Single-gene disorders of immunity

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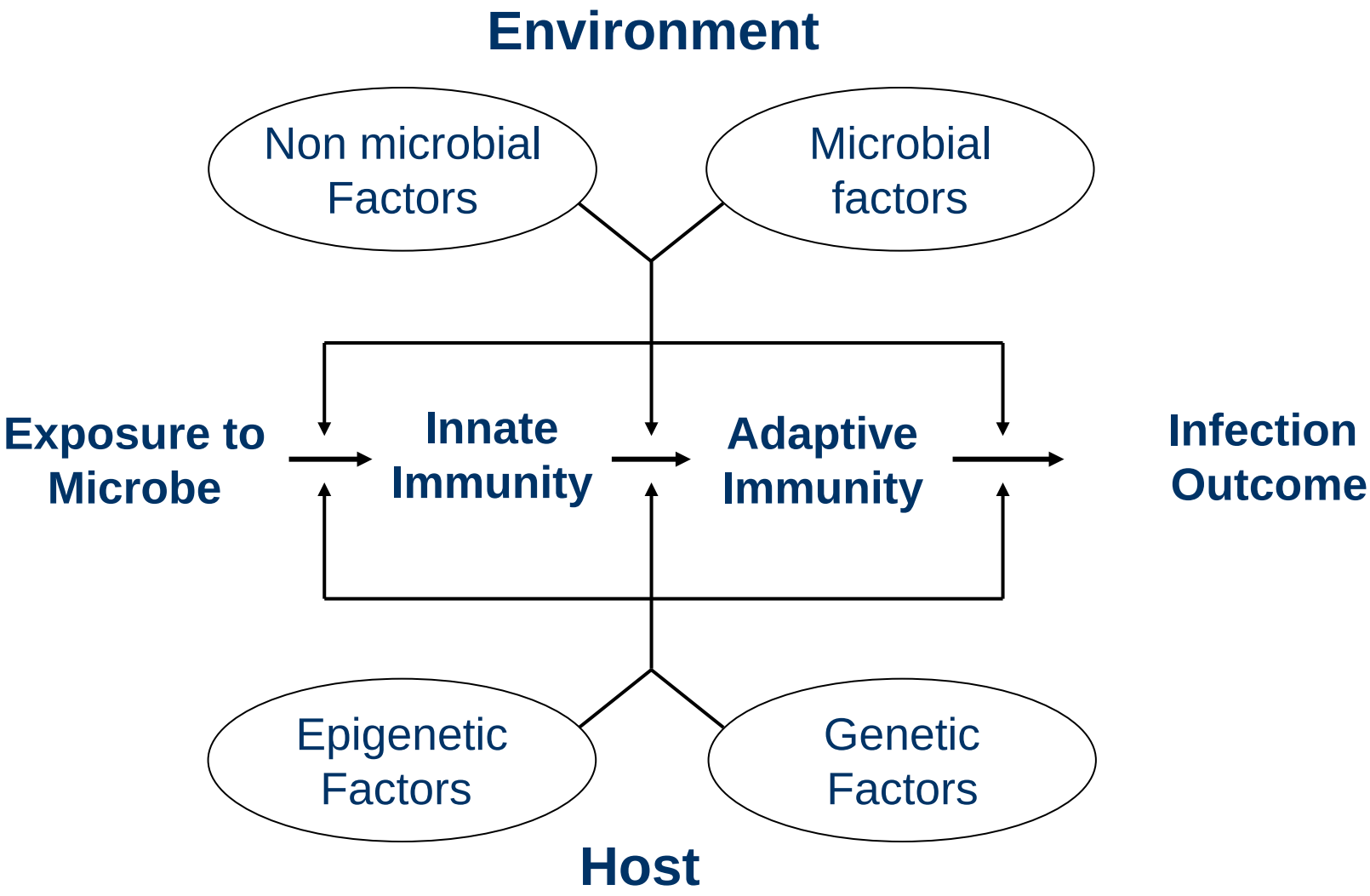
Aims

- To introduce the concept of human genetics of infectious diseases
- To introduce the concept of primary immunodeficiency
- To explain how single gene variants are important contributors to life threatening childhood infections
- To understand pathogenesis in immunological and genetic terms


Environment
Non microbial Factors
Microbial factors
Exposure to Microbe
Innate Immunity
Adaptive Immunity
Infection Outcome
Epigenetic Factors
Genetic Factors
Host

Historical Advances

Microbial theory of infectious disease

Pasteur (1865-1870)

Microbes cause disease in silkworms

Koch (1884) Koch's postulates

1. The microorganism must be found in in all suffering from the disease, but not in healthy.
2. The microorganism must be isolated from a diseased organism and grown in pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be re-isolated from the inoculated, diseased experimental host.

Genetic theory of infectious disease

Nicolle (1911-1917) Clinical variability of infected population

Described coexistence of symptomatic and asymptomatic infections in human populations

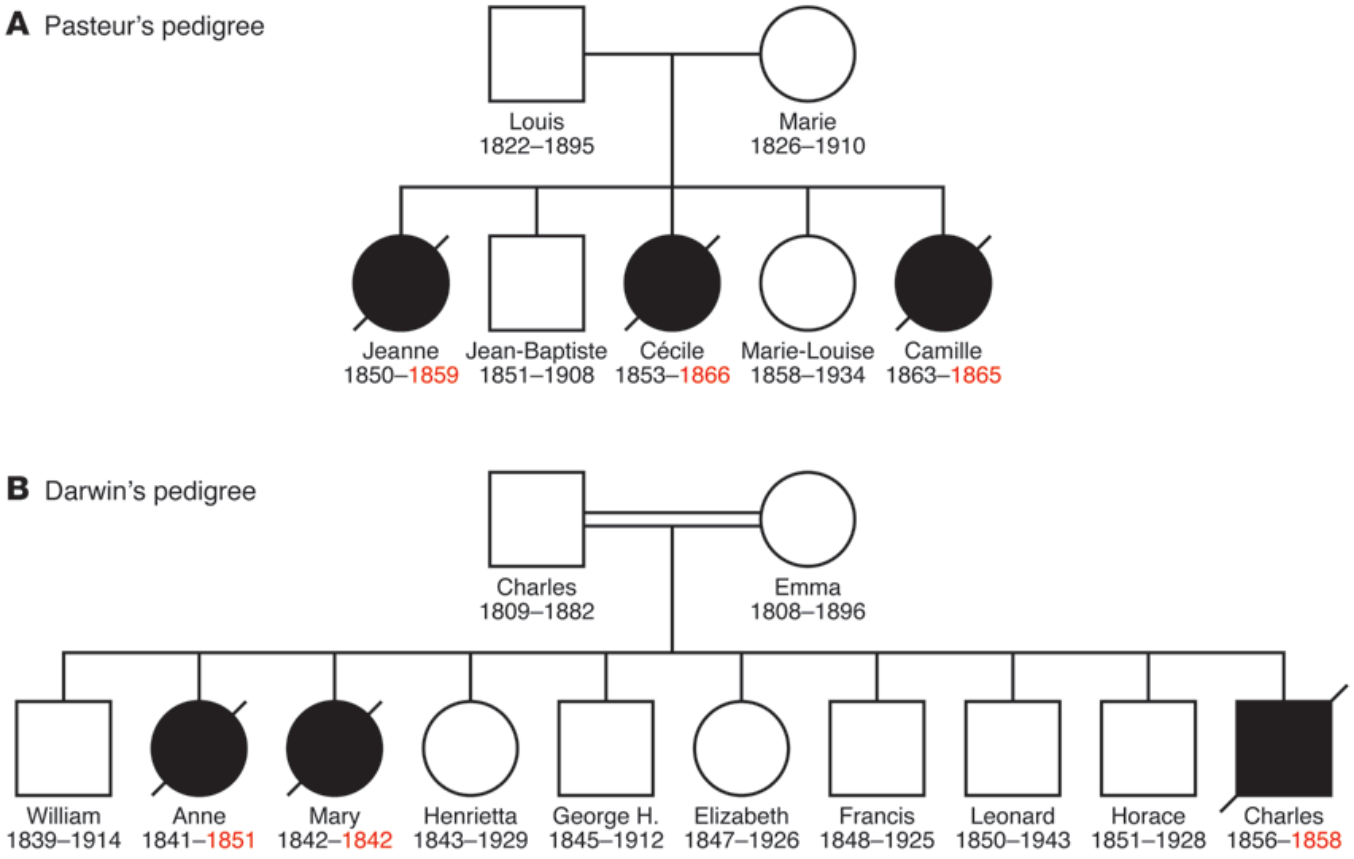
Bruton (1950s) X linked agammaglobulinemia

XLA, lack of mature B cells

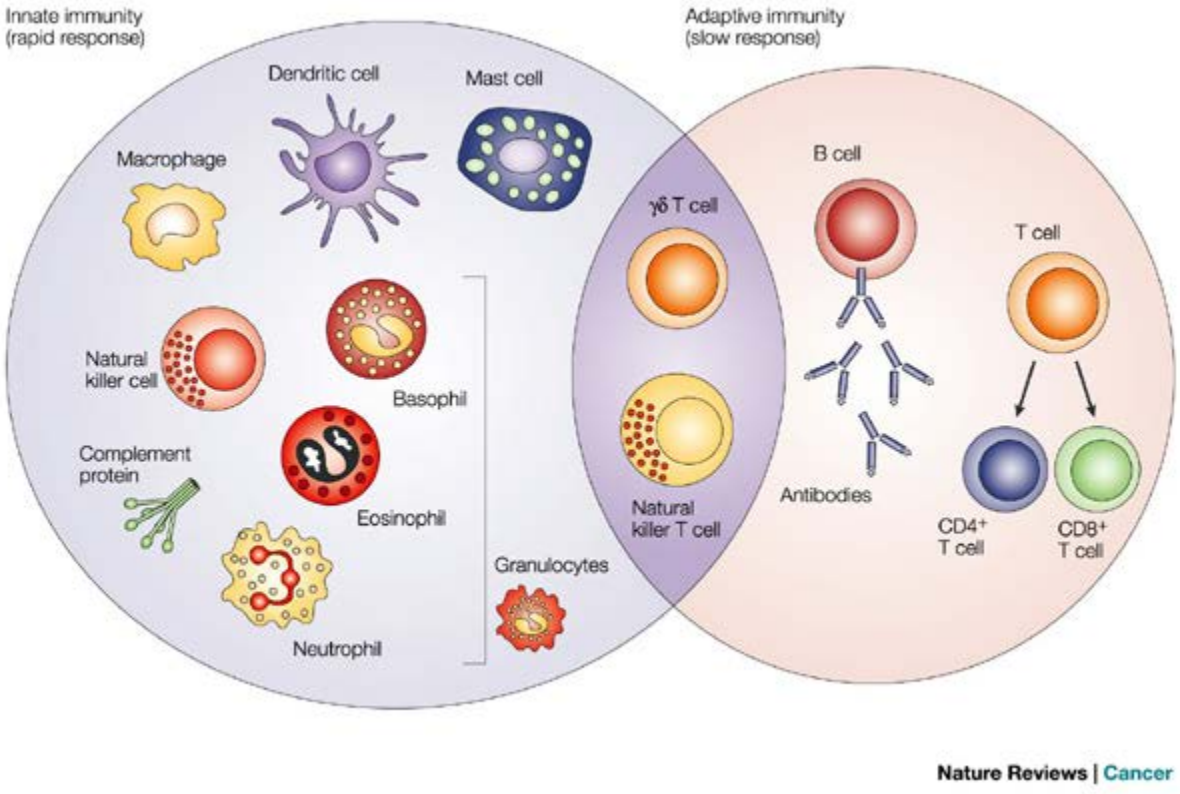
Allison (1950s) Protective role of sickle cell trait in malaria

Alcais et al (2009) JCI

Genetic theory of infectious disease



Immune response



Immunodeficiencies

Primary Immunodeficiency

Inherited or genetic disorders that affect the immune system

a number of rare diseases (that) feature a heightened susceptibility to infections from childhood onward

e.g. severe congenital neutropenia (*ELANE, HAX1, WAS*)
X-linked agammaglobulinemia (*XLA*)
severe combined immunodeficiency (*ADA, RAG1, RAG2*)

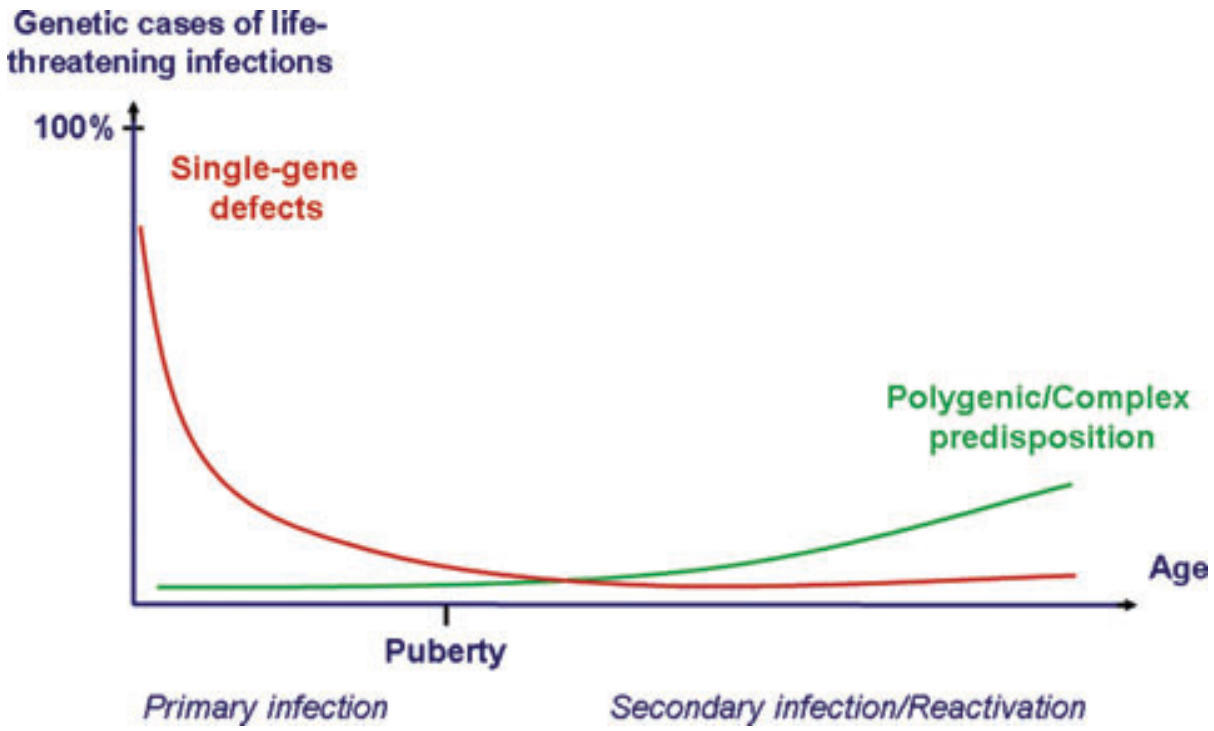
Secondary/Acquired Immunodeficiency

Compromised immune system due to environmental factors

e.g. HIV, burns, medication

The human model

a genetic dissection of immunity to infection in nature



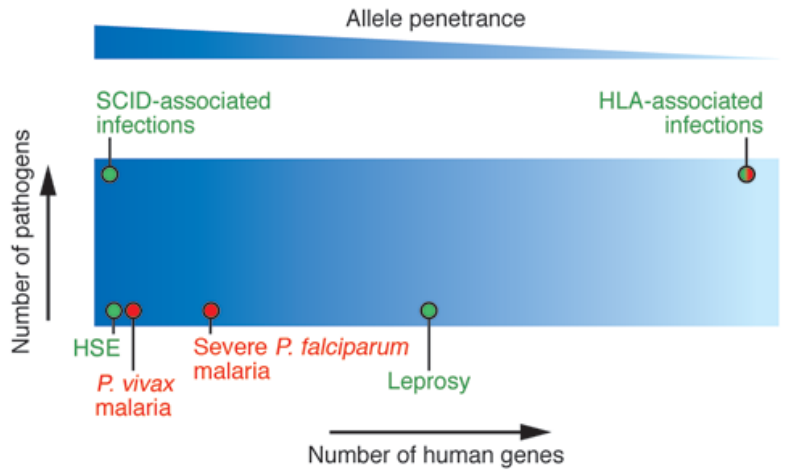
Predisposition to infectious diseases segregates in either a Mendelian or polygenic pattern of inheritance.

