Frédégonde About, Hôpital de Cayenne

Déficit immunitaire et maladies infectieuses

« Best of »

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DÉFICITS IMMUNITAIRES PRIMITIFS (DIP), HÉRÉDITAIRES

DÉFICITS IMMUNITAIRES SECONDAIRES, ACQUIS

Diabète, dénutrition, **VIH +++**
Traitements immunosuppresseurs
Maladie grave prolongée (réa,…)
Age
Perte des protéines sériques (Ig, albumine):
Maladie rénale chronique, Brûlures,
Entéropathie

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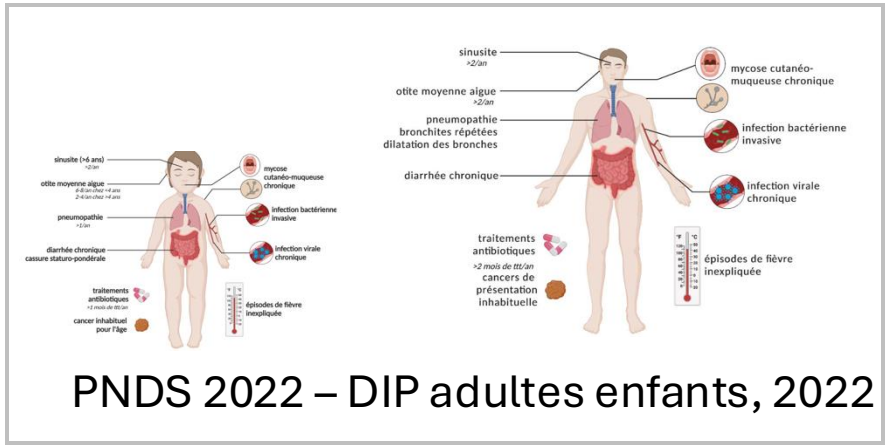
DIP



PNDS 2022 – DIP adultes enfants, 2022

Groupe hétérogène de **maladies rares**.

Génétiquement déterminé

Manifestations variables:

-infections

-ATCD familiaux (arbre, infections, auto-immunité, inflammation, décès en bas âge)

-auto-immunité

-allergie

-inflammation

-néoplasie (lymphomes)

-manifestations syndromiques (retard mental, cardiopathie, syndrome poly malformatif, eczéma, trouble de la pigmentation, signes neurologiques, troubles de la dentition,…)

