

Genetics Susceptibility to Infectious Diseases

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Learning Objectives

- Define and classify primary immunodeficiency diseases
- Review the role of clinical laboratory in the diagnosis of primary immunodeficiency diseases
- Demonstrate the utility of molecular diagnosis in primary immunodeficiency diseases
- Review the genetics of
 - (1) Mendelian susceptibility to chronic mucocutaneous candidiasis
 - (2) Mendelian susceptibility to mycobacterial infections
 - (3) Herpes simplex encephalitis

Definitions

- Primary immunodeficiency (PID): genetic

(Secondary immunodeficiency: infection, malignancy, iatrogenic)

- PID - changing definition:
from very severe Mendelian traits to
varying degree of susceptibility to infections

Identification of patients with PID

- Diagnosis of PIDs requires integration of data from clinical findings with laboratory immunological analyses and genetic testing

→ Infections

- recurrent
- life-threatening
- unusual

→ Autoimmune diseases

→ Malignancies

Primary immunodeficiencies

PIDs are like other genetic diseases, but

- Diagnosis:
 - secondary causes of ID are more common than primary (esp. in adults)
 - manifestations (infections) can be the same in both primary and secondary ID as well in “healthy” individuals
- Therapy(!):
 - Hematopoietic Stem Cell Transplantation (HSCT)
(gene therapy)
 - Replacement, anti-microbials

Diagnosis of PIDs

Clinical and family history-based diagnostic approach



Diagnostic immunology lab supports, refine phenotype

Diagnosis of PIDs

Clinical and family history-based diagnostic approach



Diagnostic immunology lab supports, refine phenotype



Molecular lab

Mutation analysis in PIDs

- Definitive diagnosis (atypical presentations)
- Presymptomatic identification
- Carrier identification, genetic counseling, prenatal diagnosis
- Prognosis (strong genotype-phenotype correlation)
- Technical considerations (DNA stability vs. live cells)

Mutations in PIDs

- ~200 recognized PIDs, >250 genes (growing fast ~1/month)
 - candidate genes
 - mapping studies
 - novel technologies (genome/exome)
- Pathways not genes - Mendelian susceptibility to:
 - chronic mucocutaneous candidiasis
 - mycobacterial infections
 - herpes simplex encephalitis
- Normal vs. immune deficient (not all-or-nothing)
 - quantitative traits/pathways

Mendelian susceptibility to chronic mucocutaneous candidiasis (CMC)

- *Candida albicans* is present in GI flora and and reproductive mucosa of **healthy** subjects
- **Immunocompromised** patients *C albicans* can cause systemic or mucosal disease
- Systemic candidiasis is an acute, disseminated, and invasive
 - Candidemia is one of the most prevalent bloodstream infections in hospital settings and is associated with significant morbidity and mortality
- CMC is localized to the skin, nails, and mucous membranes (no predisposition to invasive disease, such as sepsis or pneumonia)

Immunity to candida

- Impaired T cell immunity: HIV/AIDS, SCID, DiGeorge syndrome, DOCK8 deficiency, etc.
- Congenital neutropenias or secondary neutropenia (e.g. after chemotherapy)
- Recognition:
 - mannans (outer portion of the cell wall)
 - TLR4, Mannose Receptor, DC-SIGN, and Dectin2
 - β -glucans (inner portion of the fungal cell wall)
 - Dectin1, and MINCLE

Genetics of CMC

- Dectin-1 deficiency (AR)
- CARD-9 deficiency (AR)
- AD Hyper IgE syndrome or Job syndrome: STAT3 deficiency
- AR Hyper IgE syndrome: DOCK8 deficiency
- STAT1 mutations (AD)
- IL-17F deficiency (AR)
- IL-17RA deficiency (AR)
- APECED (or APS type I): AIRE deficiency (AR)

