Human Genetics of Tuberculosis

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Imagine Institute, Necker, Paris, France
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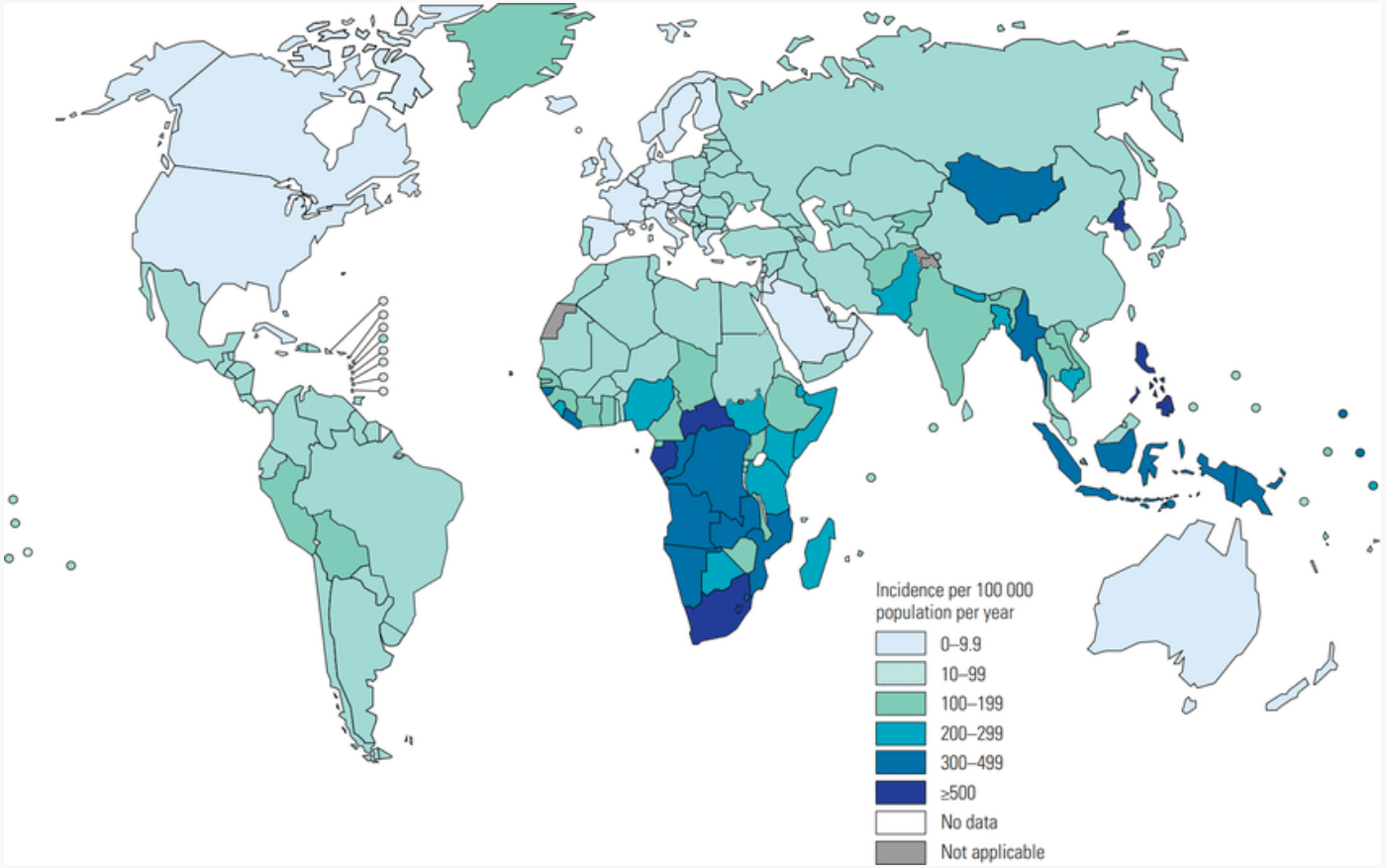
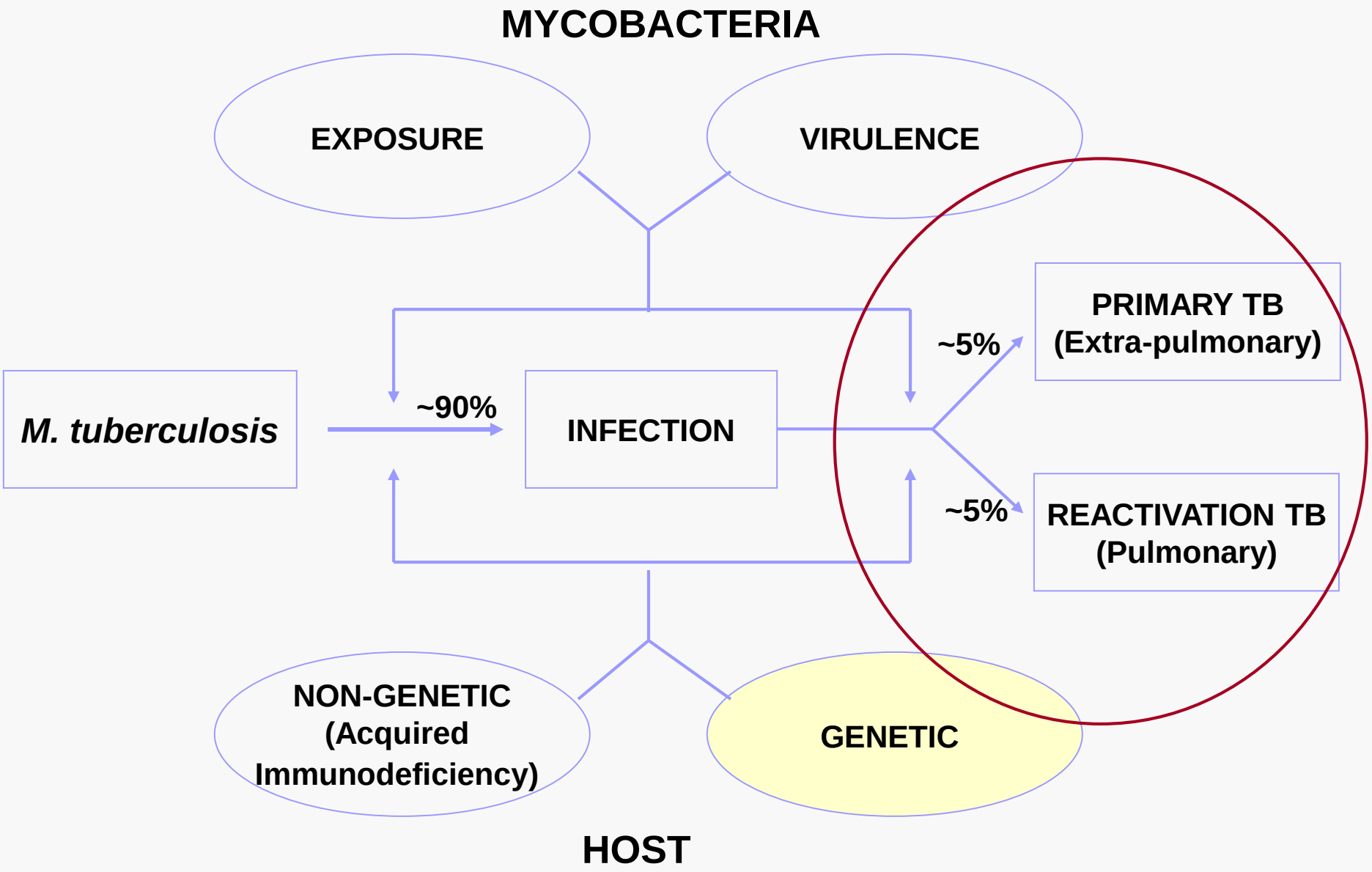
Tuberculosis (TB): Major public health problem



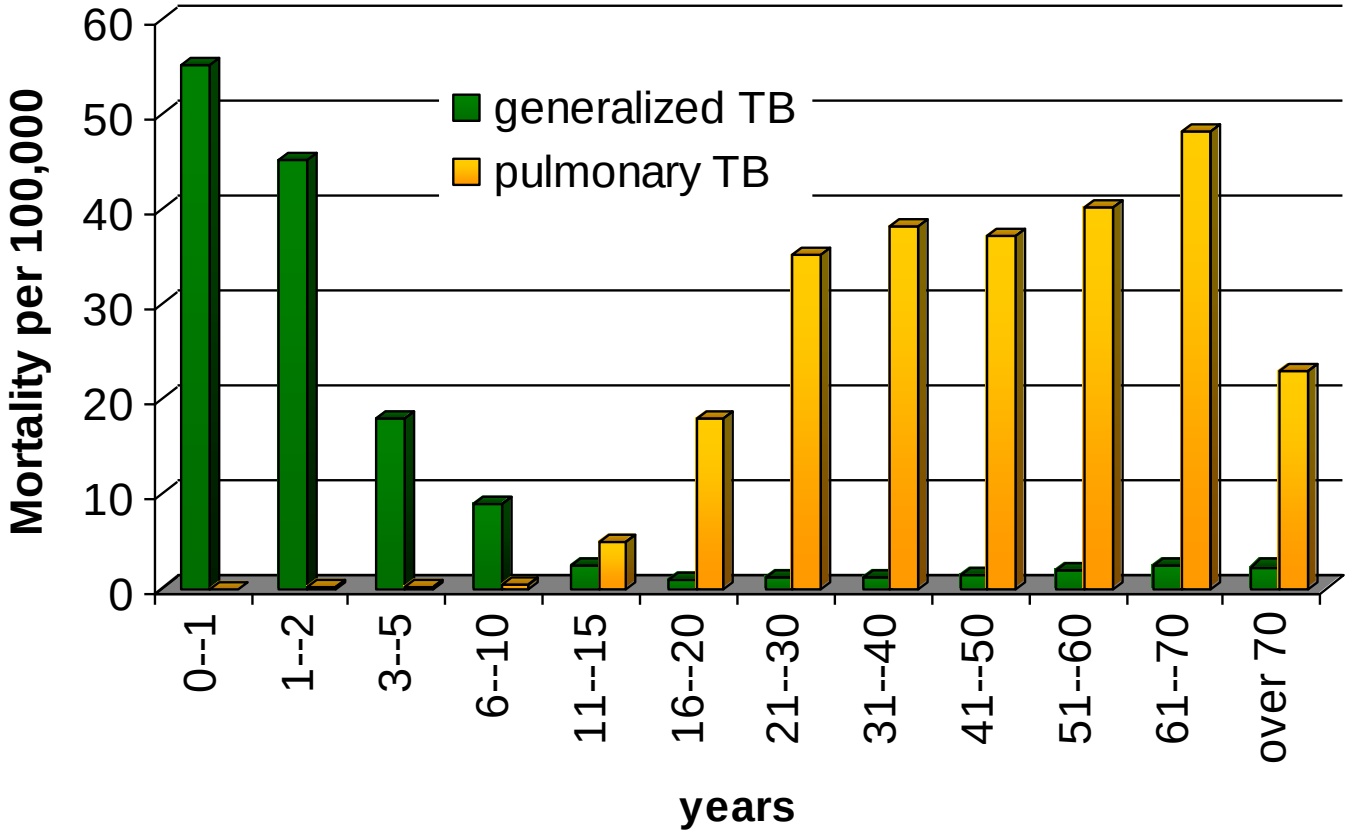
~ 1/3 world's population exposed to ***Mycobacterium tuberculosis***
~ 10 million new cases/year and ~ 2 million deaths/year
Increasing drug resistant (MDR and XDR) strains

~ 10% of infected individuals develop clinical disease
→ Pathogenesis of TB?