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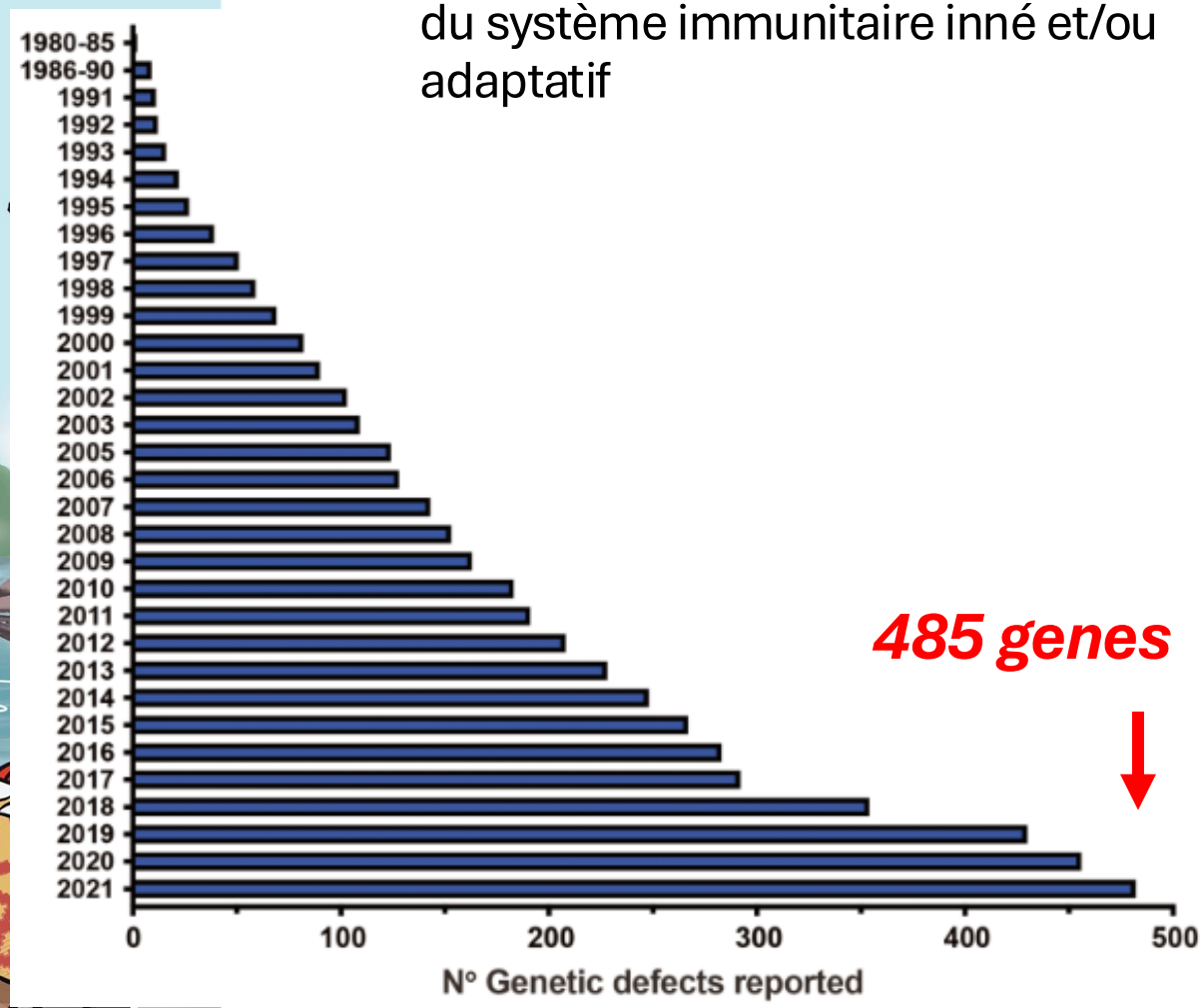
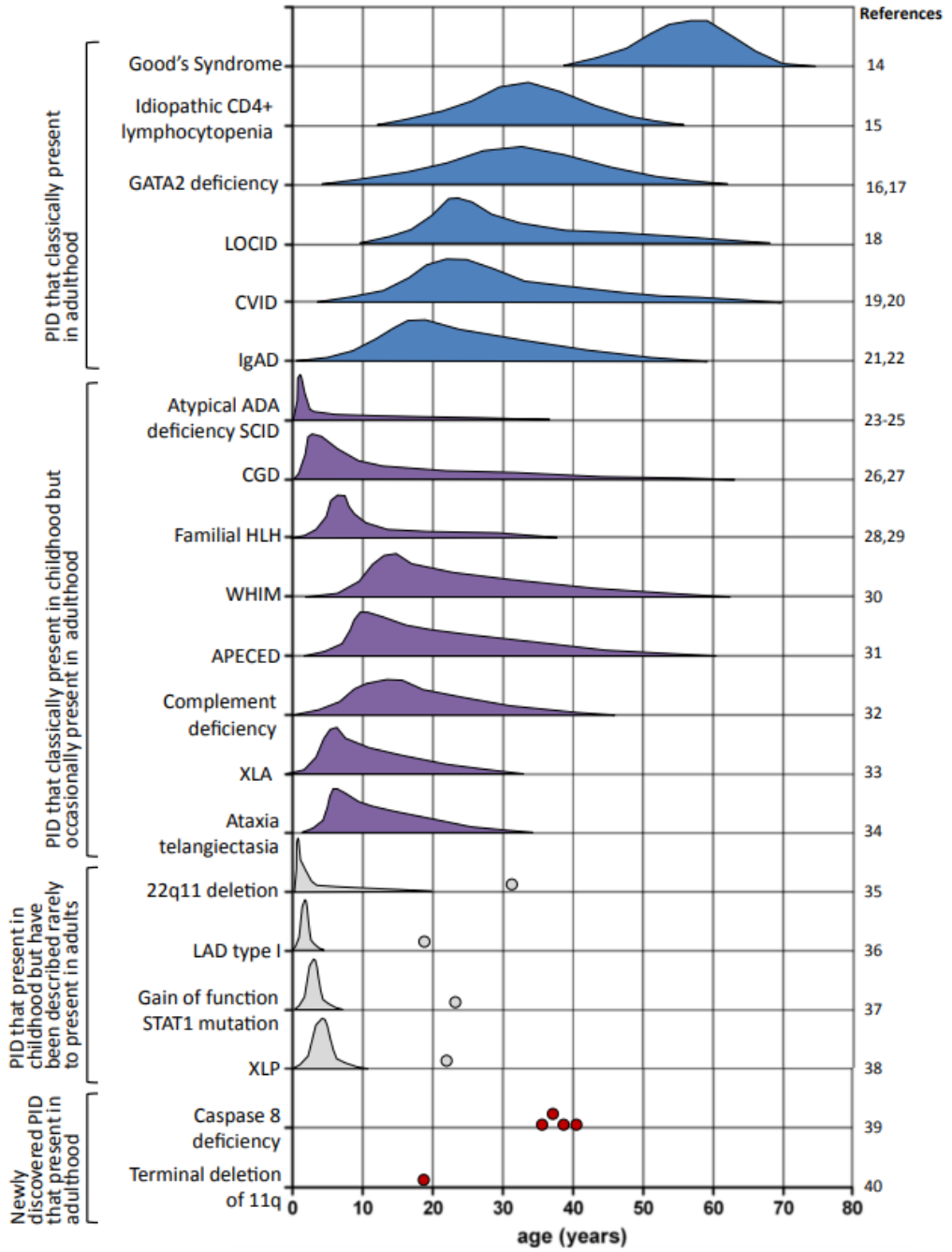
DIP