Alcais et al (2010) Ann NYAS

Single gene inborn errors of immunity

Classic PIDs:
One gene, multiple infections
Severe congenital neutropenia
XLA
SCID

Non-Classic PIDs:
One gene, single infection



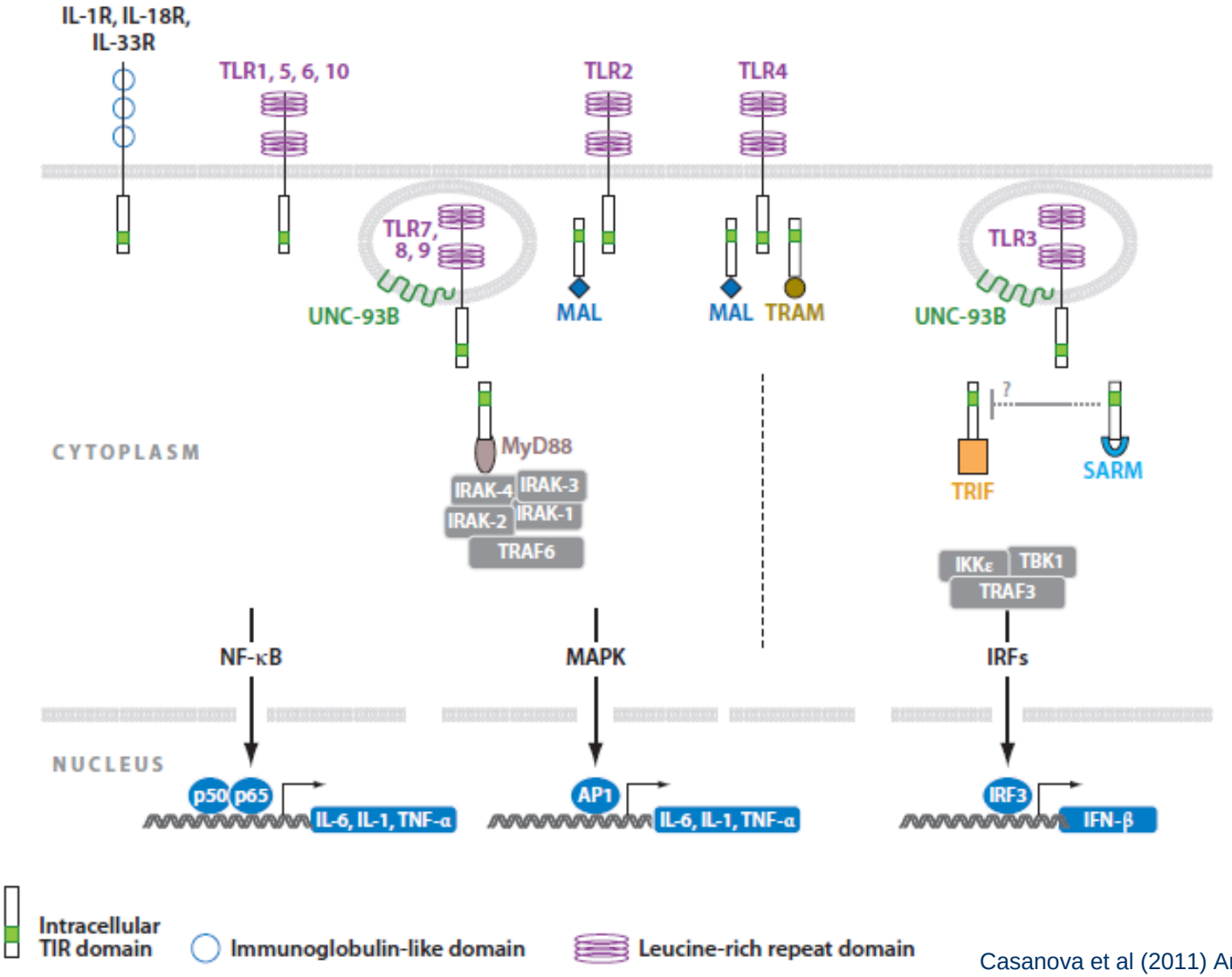
Mendelian holes in immunity to infection

Infectious agent	Clinical phenotype	Immunological phenotype	Gene	Refs.
Neisseria	Invasive disease	MAC deficiency	*C5, C6, C7, C8A, C8B, C8G, C9*	Reviewed in ref. 16
	Invasive disease	Properdin deficiency	*PFC*	
Mycobacteria	MSMD	IL-12/IL-23–IFN-γ deficiency	*IFNGR1, IFNGR2, STAT1, NEMO, IL12B, IL12RB1*	Reviewed in ref. 43
	Disseminated tuberculosis			
Streptococcus pneumoniae	Invasive disease	IRAK-4 and MyD88 deficiency	*IRAK4, MYD88*	37, 38
EBV	X-linked lymphoproliferative disease	SAP and XIAP deficiency	*SAP, XIAP*	36, 100
HPV	Epidermodysplasia verruciformis	EVER1/EVER2 deficiency	*EVER1, EVER2*	33
HSV-1	Encephalitis	Impaired production of antiviral IFNs	*UNC93B, TLR3*	46, 47
Trypanosoma evansi	Febrile episodes	No trypanolytic activity	*APOL1*	45

C, complement component; MAC, membrane attack complex; NEMO, NF-κB essential modulator; PFC, properdin factor, complement.

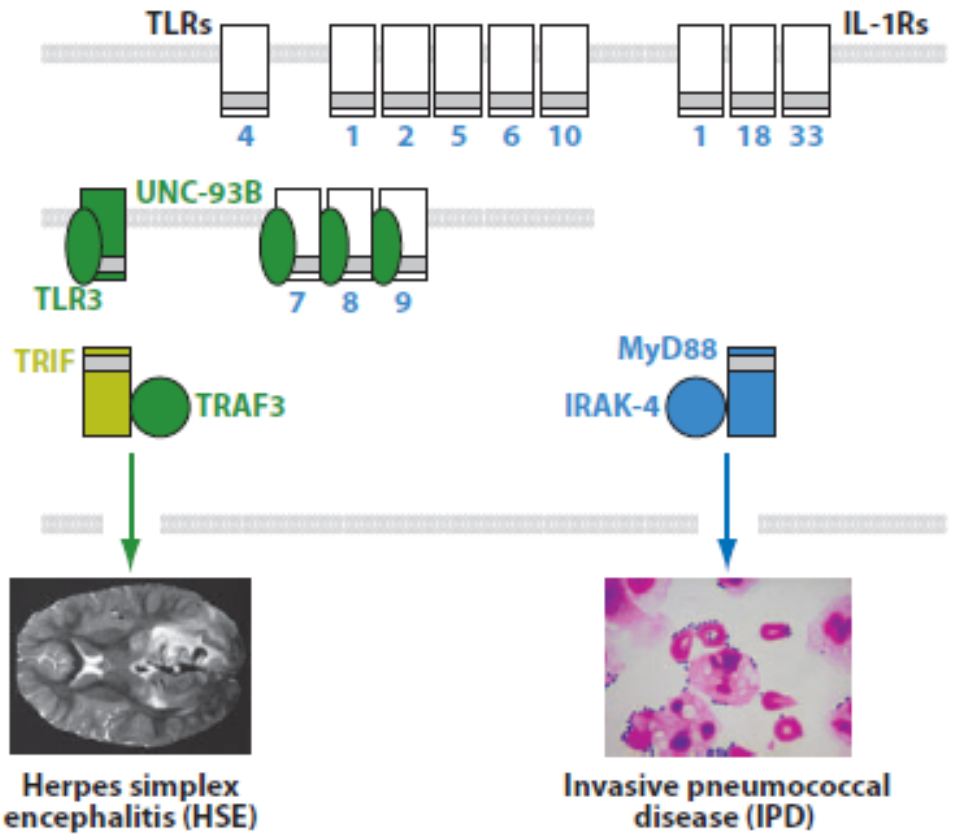
Alcais et al (2009) JCI

Innate Immunity: TLRs



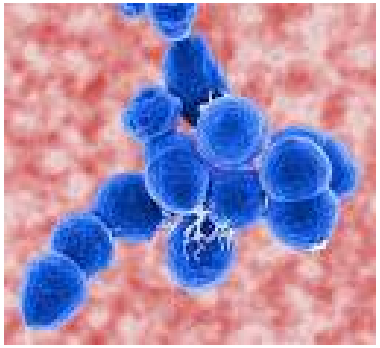
Casanova et al (2011) Annu Rev Immunol.

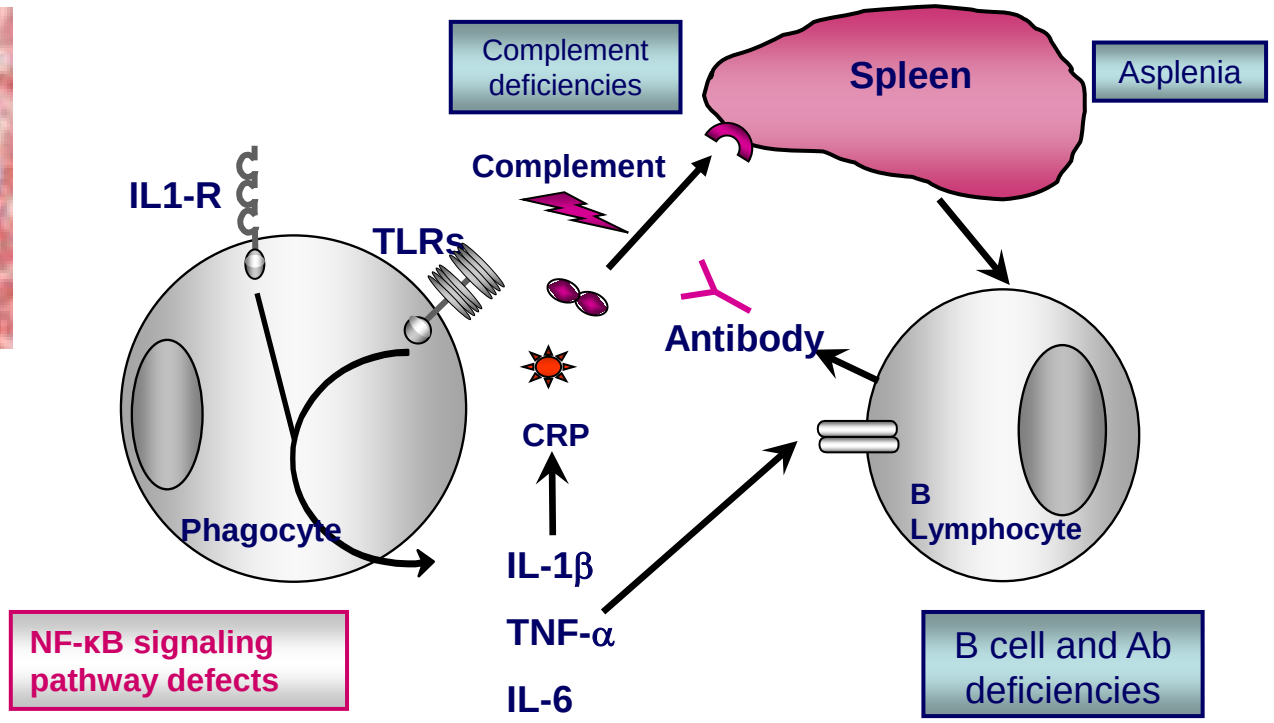
Single-gene inborn errors of TLR and IL1-R immunity



Casanova et al (2011) Annu Rev Immunol.

Invasive pneumococcal diseases (IPD)



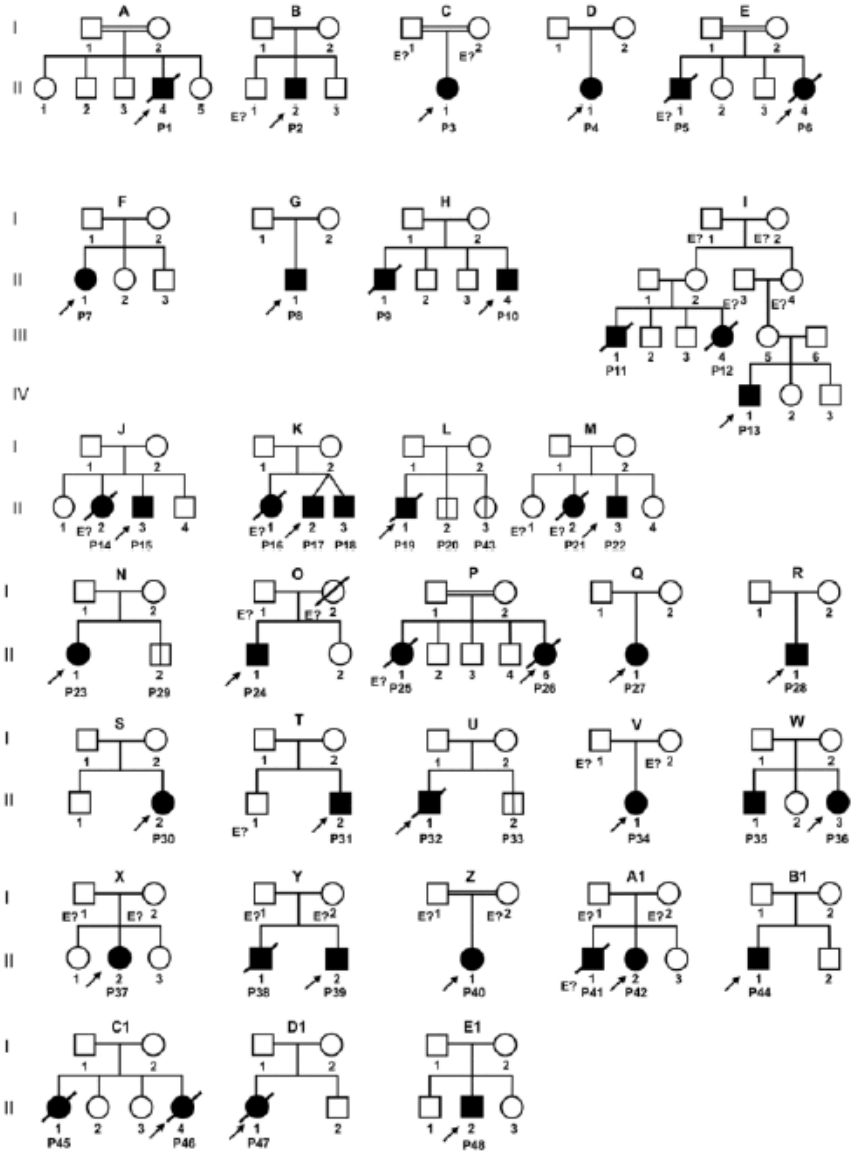


Most children colonized by *S. pneumoniae*

IPD is caused by *S. pneumoniae* resulting in pneumonia, septicemia or meningitis