Variability of response to exposure and infection



TB: Individual variability in clinical outcomes



Ranke, K. 1910. Diagnose und Epidemiologie der Lungentuberculose des Kindes. Archiv für Kinderheilkunde 54:279-306.

Familial (twin) studies (1930s)

FAMILIAL SUSCEPTIBILITY
TO TUBERCULOSIS

Its Importance as a Public Health Problem

BY

RUTH RICE PUFFER, DR.P.H.

Tennessee Department of Public Health

CAMBRIDGE, MASSACHUSETTS
HARVARD UNIVERSITY PRESS
1944

Zwillingstuberkulose

Zwillingsforschung
und
erbliche Tuberkulosedisposition

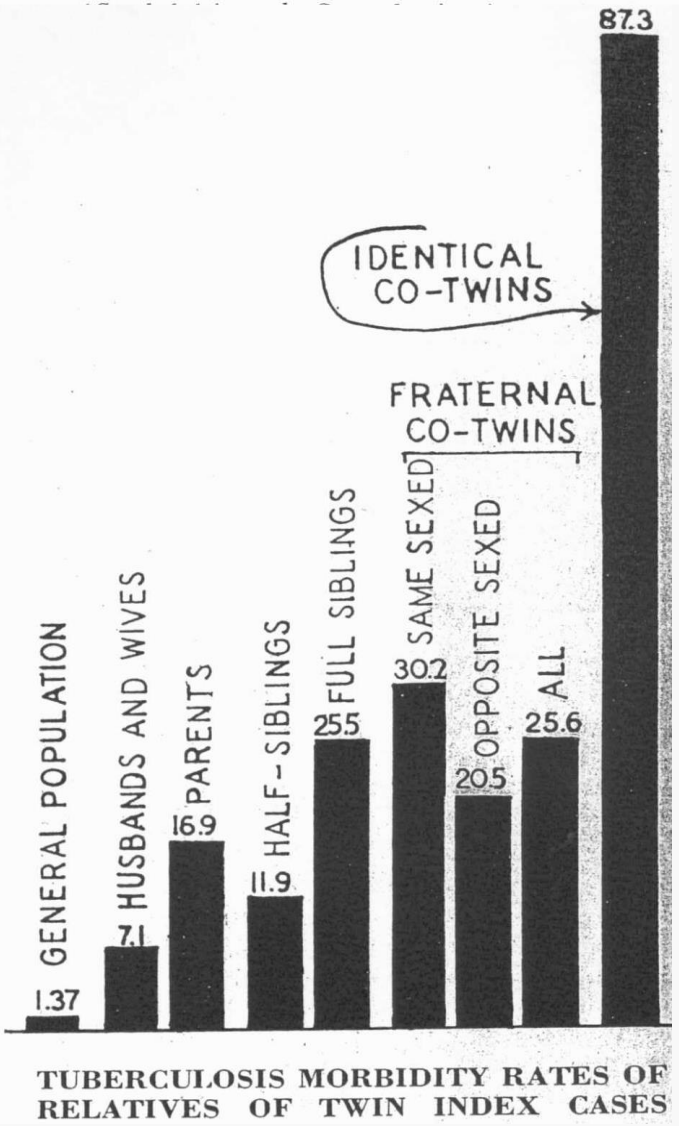
Von

Karl Diehl und Otmar Frhr. v. Verschuer

Privatdozent und Leiter der Abteilung für menschliche Erblehre des Kaiser-Wilhelm-Instituts für Anthropologie, menschliche Erblehre und Eugenik in Berlin-Dahlem

TWIN STUDIES ON GENETIC VARIATIONS IN RESISTANCE TO TUBERCULOSIS

FRANZ J. KALLMANN AND DAVID REISNER



TUBERCULOSIS MORBIDITY RATES OF RELATIVES OF TWIN INDEX CASES

Human genetics of tuberculosis

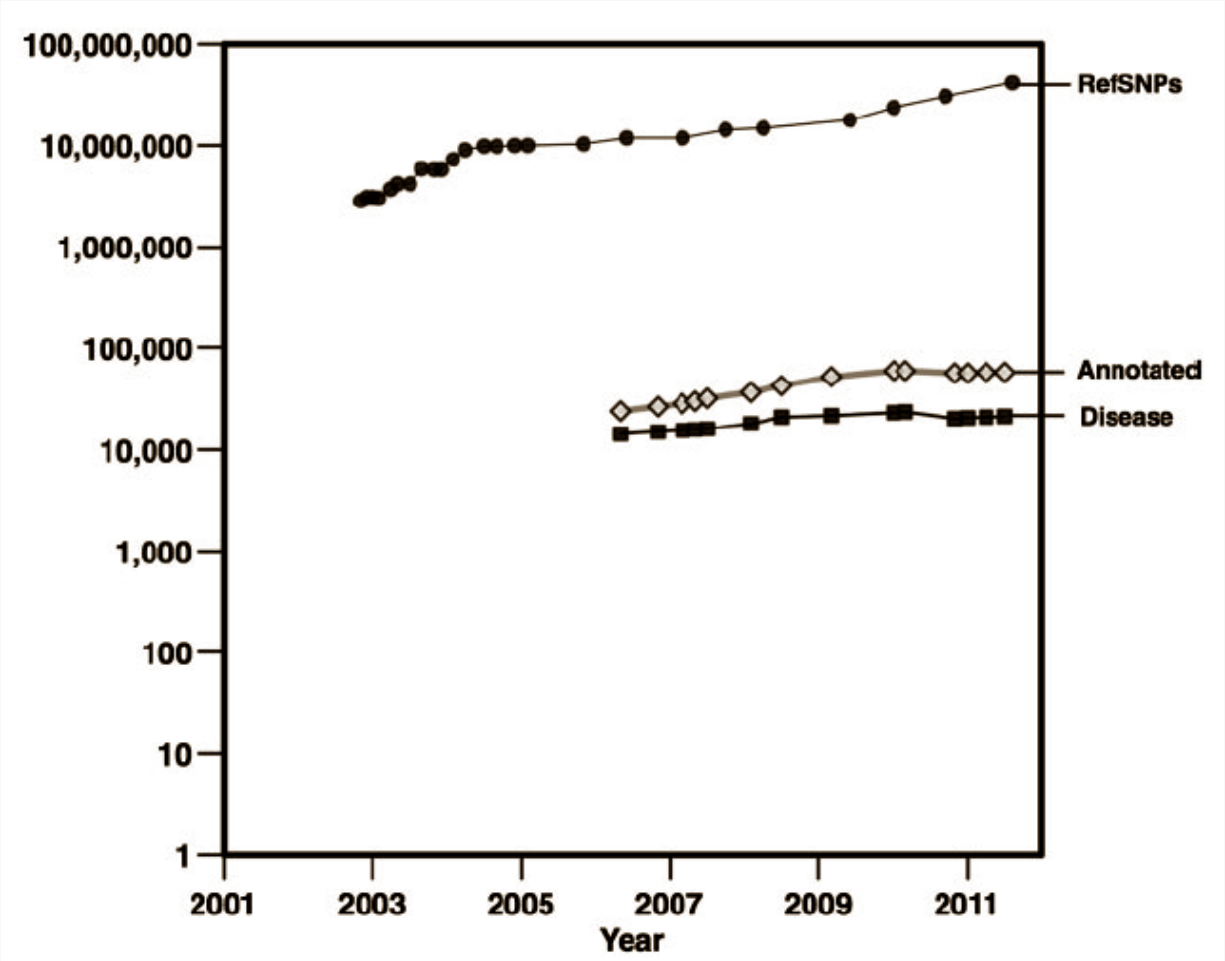
Why do some exposed individuals (and not others) get infected and develop tuberculosis?

What are the critical immunological pathways in natural conditions of infection?