Atteinte quantitative +/- qualitative du système immunitaire inné et/ou adaptatif



485 genes



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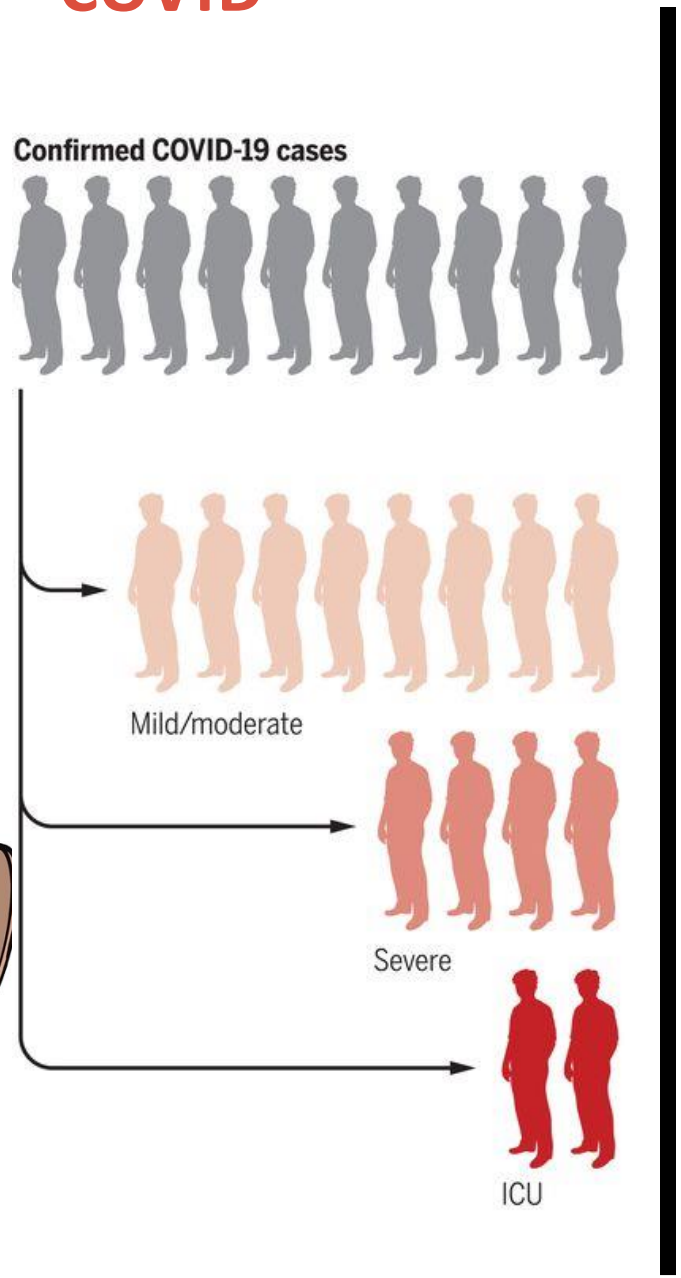
COVID