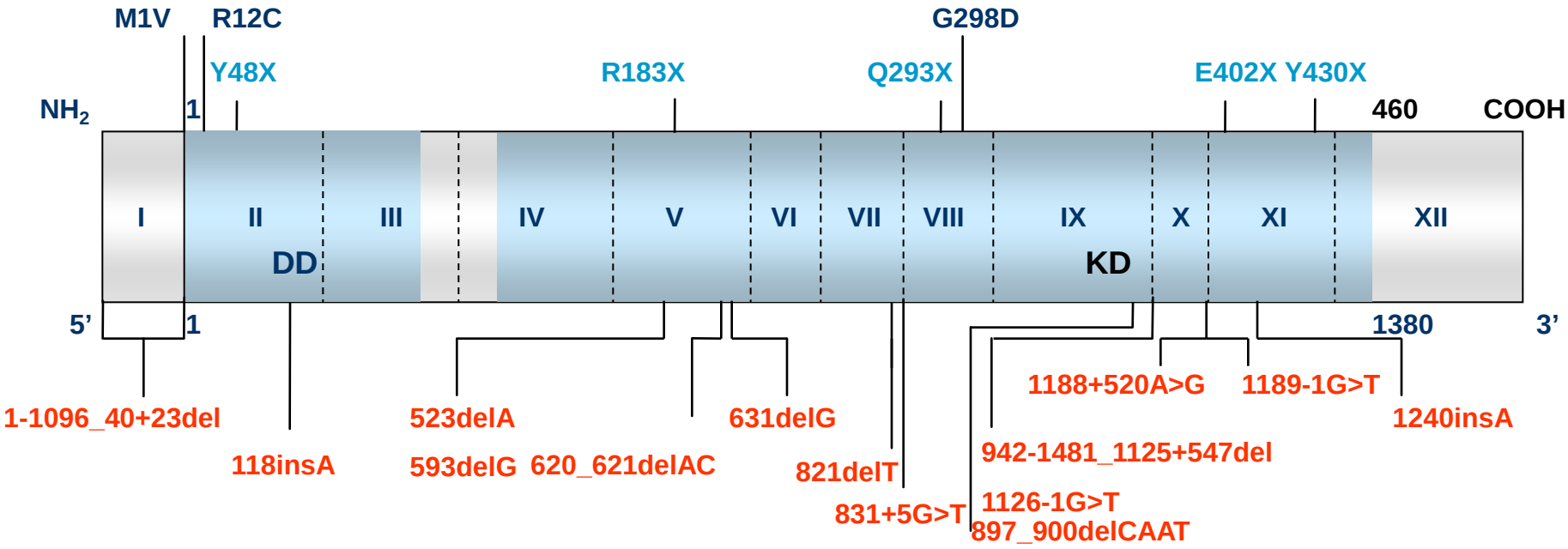
Frequency: 10/100 000 / year
Mortality rate: 1.7/100 000 / year

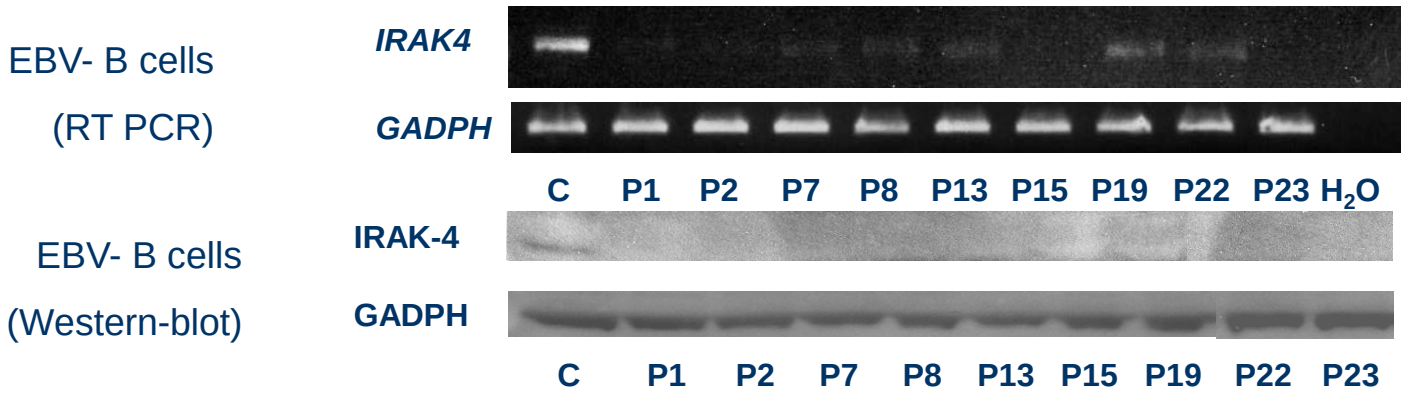
AR IRAK-4 deficiency



Picard et al (2010) Medicine

IRAK-4 deficiency - mutations

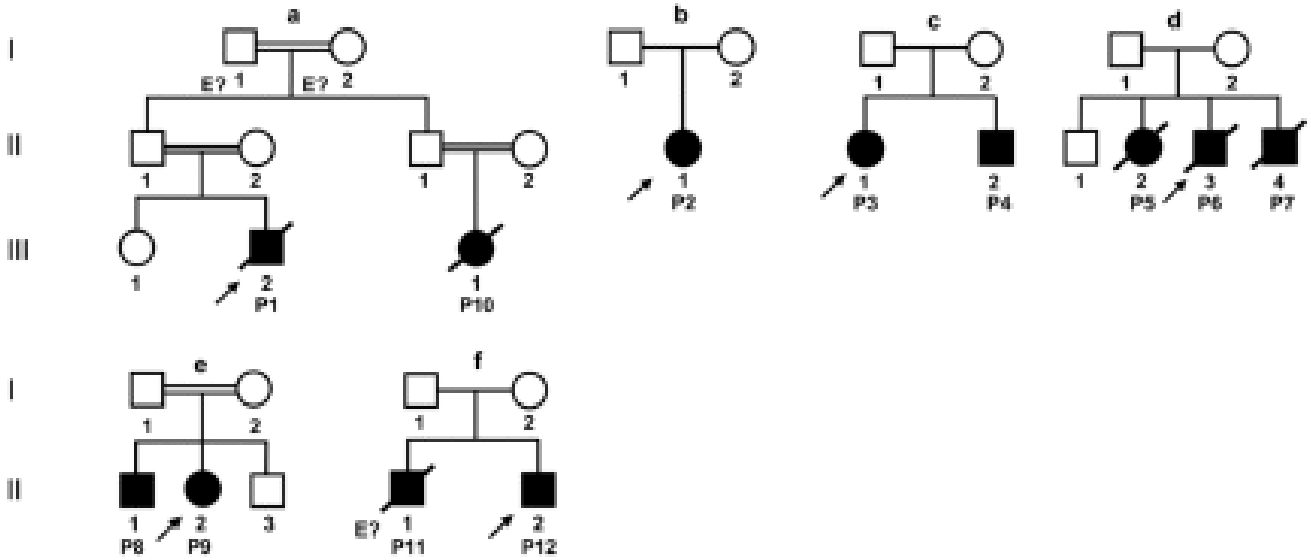




No protein expression for all mutations, except for G298D and R12C mutations

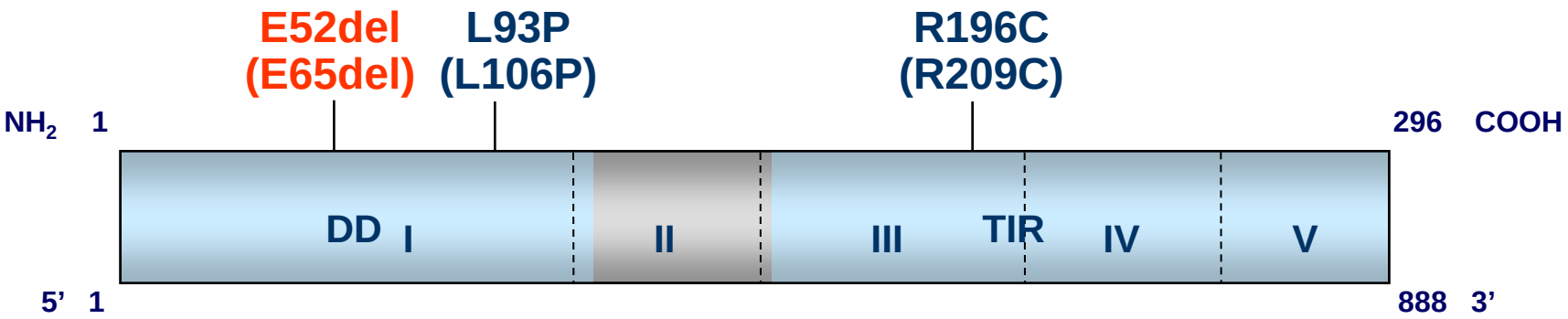
(residual IRAK-4 protein expression)