Molecular testing → diagnosis, prognosis, inheritance

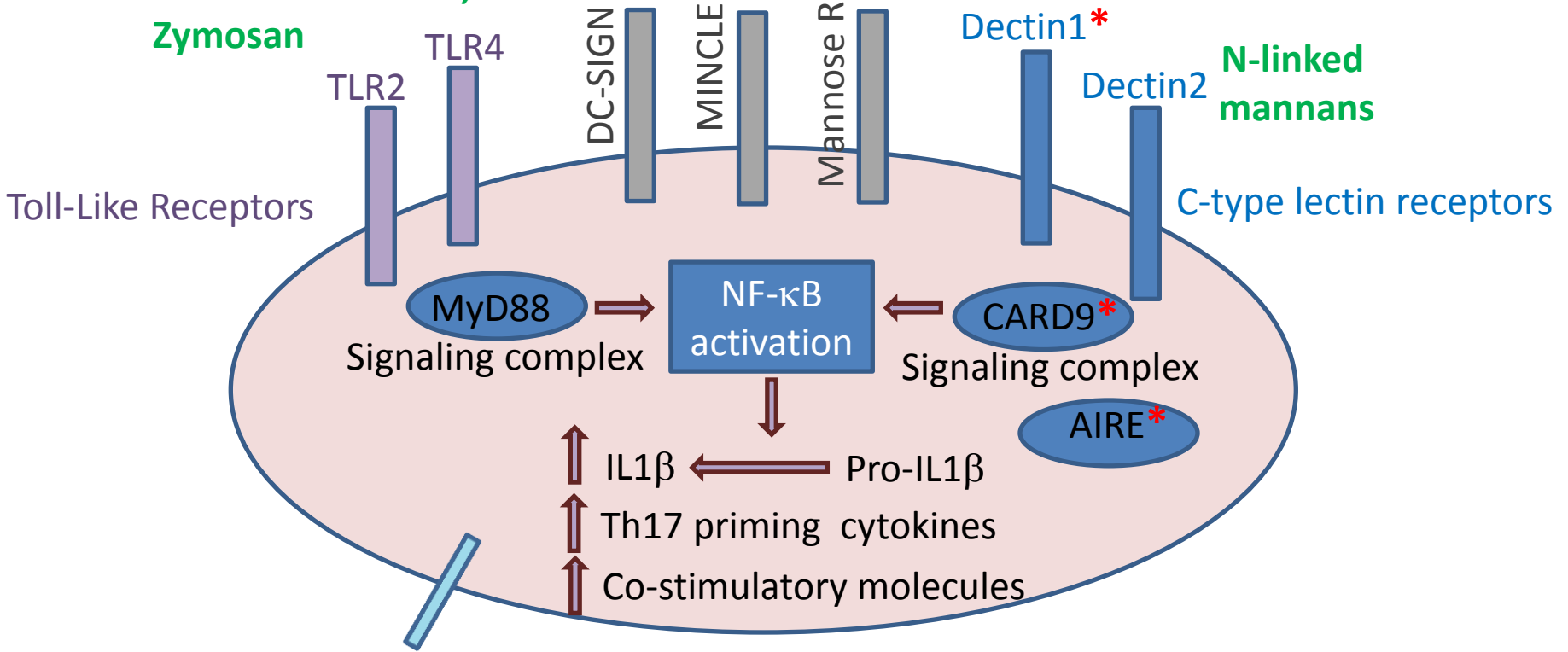
Immune response: receptors → signaling → effector functions

Fungal Pathogen Associated Molecular Patterns (PAMPs)