→ Search of genetic variants that:
- may explain differences between individuals (in part)
- are influencing the immune response to *M. tuberculosis*

Considerable number of genetic variants

Human genome is > 3000 millions base pairs (A, T, C, G)



> 300 million reported variants in humans (most of them are <1%)

Most frequent variants are single nucleotide polymorphisms (SNPs)

(simple change of one base to another, eg from A to G)

Methods of investigation in humans

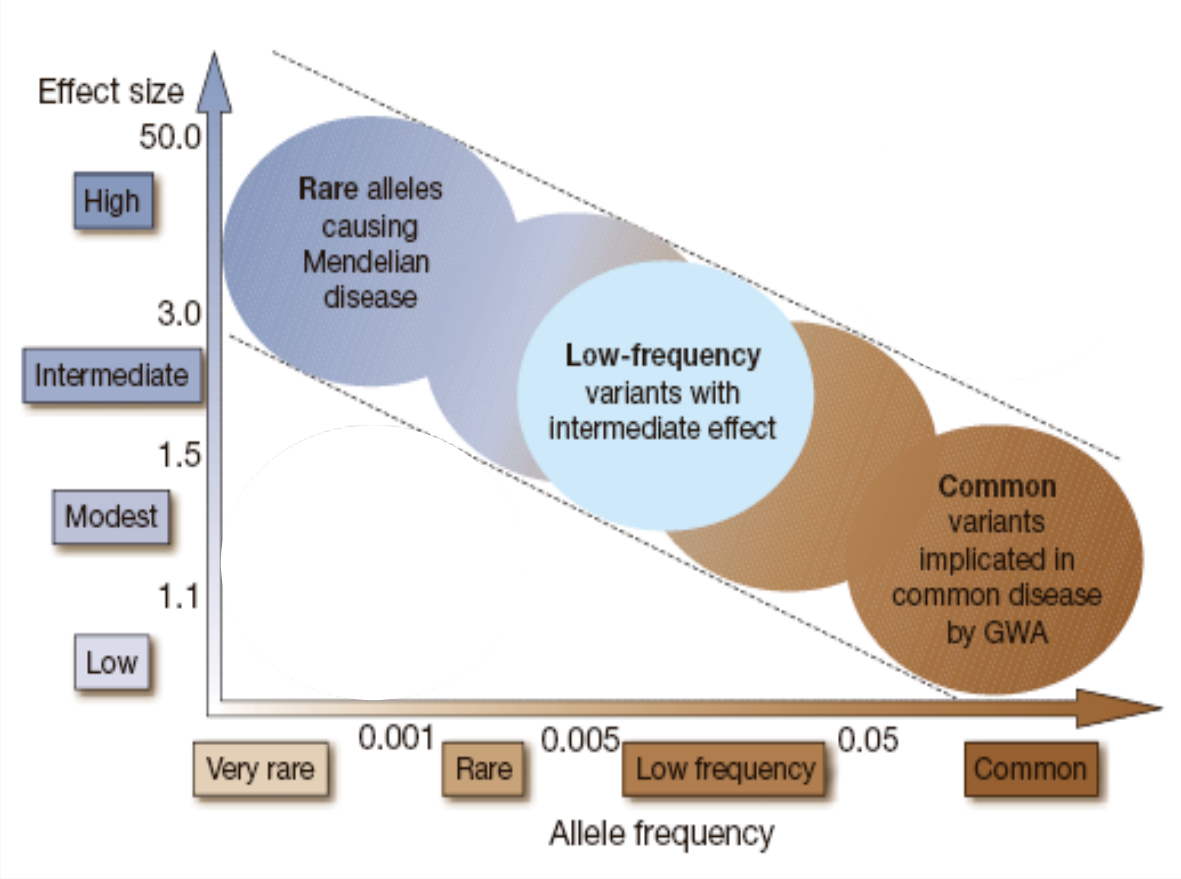
How to identify the causal genetic variant?

Phenotype	Rare: Disseminated TB (children)	Common: Pulmonary TB (adults)
Tools	**Mendelian Genetics**	**Complex Genetics**
Sample	Small	Large
	⇩	⇩
	Rare mutations **Strong individual effect**	**Common polymorphisms** **Modest individual effect**

Using the considerable progress in genomics technology:
- Ultra-high throughput genotyping: Genome-wide association studies
- Next generation sequencing: whole exome/genome sequencing

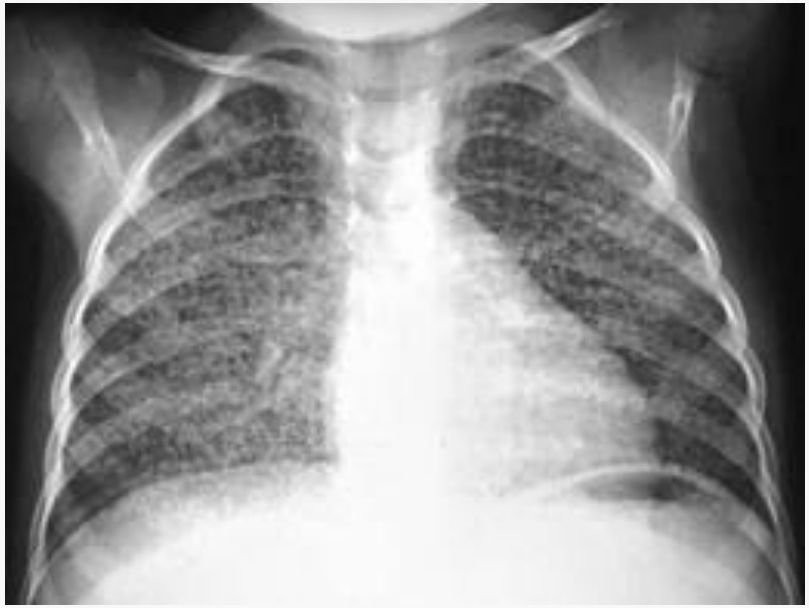
Genetic architecture of TB
→ Continous spectrum of predisposition according to individual effect and frequency of genetic variant

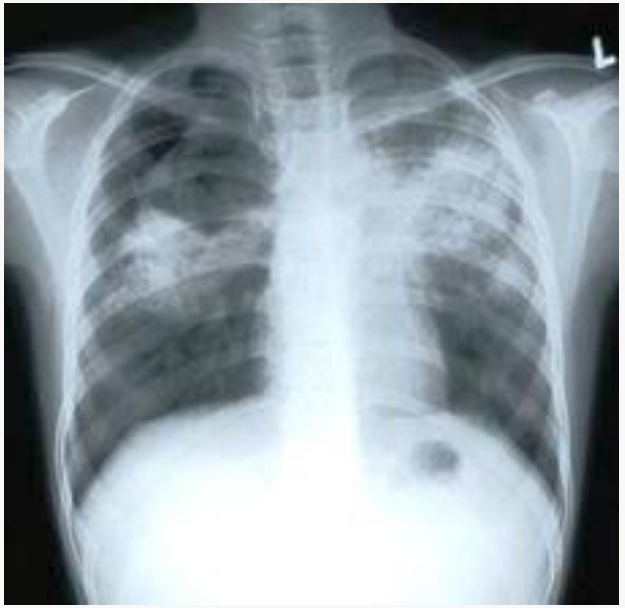
Relative risk (odds ratio, OR)



(Manolio et al, Nature, 2009)

Genetic susceptibility to TB depends on age?





Childhood TB (disseminated)

Search for rare mutations with strong individual impact

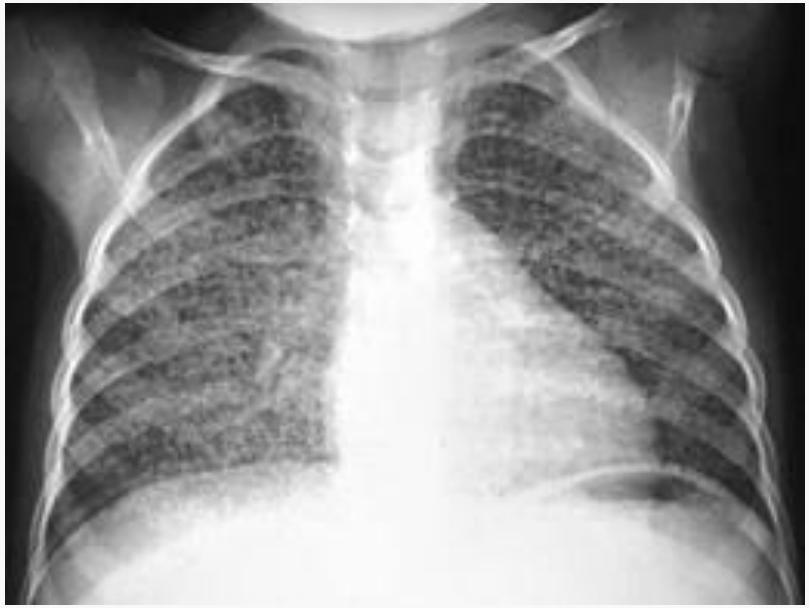
→ Mendelian/Monogenic TB

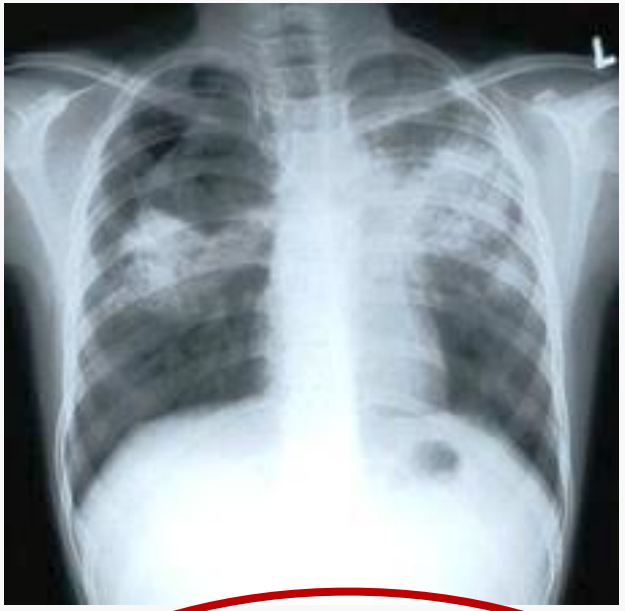
Adult PulmonaryTB

Search for common variants with modest individual effect

Very limited success

Genetic susceptibility to TB depends on age?





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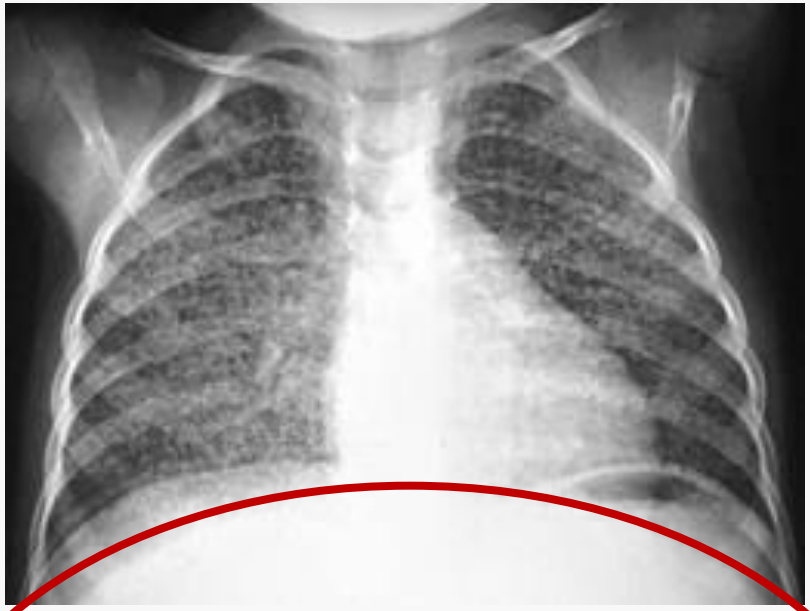

