,2,3,4,6}

The PIRO concept: P is for predisposition

Derek C Angus¹, David Burgner², Richard Wunderink³, Jean-Paul Mira⁴, Herwig Gerlach⁵, Christian J Wiedermann⁶ and Jean-Louis Vincent⁷

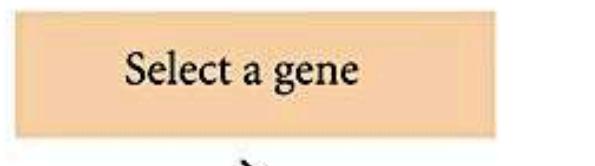
Critical Care 2003, 7:248-251 (DOI 10.1186/cc2193)



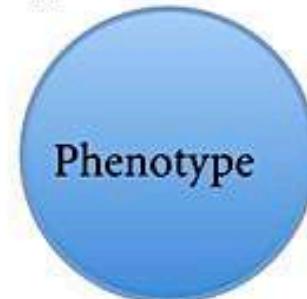




Reverse Genetics



Generate a null mutant
of the gene



Forward Genetics

Identify gene(s)
causing the phenotype

Screen a collection
of mutants





S. pneumoniae

Fighting *S. Pneumoniae*: Candidate Genes !

One phenotype may be due to different genotypes

Rajaa Sominen,^a Karl Tryggvason,^a and Lester KOBZIK^{b,c}

Patrice O. Fallon,^a and Andrew F. J. MacKenzie^c



Despite the complexity of the immune defense, one missing element may have dramatic clinical consequences

Time Post-infection (days)

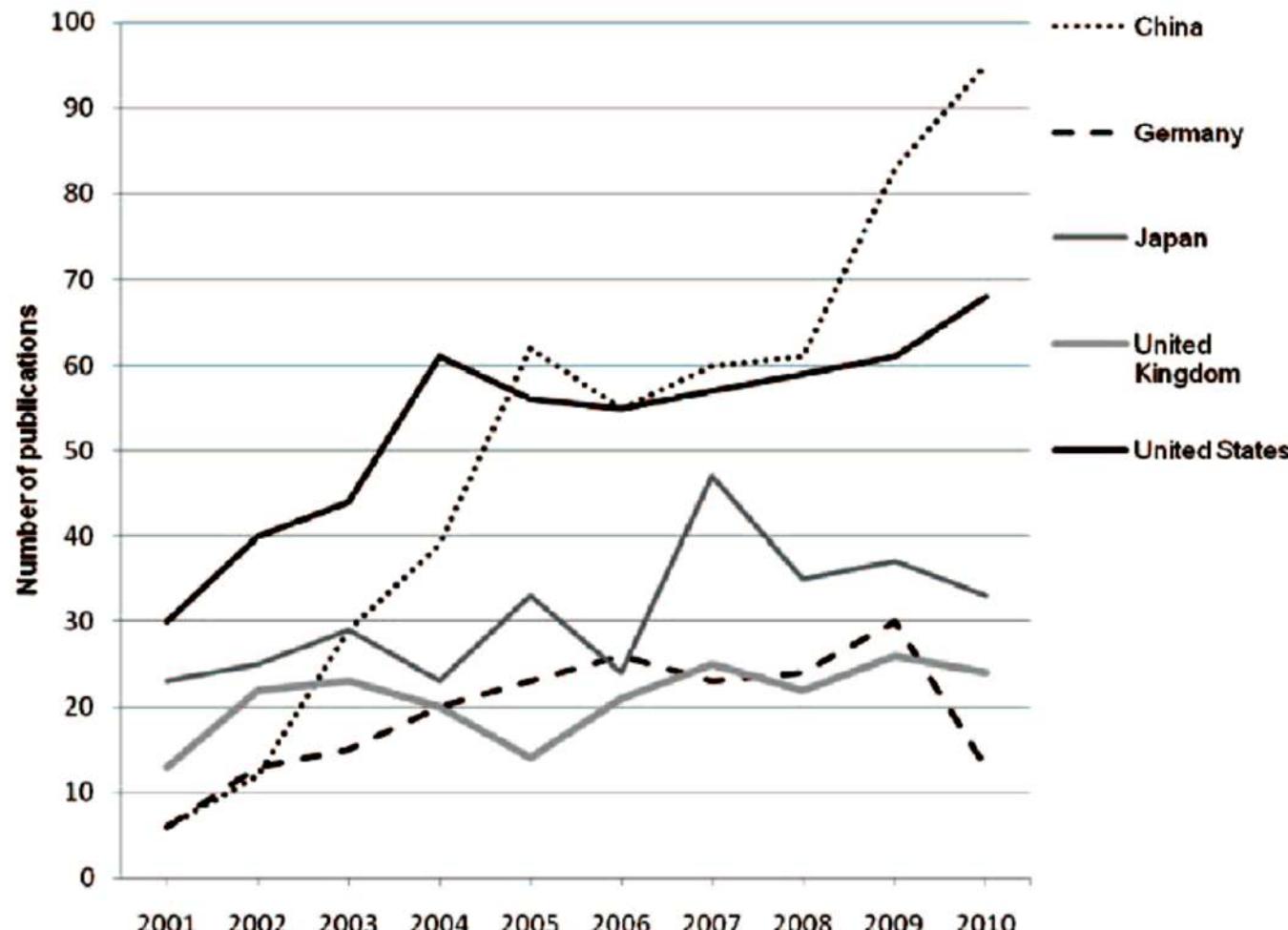
0 50 100 150
Hours post-inoculation



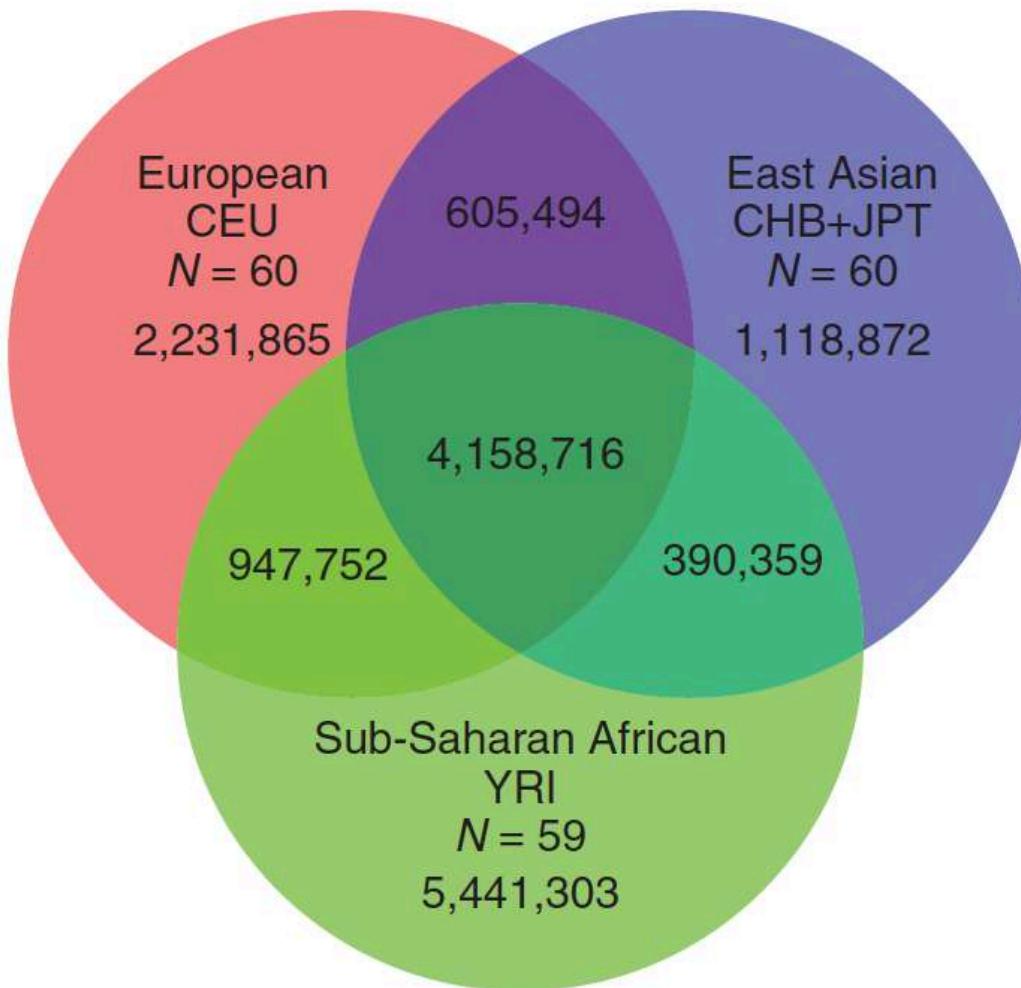


Trends in Population-Based Studies of Human Genetics in Infectious Diseases

Countries with the largest numbers of infectious disease-related publications in HUGE

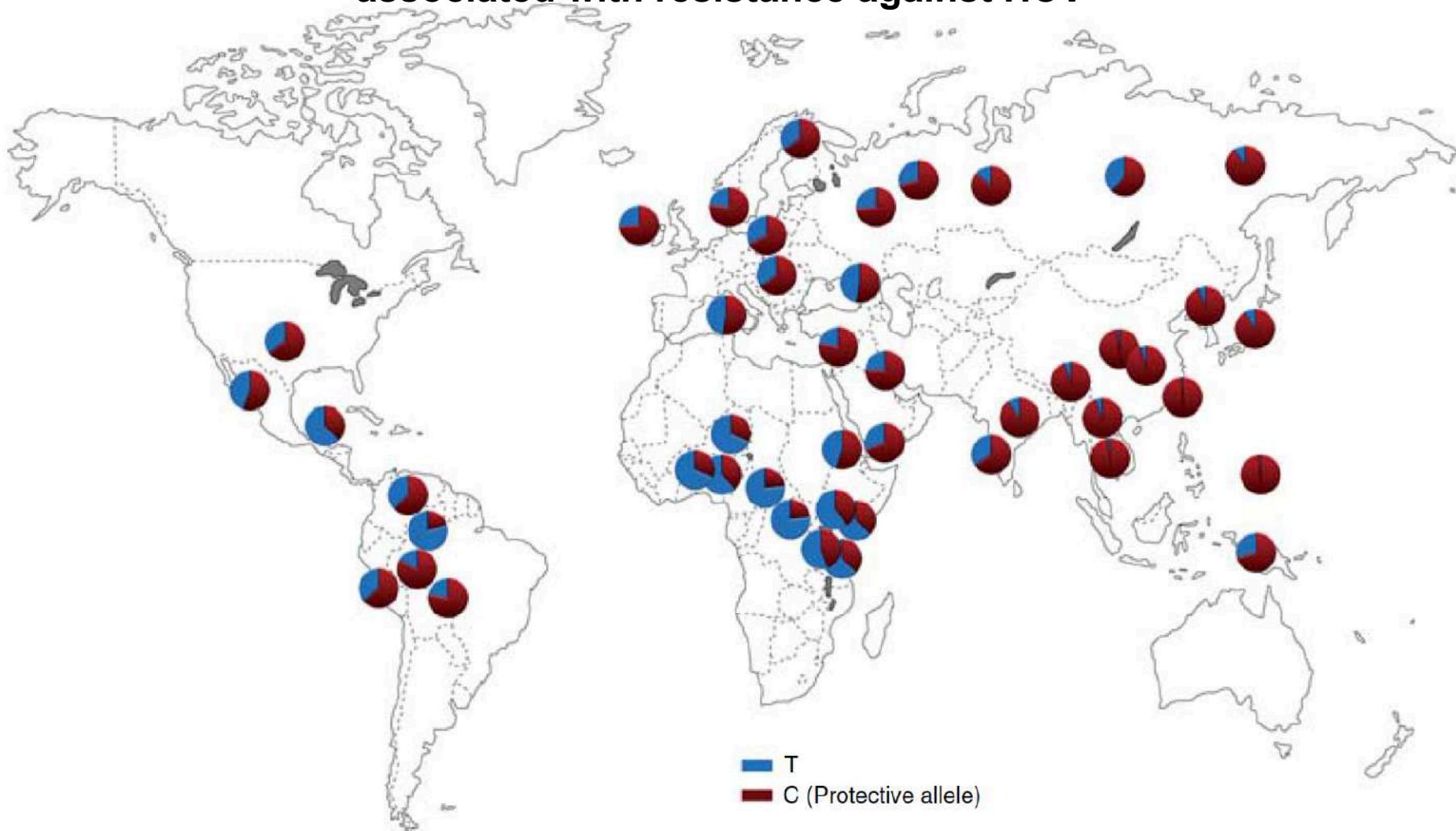


A Genome-Wide Perspective of Human Diversity and Its Implications in Infectious Disease



A Genome-Wide Perspective of Human Diversity and Its Implications in Infectious Disease

Population distribution of the IL28B rs 12979860 C allele associated with resistance against HCV



Evidences for a genetic component to sepsis

Animal Studies

- Susceptibility/resistance to certain infection in mice
- Susceptibility/resistance phenotypes of knockout mice

Human Studies

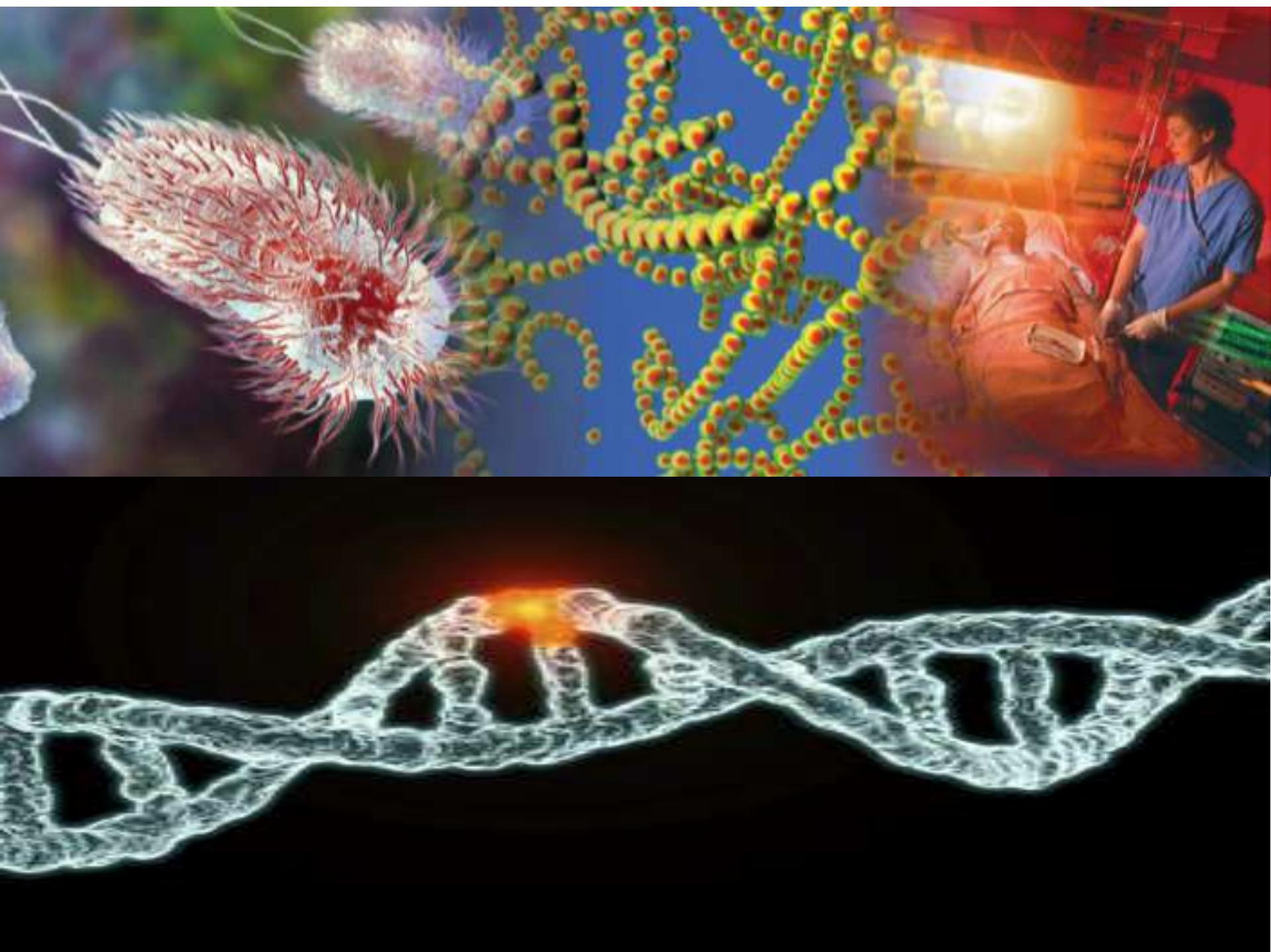
- Twin Studies
- Clinical Evidences
- Ethnic Differences
- Adoptee Studies