O-linked mannans,
Zymosan

β -glucan

N-linked
mannans

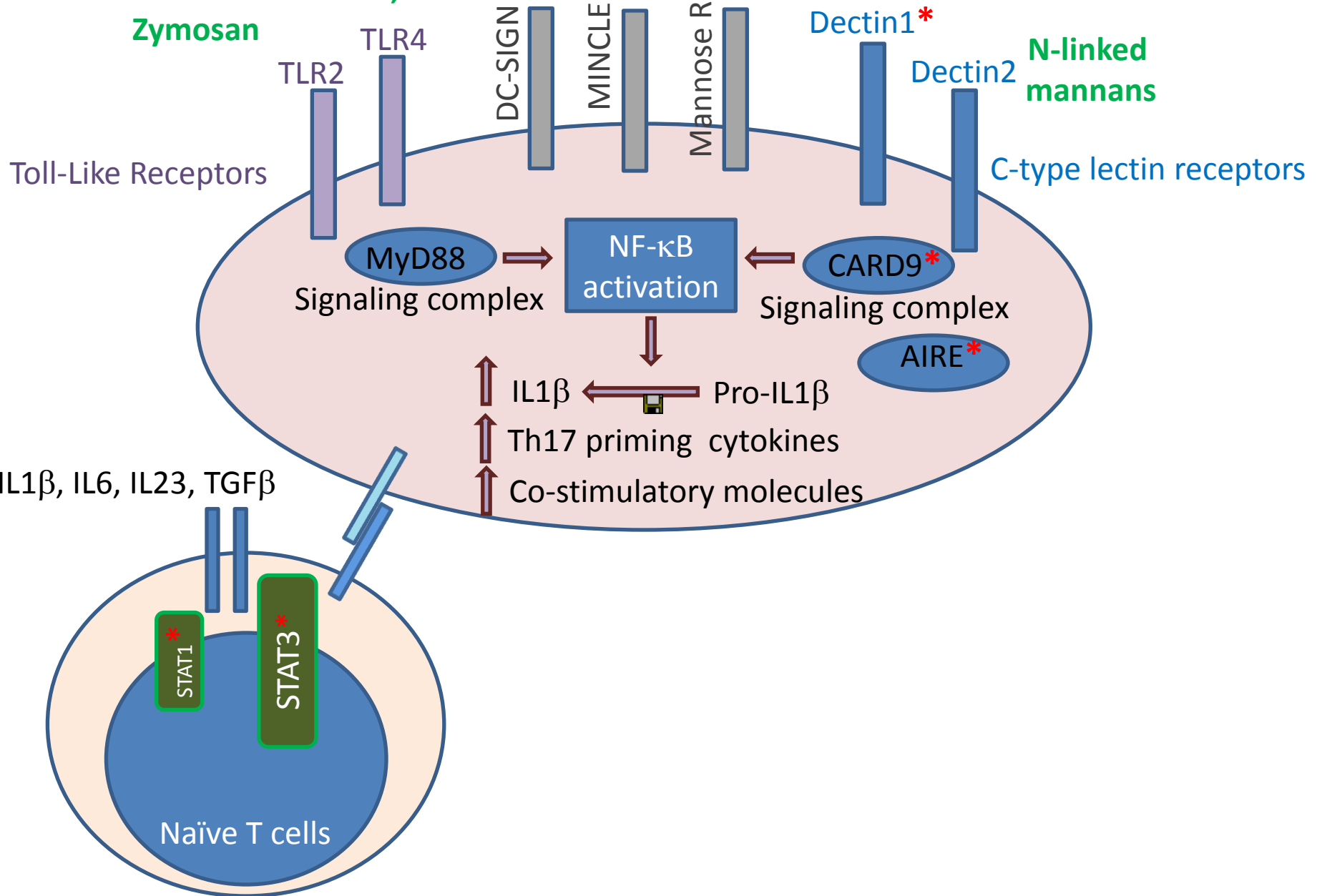


Fungal Pathogen Associated Molecular Patterns (PAMPs)