@ Science 25 Sep 2020, Vol 369, Issue 6511

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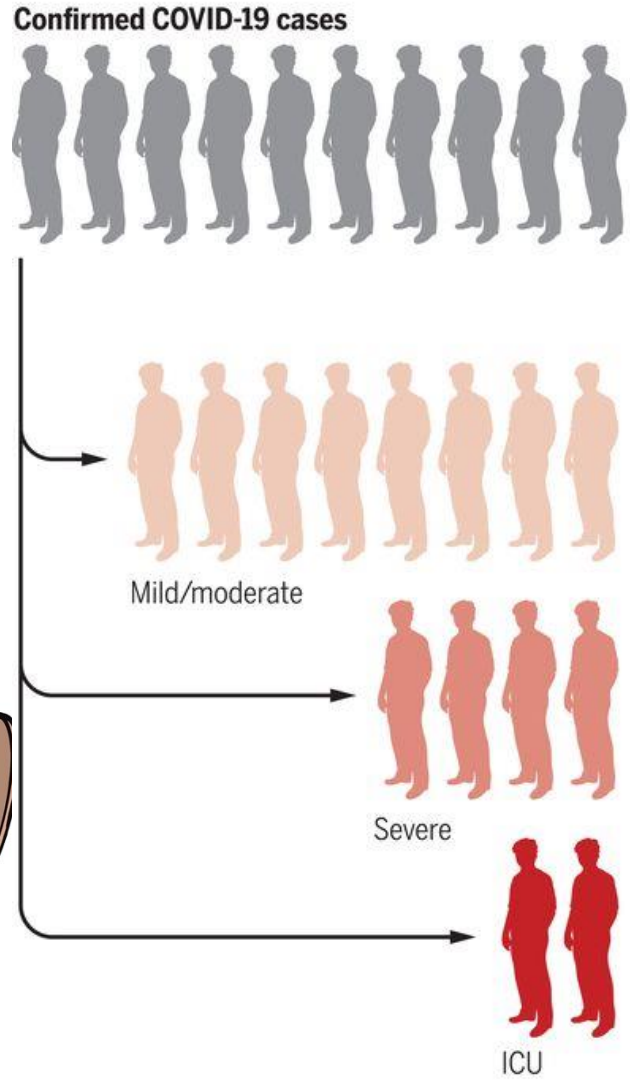
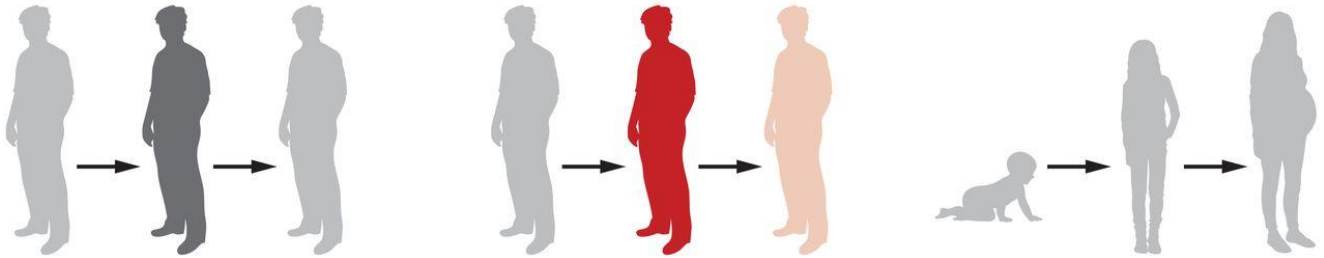
COVID