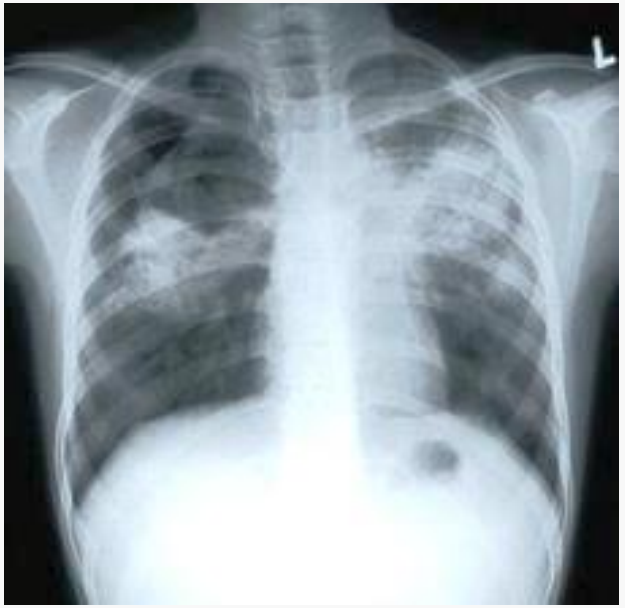

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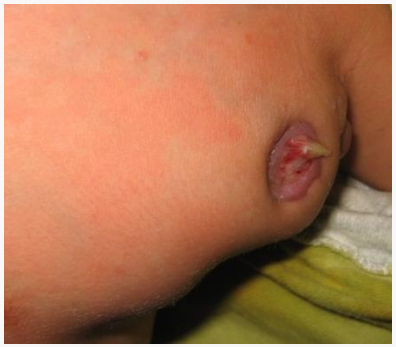
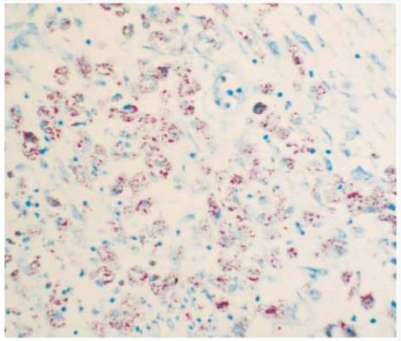
Mendelian Susceptibility to Mycobacterial Disease (MSMD)

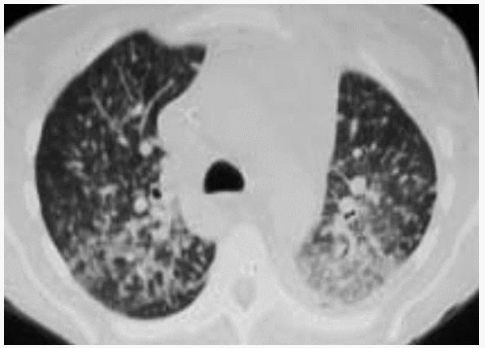
- **Rare syndrome: 1/100,000**
- **Infections by BCG and environmental mycobacteria**
- **Otherwise healthy individuals**
- **Familial forms and parental consanguinity frequent**