O-linked mannans,
Zyosan

β -glucan

N-linked
mannans



IL1 β , IL6, IL23, TGF β

STAT1*

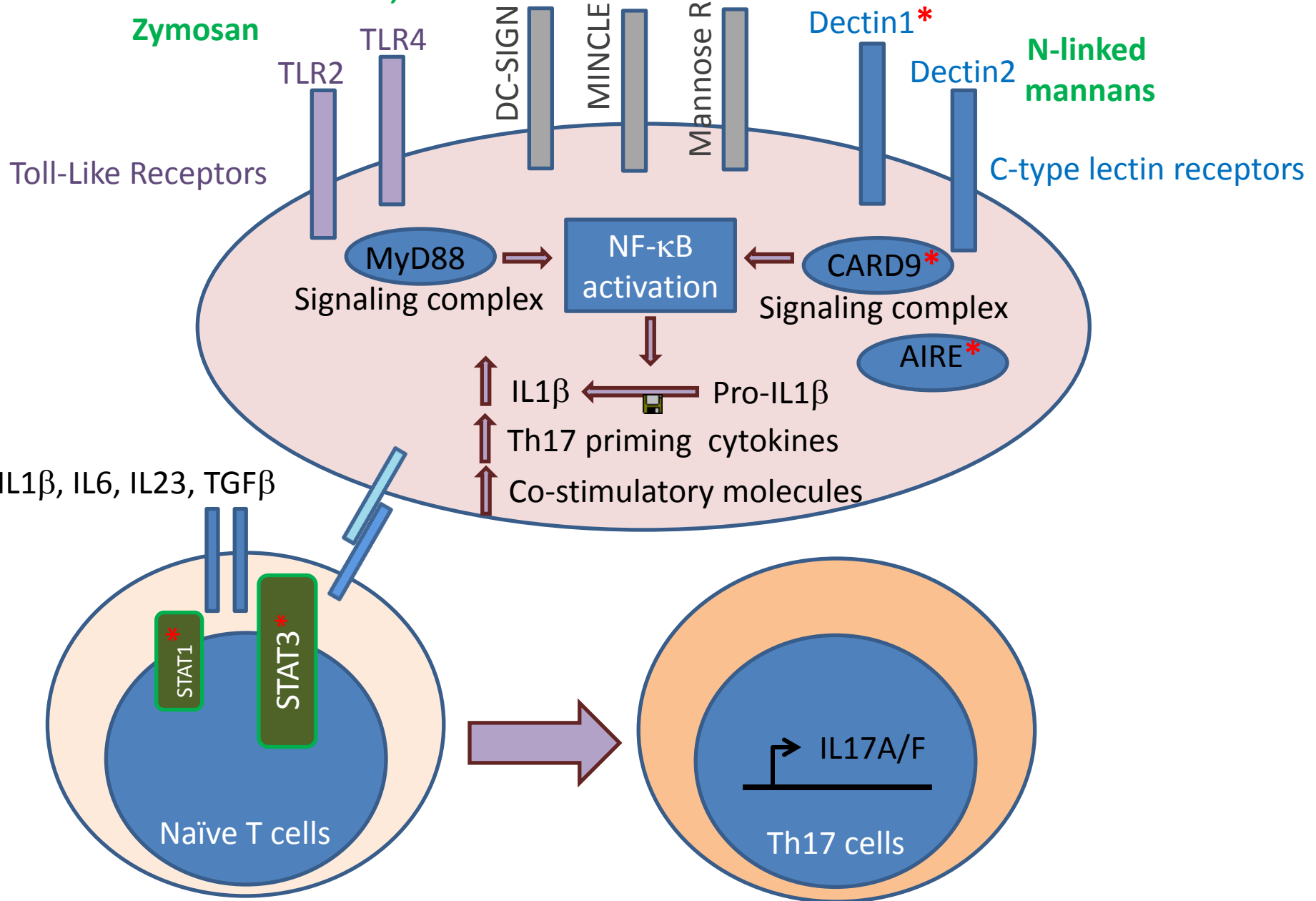
STAT3*

Naïve T cells

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O-linked mannans,
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β -glucan



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O-linked mannans,
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Toll-Like Receptors

TLR2
TLR4

DC-SIGN

MINCLE

Mannose R

Dectin1*

Dectin2

C-type lectin receptors

MyD88
Signaling complex

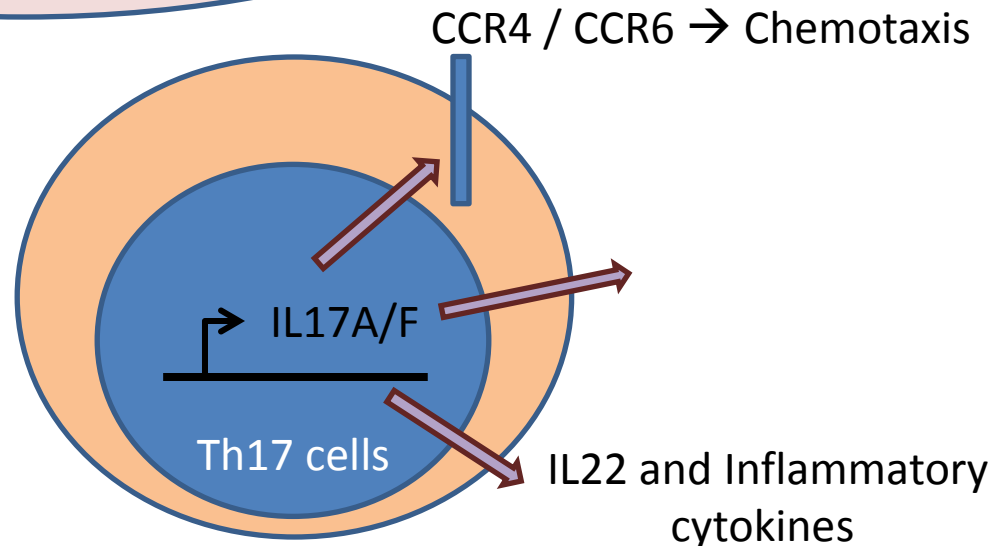
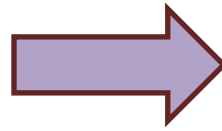
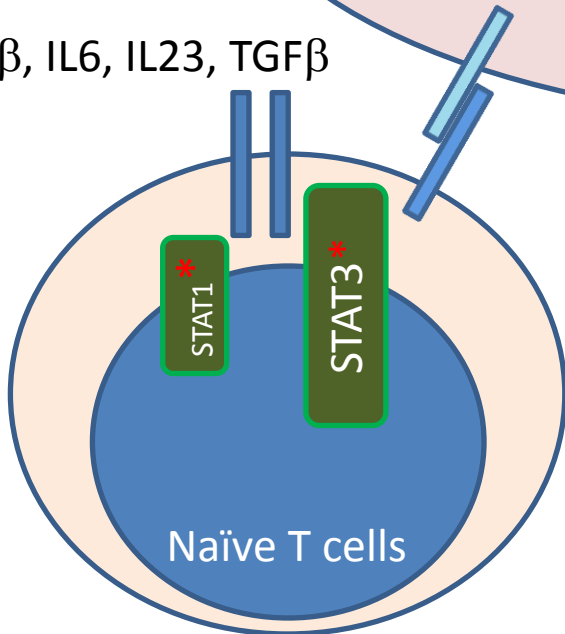
NF- κ B
activation