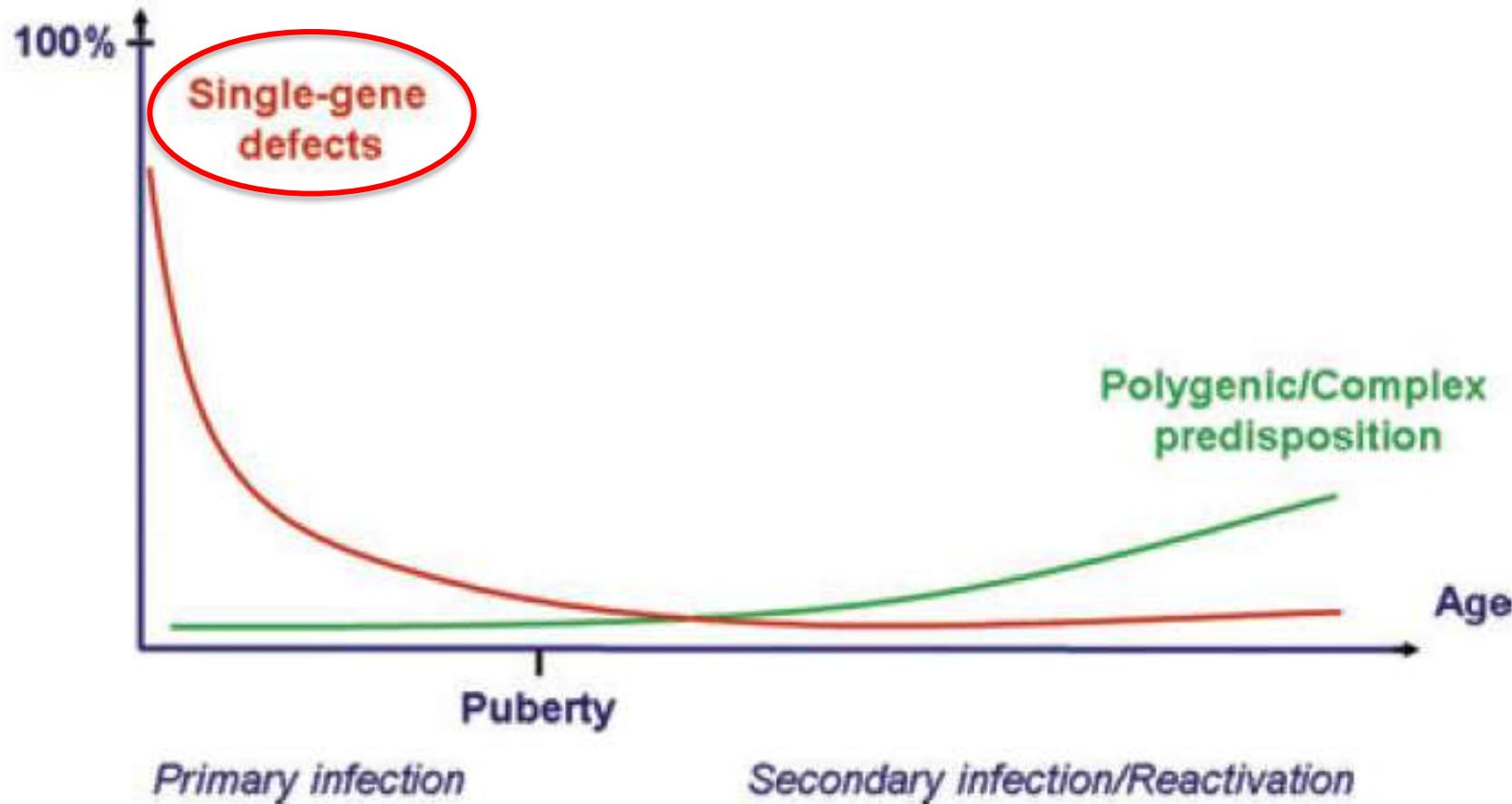
Genetic and environmental influences on premature death in adult adoptees

Cause of Death (Parent Dead before the age of 50)	Relative risk for the adoptee to die from the same cause
All causes	
Biologic	1.71
Adoptive	0.71
Infection	
Biologic	5.8
Adoptive	0.73
Vascular	
Biologic	4.5
Adoptive	3.1



Life-threatening infectious diseases of childhood: single-gene inborn errors of immunity?

Genetic cases of life-threatening infections



Primary immunodeficiencies associated with pneumococcal disease

Capucine Picard^{a,b}, Anne Puel^b, Jacinta Bustamante^b, Cheng-Lung Ku^b and Jean-Laurent Casanova^{a,b}

Inherited disorders of NF-κB-mediated immunity in man

Anne Puel¹, Capucine Picard^{1,2}, Cheng-Lung Ku¹, Asma Smahi³ and Jean-Laurent Casanova^{1,2,4}

GENETIC DISSECTION OF IMMUNITY TO MYCOBACTERIA: The Human Model

Primary immunodeficiencies of protective immunity to primary infections

Aziz Bousfiha^a, Capucine Picard^{b,c}, Stéphanie Boisson-Dupuis^{c,d},

Genetic deficiencies of innate immune signalling in human infectious disease

[View abstract](#) [View full article](#)

TLR3 Deficiency in Patients with Herpes Simplex Encephalitis

Shen-Ying Zhang,^{1,2,3} Emmanuelle Jouanguy,^{1,2,3} Sophie Ugolini,⁴ Asma Smahi,⁵

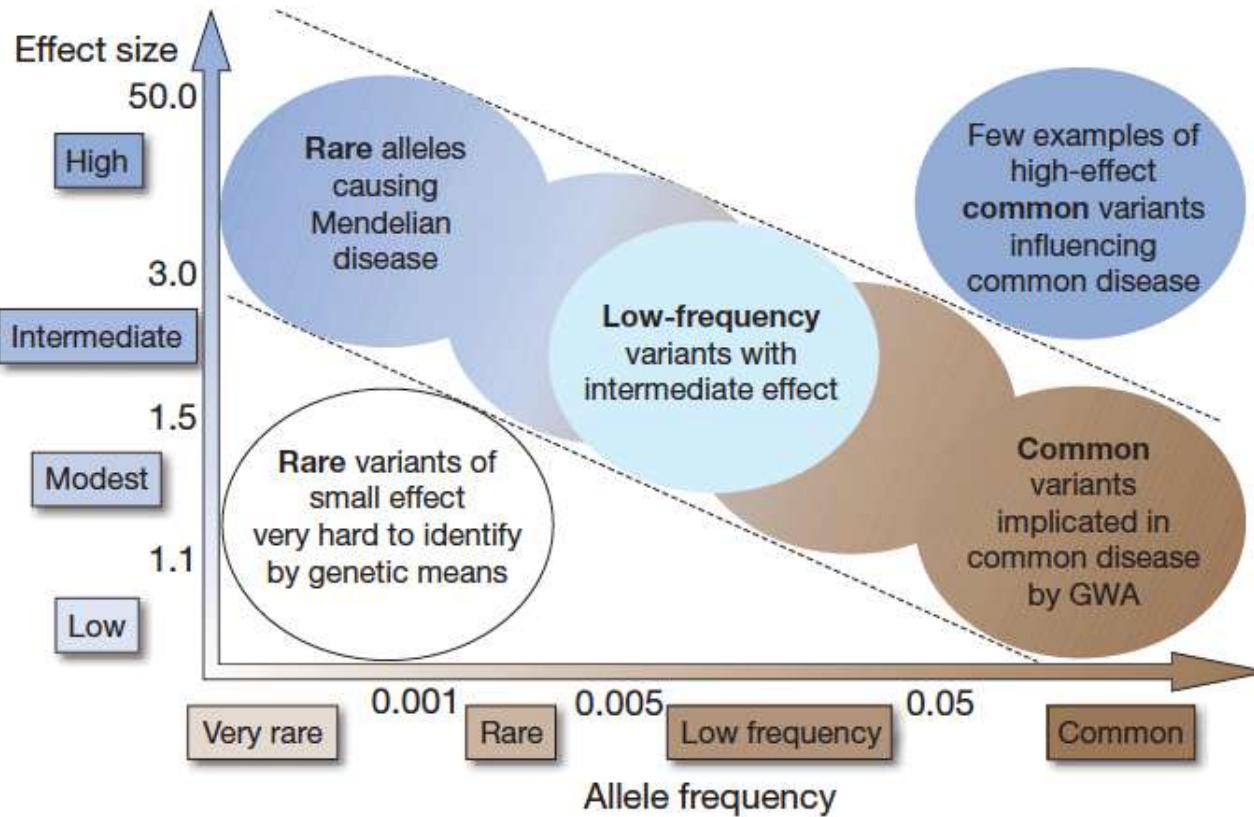
Life-threatening infectious diseases of childhood: single-gene inborn errors of immunity?

Alexandre Alcaïs,^{1,2} Lluis Quintana-Murci,³ David S. Thaler,⁴ Erwin Schurr,⁵ Laurent Abel,^{1,2}

Immunodeficiency and Genetic Defects of Pattern-Recognition Receptors

Mihai G. Netea, M.D., Ph.D., and Jos W.M. van der Meer, M.D., Ph.D.

Finding the missing heritability of complex diseases

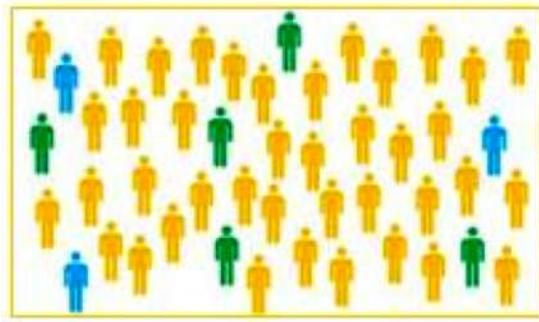


Research strategies:

- SNPs
- GWAs
- Sequencing studies

How to choose candidate genes?