Longitudinal variation within an individual

Stochastic, environmental, developmental changes



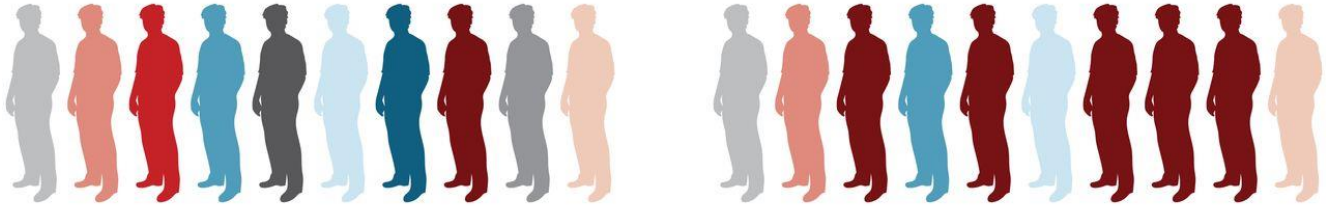
Stochastic variation
(stochastic gene regulation, epigenetic changes; de novo mutations)

Environmental perturbation
(vaccination, infection, diet)

Developmental change
(maturation, puberty, pregnancy, aging)

Interindividual variation within the same population or between different populations

Host genetic, environmental, microbiome differences



Population A

Population B

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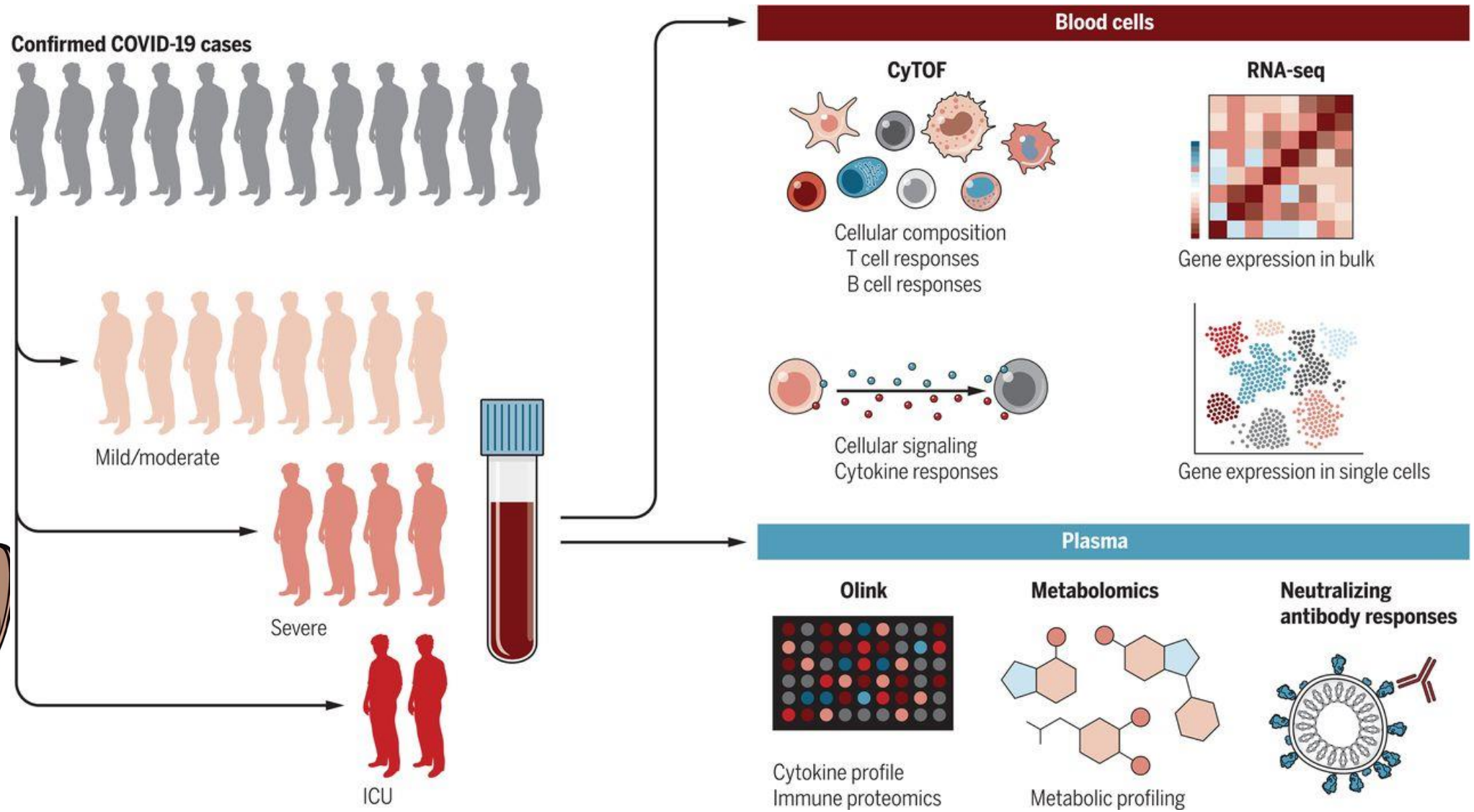
COVID