CARD9*
Signaling complex

AIRE*

IL1 β ← Pro-IL1 β
Th17 priming cytokines
Co-stimulatory molecules

IL1 β , IL6, IL23, TGF β

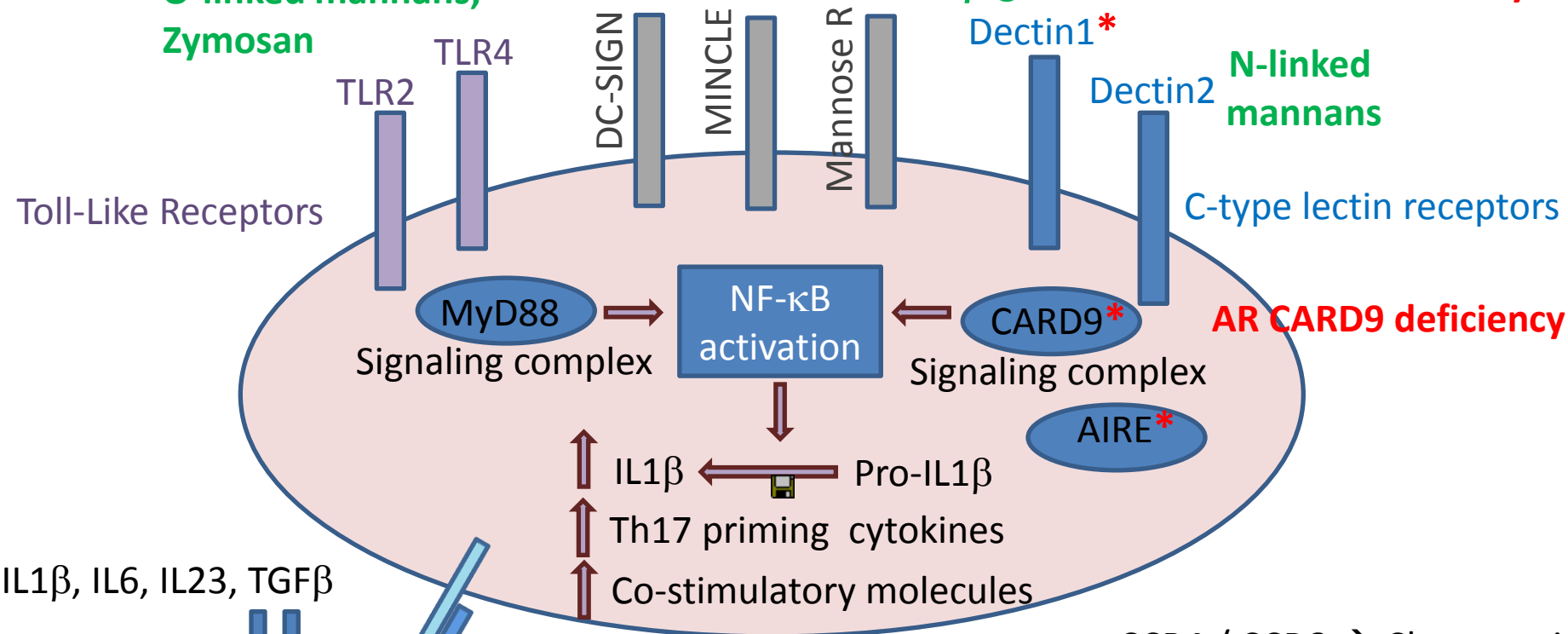


Fungal Pathogen Associated Molecular Patterns (PAMPs)

O-linked mannans,
Zymosan

β -glucan

AR Dectin1 deficiency



IL1 β , IL6, IL23, TGF β

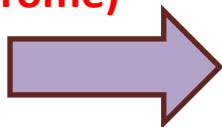
Gain-of-Function
STAT1

STAT1*

Dominant neg.
(Job syndrome)

STAT3*

Naïve T cells



CCR4 / CCR6 \rightarrow Chemotaxis

AR IL17RA deficiency

anti-IL17
Autoantibody
(APECED)