AR MyD88 deficiency

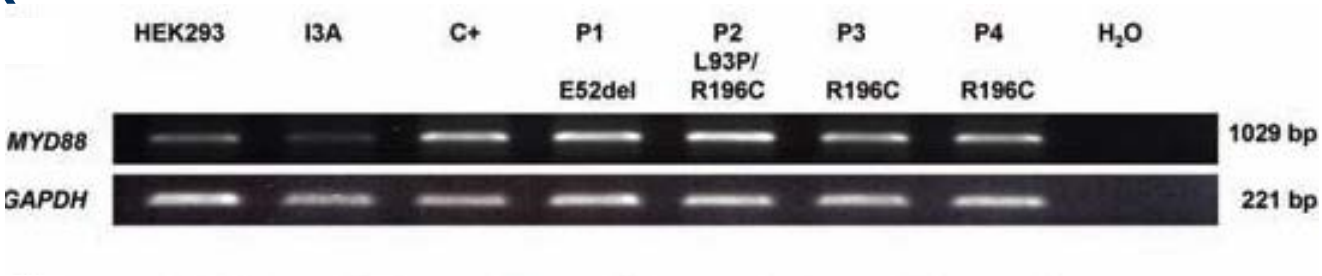


Picard et al (2010) Medicine

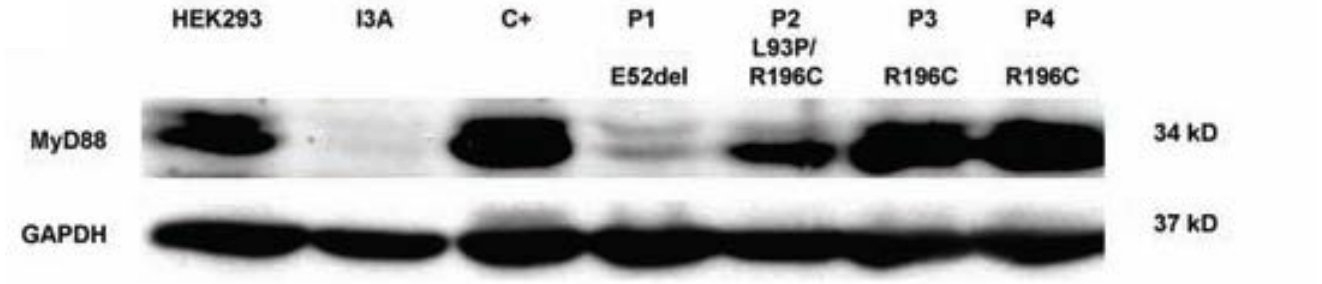
MyD88 deficiency - mutations



RT PCR



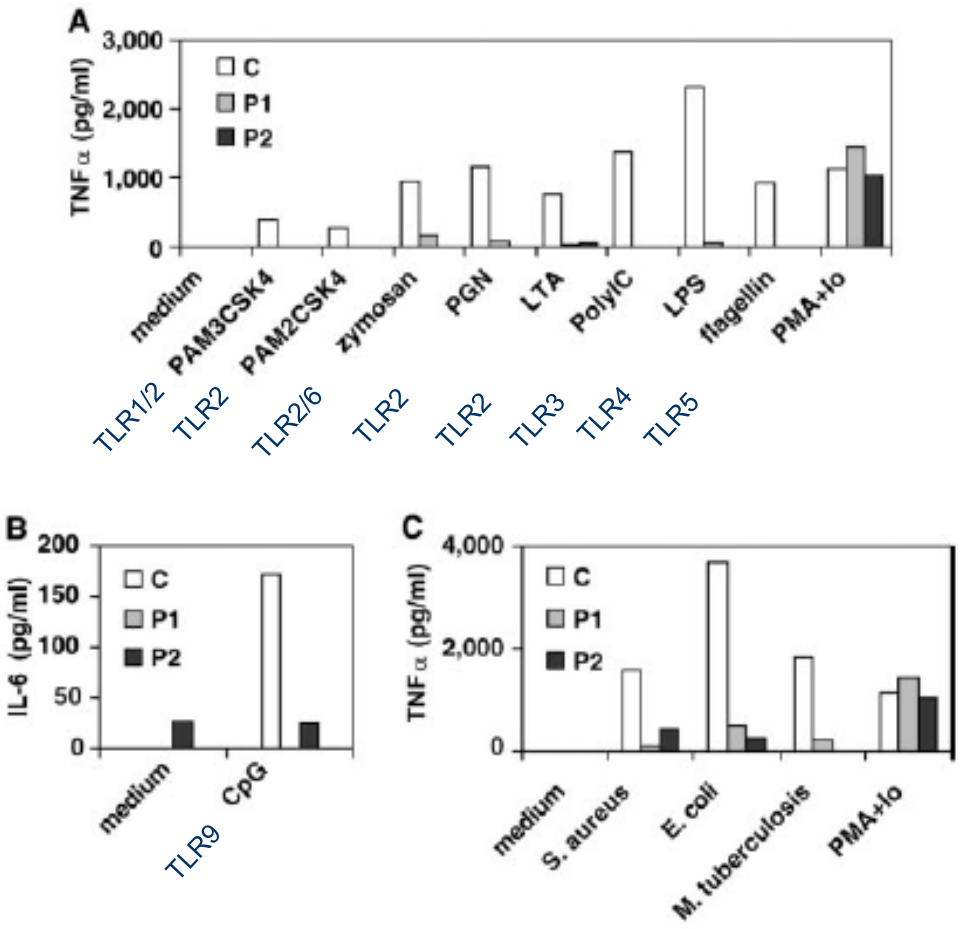
WB



von Bernuth et al. Science 2008

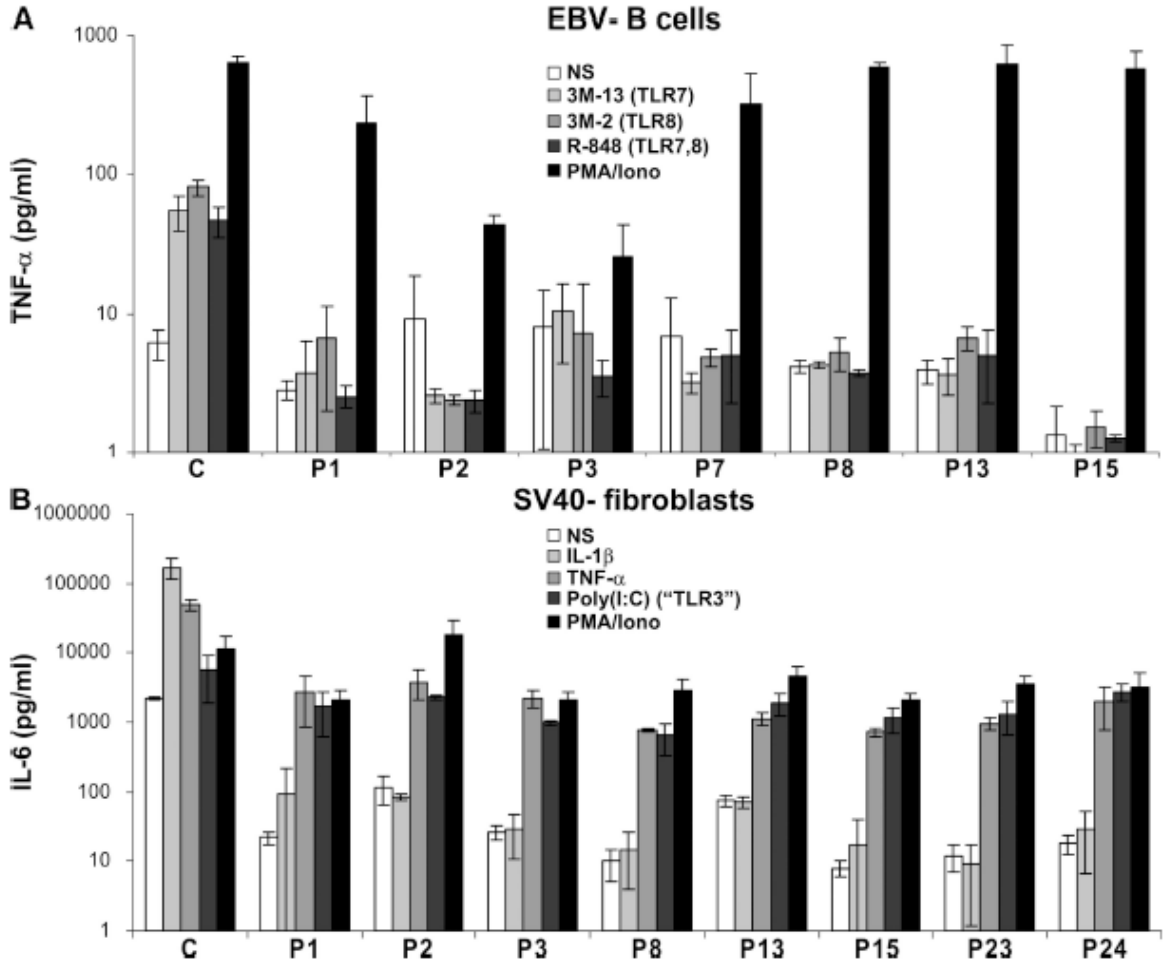
Whole blood phenotype

IRAK4$^{-/-}$ and MYD88$^{-/-}$



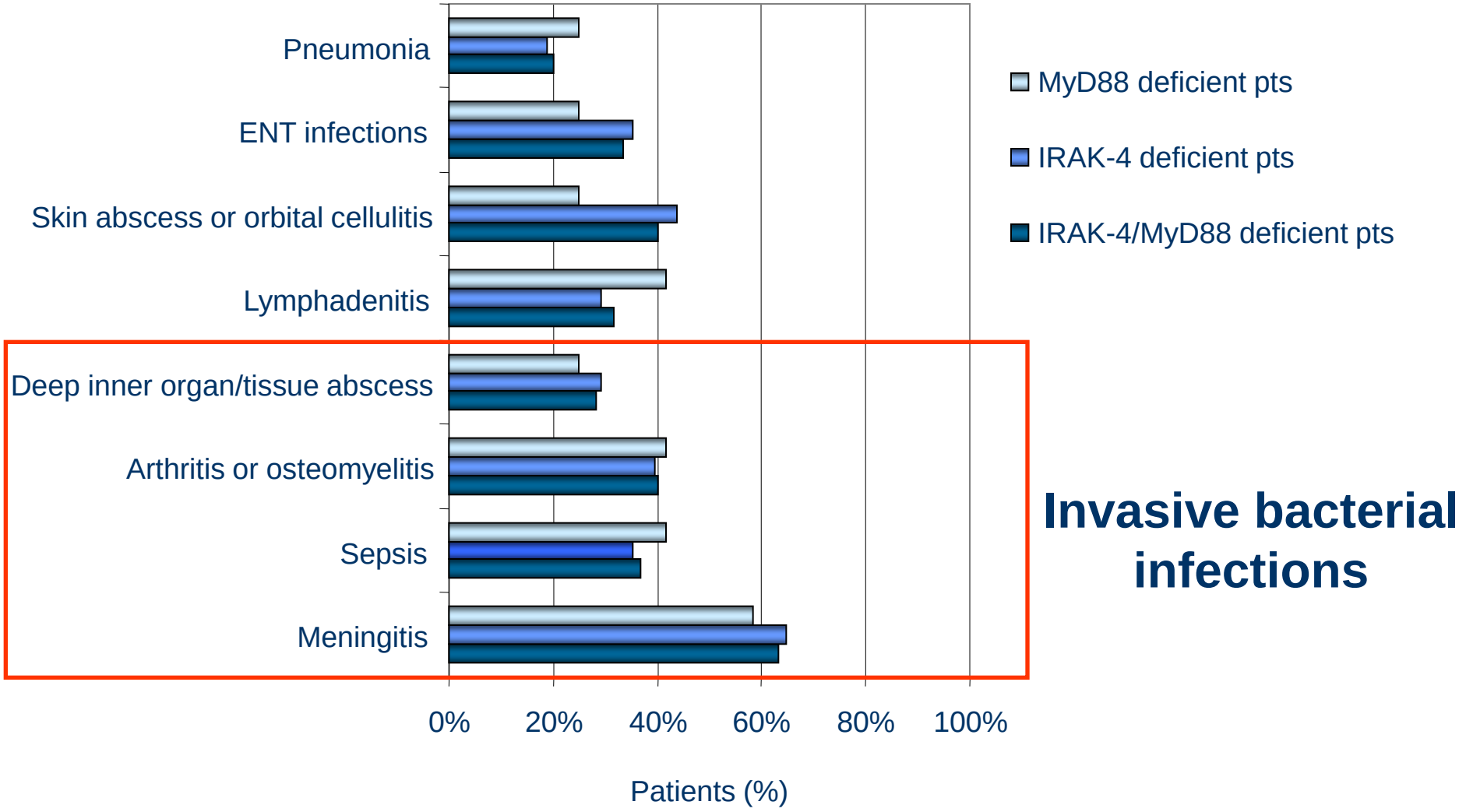
Picard et al (2003) Science

Cellular phenotype



Ku et al (2007) JEM

IRAK-4/MyD88 deficiencies: Clinical manifestations (60 patients)

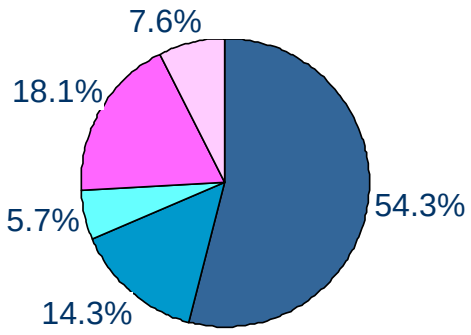


Invasive bacterial infections

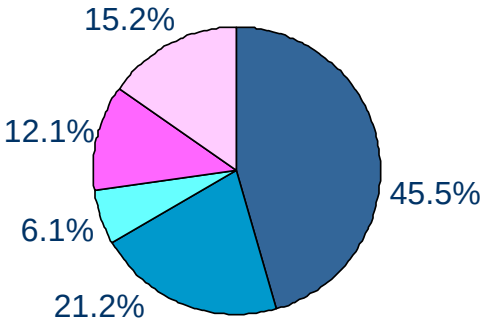
IRAK-4/MyD88 deficiencies: Bacterial infections

Invasive infections

IRAK-4 déficient pts

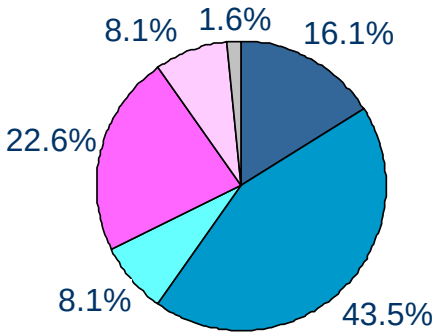


MyD88 deficient pts

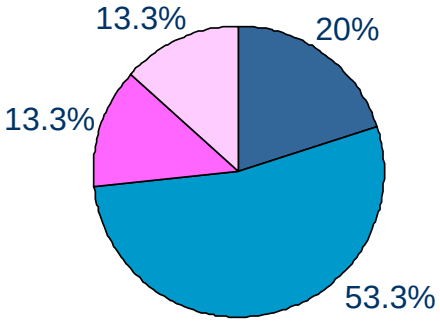


Non invasive infections

IRAK-4 deficient pts



MyD88 deficient pts



- ***S. pneumoniae***
- ***S. aureus***
- **Other Gram-pos**
- ***P. aeruginosa***
- **Other Gram-neg**

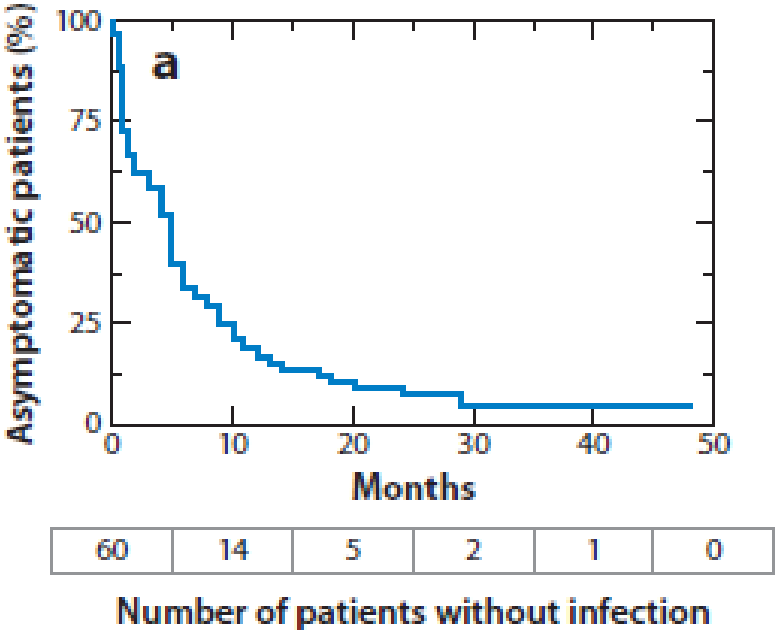
S. pneumoniae = 52.2% of <u>invasive bacterial infections</u>

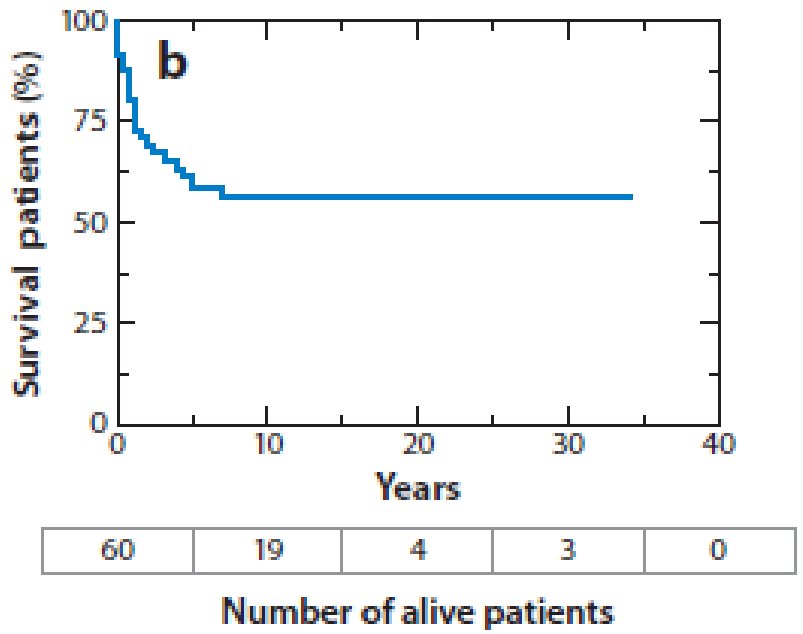
(Meningitis, sepsis, arthritis, osteomyelitis, deep abscess)

S. aureus = 45.5% of <u>non invasive bacterial infections</u>

(Cellulitis, omphalitis, sinusitis, ENT infections, pneumonia)

IRAK-4/MyD88 deficiencies: Severe, narrow and transient phenotype





Early clinical phenotype : first invasive infection occurred < 2 years
Transient clinical phenotype : no severe invasive infections > 14 years

IRAK-4/MyD88 deficiencies and IPD

MyD88 and IRAK-4 patients :

- same clinical and cellular phenotype
- Susceptibility to invasive pyogenic bacteria but improves with age
- Deficient IL-1β and TLR signalling (except for TLR3, partially for TLR4)

The TIR signalling pathway:

- Crucial role in resistance to invasive infections by pyogenic bacteria
- Redundant role in resistance to other common microorganisms (viruses, mycobacteria, fungi)

Children with invasive pneumococcal disease must be screened for defects in the TIR signalling pathway

Human versus Mouse MyD88 deficiency

Table 2. Thirty-three pathogens for which the mortality of MyD88-deficient mice in vivo was greater than that of wild-type controls in experimental conditions

Pathogen group	Strain	References
Gram-positive bacteria	*Bacillus anthracis*	[77]
	Listeria monocytogenes	[33]
	Staphylococcus aureus	[32]
	Streptococcus agalacticae	[37]
	Streptococcus pneumoniae	[45,48]
	Streptococcus pyogenes	[72]
Gram-negative bacteria	Anaplasmataceae	[73]
	Borrelia hermsii	[52]
	Burkholderia pseudomallei	[67]
	Chlamydia muridarum	[71]
	Chlamydia pneumoniae	[47]
	Francisella tularensis	[53,68]
	Klebsiella pneumoniae	[69]
	Pseudomonas aeruginosa	[36,44,57,63]
Mycobacteria	*Mycobacterium avium*	[35]
	Mycobacterium bovis	[39]
	Mycobacterium tuberculosis	[40,41,58,65]
Viruses	*Herpes simplex virus 1*	[80]
	Herpes simplex virus 2	[83]
	Influenza A virus	[84]
	Lymphocytic choriomeningitis virus	[81,85]
	Murine cytomegalovirus	[78,82]
	Rabies virus	[90,91]
	SARS coronavirus	[89]
	Vesicular stomatitis virus	[87,88]
Parasites	*Cryptosporidium parvum*	[101]
	Toxoplasma gondii	[92,93,96,98, 103,106]
	Trypanosoma brucei	[99]
	Trypanosoma cruzii	[97,102]
Fungi	*Aspergillus* spp.	[108]
	Candida albicans	[108,109,112]
	Cryptococcus neoformans	[110,111]
	Paracoccidioides brasiliensis	[113]

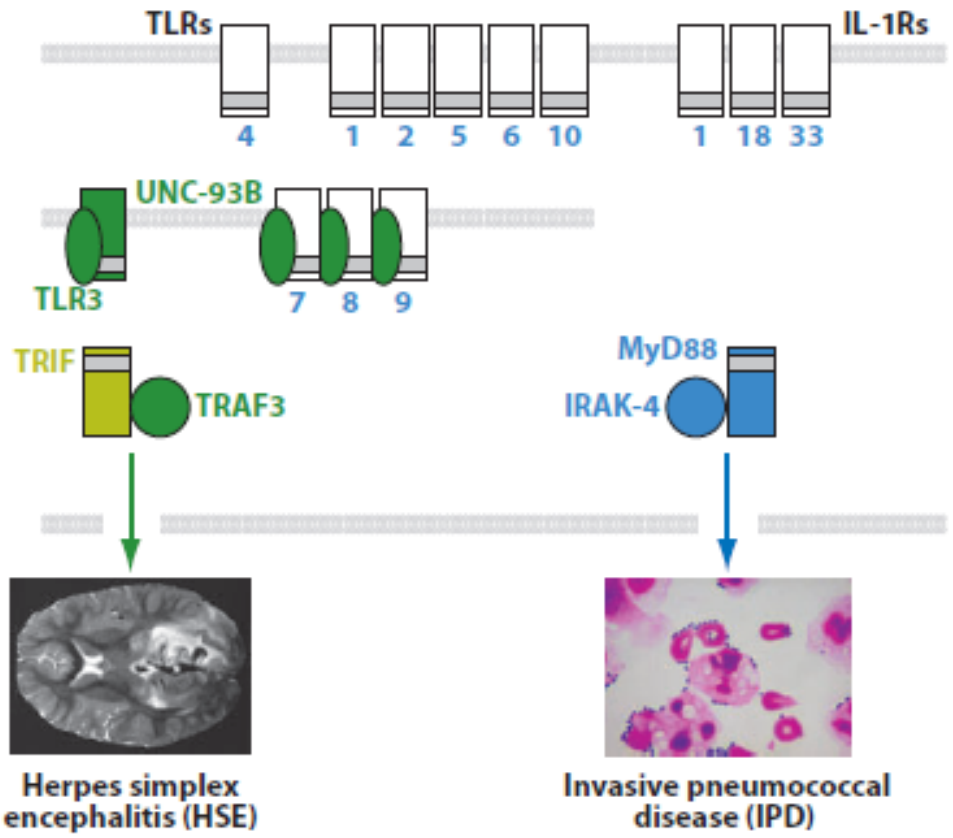
Table 3. Invasive infections in patients with impaired MyD88-IRAK-4 signaling caused by six Gram-positive and 13 Gram-negative bacteria