BCGitis

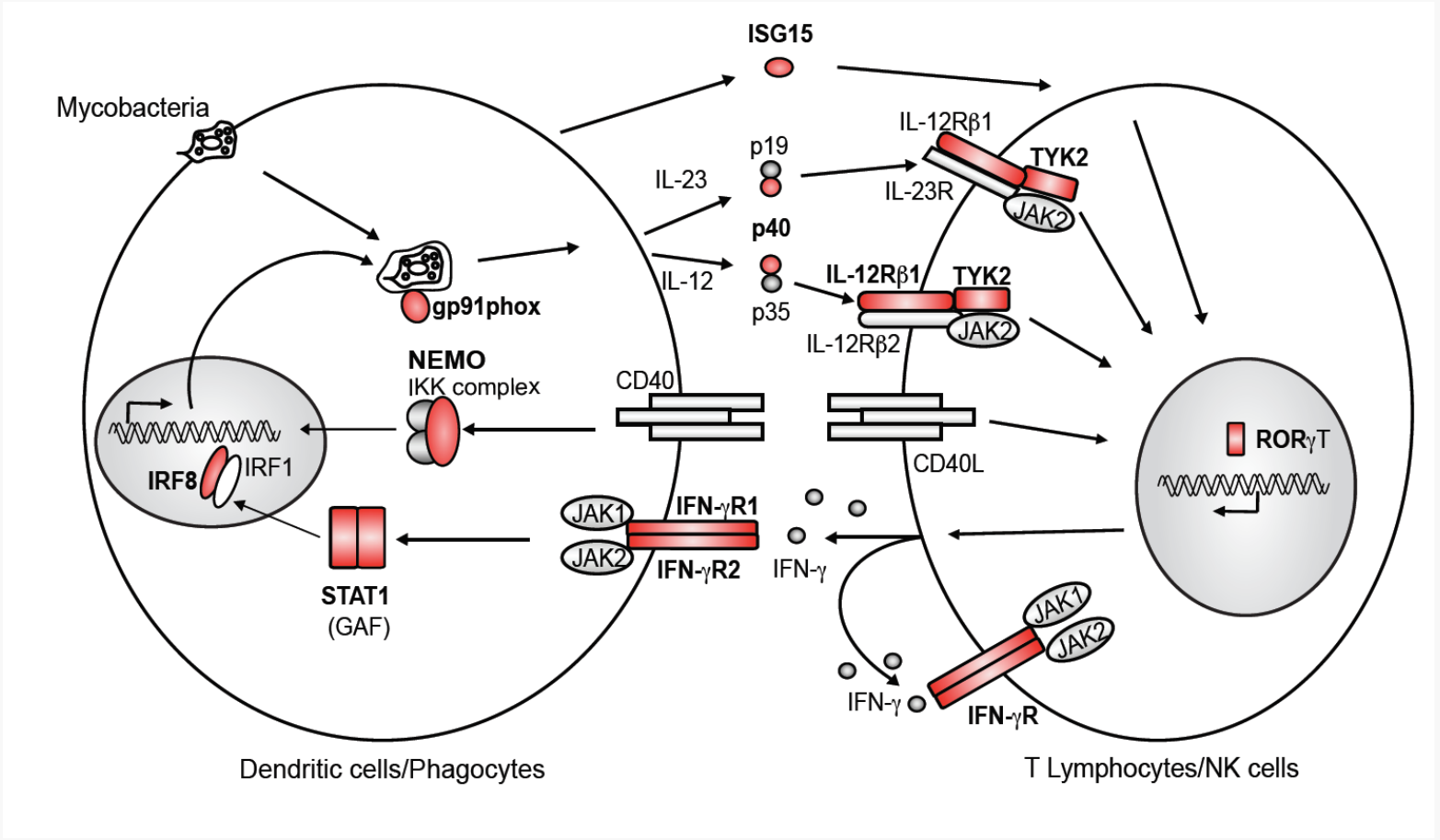


Poor granulomatous reaction



Disseminated *M. avium* infection

MSMD: genetic defects in IL-12/-23 /IFN-γ pathway



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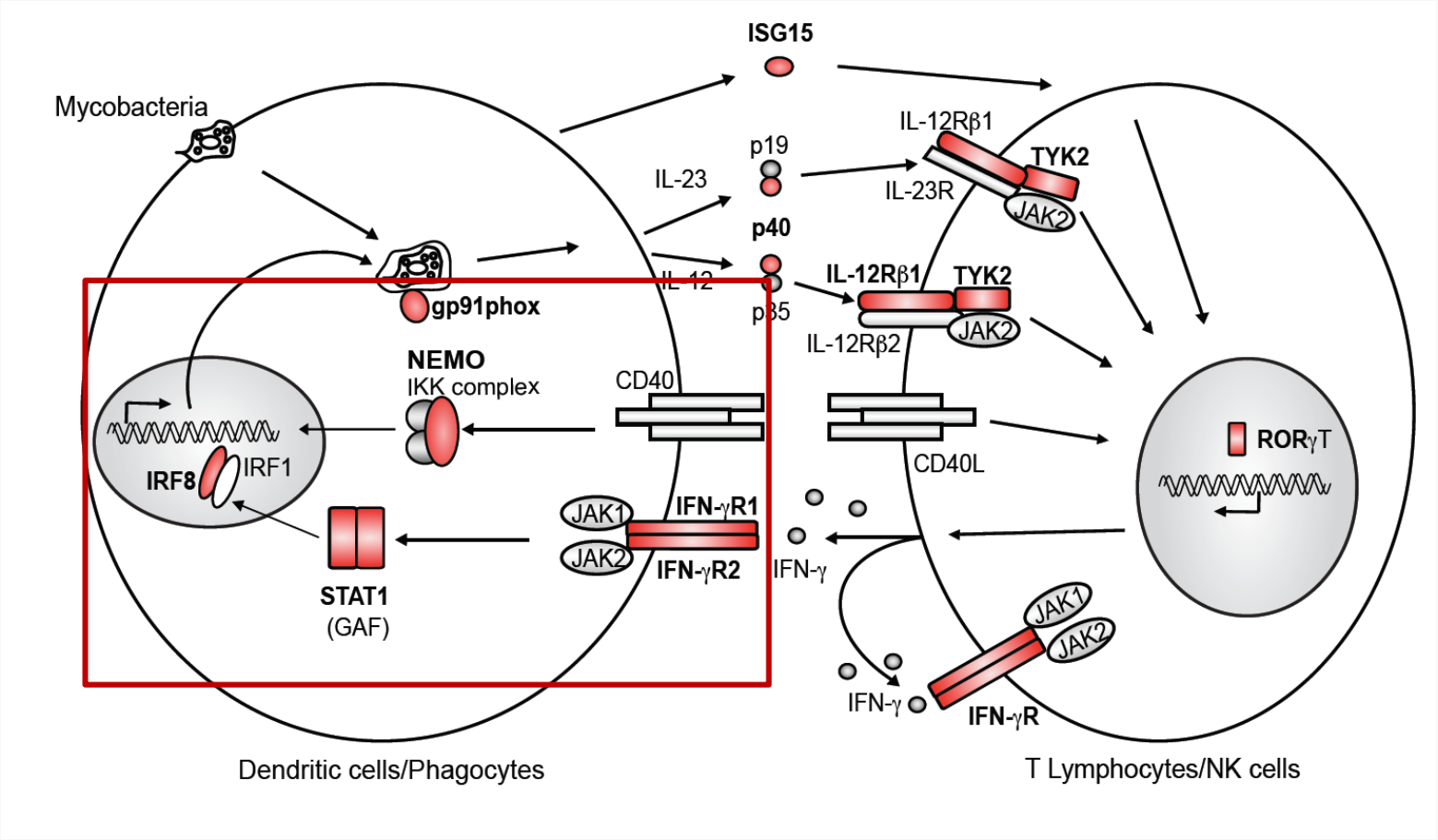
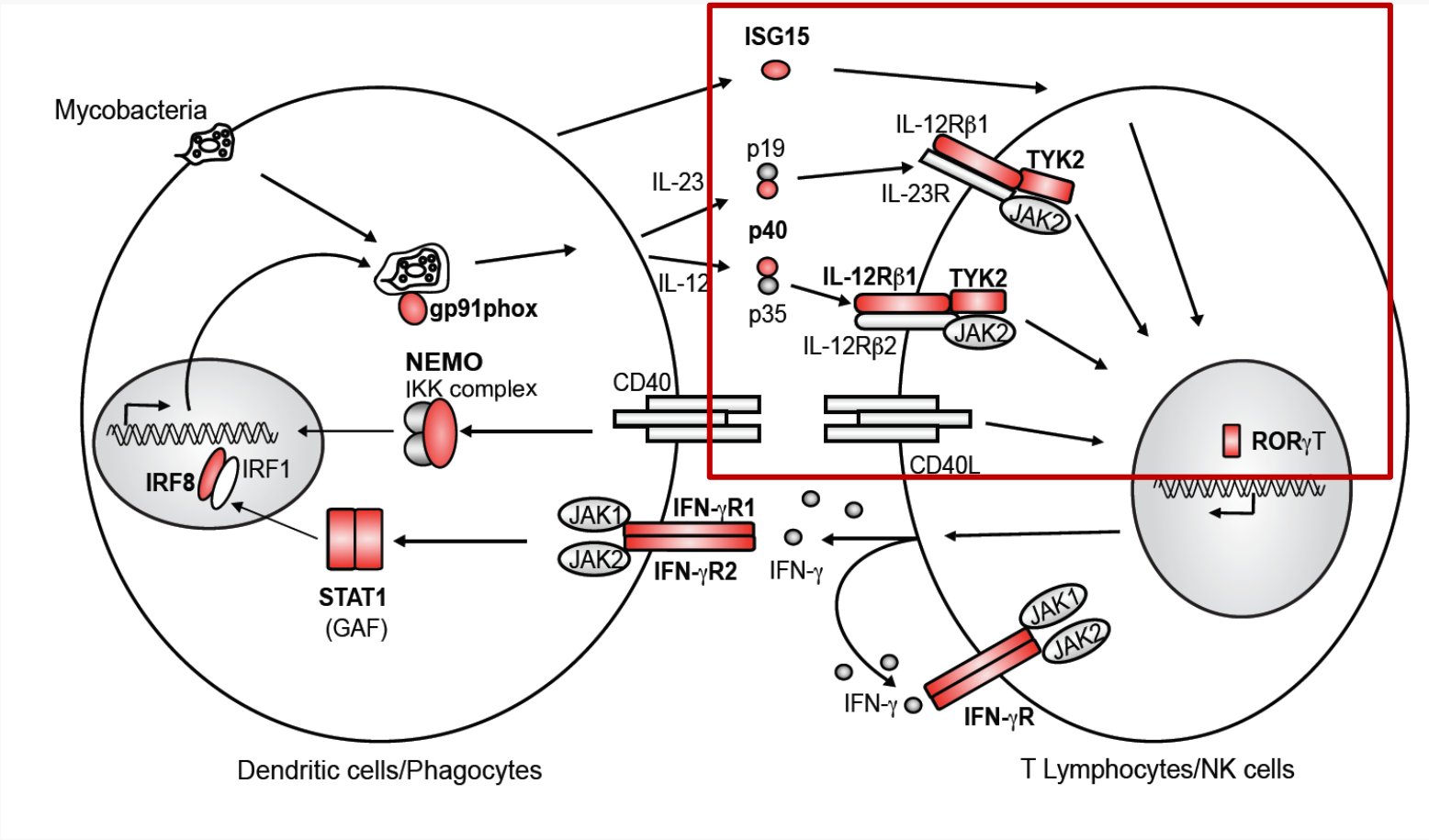


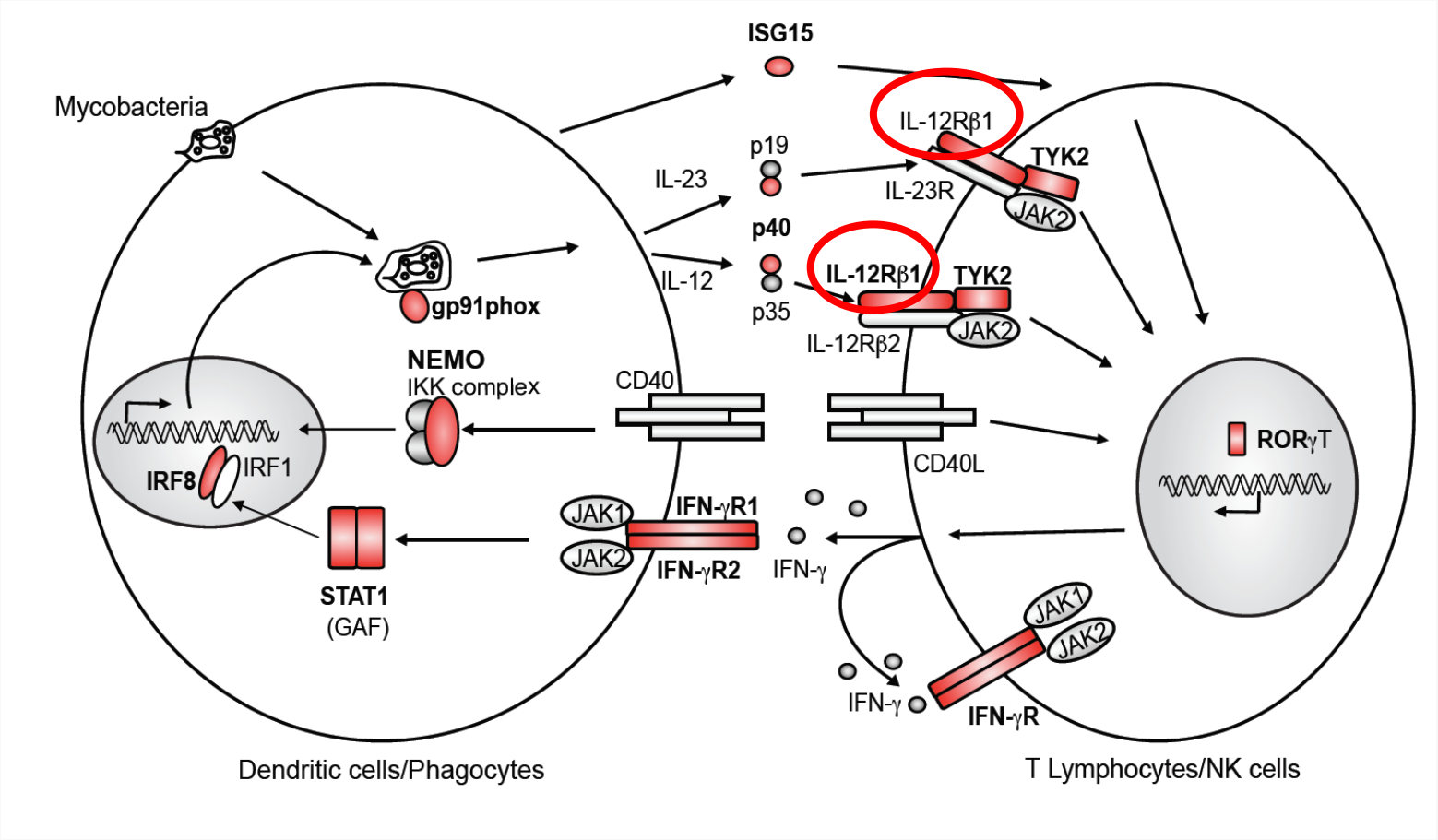
→ **Impaired response to IFN-γ**

MSMD: genetic defects in IL-12/-23 /IFN-γ pathway

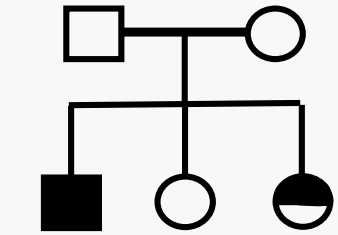


→ **Impaired production of IFN-γ (amenable to IFN-γ treatment)**

First evidence of Mendelian TB



→ **Complete autosomal recessive (AR) IL-12Rβ1 deficiency**

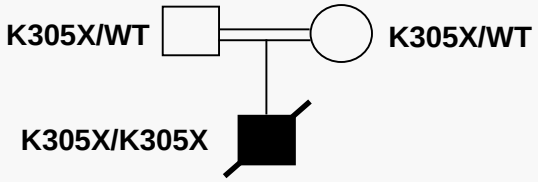


MSMD **Abdominal TB**

Mendelian TB → Candidate gene : *IL12RB1*

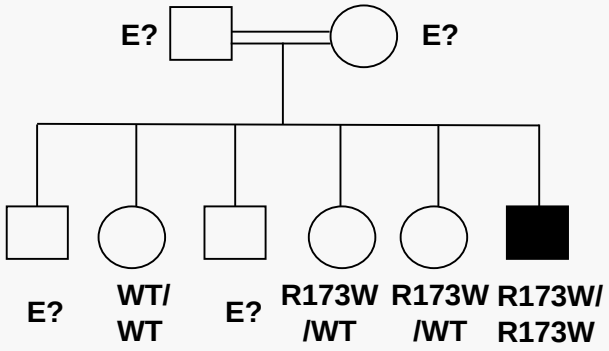
50 TB severe children patients from Turkey, Iran and Morocco

→ Identification of TWO patients with complete autosomal recessive (AR) IL-12Rβ1 deficiency



P1

From Morocco
BCG vaccinated at birth (no adverse effect)
Severe pulmonary TB at 13 years