AIRE*

IL17A/F

Th17 cells

IL22 and Inflammatory
cytokines

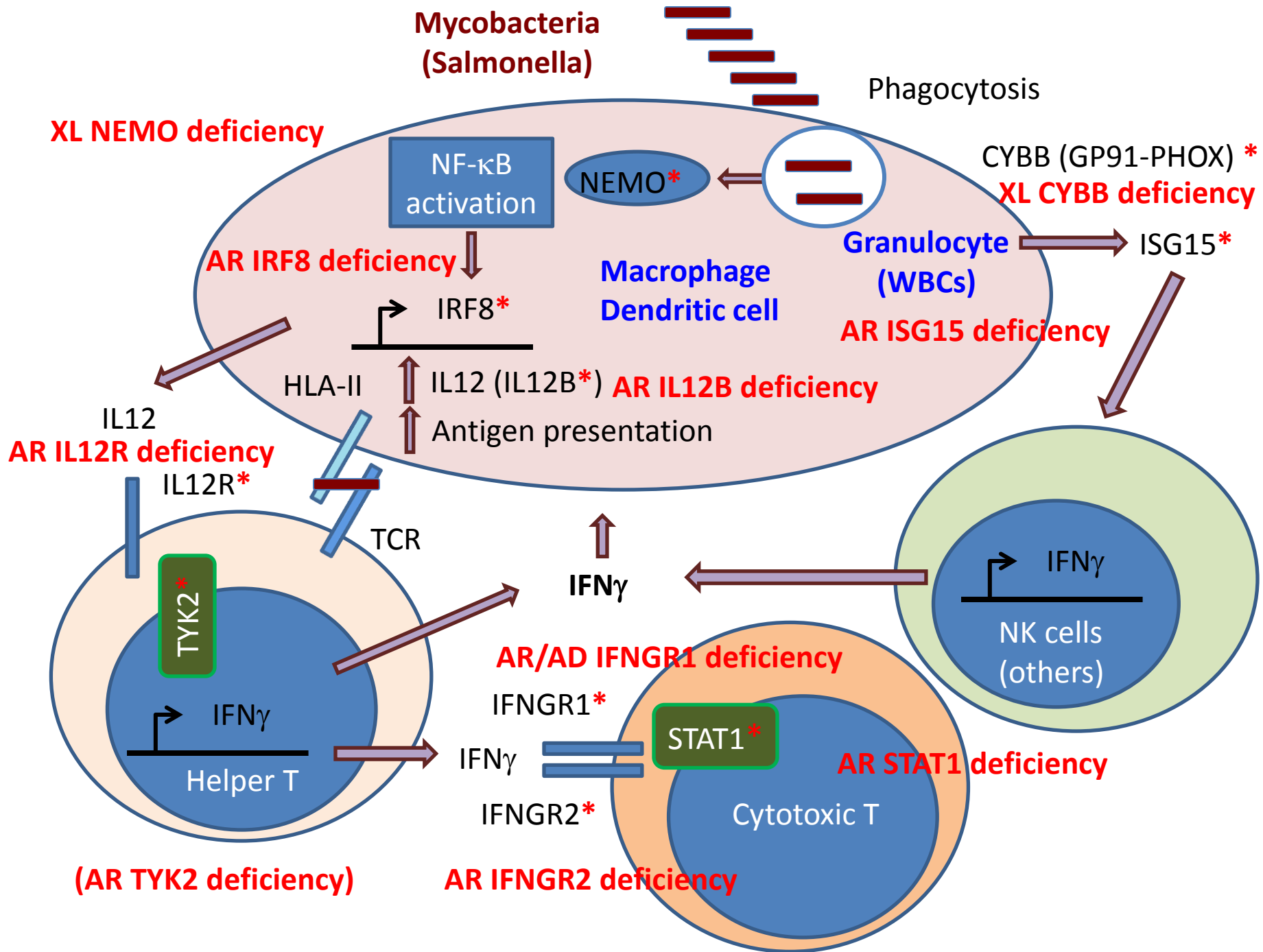
Immunity to candida

- Gain-of-function STAT1 mutations:
 - dimorphic fungi: - coccidioidomycosis
- histoplasmosis
- CARD9 deficiency:
 - increased risk of invasive candidiasis
(*Candida dubliniensis* meningoencephalitis)

(Sampaio EP et al. JACI 2013; Drewniak A et al. Blood 2013)