Pathogen group	Strain	References
Gram-positive bacteria	*Staphylococcus aureus*	[29–31,115, 117,119, 121,125, 126,128]
	Streptococcus agalacticae	[30,31,127, 128]
	Streptococcus milleri	[125]
	Streptococcus parasanguis	[118]
	Streptococcus pneumoniae	[29–31,114–126,128]
	Streptococcus pyogenes	[31,128]
Gram-negative bacteria	*Acinetobacter baumanii*	[128]
	Citrobacter freundii	[31]
	Clostridium septicum	[31,114,116]
	Escherichia coli	[31]
	Haemophilus influenzae	[31]
	Klebsiella pneumoniae	[31]
	Moraxella catarrhalis	[31]
	Neisseria meningitidis	[31,114,116, 125]
	Proteus spp.	[30,31]
	Pseudomonas aeruginosa	[30,31,120–122,125, 128]
	Salmonella enterica	[30,31]
	Serratia marcescens	[31]
	Shigella sonnei	[31,119,125, 127]

MyD88-dependent TLR and IL-1R immunity is vital in both mice and humans, but its role in the course of naturally occurring infections in humans seems to be much more restricted

Von Bernuth et al (2012) Eur J Imm

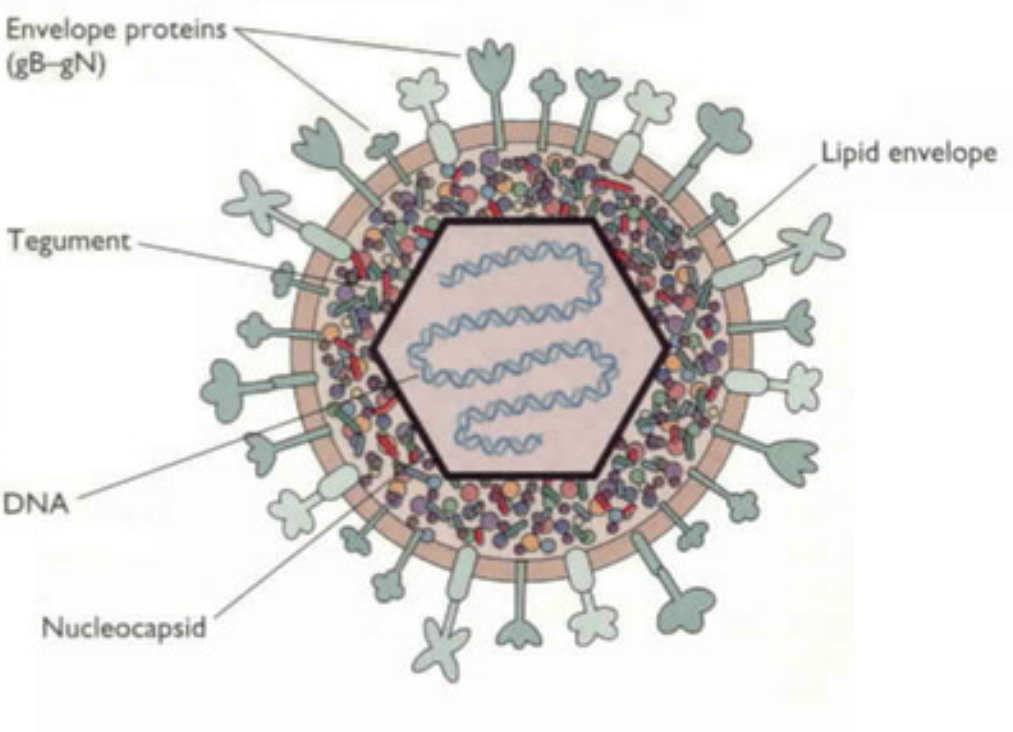
Single-gene inborn errors of TLR and IL1-R immunity

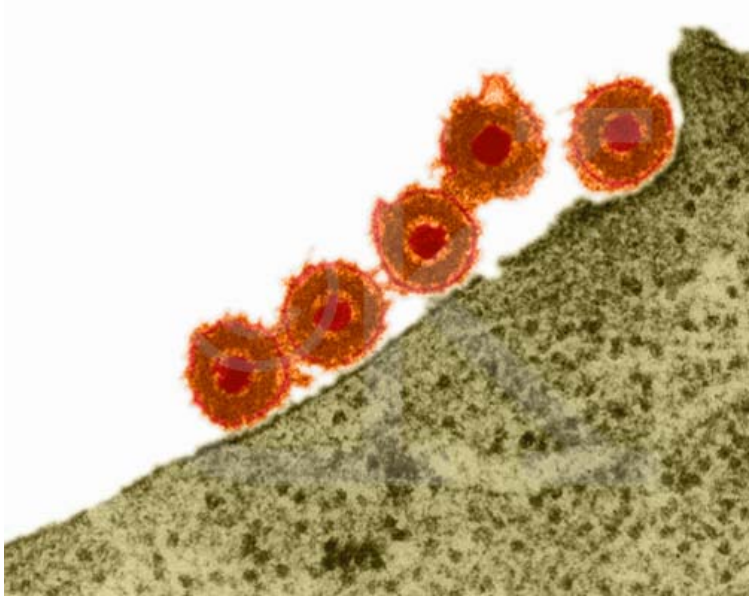


Casanova et al (2011) Annu Rev Immunol.

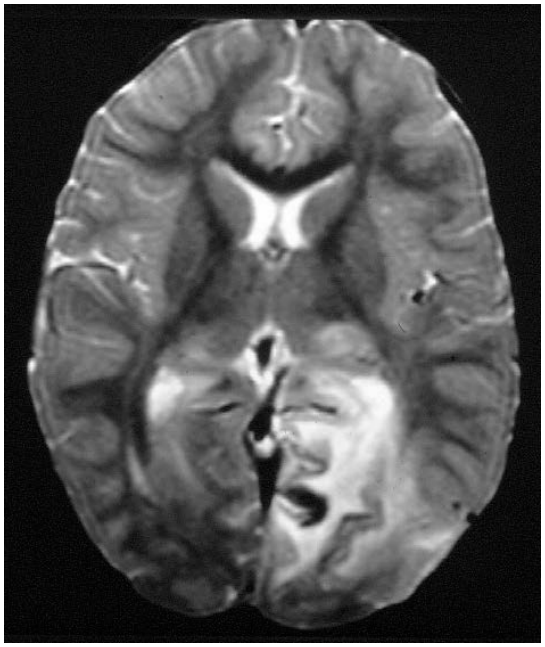
Herpes Simplex Virus (HSV)

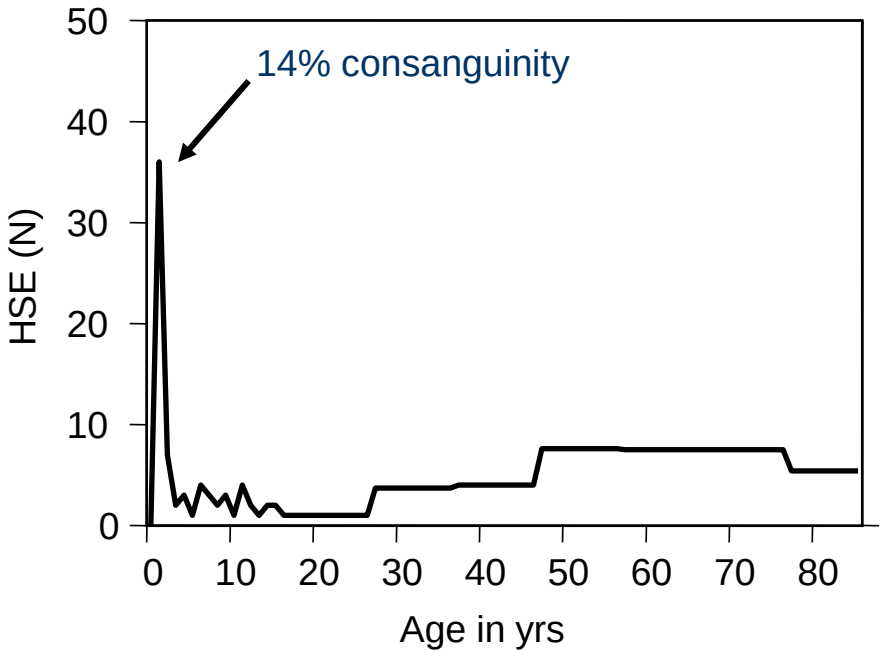
Alpha Herpetoviridae family
Envelopped virus with ds DNA genome
Binds to cell surface via surface glycoproteins
Causes lytic or latent infection
1960s: HSV-1 & HSV-2





Herpes Simplex Encephalitis (HSE)





HSE patients carry a genetic predisposition to HSE

HSE Patients

Recruitment

Functional Screen

Impaired Phenotype

Consanguinity

↓

Positional Cloning

Linkage

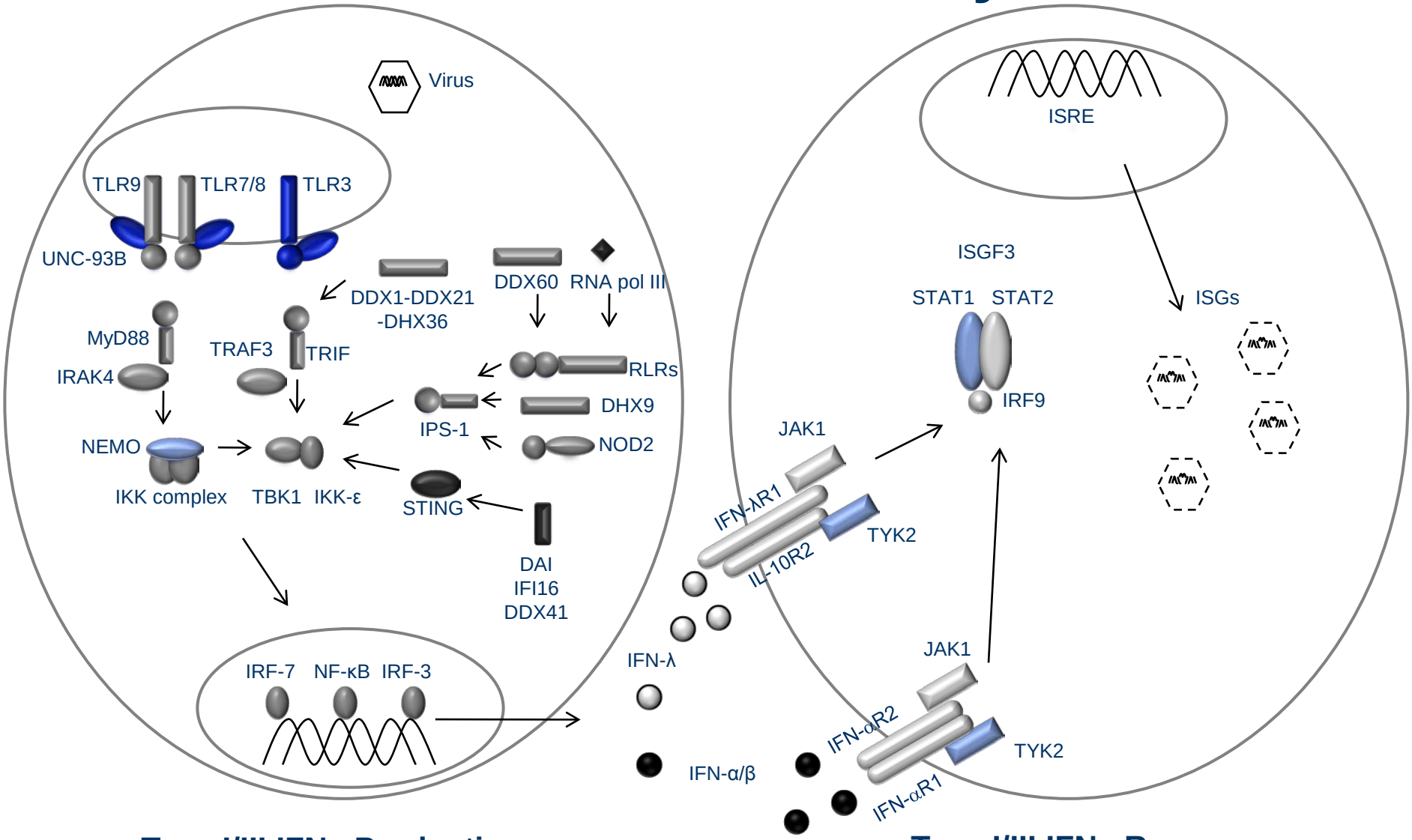
Candidate Pathway

Sequencing

↓

Characterization of Mutation

Antiviral Immunity



Type I/III IFNs Production

Type I/III IFNs Response

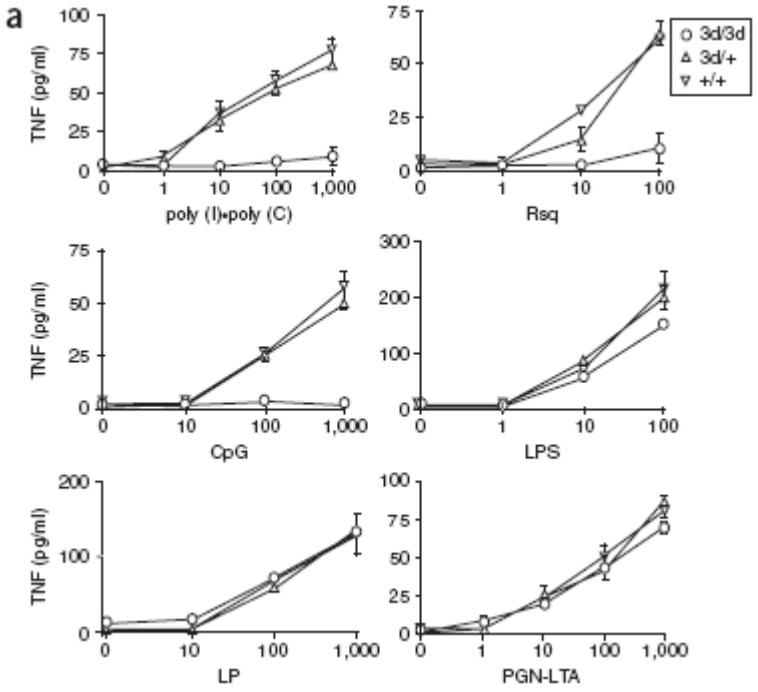
Sancho-Shimizu et al. 2011 *Curr Opin Vir* 1(6): 487-96,

nature immunology

The *Unc93b1* mutation 3d disrupts exogenous antigen presentation and signaling via Toll-like receptors 3, 7 and 9

Koichi Tabeta[1], Kasper Hoebe[1], Edith M Janssen[2], Xin Du[1], Philippe Georgel[1], Karine Crozat[1], Suzanne Mudd[1], Navjiwan Mann[1], Sosathya Sovath[1], Jason Goode[1], Louis Shamel[1], Anat A Herskovits[3], Daniel A Portnoy[3], Michael Cooke[4], Lisa M Tarantino[4], Tim Wiltshire[4], Benjamin E Steinberg[5], Sergio Grinstein[5] & Bruce Beutler[1]