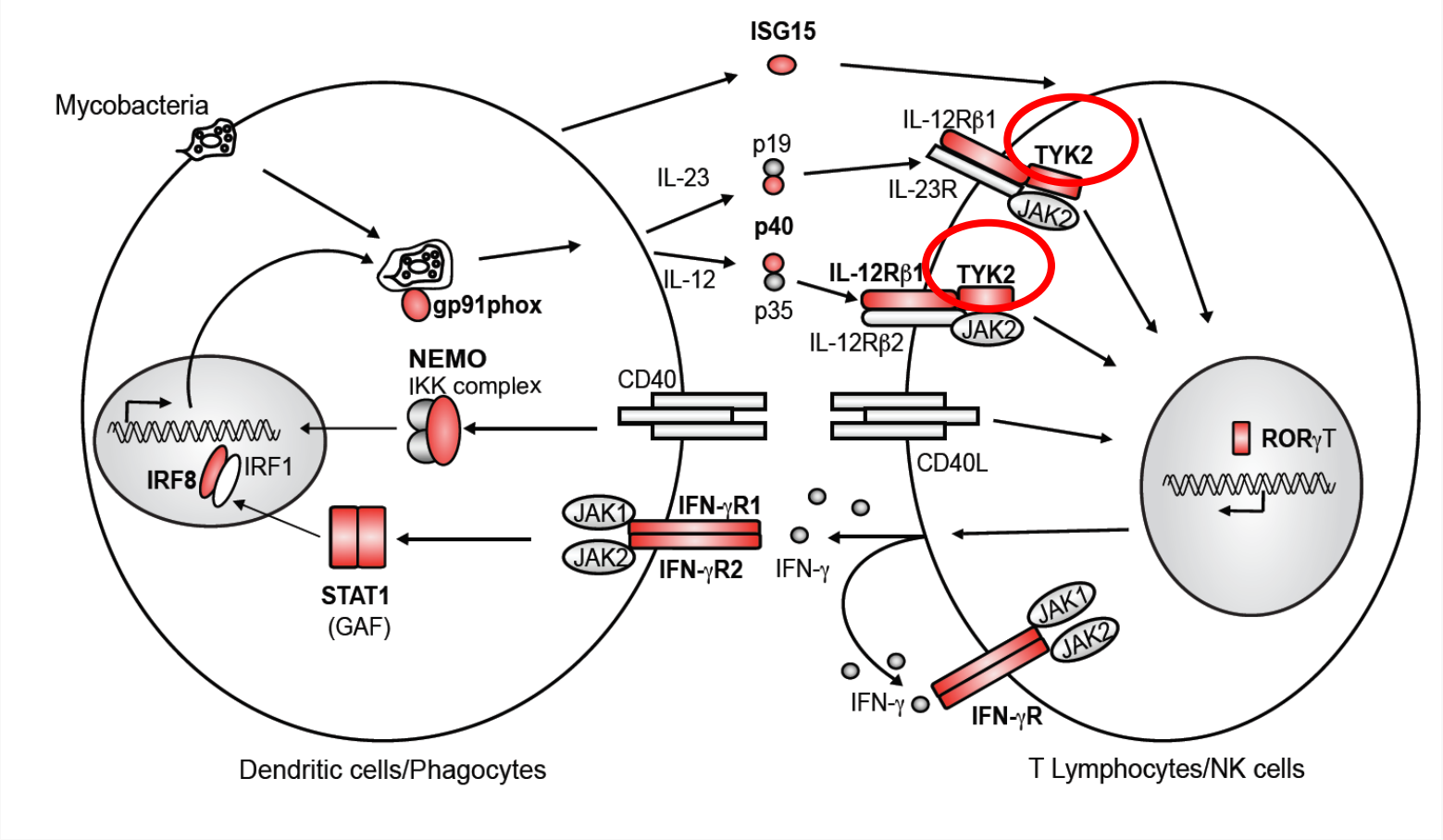
P2

From Iran
BCG vaccinated at birth (no adverse effect)
Severe pulmonary TB at 7 months of age
Extrapulmonary TB at 6 years

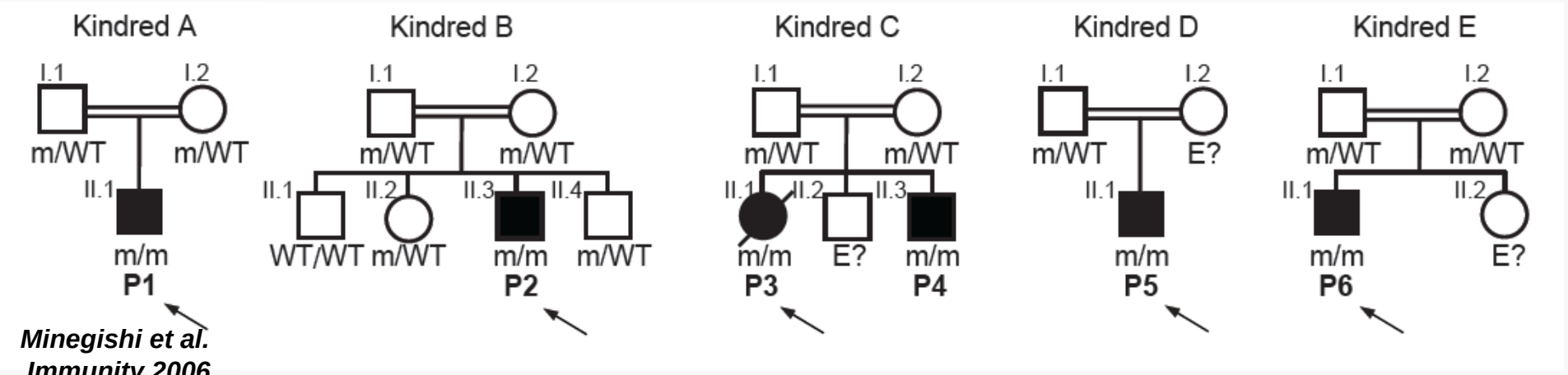
→ Proof of principle for Mendelian TB

→ Search for other genes by next generation sequencing approaches

From rare to common monogenic causes of TB: TYK2 deficiency



AR TYK2 complete deficiency in 4 new families

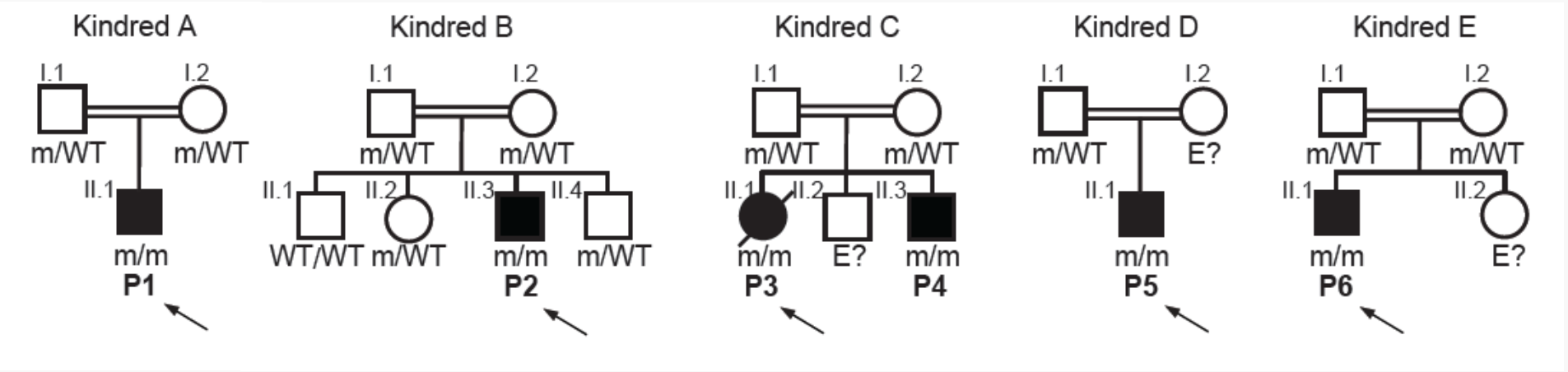


Minegishi et al. Immunity 2006

	P1	P2	P3	P4	P5	P6
Sex	Male	Male	Female	Male	Male	Female
Country	Japan	Turkey	Morocco	Morocco	Iran	Iran
Atopy/Dermatitis	yes	no	no	no	no	no
Elevated IgE	yes	no	no	no	no	no
S. aureus infections	yes	no	no	no	no	no
Viral infections	HSV, PI3, MC	VZV	no	yes?	no	no
Intracellular bacteria	BCG, Salmonella	BCG, Brucella	*M. tuberculosis*	yes?	BCG	*M. tuberculosis*
Fungal infections	C. albicans	no	no	no	no	no
Homozygous mutati	C70HfsX21	767X	T1106HfsX4	T1106HfsX4	E154X	S50HfsX1

Kreins et al
J Exp Med 2015

AR TYK2 complete deficiency in 4 new families



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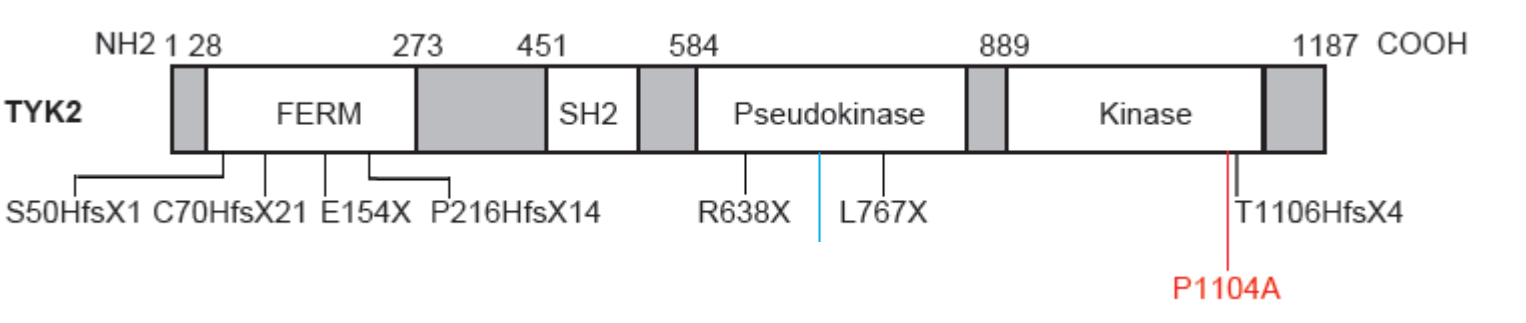
Abdominal TB ***Miliary***