Mendelian susceptibility to mycobacterial disease

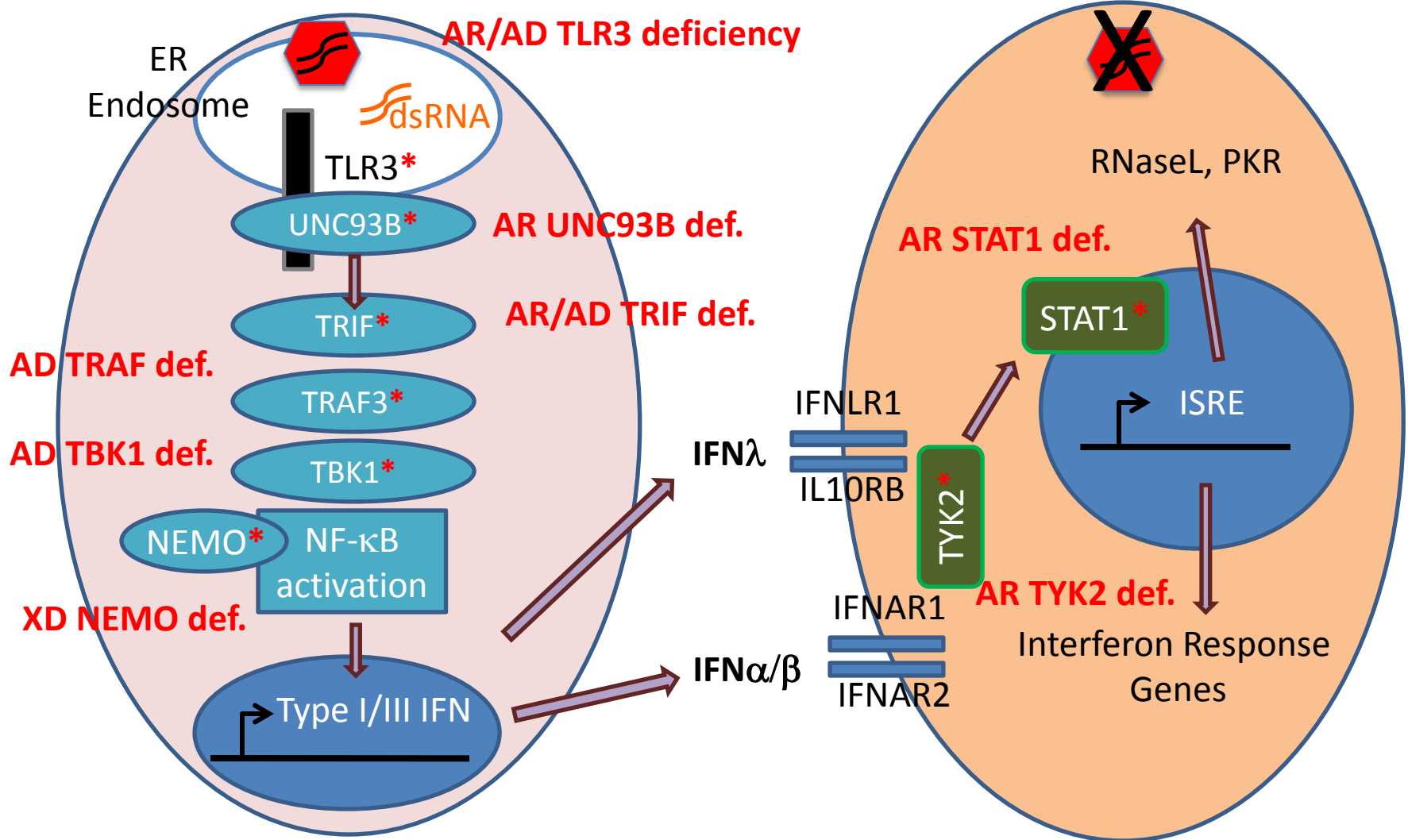
- Predisposition of otherwise apparently healthy individuals to infections caused by weakly virulent mycobacteria Bacille Calmette Guerin (BCG) and atypical (or nontuberculous) mycobacteria, *M. tuberculosis* and Salmonella
 - Genes:
 - IFNGR1 (AR/AD)
 - IFNGR2 (AR)
 - STAT1 (AD)
 - IL12B (AR)
 - IL12RB1 (AR)*
 - NEMO (IKBKG) (XL)
 - CYBB (XL)
 - IRF8 (AR/AD)
 - ISG15 (AR)
 - TYK2 (AR)
- Impaired IFN- γ -mediated immunity (~50 % have unknown genetics)



Herpes Simplex Encephalitis

- HSE is the most common cause of sporadic fatal encephalitis worldwide (70% mortality if untreated)
- Acyclovir
- Lifelong neurological sequelae of varying severity in survivors is common (>30%)
- Genes:
 - TLR3 (AR/AD)
 - UNC-93B (AR)
 - TRIF (AR/AD)
 - TRAF3 (AD)
 - TBK1 (AD)
 - NEMO (XR)
 - STAT1 (AR)
 - TYK2 (AR)

Herpes Simplex Encephalitis



Different genes – same/similar clinical phenotype

- **CMC:**

- IL-17RA, IL-17F, STAT1, DECTIN1, CARD9, STAT3, DOCK8, AIRE

- **MSMD:**

- IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, NEMO, CYBB, IRF8, ISG15, TYK2