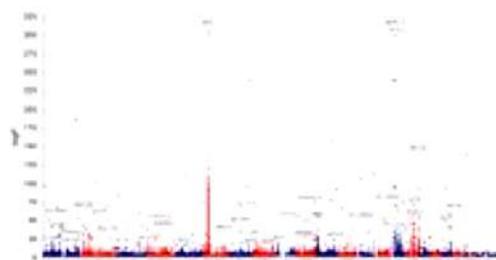
General Population



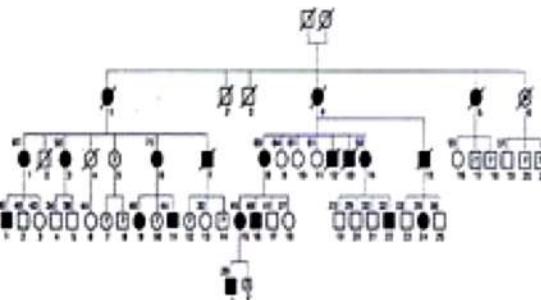
Controls and Cases



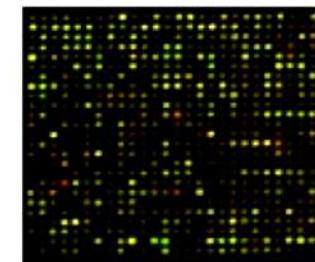
Genome-Wide Association Studies



Linkage Studies



Microarrays



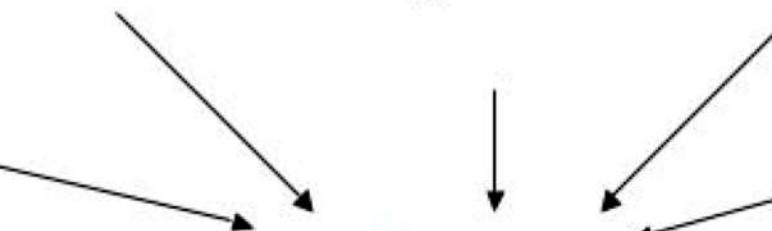
Litterature



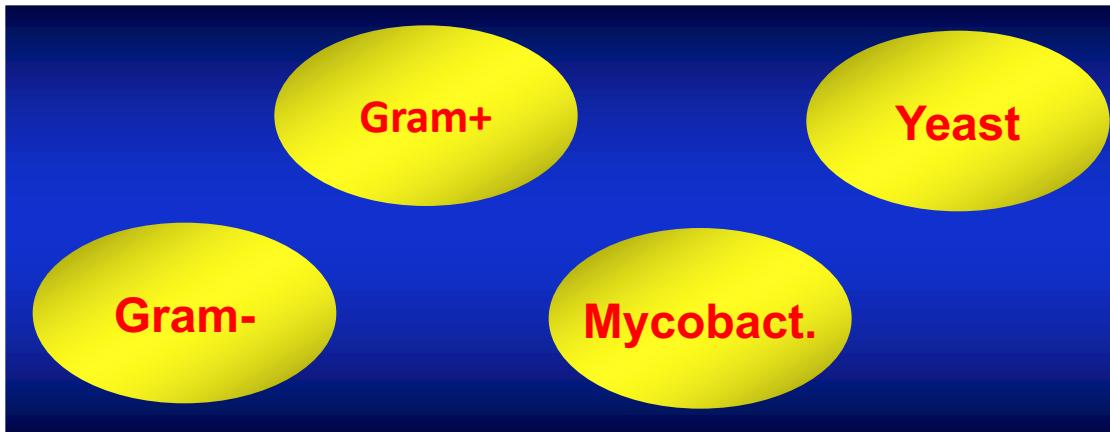
Other Related Diseases



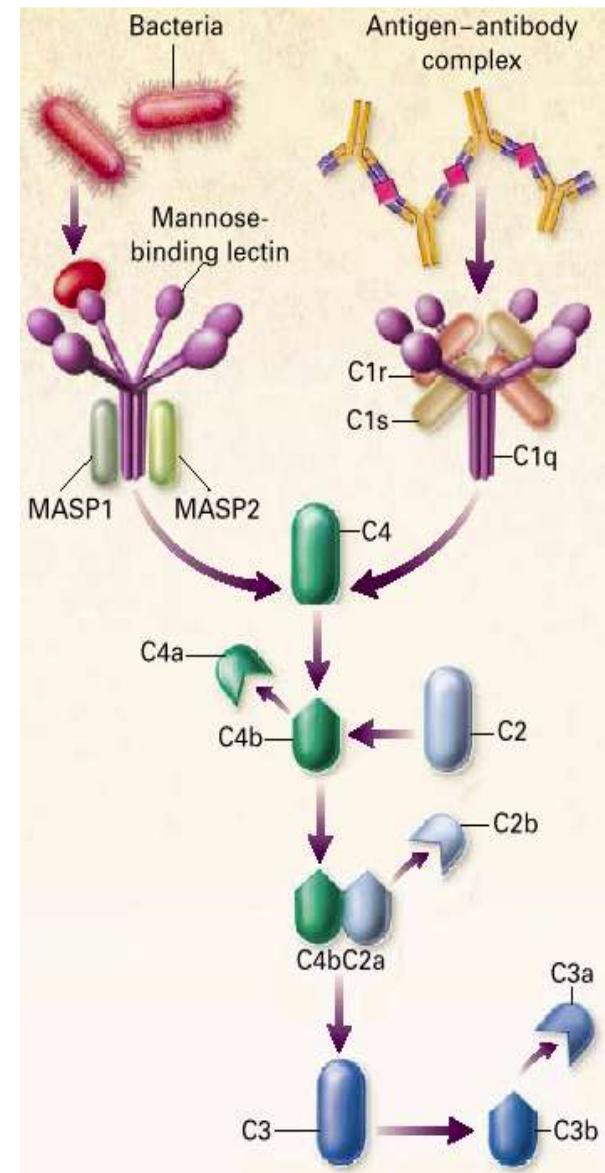
Gene and Variants Selection



Mannose-Binding Lectin

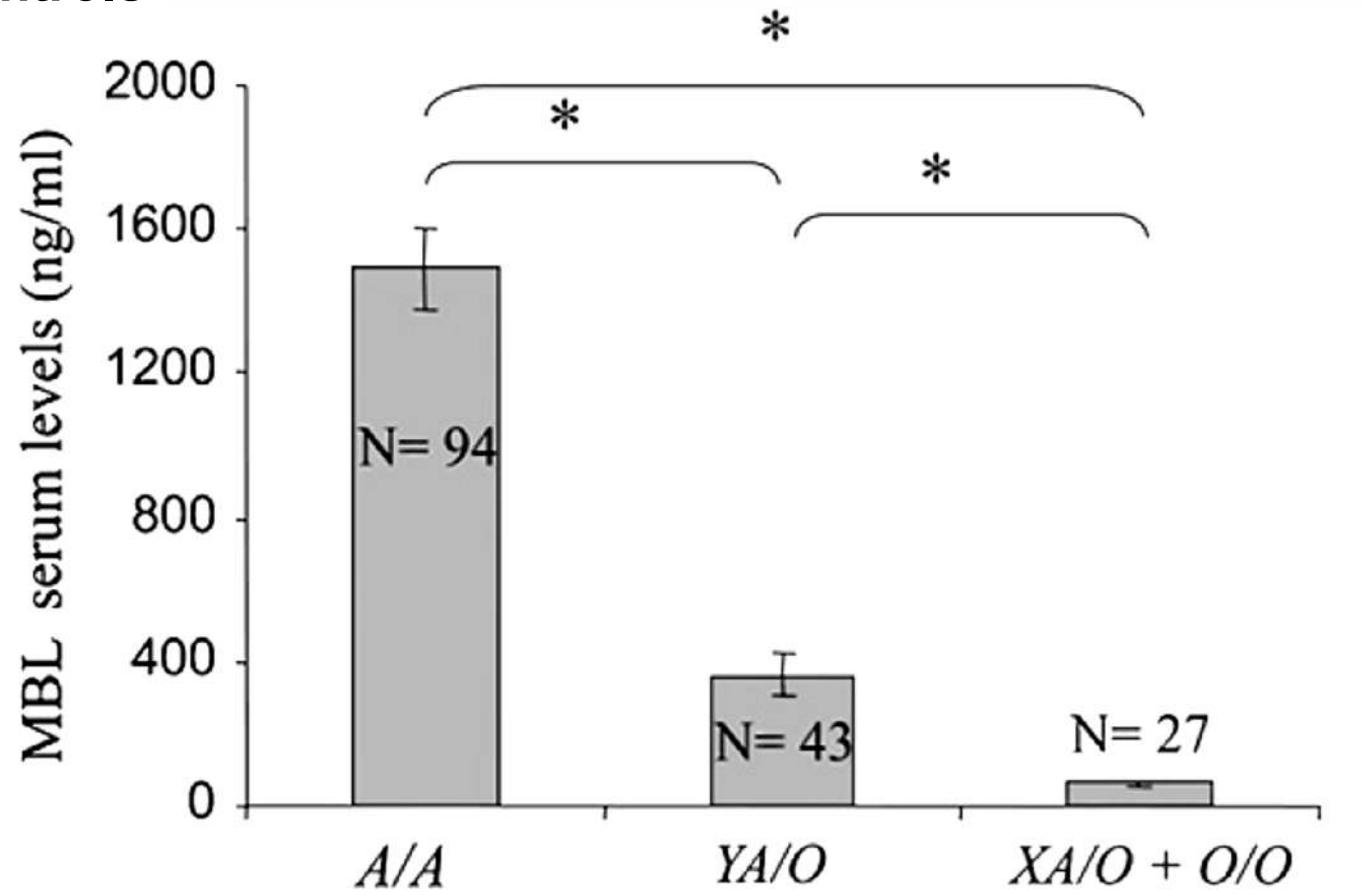


- Collectin
- Structural homology with C1q
- Associated to 2 serine proteases
- Variability:
 - Point mutations codons 52, 54, 57
 - Polymorphisms in the promoter

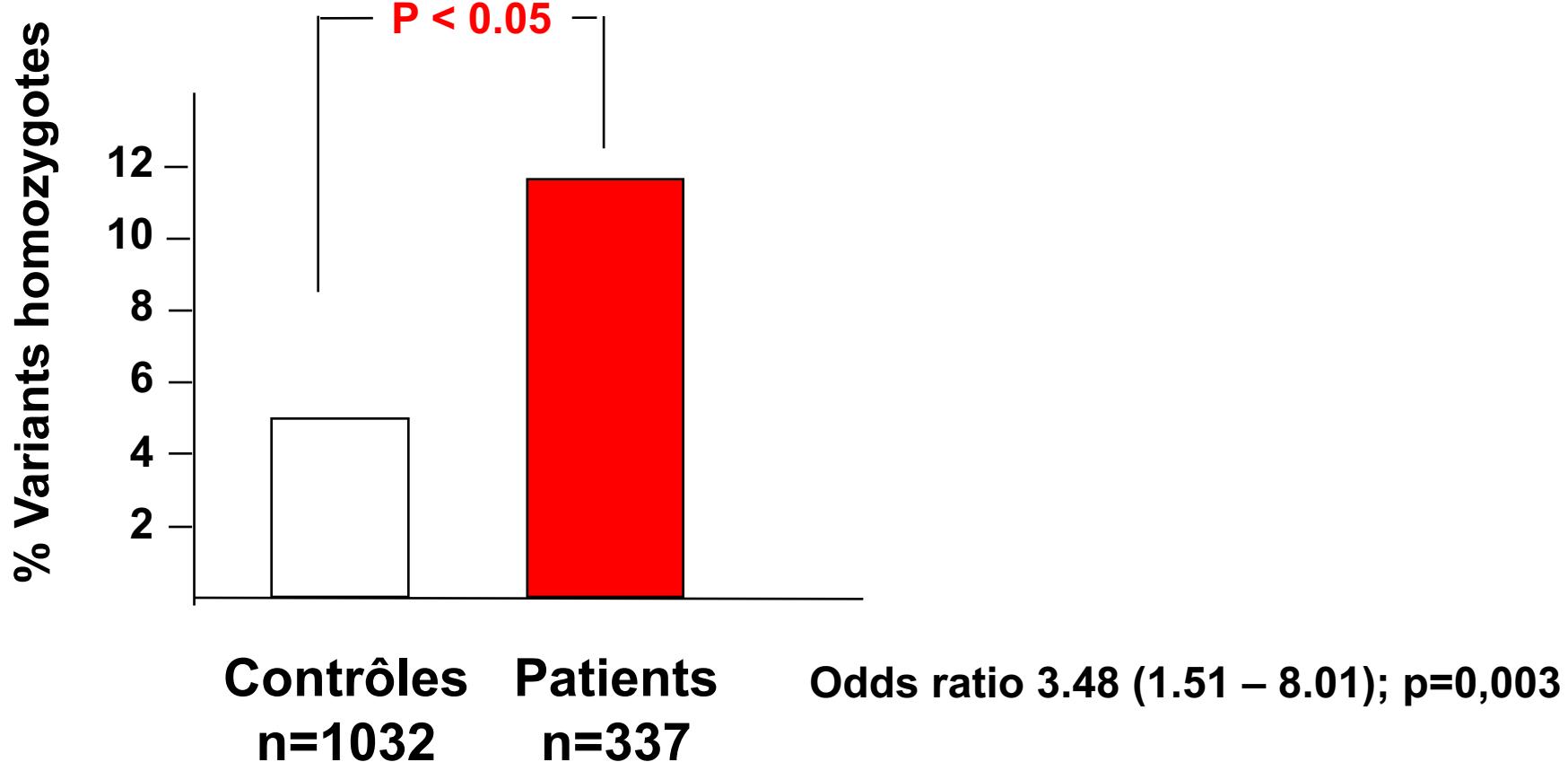


MBL genotypes and protein levels

164 controls

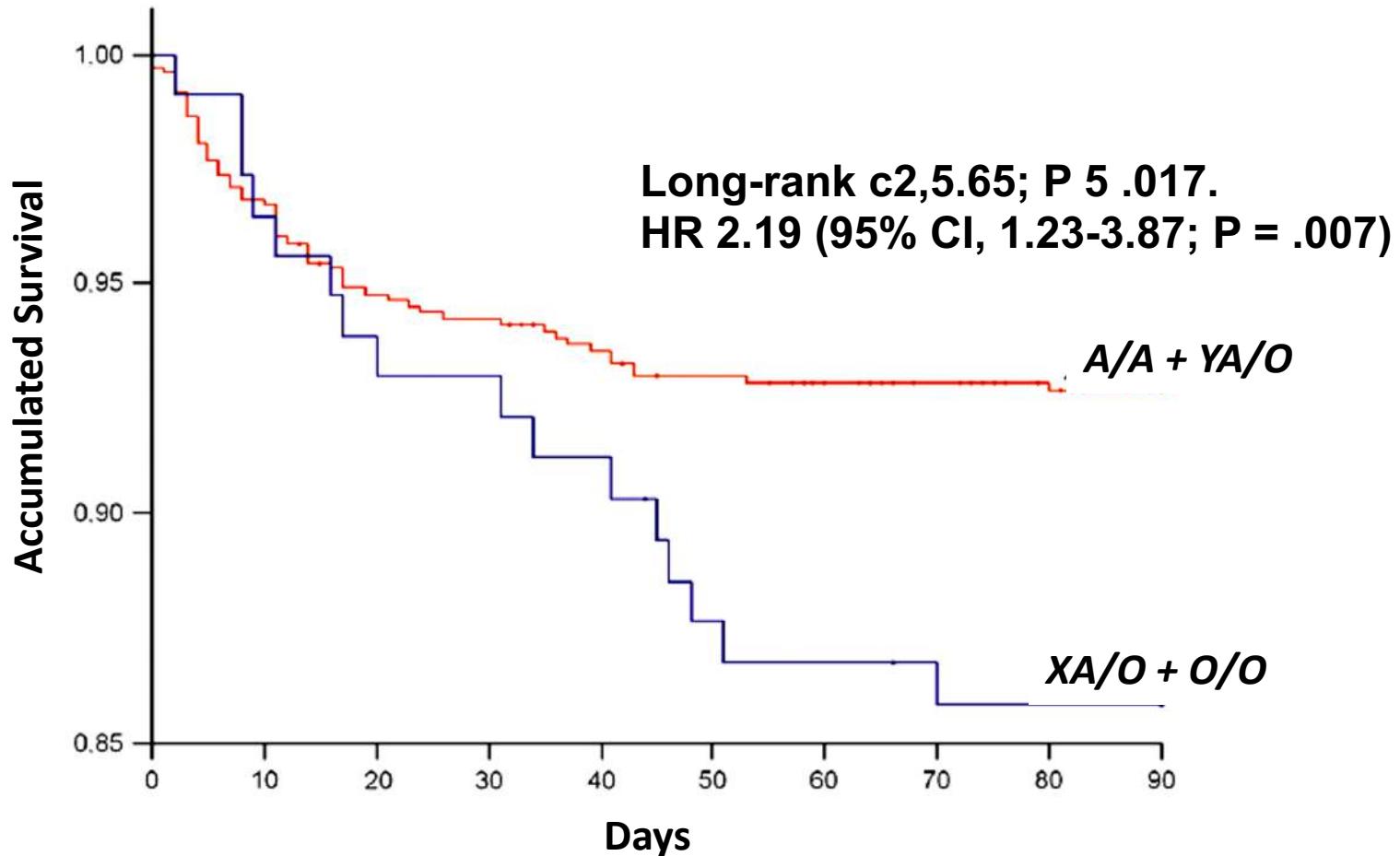


MBL genotype and risk of invasive pneumococcal disease



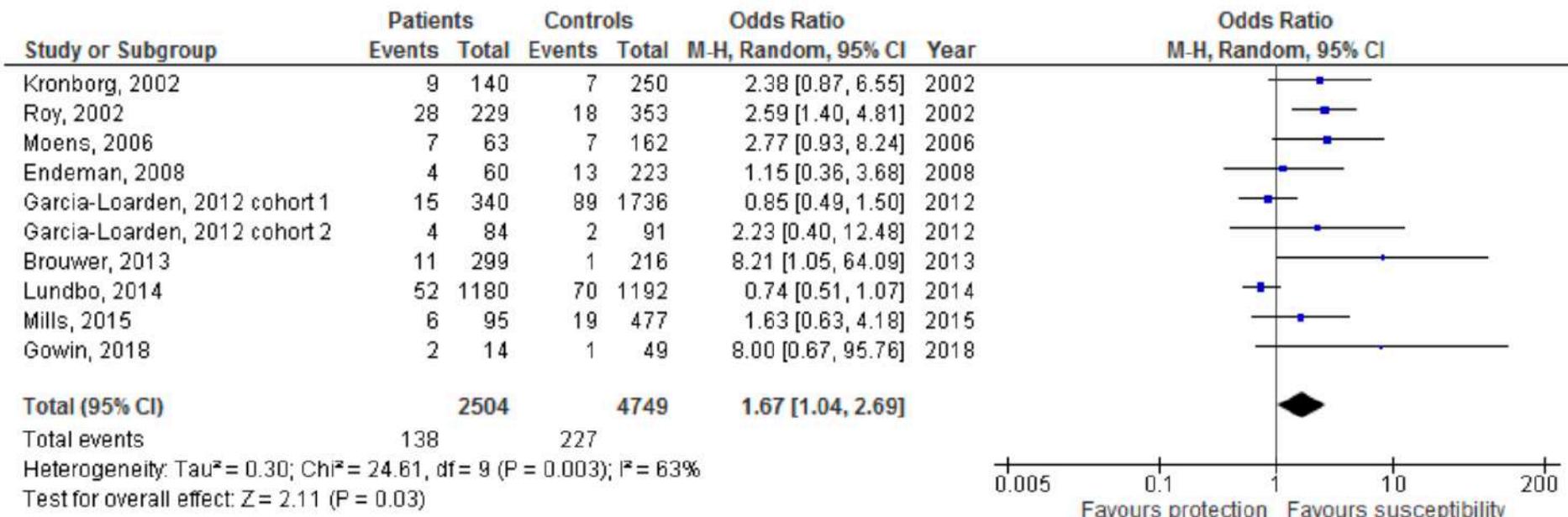
MBL haplotypes and 90 days mortality

848 CAP

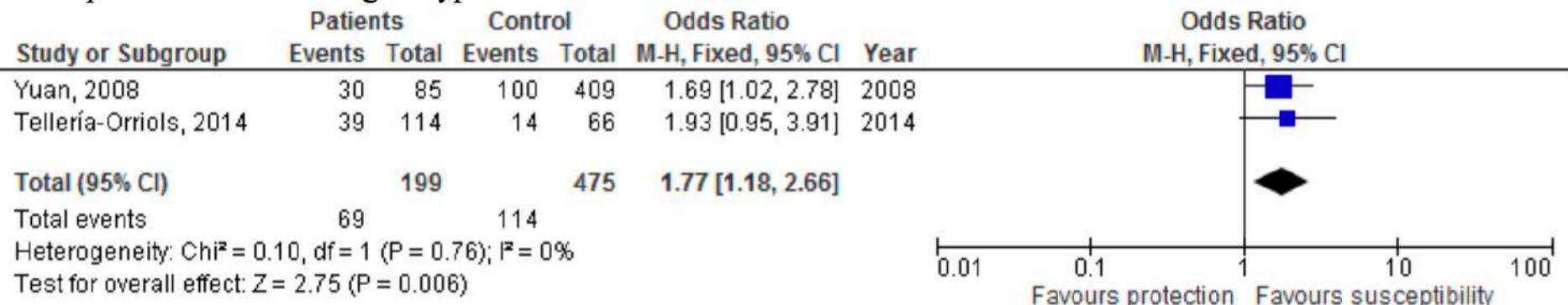


Host genetic variability and pneumococcal disease: a systematic review and meta-analysis