Investigation of a more common TYK2 variant: P1104A

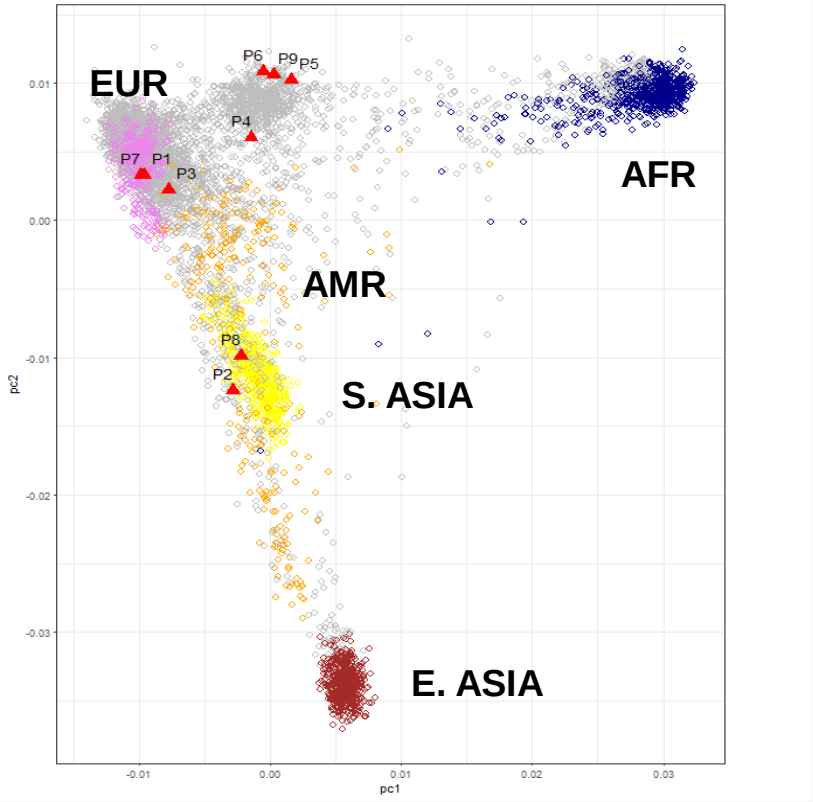


In our exome database of >6000 subjects:
11 P1104A homozygotes including 10 in mycobacterial diseases:

- **7 in TB (out of 455 patients)**
- **3 in MSMD (out of 463 patients)**
- **1 in other conditions (out of 5359)**

Highly significant when accounting for ethnic heterogeneity (PCA):

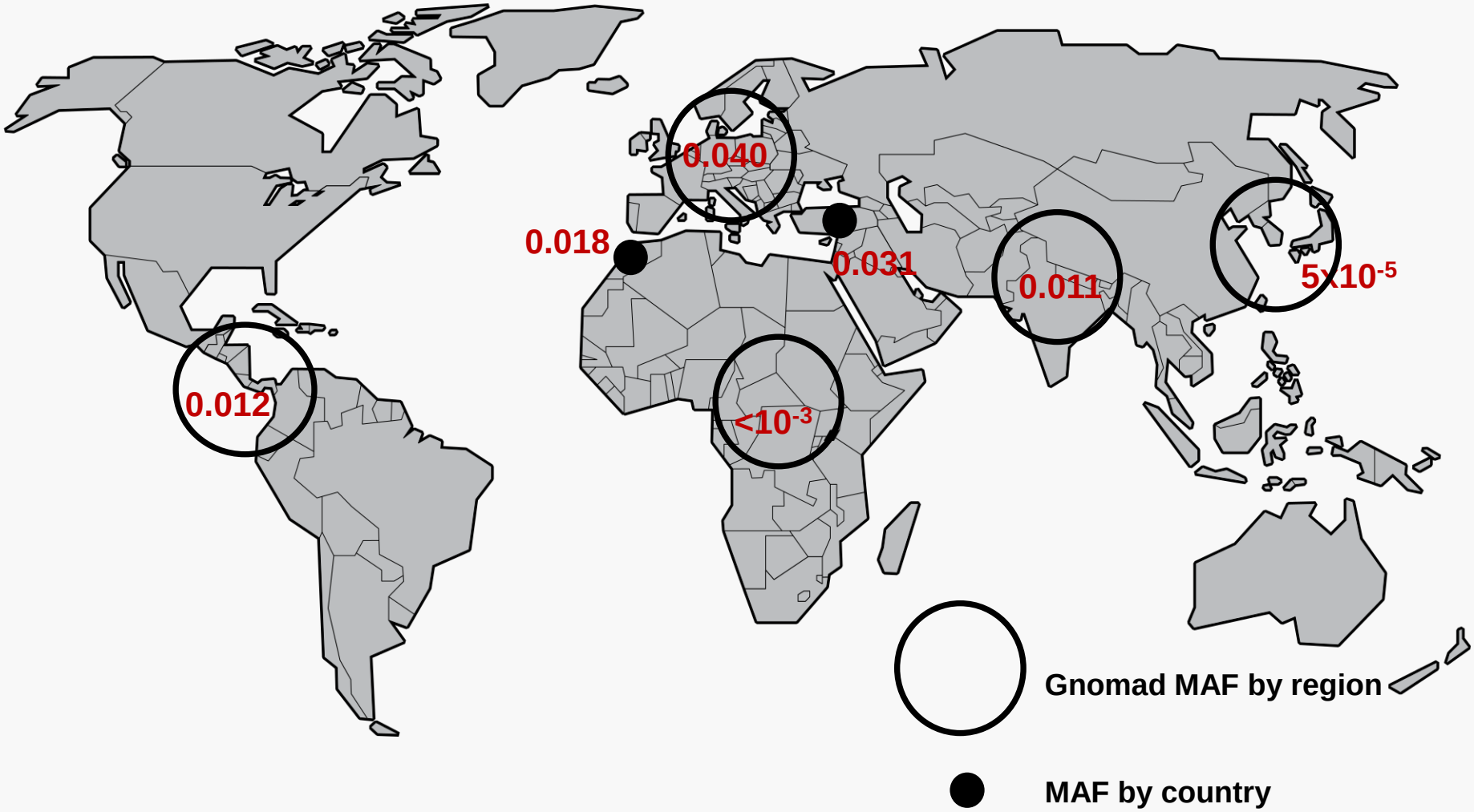
- TB: OR ~ 90, p = 8×10^{-8}
- TB+MSMD: OR ~ 60, p = 3×10^{-8}



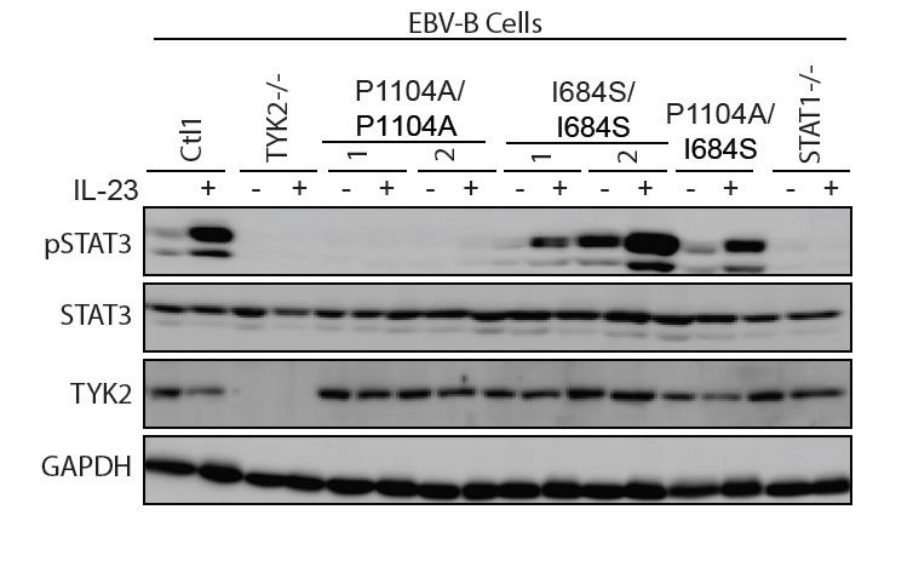
→ **Strong enrichment of P1104A homozygotes in TB**

Boisson-Dupuis et al Science Immunol 2018

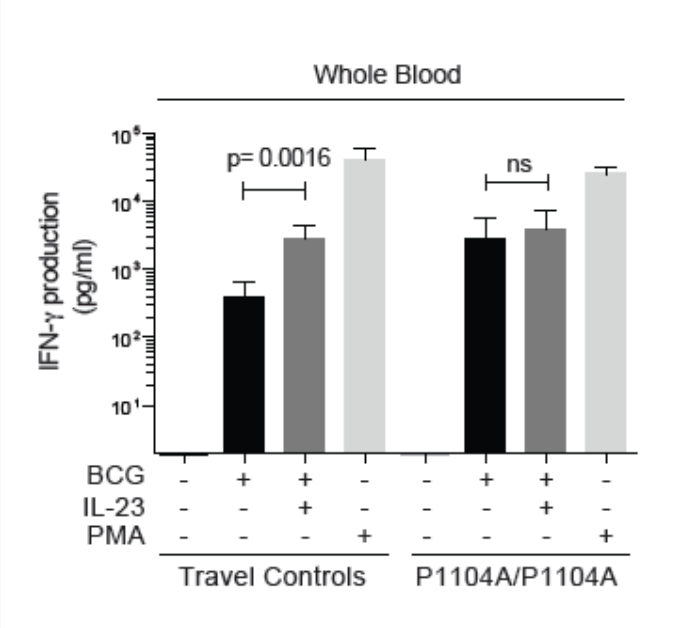
Worldwide P1104A frequency



Impaired response to IL-23



Impaired response to IL-23
for P1104A homozygotes
in EBV-B cells



Impaired IFN-γ production
in response to IL-23
in whole blood

→ **Impairment of IL-23 mediated IFN-γ immunity**

Replication in the UK Biobank data

503,000 participants

40-69 years old

22 recruitment centres

89% England

7% Scotland

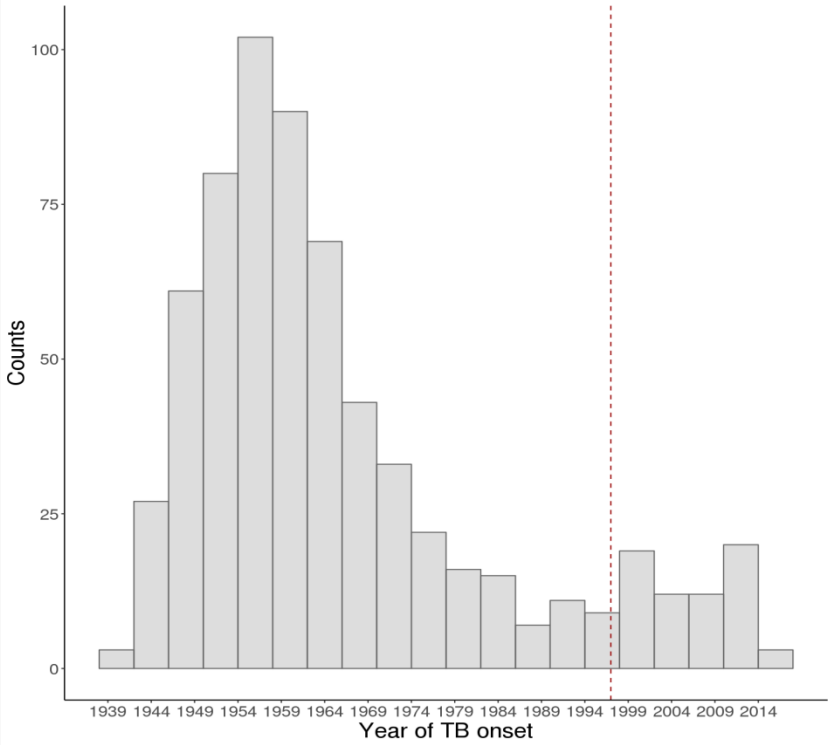
4% Wales

Enrichment of P1104A homozygotes in TB

GWAS array with imputed data.