TLR3



TLR7/8

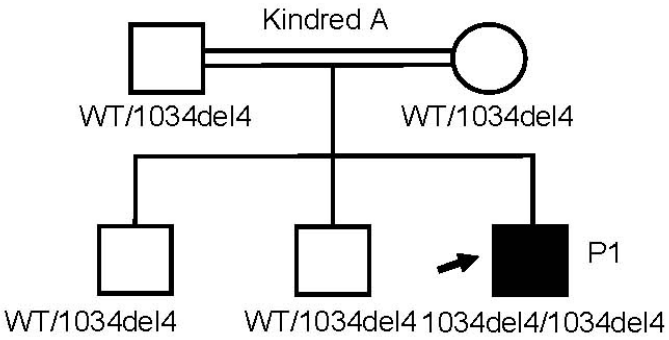
TLR9

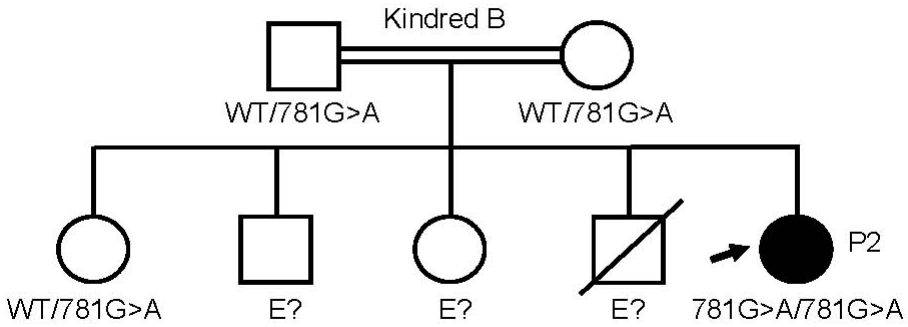
TLR4

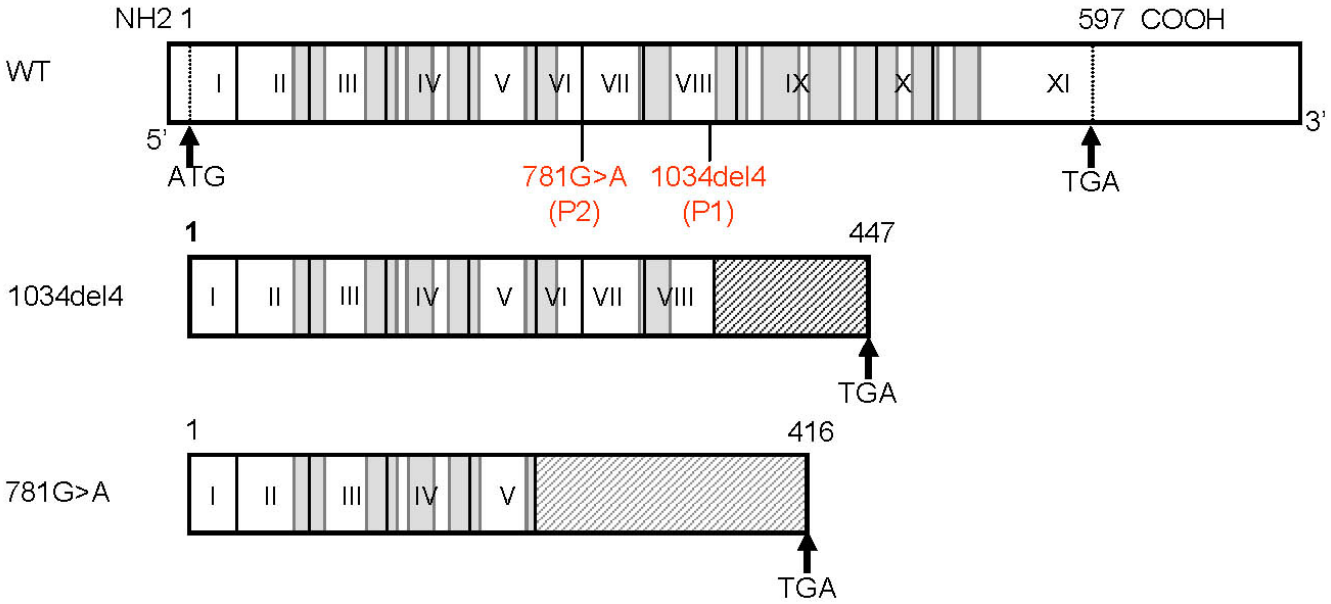
TLR2

TLR2/6

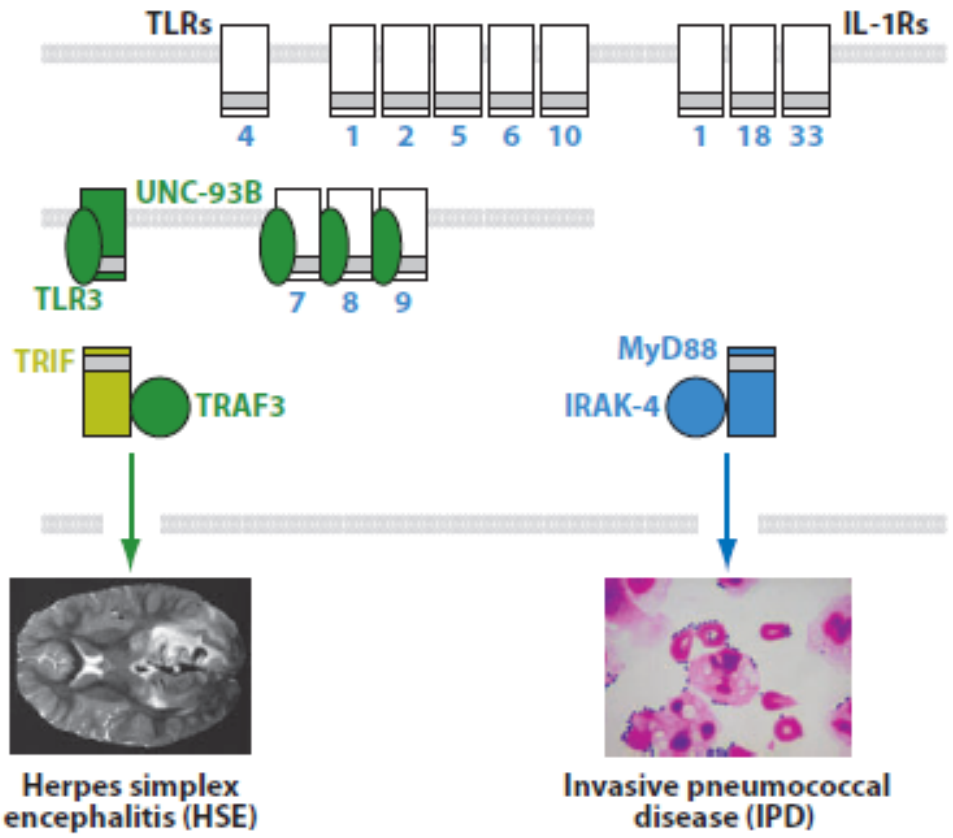
AR UNC93B deficiency





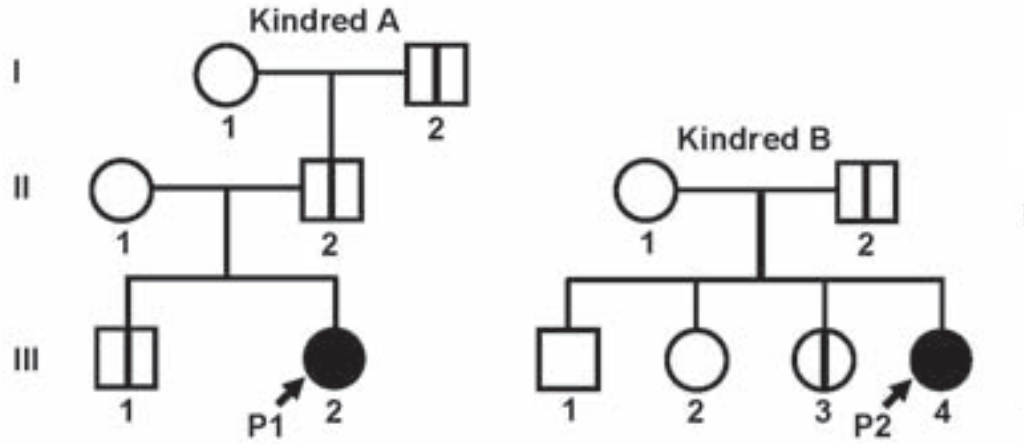


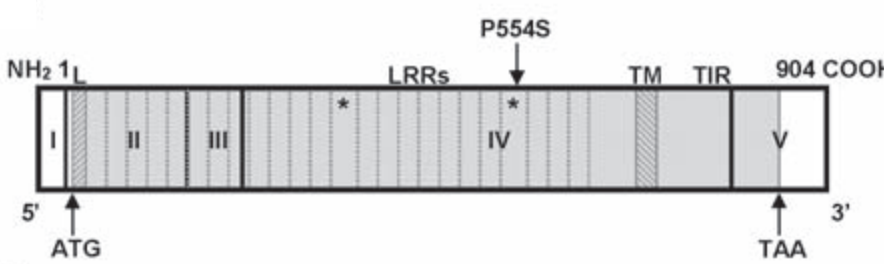
Single-gene inborn errors of TLR and IL1-R immunity



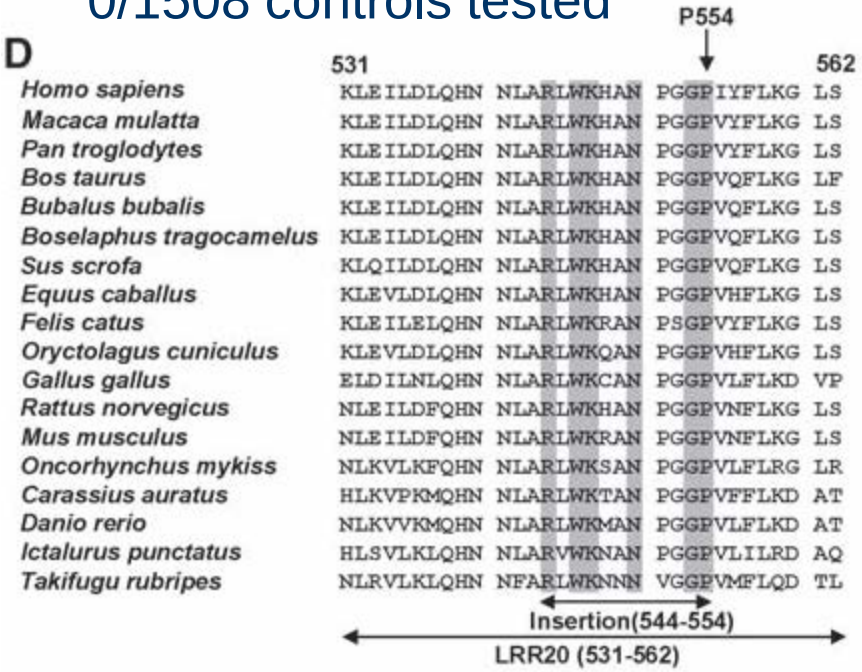
Casanova et al (2011) Annu Rev Immunol.