MBL2 – variant alleles (O/O genotype) of rs1800450, rs1800451 or rs5030737



Forest plot a.1 CD14 – CC genotype of rs2569190*

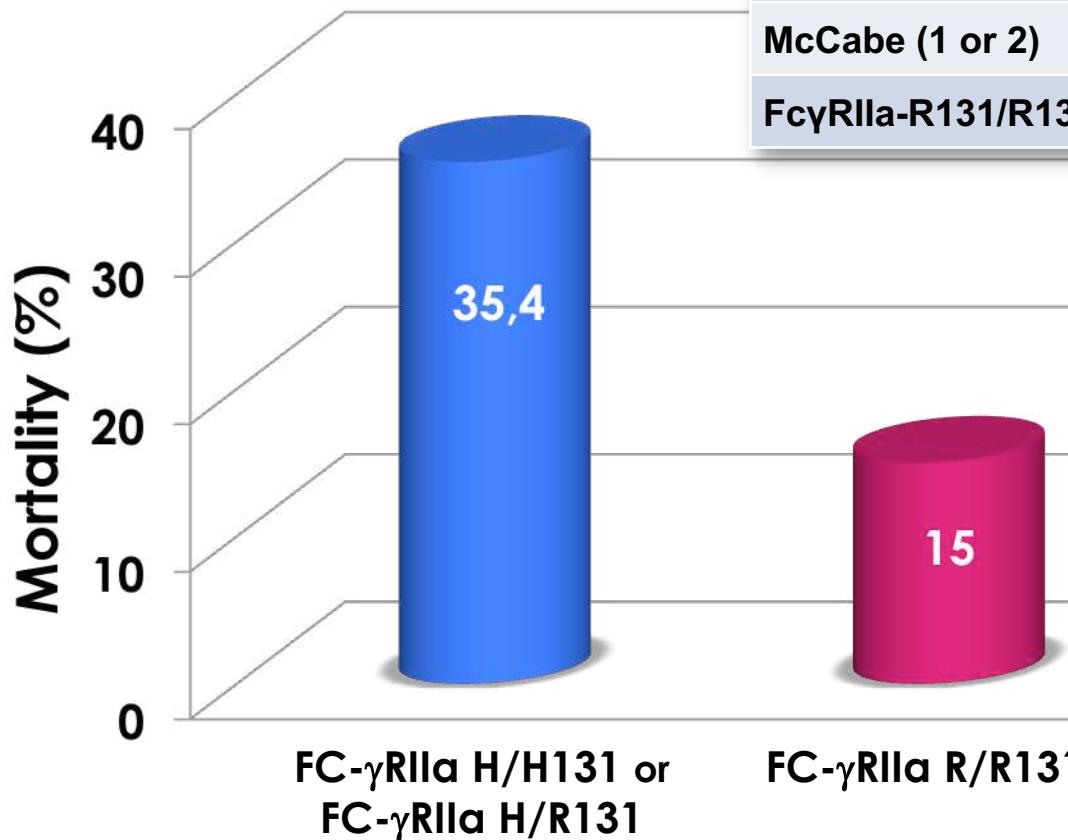




Protective Effects of *FCGR2A* Polymorphism in Invasive Pneumococcal Diseases

Adrien Bouglé, MD; Adeline Max, MD; Nicolas Mongardon, MD; David Grimaldi, MD; Frédéric Pène, MD, PhD; Christophe Rousseau, MSc; Jean-Daniel Chiche, MD, PhD; Jean-Pierre Bedos, MD; Eric Vicaut, MD, PhD; and Jean-Paul Mira, MD, PhD

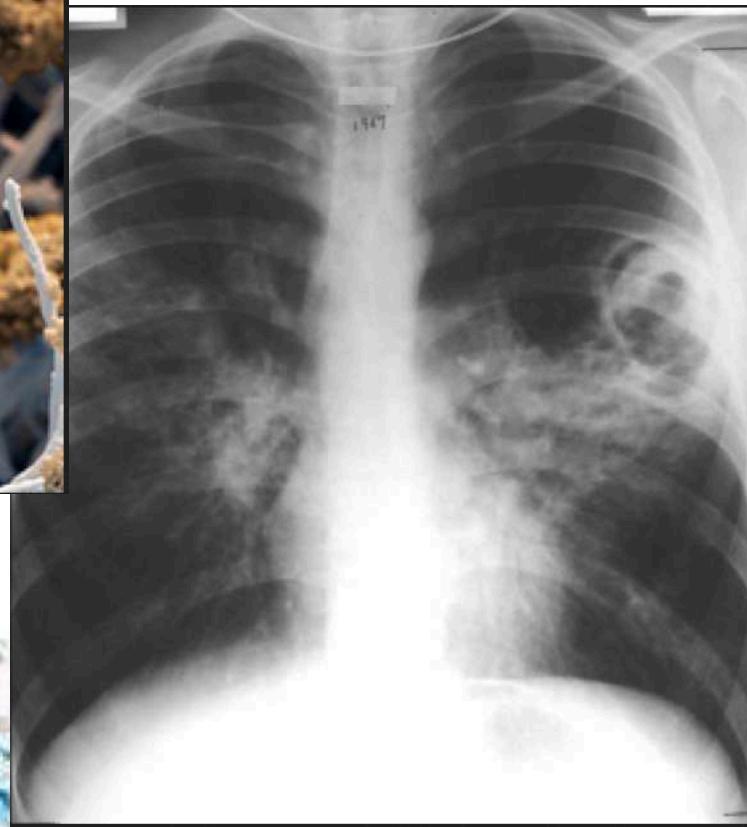
- 243 caucasian pts with proven IPD & no comorbidity



	Adjusted OR [95% CI]	P
SAPS II	1.068 [1.044; 1.091]	<0.0001
McCabe (1 or 2)	2.725 [1.302; 5.700]	0.0078
Fc γ R IIa -R131/R131	0.256 [0.097; 0.673]	0.006

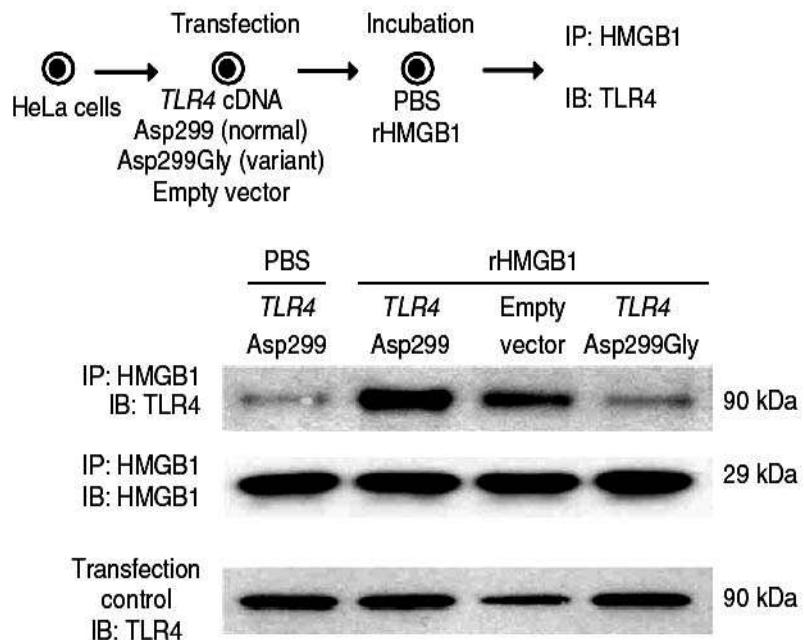
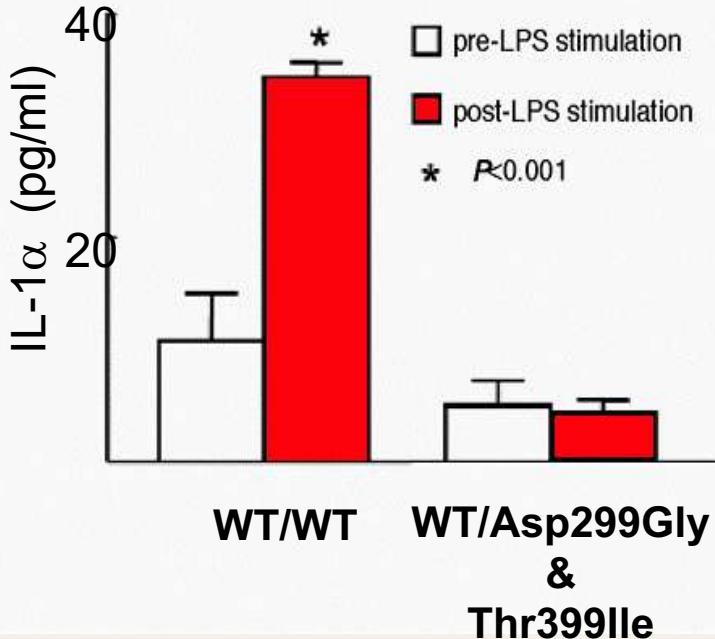
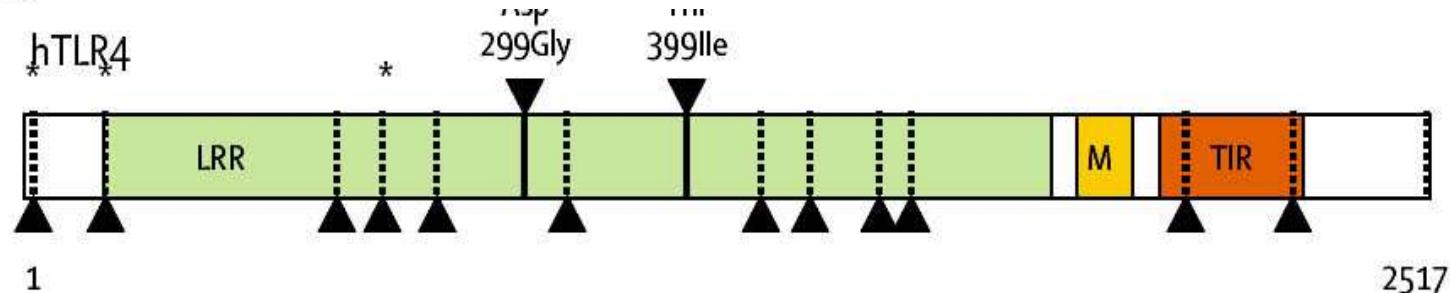
FC- γ R IIa R/R131 confers higher binding affinity for CRP-opsonized bacteria & increased bacterial clearance

Invasive Aspergillosis



Single nucleotide polymorphisms of Toll-like receptors and susceptibility to infectious disease

Lancet Infect Dis 2005; Nicolas WJ Schröder and Ralf R Schumann
5: 156-64



Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation

Hypothesis : polymorphisms in *TLR* genes from the donor and the recipient may influence

susceptibility to invasive aspergillosis in stem cell transplantation

Discovery study: DNA from 336 patients and their unrelated donors (1995 – 2003)

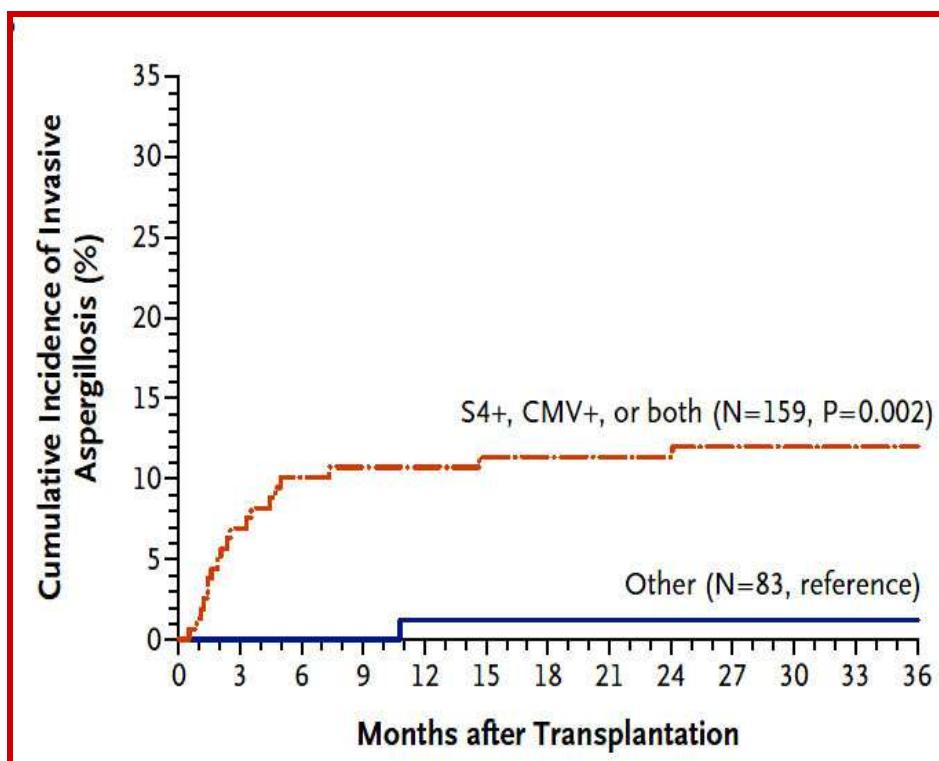
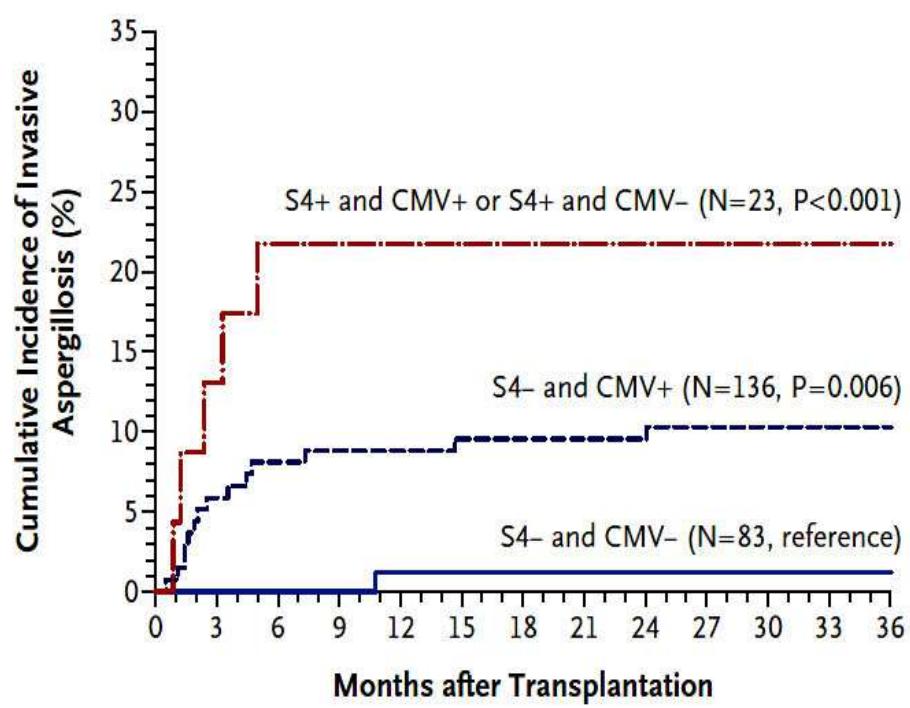
33 cases of aspergillosis

Validation study: matched case-control study with recipients of donors

103 patients with invasive aspergillosis and 263 recipients without aspergillosis.