Doctor-diagnosed TB:
620 with TB and 114,473 without

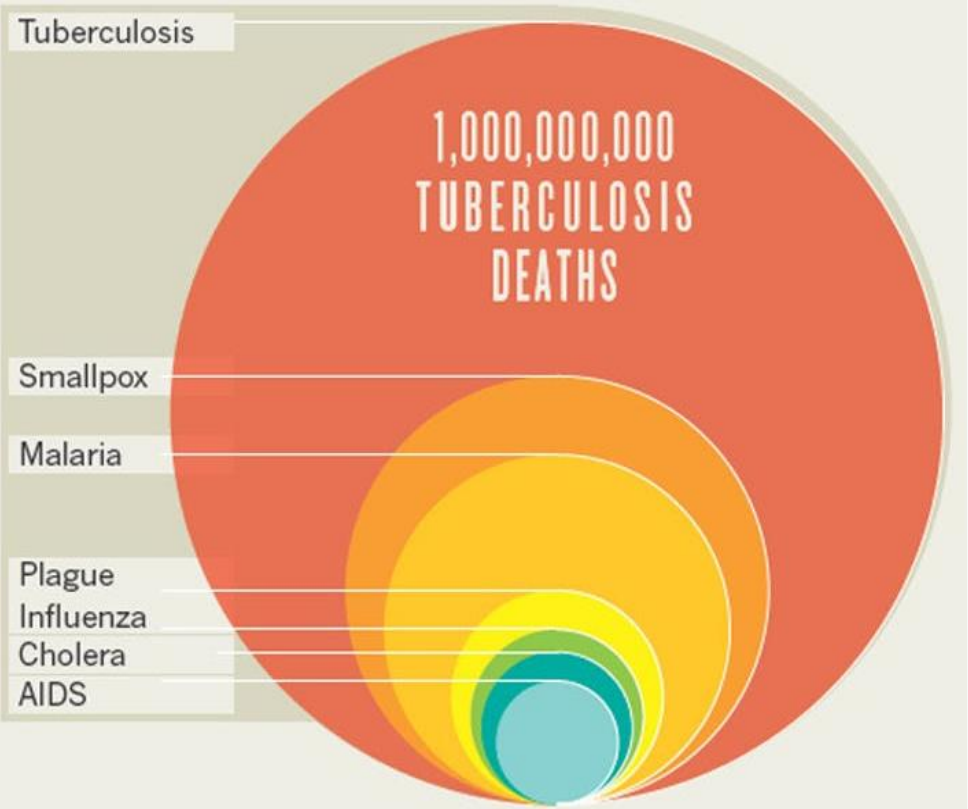
P1104A	TB	Controls
Homozygous	**6 (1%)**	**228 (0.2%)**
Non homozygous	614	114,245



Odd ratio of developing TB adjusted for ethnic origin:
OR= 5.0 (1.96-10.31), p=0.002

Kerner et al
PNAS 2019

TYK2 P1104A: Population genetic studies
(*Quintana-Murci lab*)



TB has killed more than any other infectious disease during the last 200 years

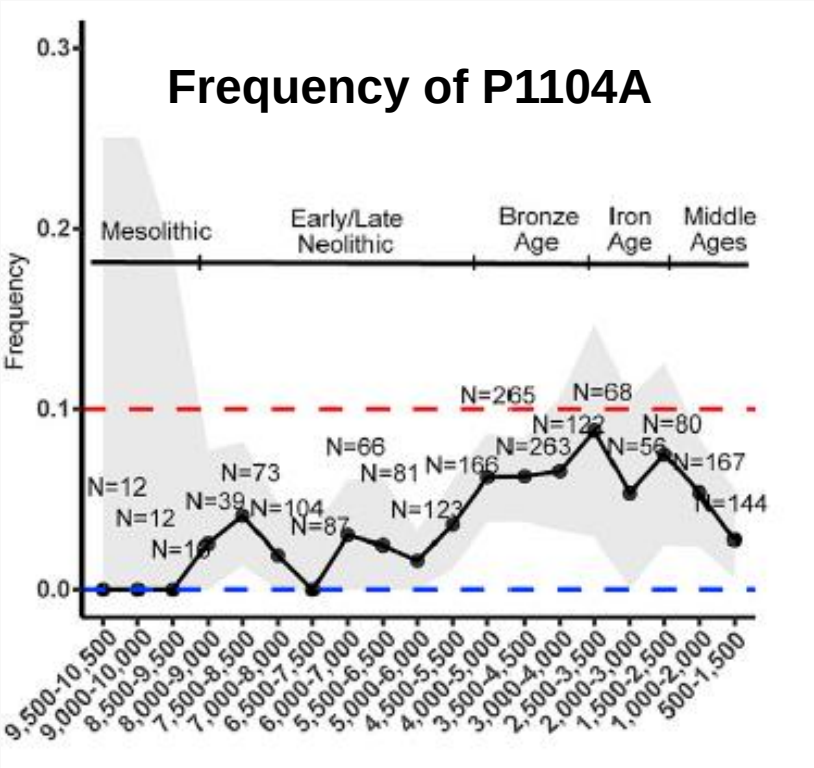
→ Selection pressure exerted by TB

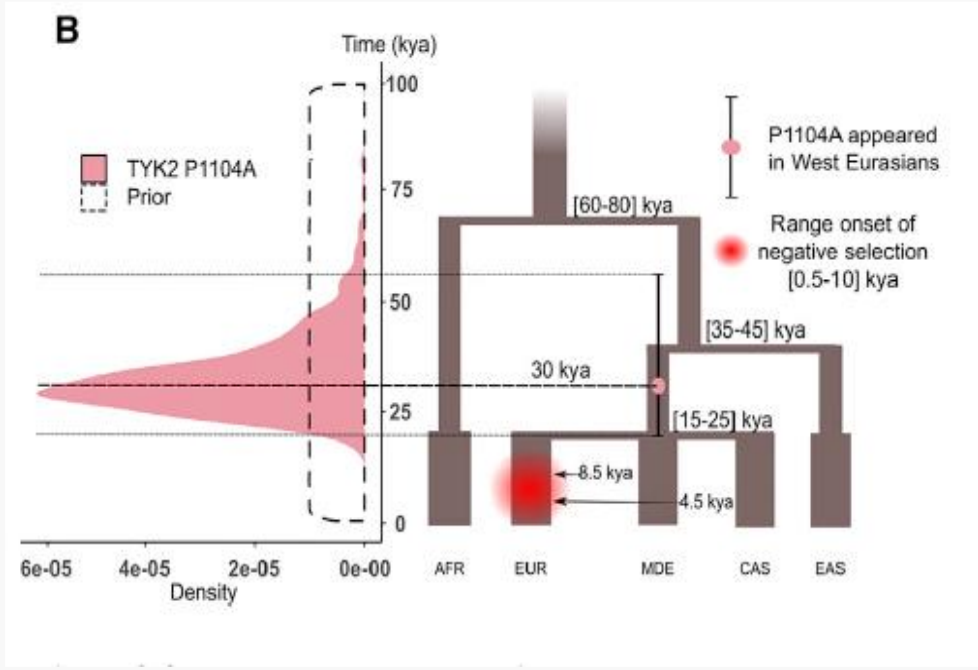
WHO, 2020;
Paulson T. Nature 2013

Human ancient DNA analyses reveal the high burden of tuberculosis in Europeans over the last 2,000 years

Gaspard Kerner,[1,2,3,*] Guillaume Laval,[1] Etienne Patin,[1] Stéphanie Boisson-Dupuis,[2,3,4] Laurent Abel,[2,3,4] Jean-Laurent Casanova,[2,3,4,5,7] and Lluis Quintana-Murci[1,6,7,*]

The American Journal of Human Genetics *108*, 517–524, March 4, 2021





Using ~1000 ancient DNAs

Increase in frequency until 2000-3000 BC
Strong decline since then

Origin of P1104A ~30,000 yrs ago

Strong negative selection starting ~2000 yrs ago

Conclusions

Recessive TYK2 P1104A condition represents a common monogenic etiology of TB
It may underlie TB in about 1% of Europeans (up to 0.5% elsewhere except East Asia and Subsaharan Africa)

Blurs the dichotomy between rare monogenic and common complex predisposition

P1104A selectively impairs IL23-dependent IFN-γ anti-mycobacterial immunity
→ Implications for treatment (recombinant IFN-γ), prevention

Opposite protective effect (ORs ~0.2 for homozygous) in several inflammatory or autoimmune disorders (Crohn, ankylosing spondylitis, rheumatoid arthritis…):
- Growing incidence of inflammatory conditions due to selection of stronger immune responses by deadly infectious diseases as TB.
- Advantages and disadvantages of TYK2 inhibitors:
  may need similar procedures as anti-TNF drugs

→ Search for other monogenic causes of TB

S. Boisson-Dupuis
Xiao-Fei Kong
Alexandra Kreins
Masato Ogishi
Quentin Philipot
Rui Yang

Alexandre Alcaïs
Jacinta C. Bustamante
Aurélie Cobat
Clement Conil
Gaspard Kerner
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Medical clinicians around the world