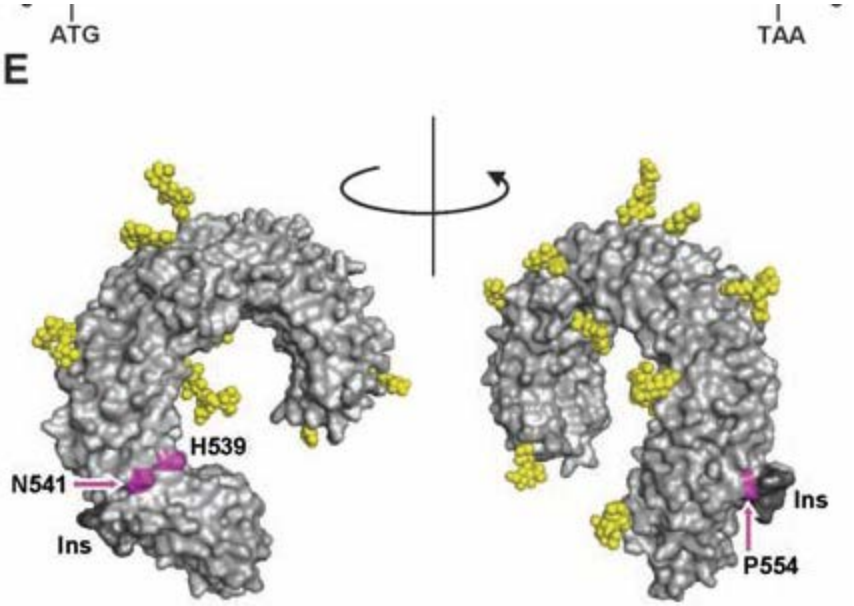
TLR3 deficiency





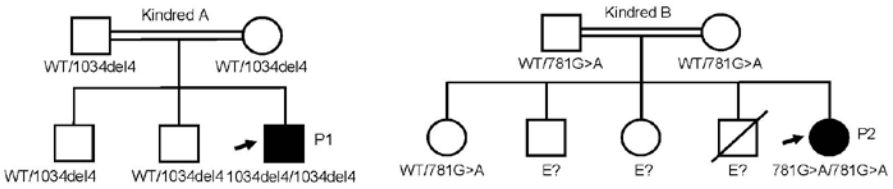
0/1508 controls tested



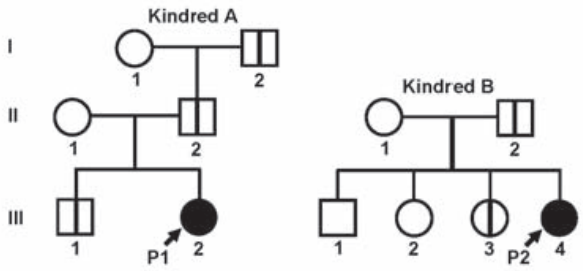


UNC93B$^{-/-}$ vs TLR3$^{+/-}$ Deficiencies

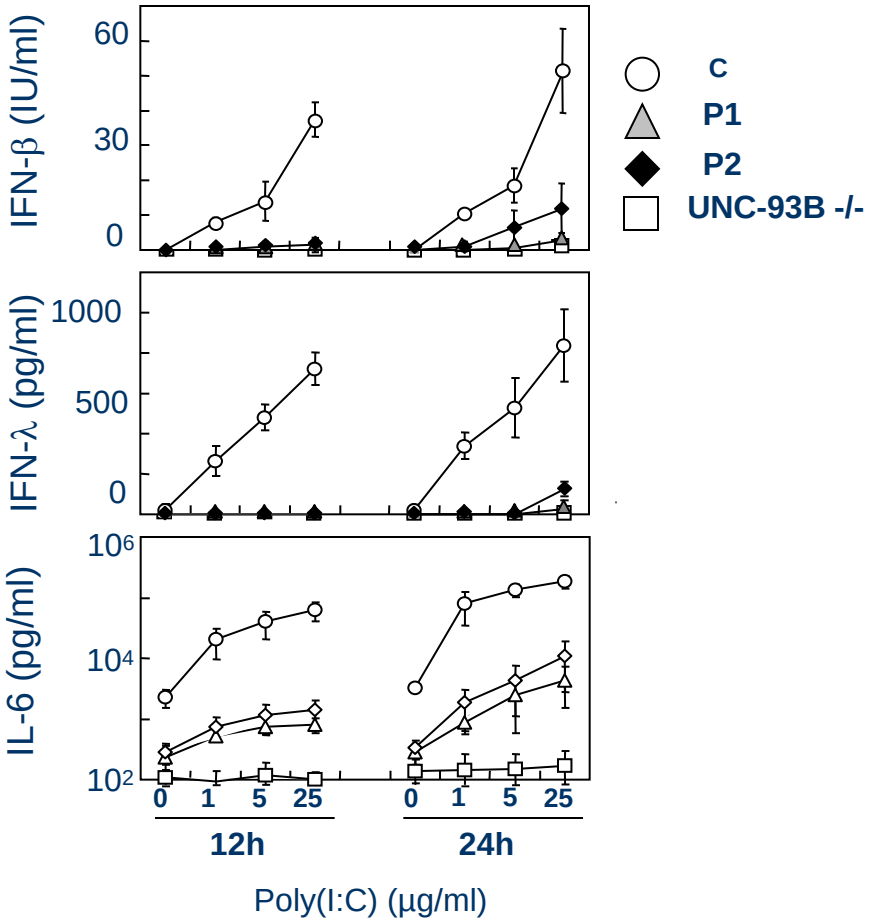
AR UNC93B$^{-/-}$



AD TLR3$^{+/-}$



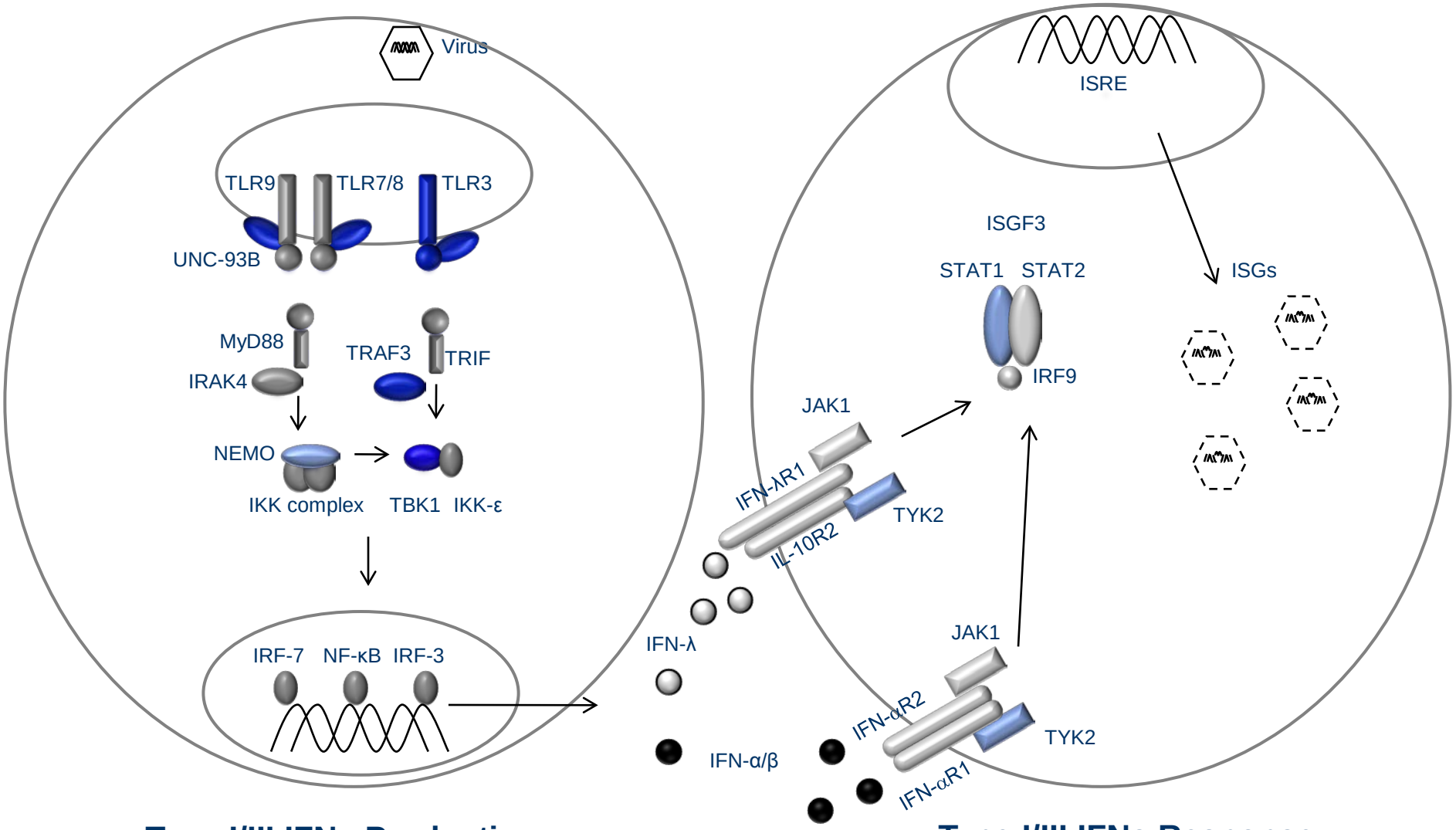
SV40 Fibroblasts



Casrouge et al. 2006 *Science* 314 (5797):308-12

Zhang et al. 2007 *Science* 317(5844):1522-7

HSE Immunity



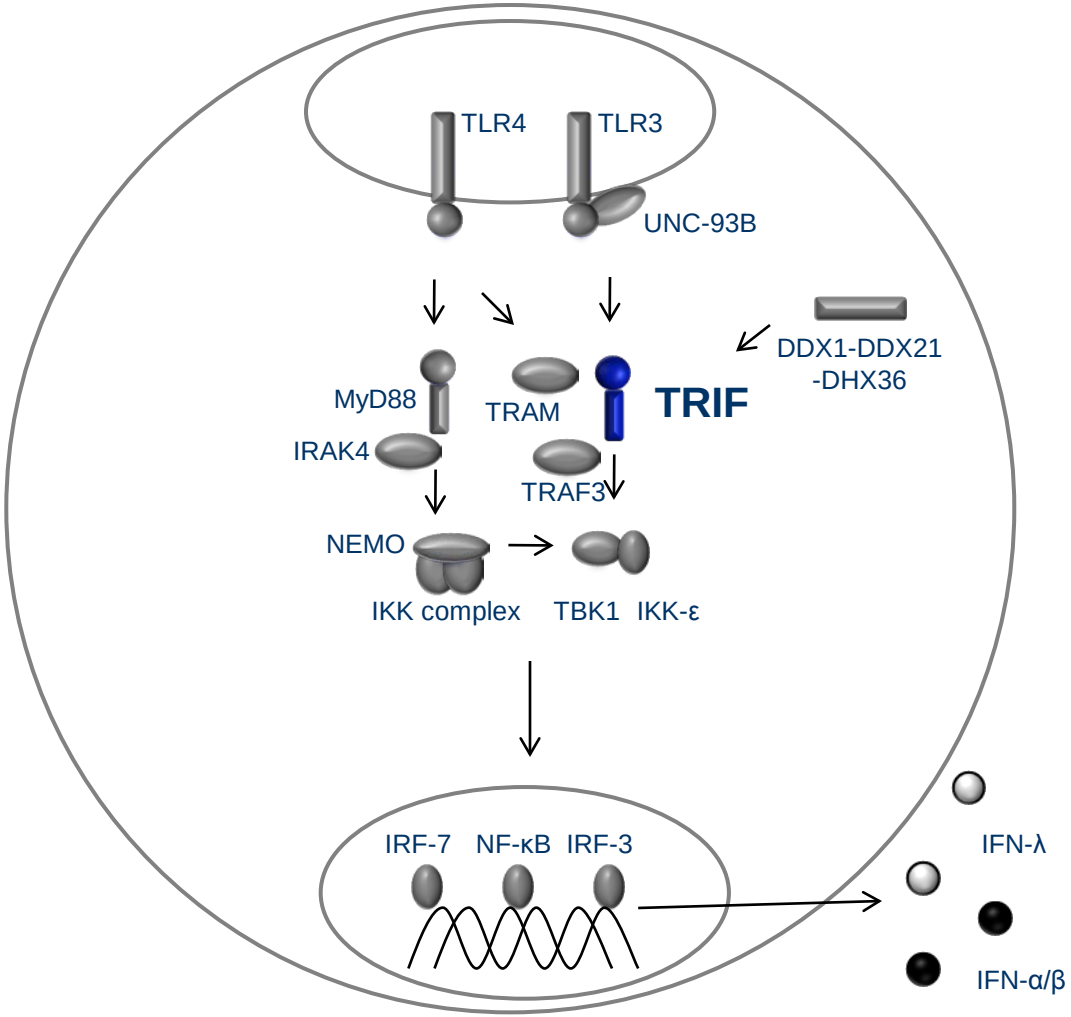
Type I/III IFNs Production

Type I/III IFNs Response

Perez de Diego et al. 2010 *Immunity*. Sep 24;33(3):400-11

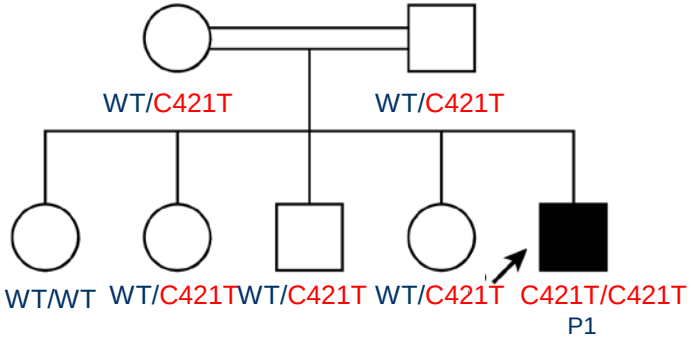
Guo et al. 2011 *J Exp Med*. Sep 26;208(10):2083-98