Genes: 20 SNPs in *TLR2*, *TLR3*, *TLR4* and *TLR9*

Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation



Protective role of interleukin-10 promoter gene polymorphism in the pathogenesis of invasive pulmonary aspergillosis after allogeneic stem cell transplantation

KW Seo¹, DH Kim^{1,2}, SK Sohn^{1,2}, NY Lee^{2,3}, HH Chang⁴, SW Kim⁴, SB Jeon¹, JH Baek¹, JG Kim^{1,2}, JS Suh^{2,3} and KB Lee^{1,2}

Bone Marrow Transplantation (2005) 36, 1089–1095

Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation

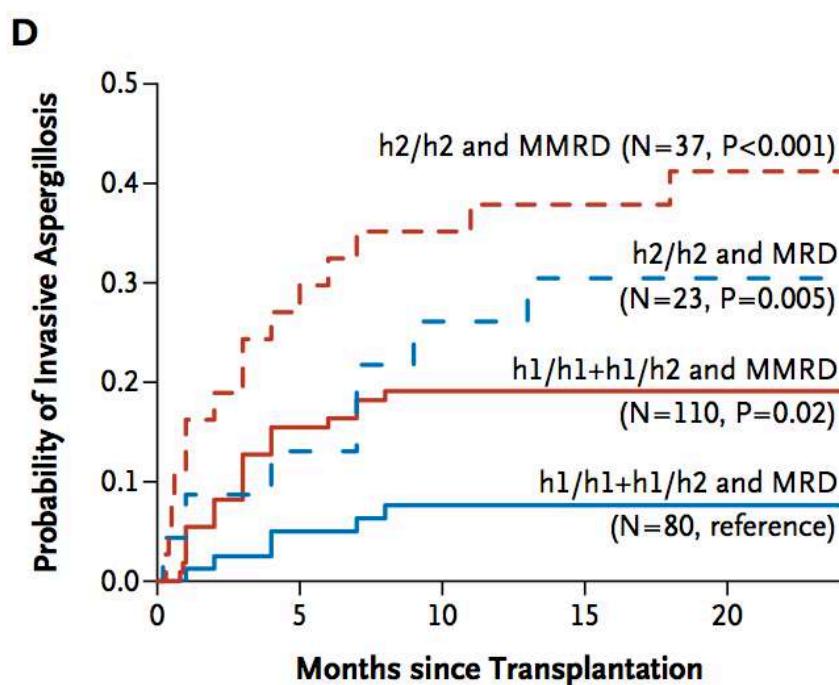
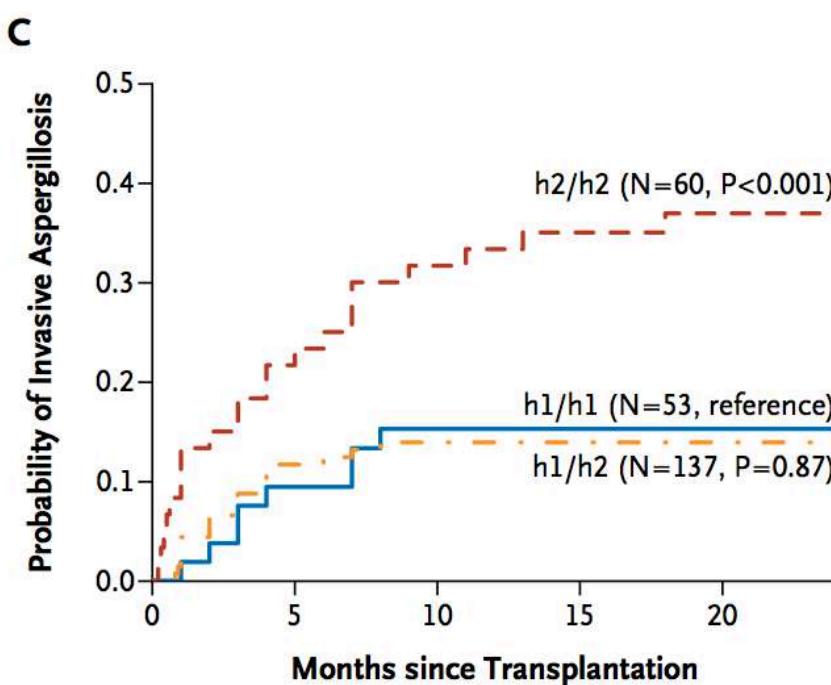
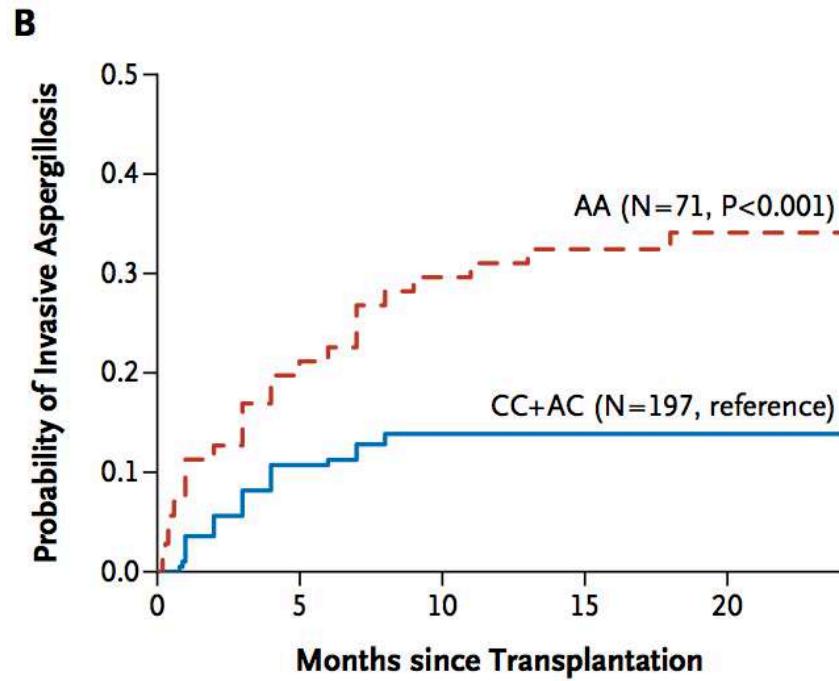
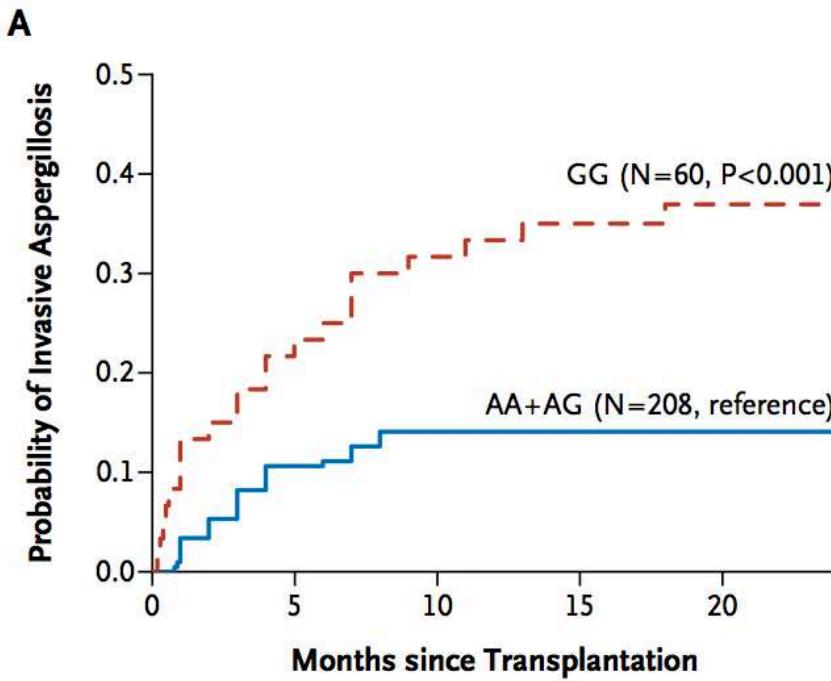
Bochud PY. *N Engl J Med* 2008; 359:1766

ORIGINAL ARTICLE

Genetic PTX3 Deficiency and Aspergillosis in Stem-Cell Transplantation

Cristina Cunha, Ph.D., Franco Aversa, M.D., João F. Lacerda, M.D., Ph.D.,

N Engl J Med 2014;370:421-32.

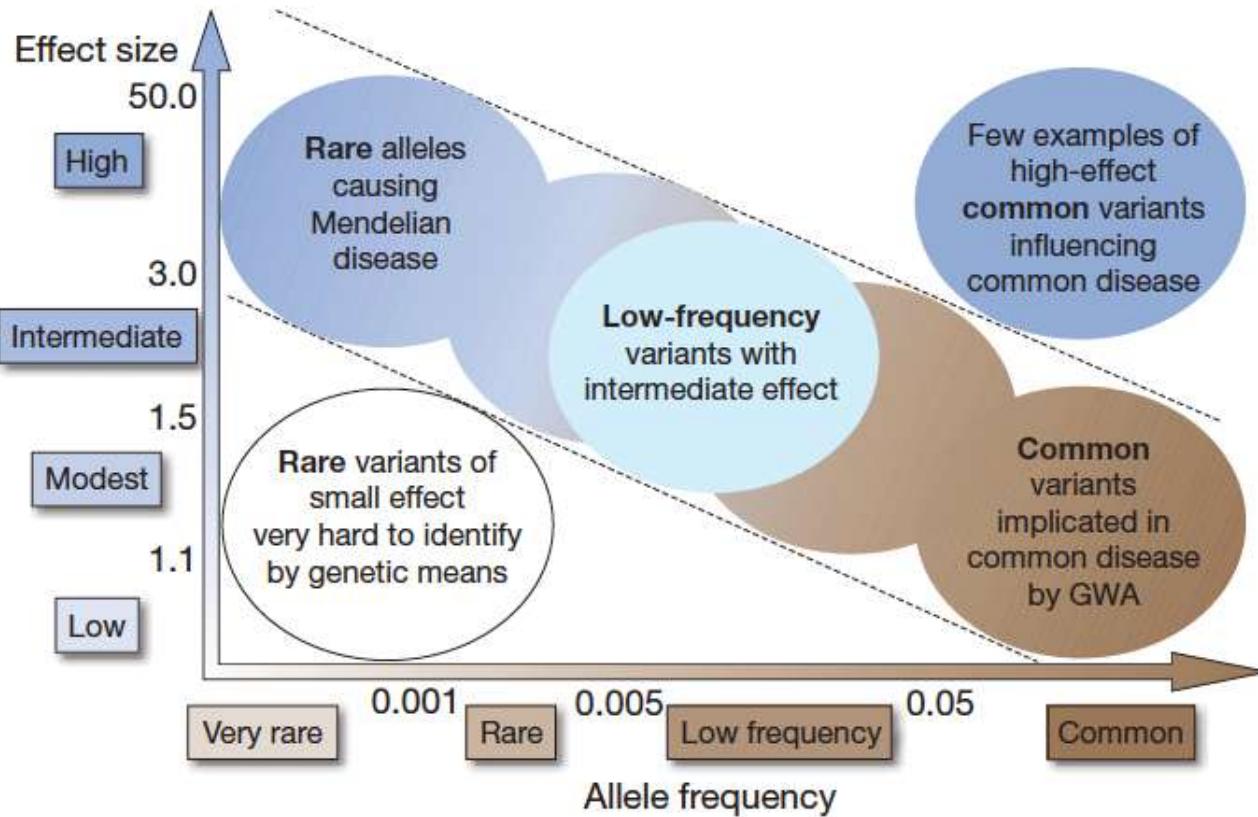


PREVENTION AVE

THIS WAY



Finding the missing heritability of complex diseases



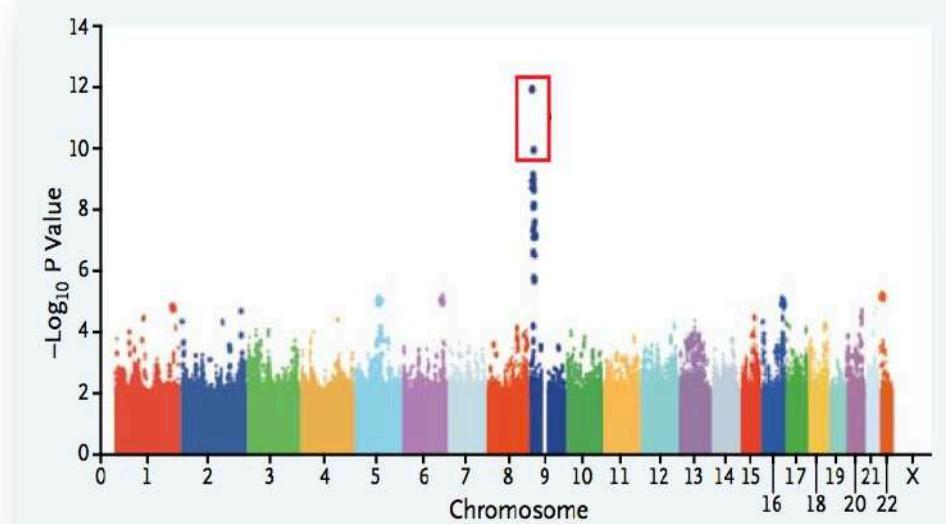
Research strategies:

- SNPs
- **GWAs**
- Sequencing studies

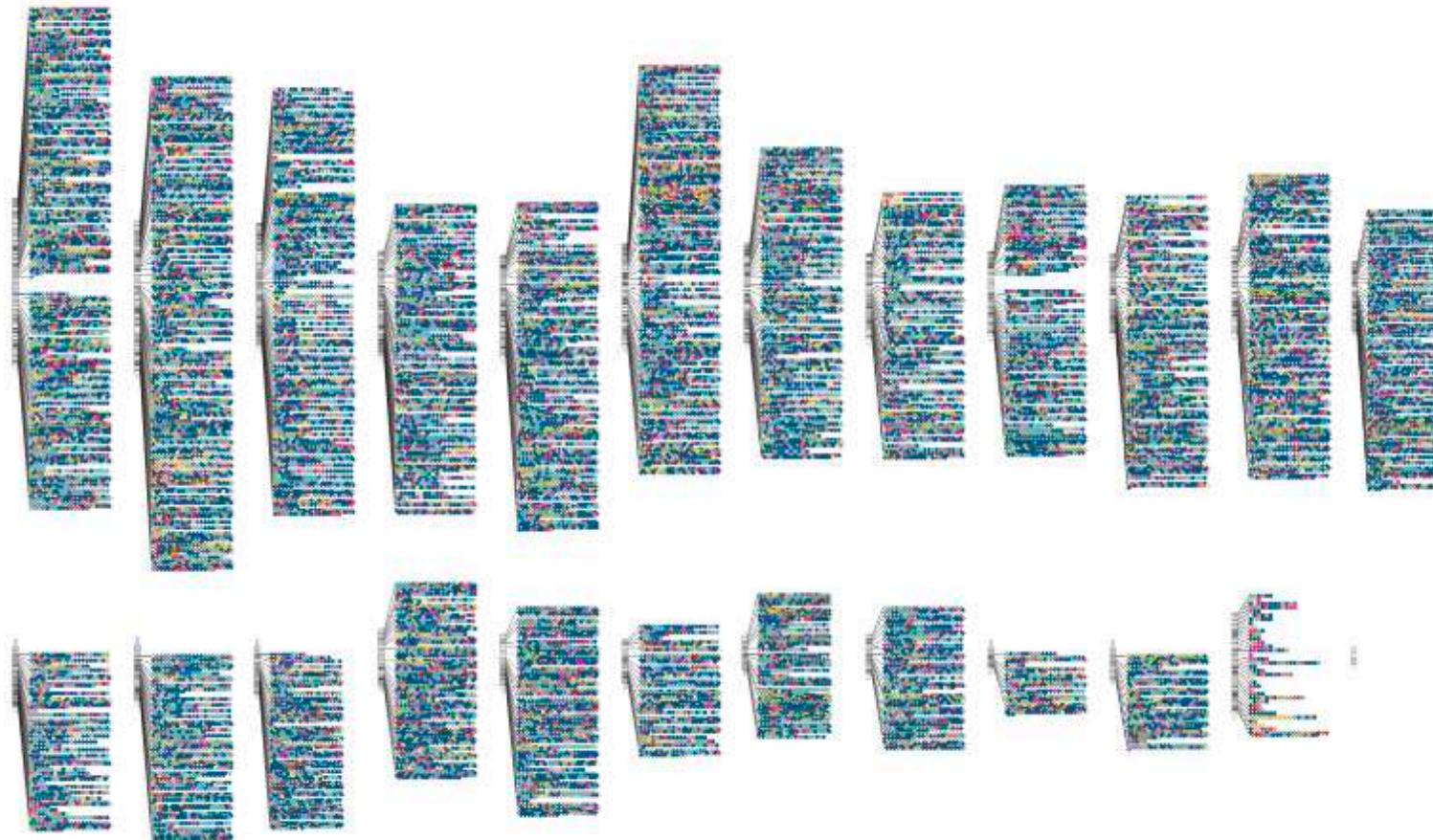
The power of whole-genome scans



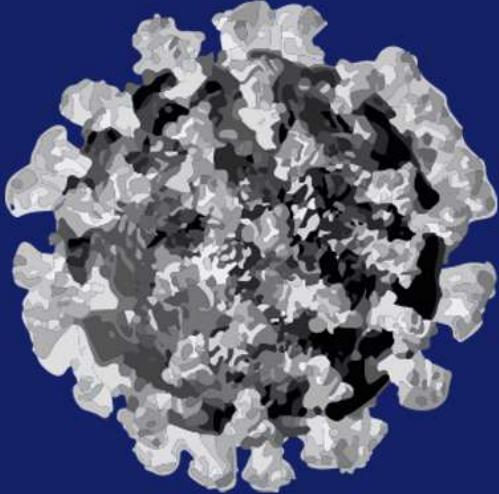
- *1 Million SNPs*
- *Automated devices*



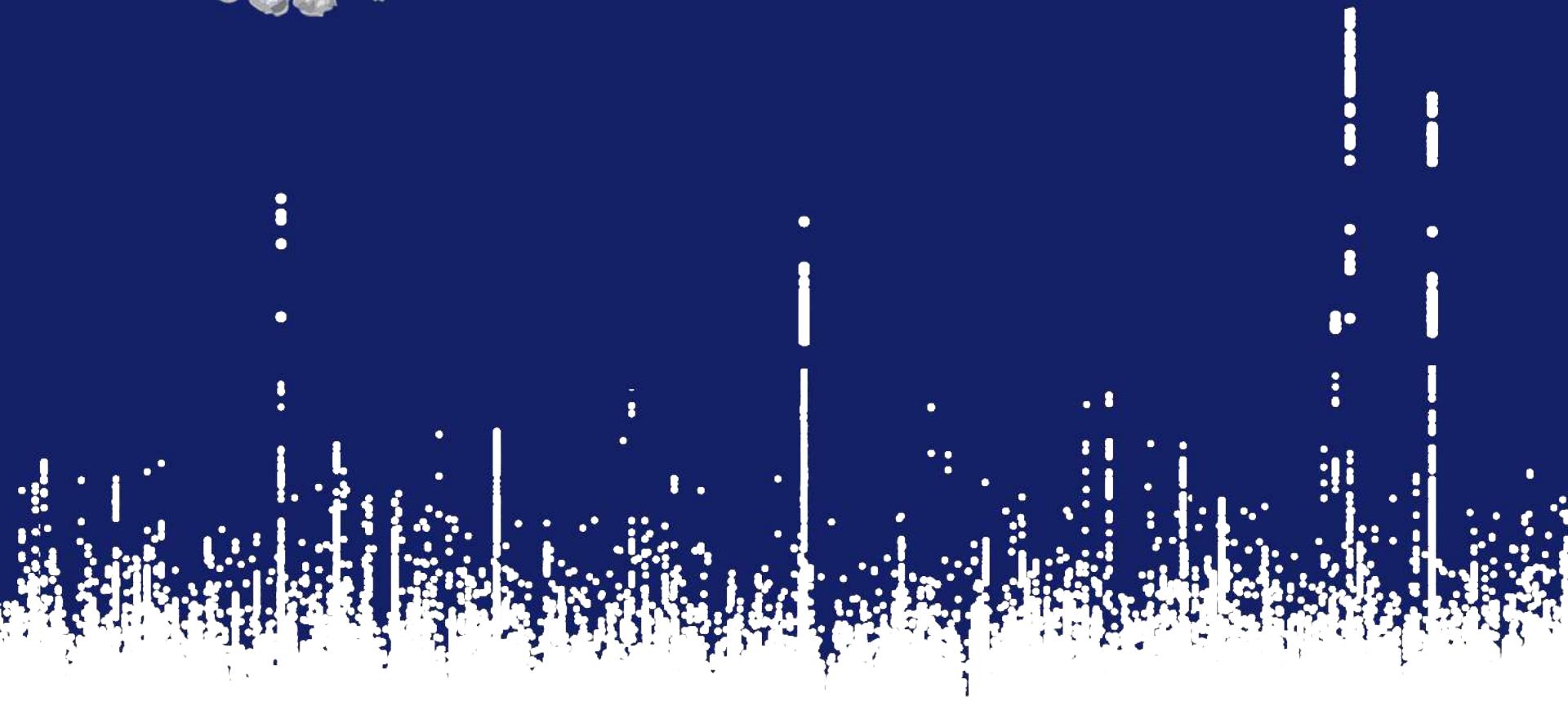
The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019



Sept 2018: 5687 GWAS comprising 71673 variant-trait associations from 3567 publications



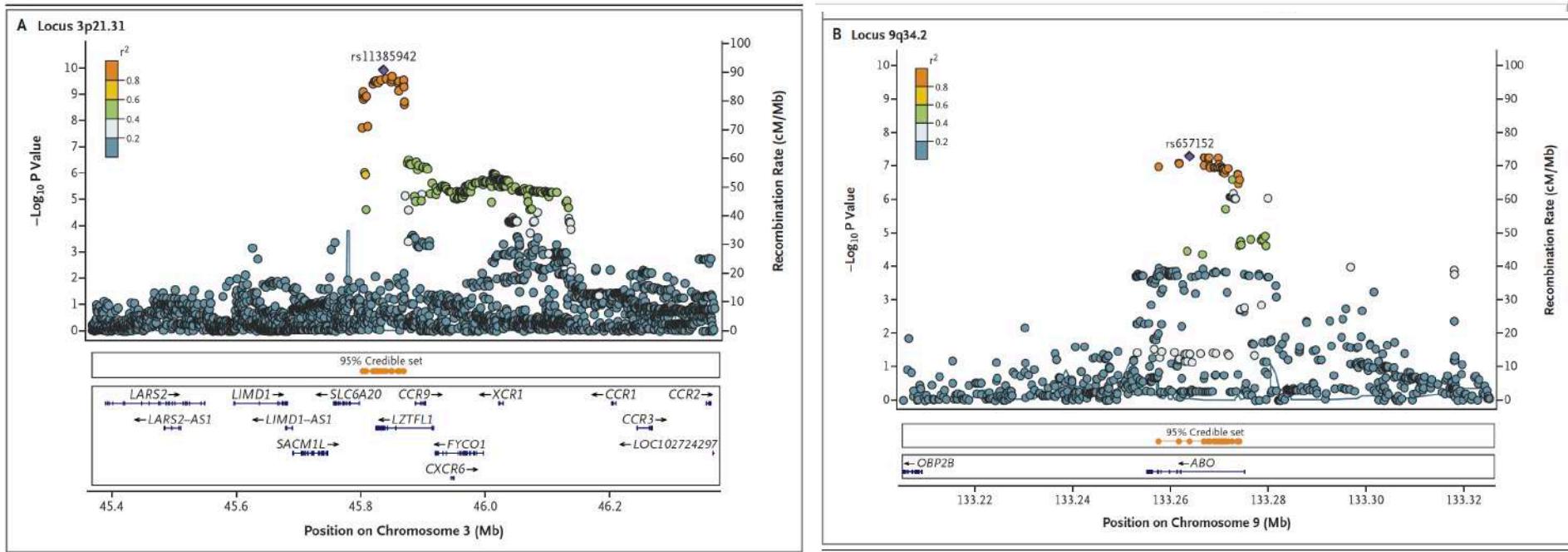
The COVID-19 Host Genetics Initiative



Genomewide Association Study of Severe Covid-19 with Respiratory Failure

The Severe Covid-19 GWAS Group*

**1980 Covid-19 severe patients - 7 hospitals in Italy and Spain
(Italy: 835 patients and 1255 controls/Spain 775 patients and 950 controls)**



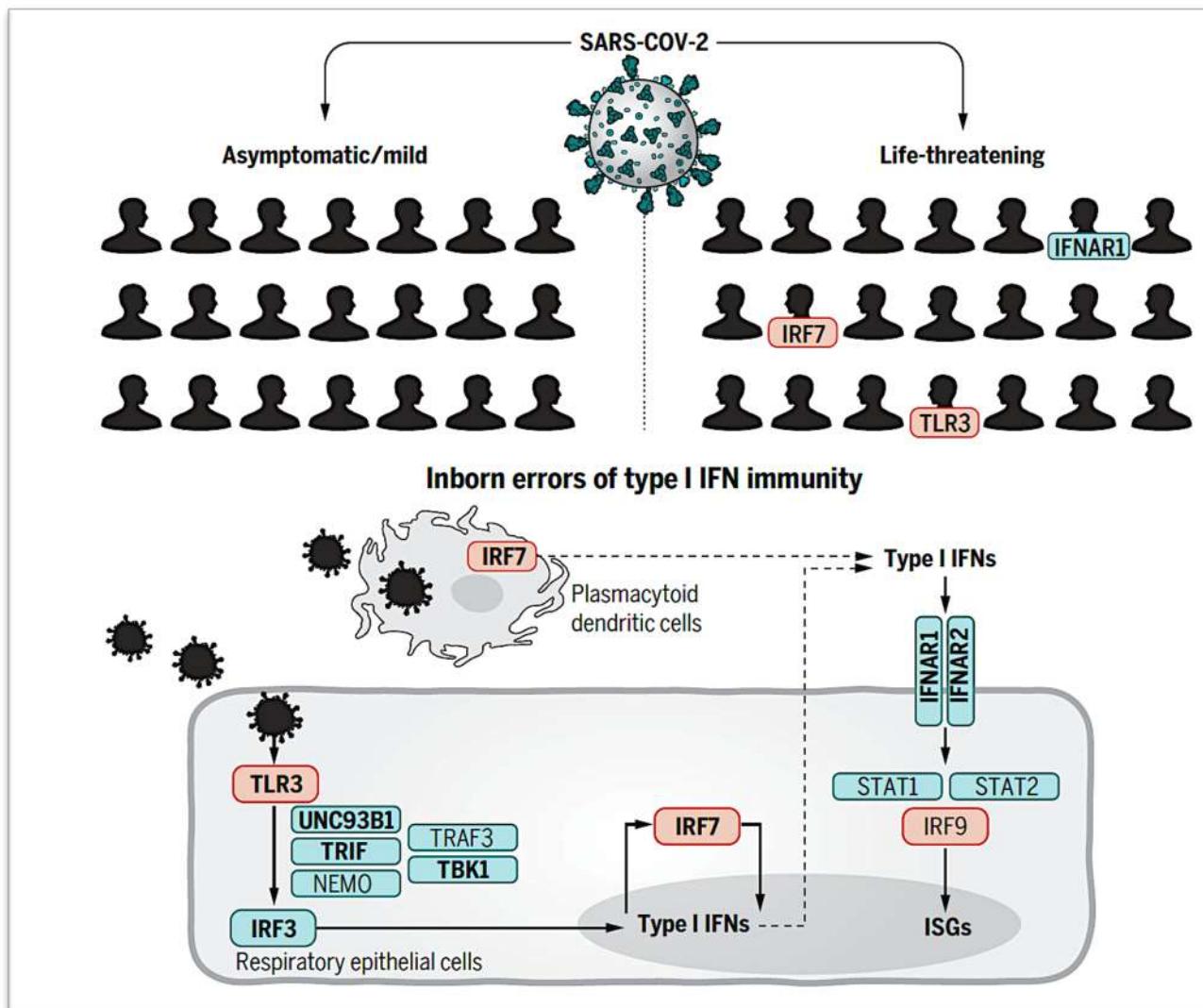
Higher risk with blood group A than other blood groups. (odds ratio, 1.45; 95% CI, 1.20 to 1.75; $P = 1.48 \times 10^{-4}$)

Protective effect for blood group O as compared with the other blood groups (odds ratio, 0.65; 95% CI, 0.53 to 0.79; $P = 1.06 \times 10^{-5}$).