- **HSE:**

- TLR3, UNC-93B, TRIF, TRAF3, TBK1, NEMO, STAT1

→ Molecular networks/pathways, not genes

→ Single gene testing vs. gene panels

One gene – multiple phenotypes

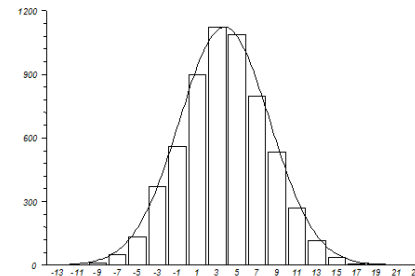
- AD **STAT1** deficiency: **dominant negative** mutations
→ susceptibility to mycobacterial and salmonella infections
- AD **STAT1** deficiency: **gain-of-function** mutations
→ chronic mucocutaneous candidiasis
- AR **STAT1** deficiency: **loss-of-function** mutations
→ susceptibility to severe viral and mycobacterial disease

Genetic susceptibility

- Monogenic primary immunodeficiency diseases
 - Classic PIDs: opportunistic infections
 - Novel PIDs: restricted susceptibility/single organisms (e.g. HSE is genetic)

→ rare
- Immune response is a complex trait
 - complex traits (such as height and weight), arise from the combination of large number of (hundreds/thousands) of individual small genetic effects across the genome
 - Genome Wide Association Studies (GWAS) Increasing knowledge

→ Common (everybody!)



Genetic susceptibility

- Candida infections (Smeekens et al. 2013):
 - Dectin1 → Candida colonization
 - TLR1/2/3/4 → Susceptibility candidemia
 - IL4/MBL2/NLPR3 → Recurrent vulvo-vaginal candidiasis
- Tuberculosis susceptibility (Barreiro et al. 2012; Qu et al. 2011):
 - MSMD and TB: monozygotic/dizygotic twin studies
 - DUSP14 → pulmonary TB
 - HLA/NRAM1/IFNG/IL12B/NOS2A
- Susceptibility to HSV encephalitis:
 - HSE (de Diego et al. 2013)
 - TLR3 variants → Resistance to HSV2 (Svensson et al. 2012)

→ Pathways

Genetic susceptibility

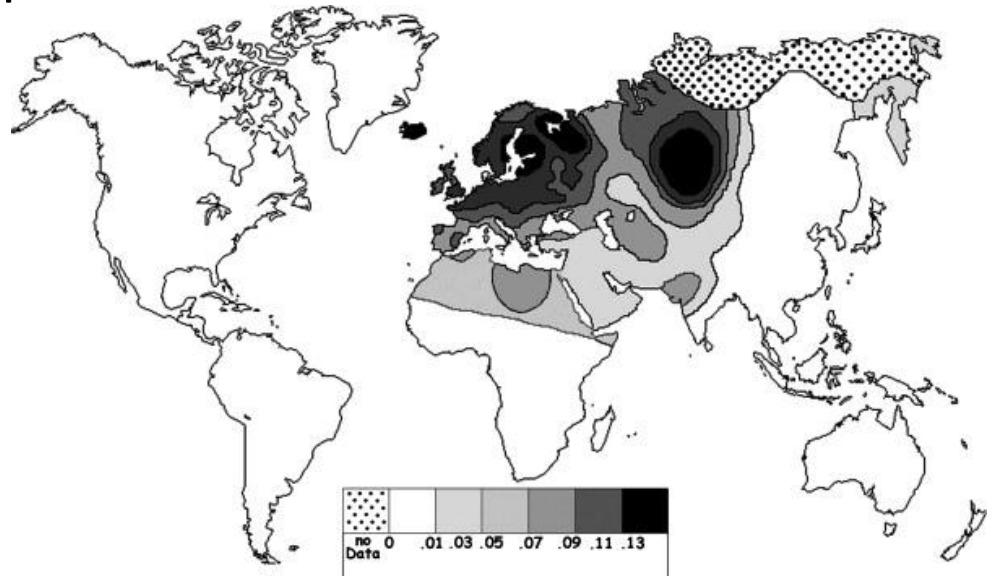
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→ Pathways

Genetic susceptibility - Environment

- Genetic variants: 'pathogenic', 'neutral', 'beneficial'
- HbS, HbC, and α -thalassemia → protection from malaria
- CCR5 Δ 32
 - Protection against HIV infection (Liu et al. 1996)
 - Increases risk of symptomatic West Nile virus infection (Glass et al. 2006)

→ Europe 3-16%
allele frequencies
(south to north)



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