TRIF deficiency

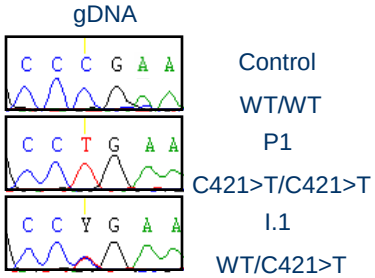


AR TRIF

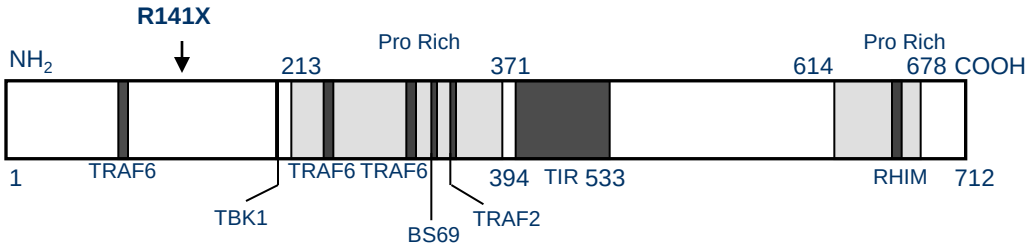
Saudi Arabian



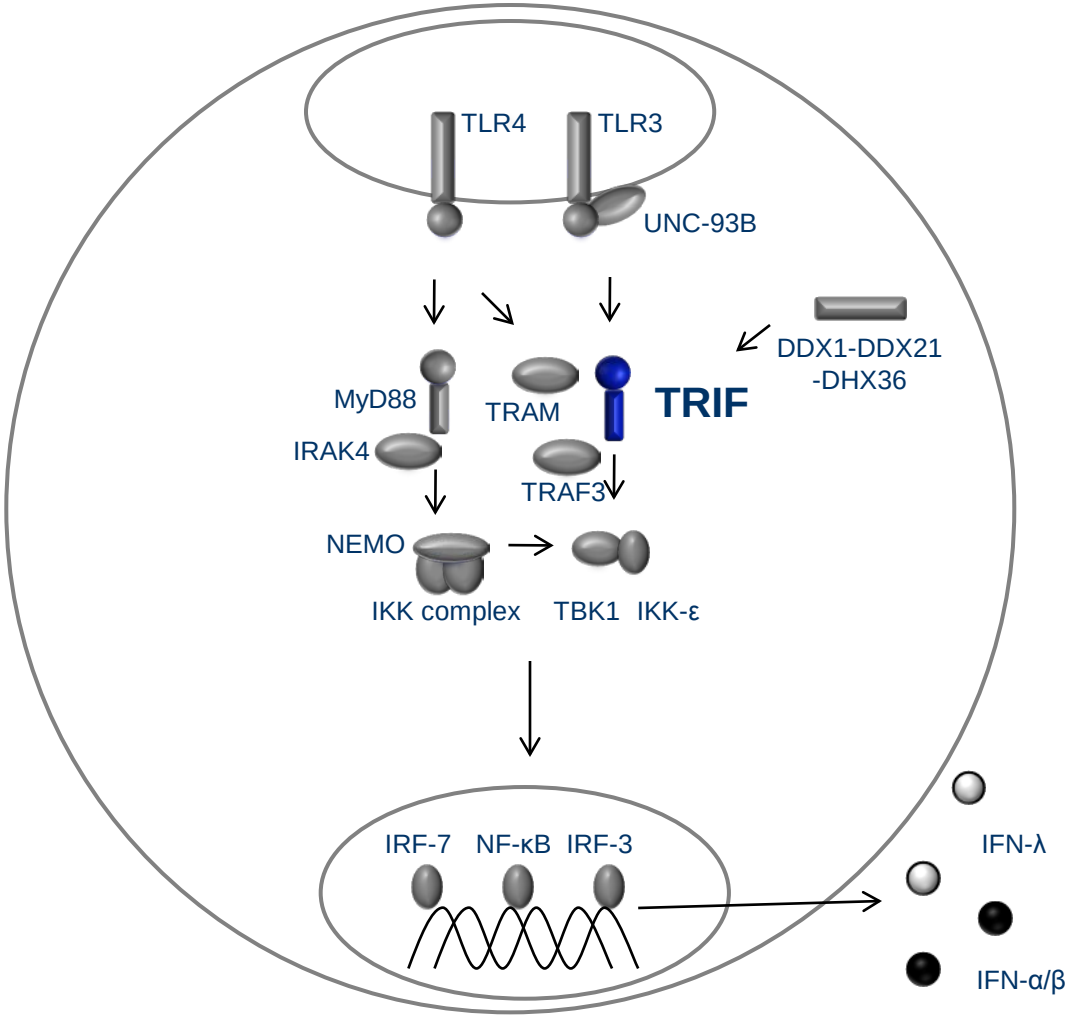
HSE at 3yrs



1050 CEPH + 182 Saudi Arabian Controls



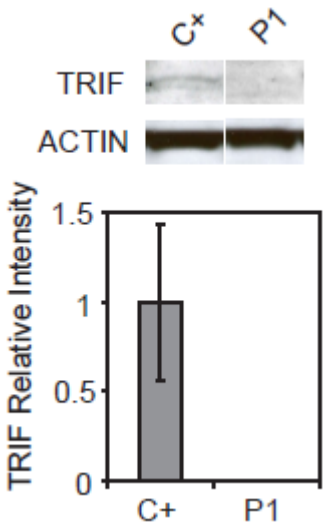
TRIF deficiency

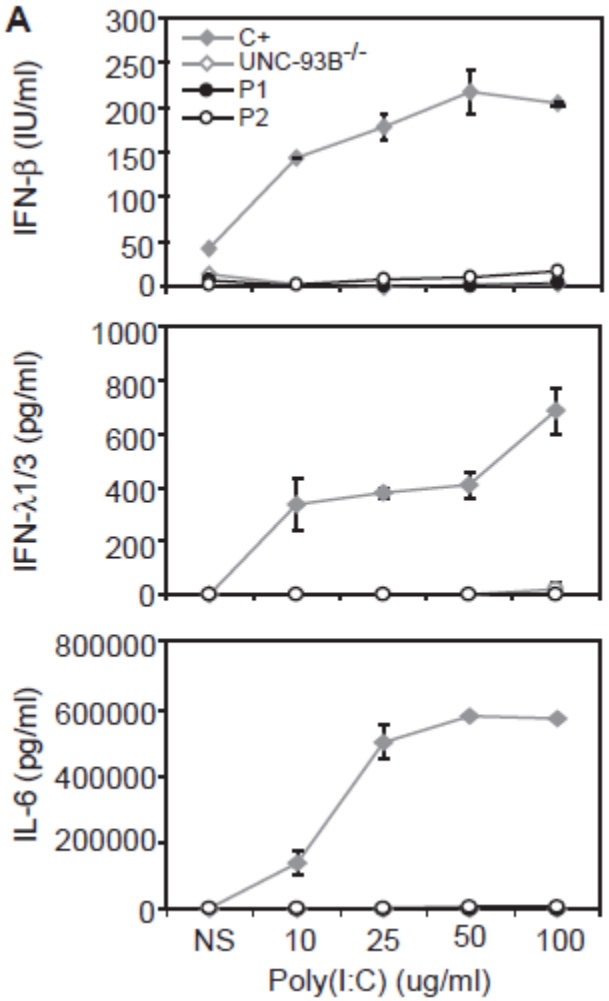


TRIF Expression/Function

SV40 Fibroblasts

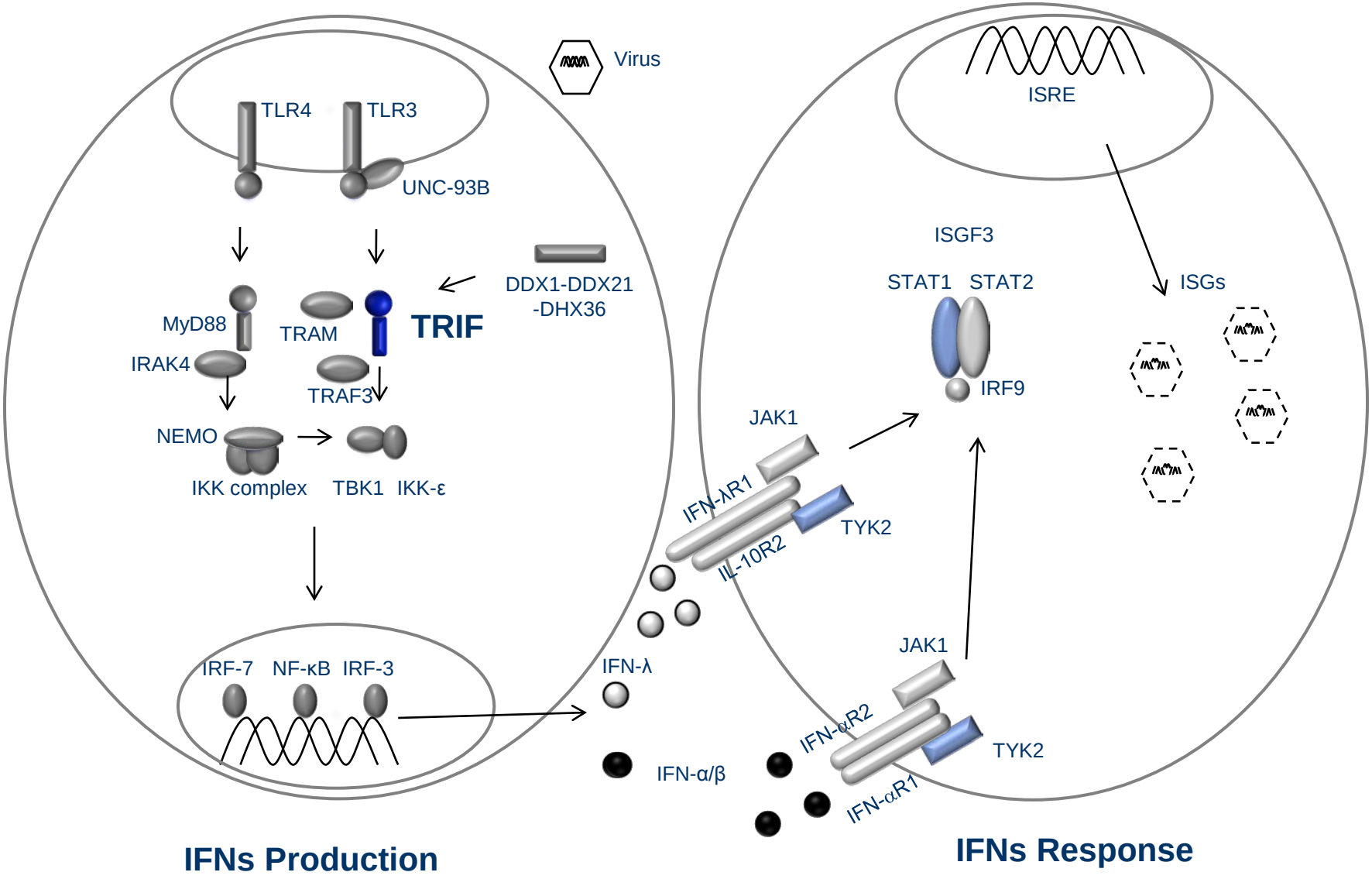
Western





Sancho-Shimizu et al. 2011 *JCI*.

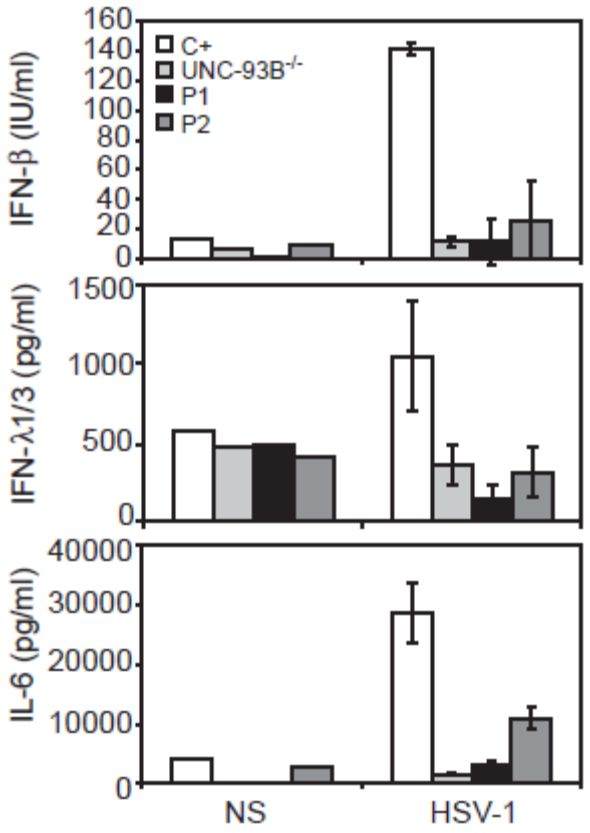
Viral Infection



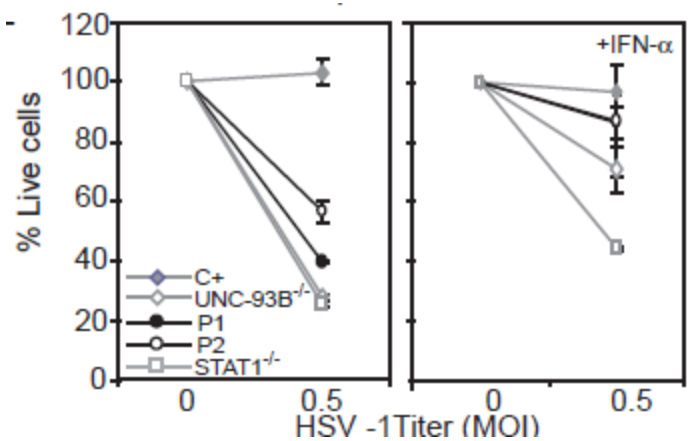
HSV-1 Infection

SV40 Fibroblasts

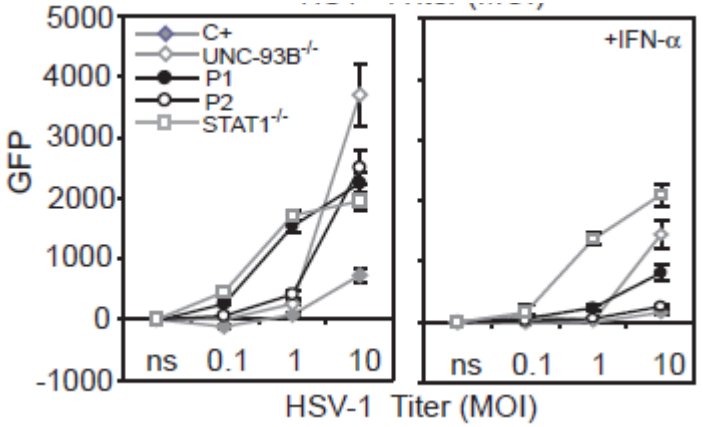
Cytokine



Cellular Mortality



Viral Replication

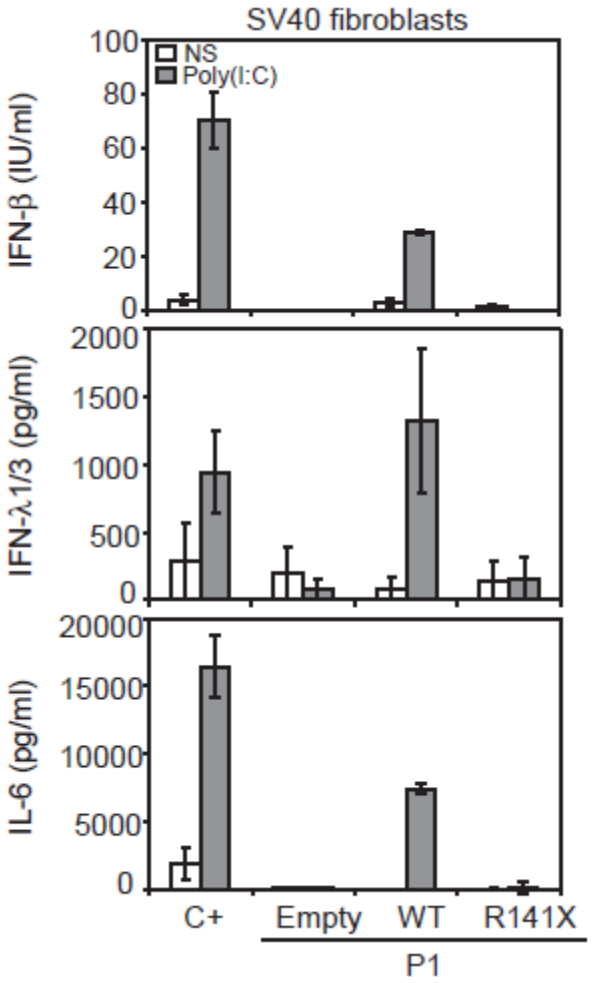


Susceptible to HSV1 due to lack of IFN production

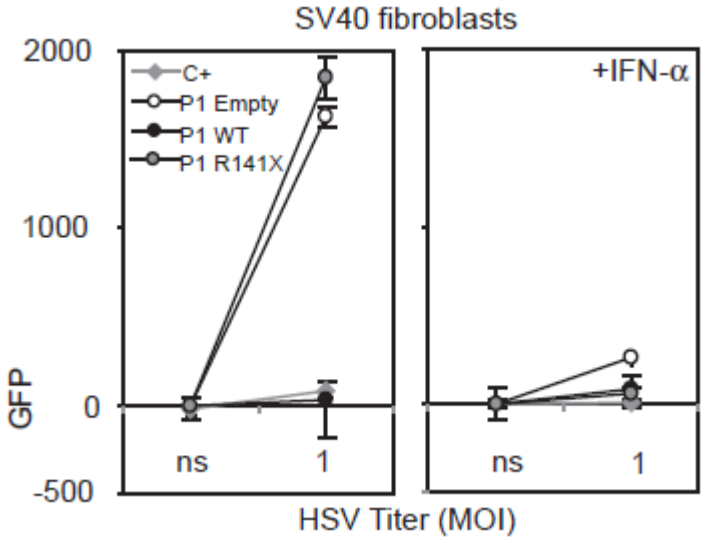
Retroviral transfection R141X

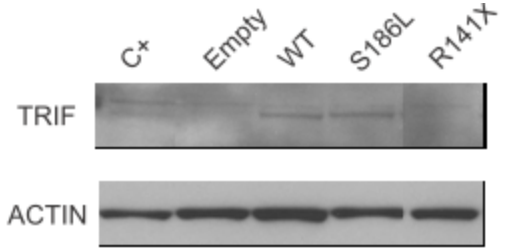
P1 SV40 Fibroblasts

PolyI:C



HSV1 Replication

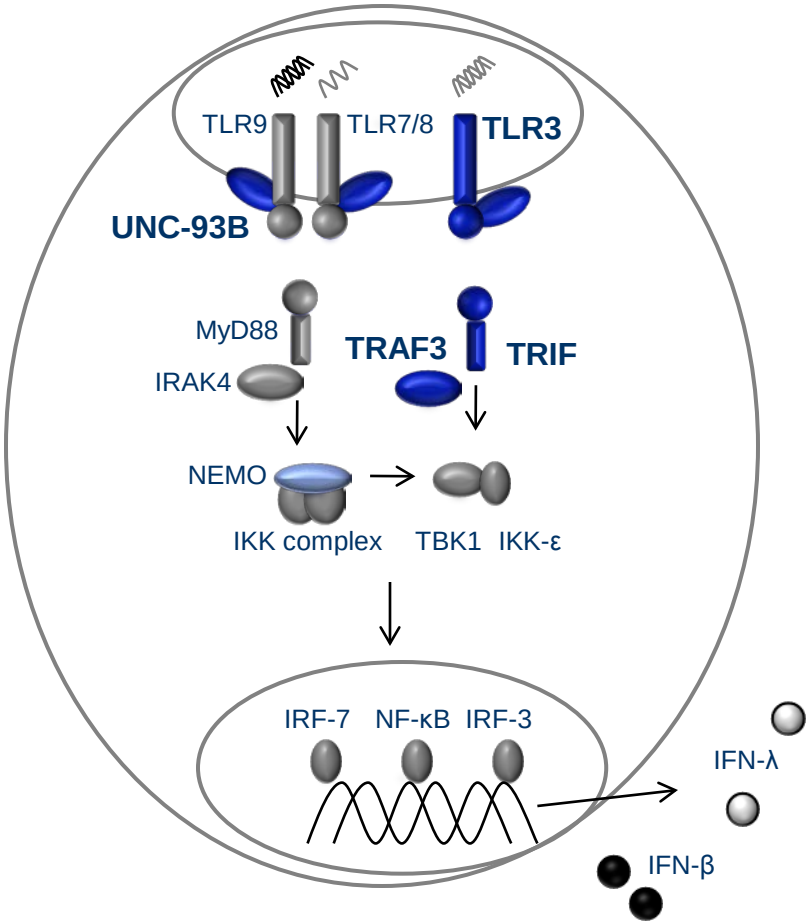




WT TRIF complements P1's cells

R141X is a null allele

TLR3-IFN deficiencies and HSE



AR UNC93B
AR & AD TLR3
AR & AD TRIF
AD TRAF3

Narrow defects in antiviral IFNs
(UNC93B, TLR3, TRAF3 and TRIF)

↓

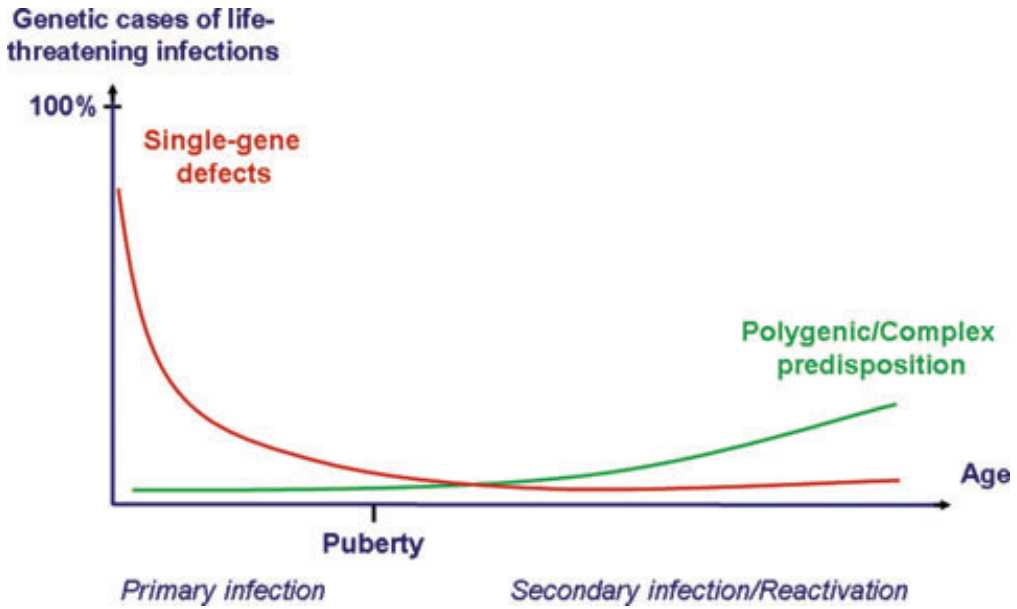
Single viral infection HSE

Incomplete penetrance

The host has evolved towards maximizing detection of HSV-1 in the CNS where infections are potentially lethal.

Conclusions

Inborn errors of immunity underlying infectious diseases



Life threatening infectious disease in childhood, due to primary infection, result from individually rare singe-gene variations of variable clinical penetrance

- conventional PIDs

(one gene, multiple infections)

- Nonconventional or ‘novel’ PIDs

(one gene, one infection)

Secondary or reactivation infections in adults is more complex

Alcais et al (2010) Ann NYAS