RESEARCH ARTICLE

CORONAVIRUS

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19





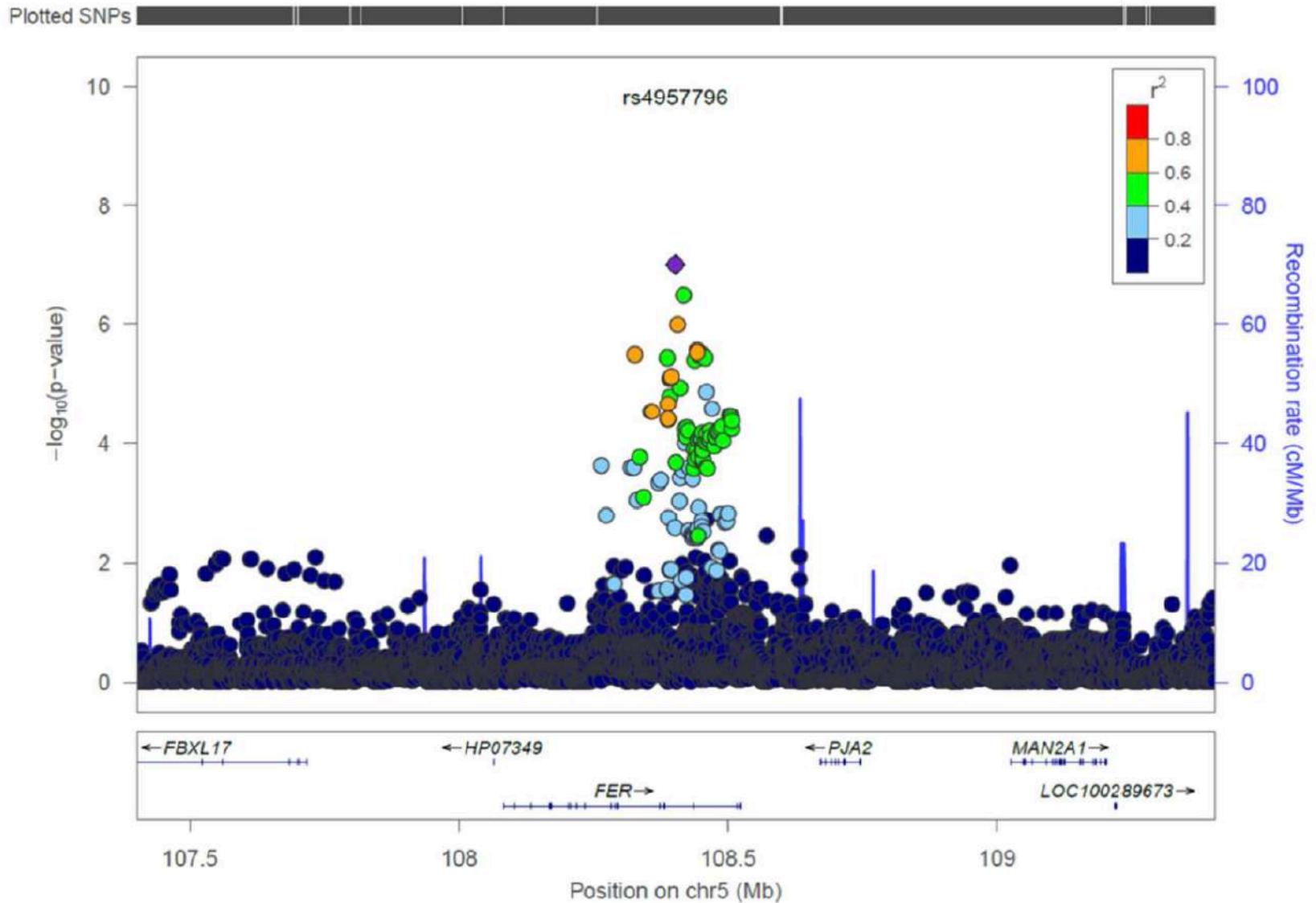
Study Design: Multiple Step Design

1. GWAS: genome wide association study
2. Replication of most significant Markers from Step 1



	GenOSept/GAinS; Discovery	VASST; Discovery	PROWESS; Discovery	GAinS; Replication
N	1766	361	407	1002
N deaths	328 (18.6%)	115 (31.9%)	129 (31.7%)	174 (17.4%)
Males	1055 (59.7%)	226 (62.6%)	247 (60.7%)	505 (50.4%)
Females	711 (40.3%)	135 (37.4%)	160 (39.3%)	497 (49.6%)
Age (mean)	63.1	62.2	63.1	63.8
N Pneumonia	1035 (58.6%)	217 (60.1%)	301 (74.0%)	538 (53.7%)
N deaths among patients with pneumonia	185 (17.9%)	74 (34.1%)	100 (33.2%)	106 (19.7%)
APACHE II score; median (range)	17 (2-44)	26 (10-49)	24 (10-50)	16 (3-41)
Pathogen identified*	60.2%	81.1%	61.5%	44.4%
Bacterial infection*	33.6%	62.7%	56.5%	32.4%
Gram positive infection*	23.5%	51.2%	36.3%	22.3%
Gram negative infection*	11.7%	25.3%	30.9%	11.0%
Viral infection*	3.3%	1.8%	0	6.8%

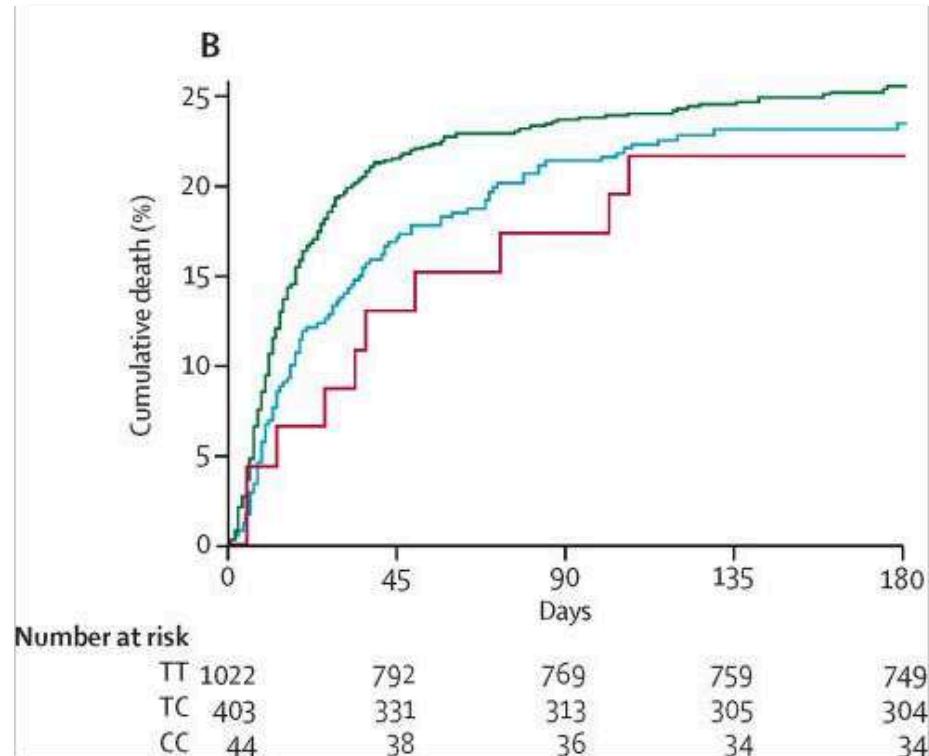
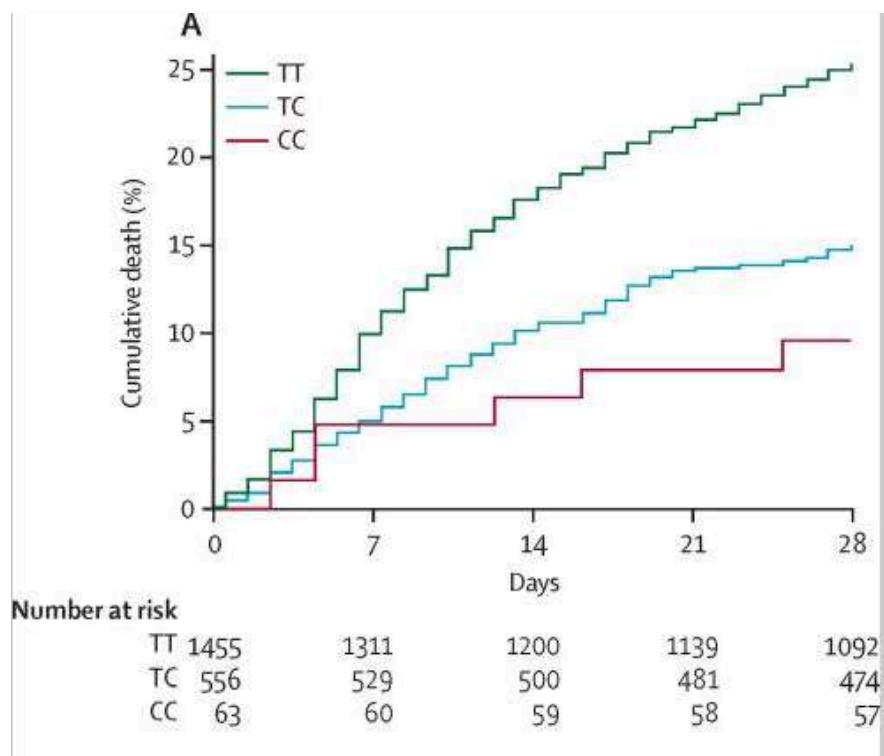
*among patients with sepsis due to pneumonia



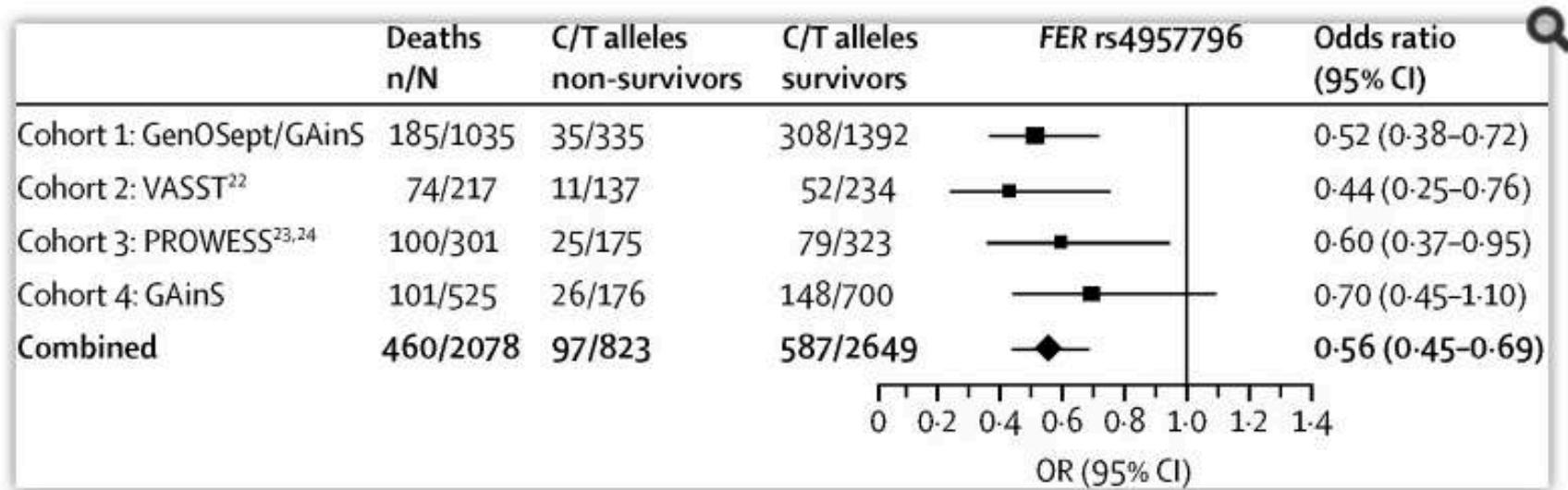
FER plays a role in the regulation of the actin cytoskeleton, cell adhesion, migration and invasion, and chemotaxis

Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study

Effect on FER rs4957796 on pneumonia mortality



Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study



SCIENTIFIC REPORTS



OPEN

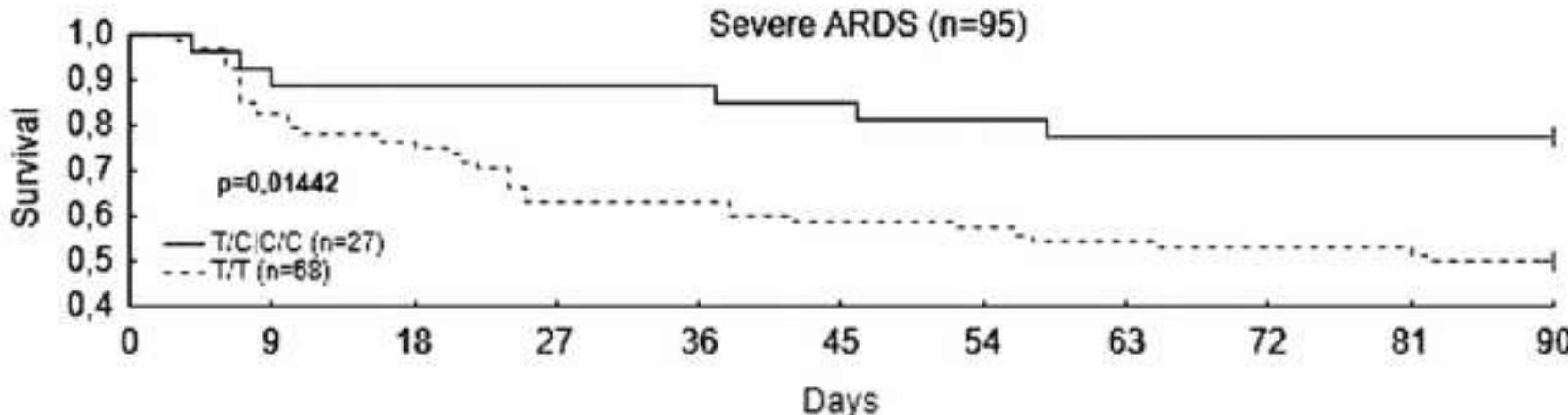
The FER rs4957796 TT genotype is associated with unfavorable 90-day survival in Caucasian patients with severe ARDS due to pneumonia

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José Hinz¹, Benedikt Büttner¹, Fabian Kriesel¹, Maximilian Steinau¹, Aron Frederik Popov^{2,3}, Michael Ghadimi⁴, Tim Beissbarth⁵, Mladen Tzvetkov⁶, Ingo Bergmann¹ & Ashham Mansur¹



Conclusions & Perspectives

- Identification of genetic markers of susceptibility and severity
 - Evaluation of the individual risk
 - Prevention, immunization
 - Personalized physiopathology
 - Pharmacogenomics

Recurrent Purpura Fulminans

15 yo girl admitted in ICU

- Temperature 40° C; HR 125; BP 74/45; RR 38
- Meningitis with purpura fulminans
- MOF (Shock, ARDS, ARF, DIC, Lactic acidosis)
- Meningococcus type N in the skin biopsy
- Survival with multiple finger amputations and skin grafting
- 6 month hospitalization

One year after:

- Temperature 39° C; HR 125; BP 83/48; RR: 33
- Meningitis with purpura fulminans
- Lumbar puncture → meningococcus type Y
- Shock and DIC
- Survival (Xigris) with new skin grafting
- 3 month hospitalization

Recurrent Purpura Fulminans

Genetic predisposition?