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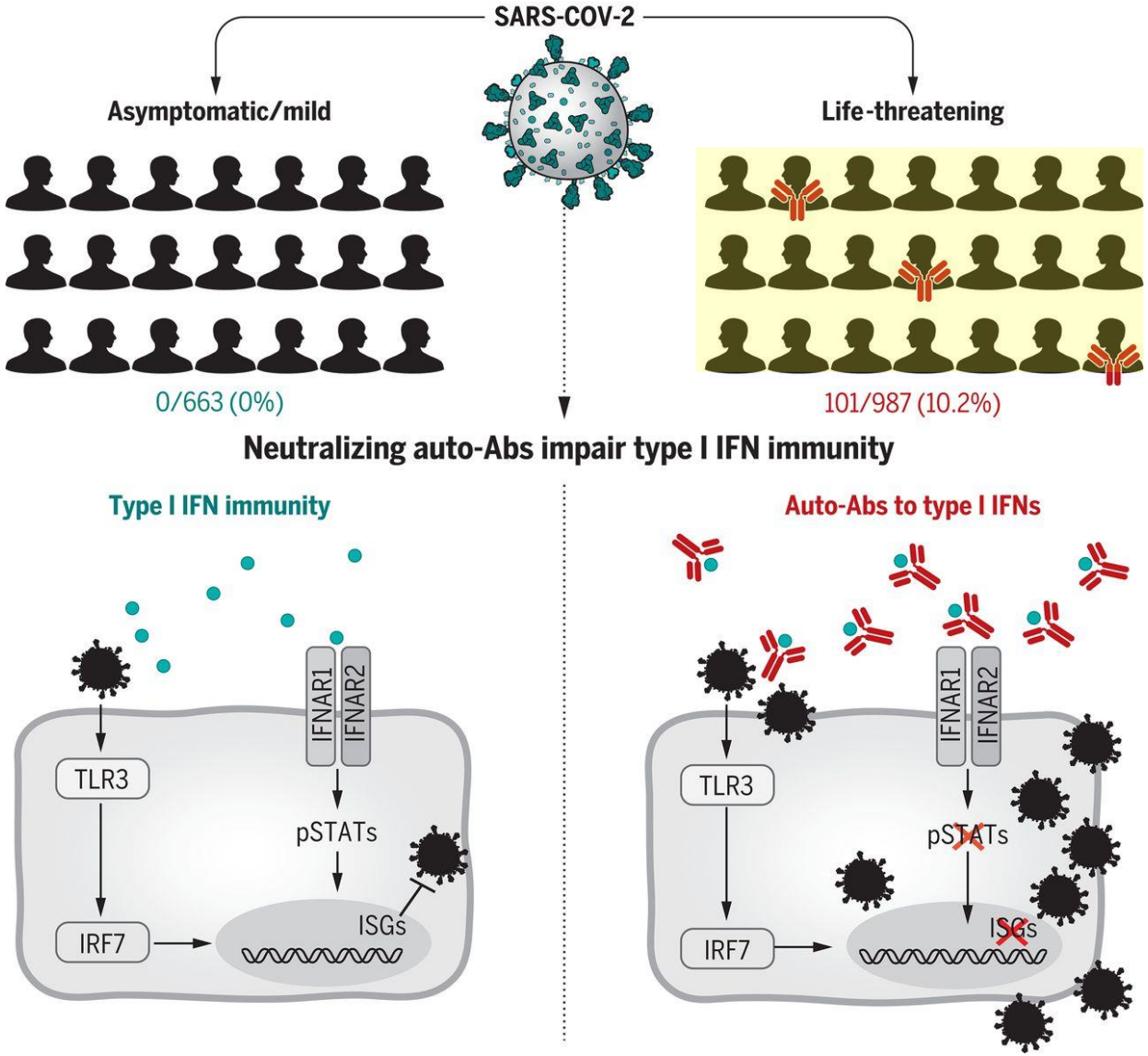
Neutralizing auto-Abs to type I IFNs underlie life-threatening COVID-19 pneumonia.