Innate immunity

Inflammation

Coagulation

Innate Immunity

TLR4

CD14

Fc γ RIIa

Fc γ RIII

MBL

Complement

C7 deficiency

Inflammation

TNF α

LT α

IL-1

IL-6

IL-10

ACE

Coagulation

Tissue Factor

Prothrombin

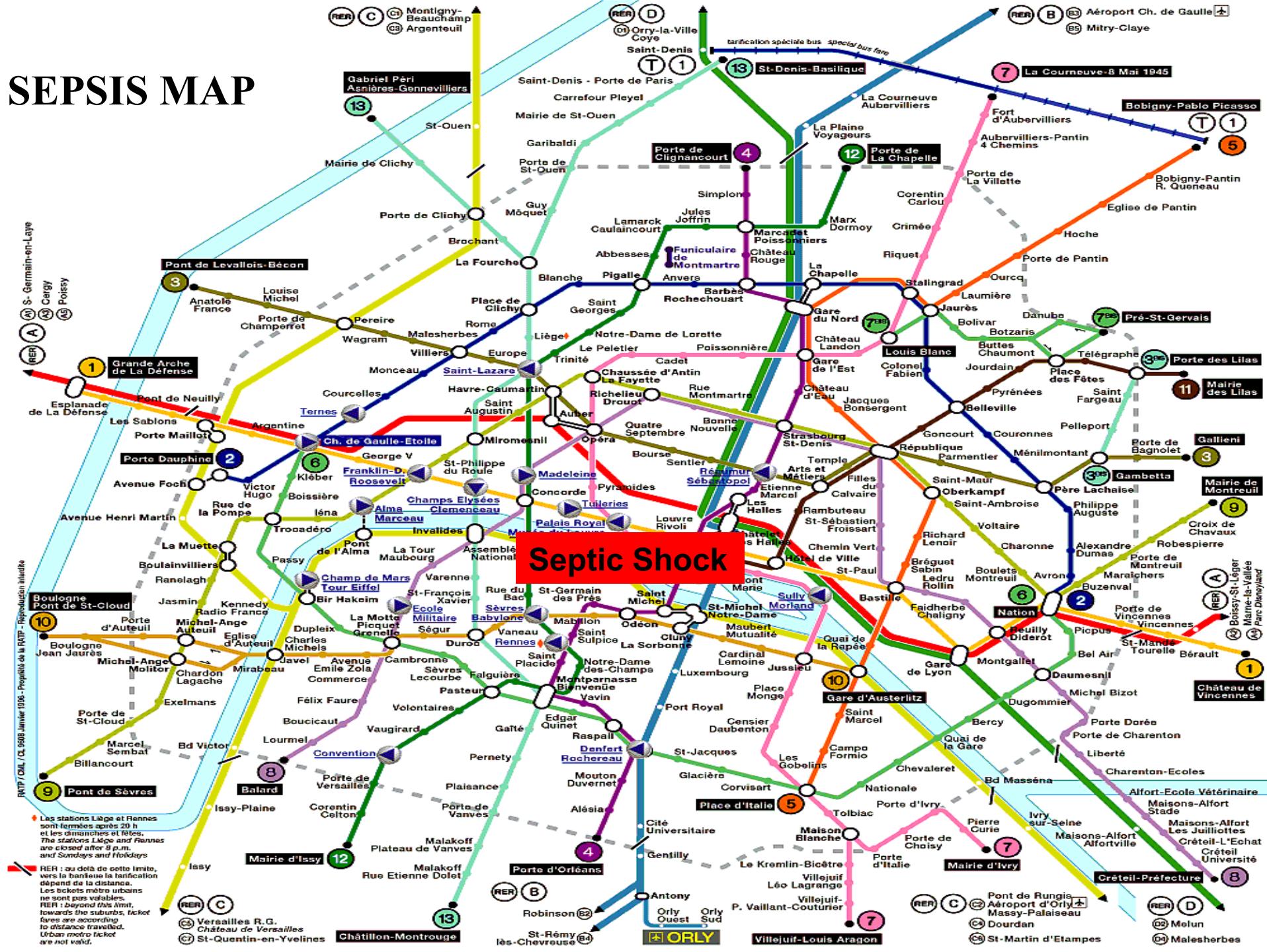
Factor V

Factor VII

Factor XIII

PAI-1

SEPSIS MAP



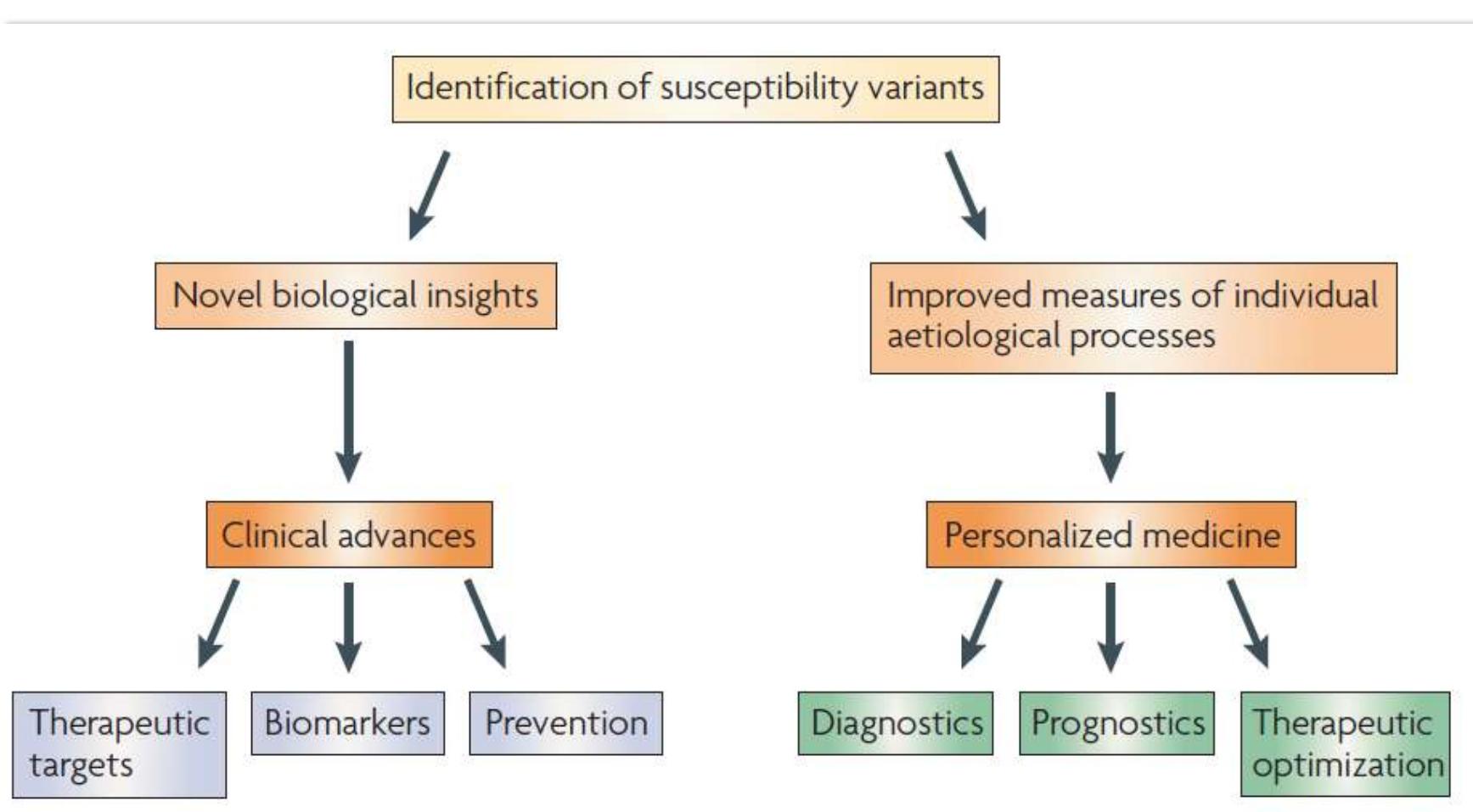
PUTTING SCIENCE
RIGHT
TO WORK!



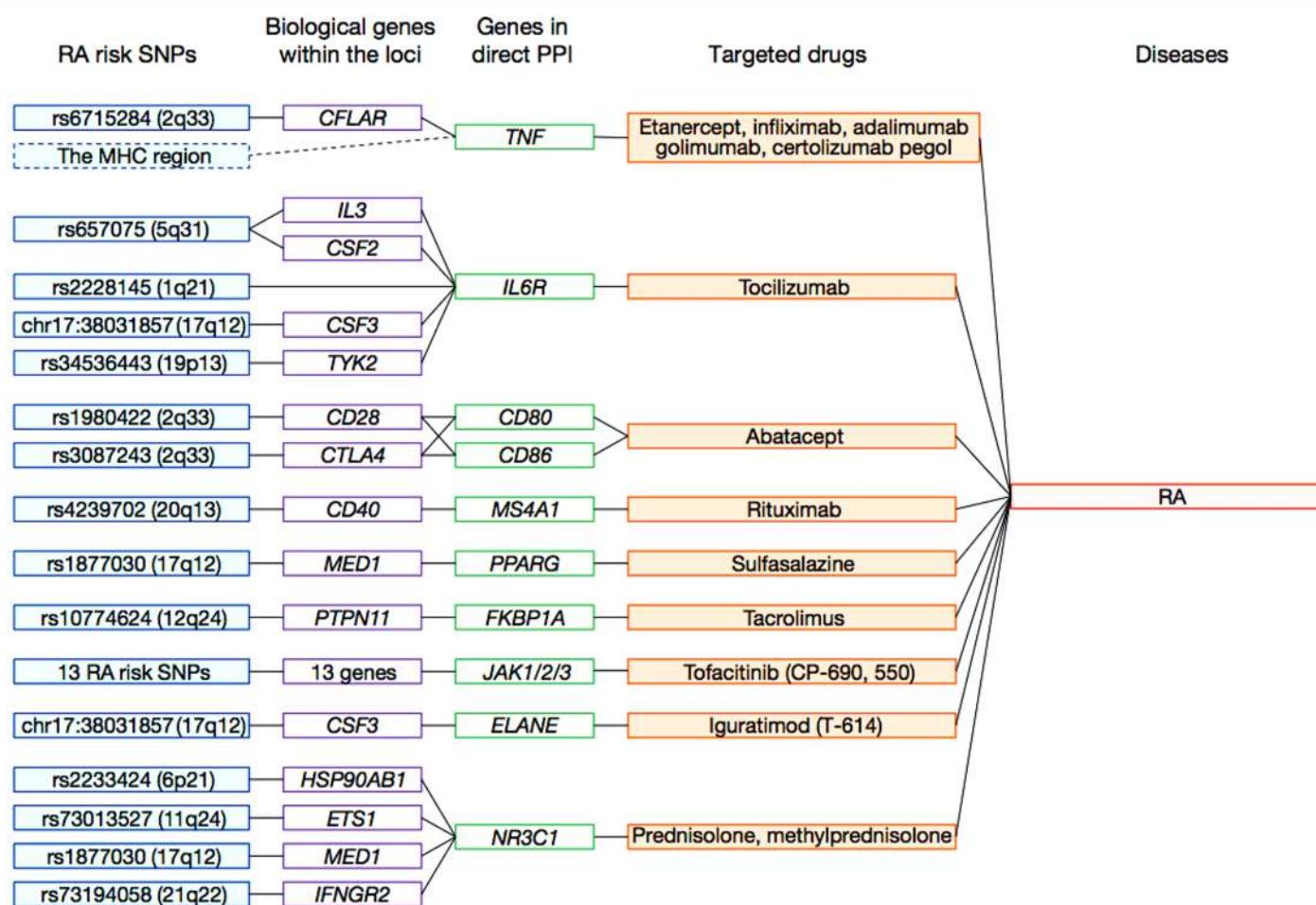


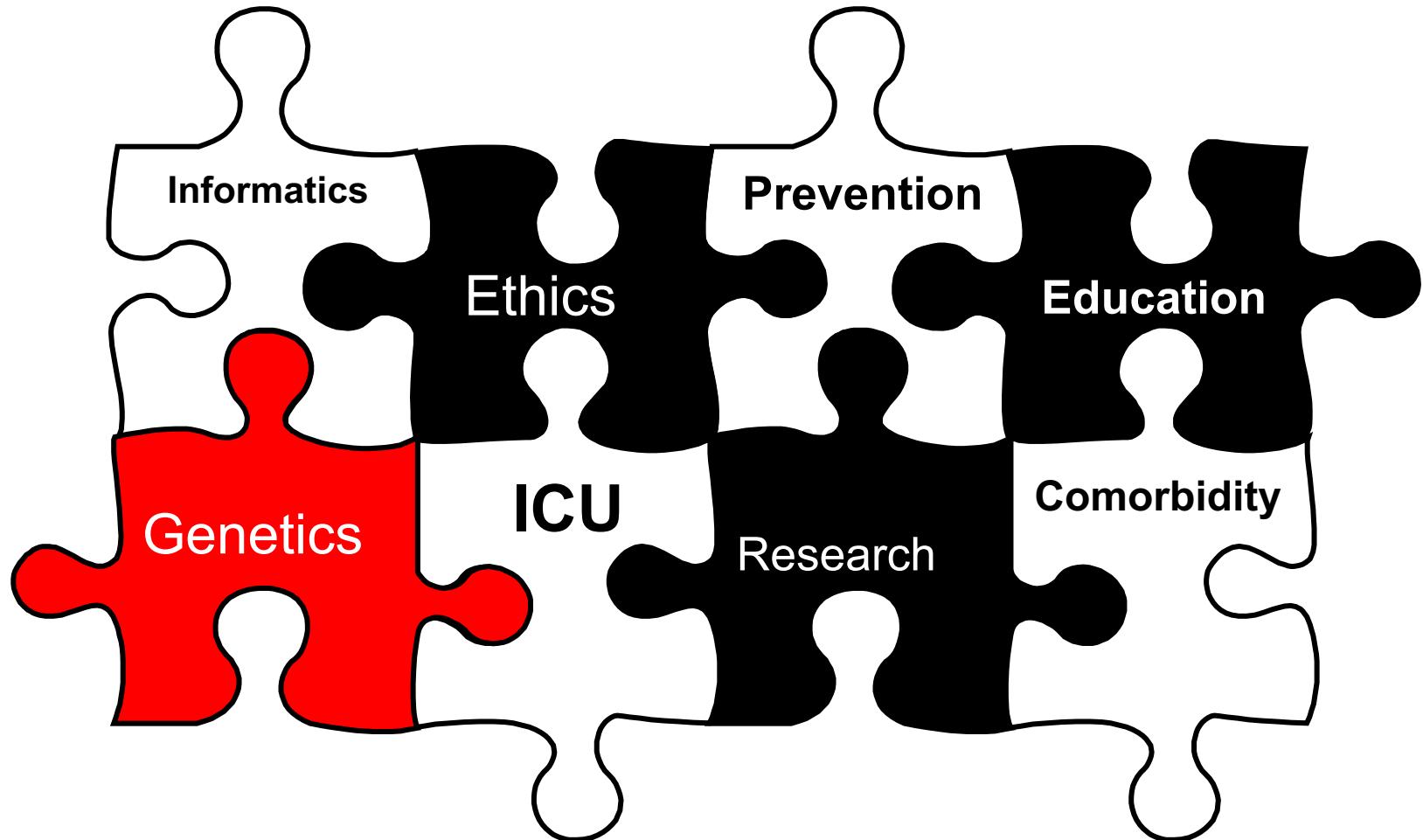


Clinical Translation of Findings from Whole Genome Studies



Genetics of rheumatoid arthritis contributes to biology and drug discovery



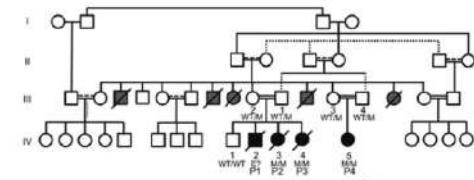


Consider Genetic Testing

**Sepsis
Recurrence**

**Family
History**

**Extreme
Phenotype**



UPGRADE
MAN!



謝謝您

MERCI!
THANK you!





**« Man is a tool-using animal...
Without tools he is nothing,
with tools he is all .»**

Thomas Carlyle

19th-century