Bastard, P. et al. Science 370, eabd4585 (2020)

We tested the hypothesis that neutralizing auto-Abs against type I IFNs may underlie critical COVID-19 by impairing the binding of type I IFNs to their receptor and the activation of the downstream responsive pathway. Neutralizing auto-Abs are represented in red, and type I IFNs are represented in blue. In these patients, adaptive autoimmunity impairs innate and intrinsic antiviral immunity. ISGs, IFN-stimulated genes; TLR, Toll-like receptor; IFNAR, IFN-α/β receptor; pSTAT, phosphorylated signal transducers and activators of transcription; IRF, interferon regulatory factor.

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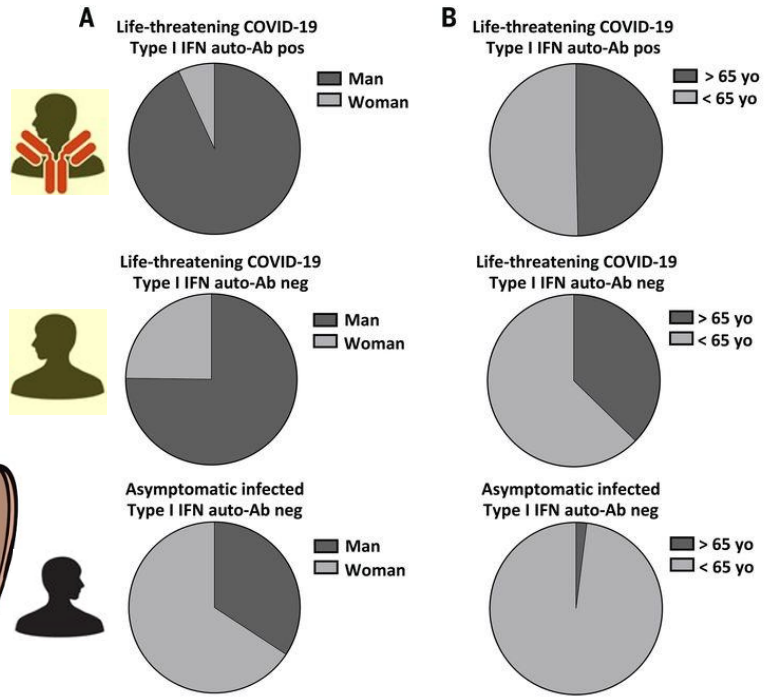

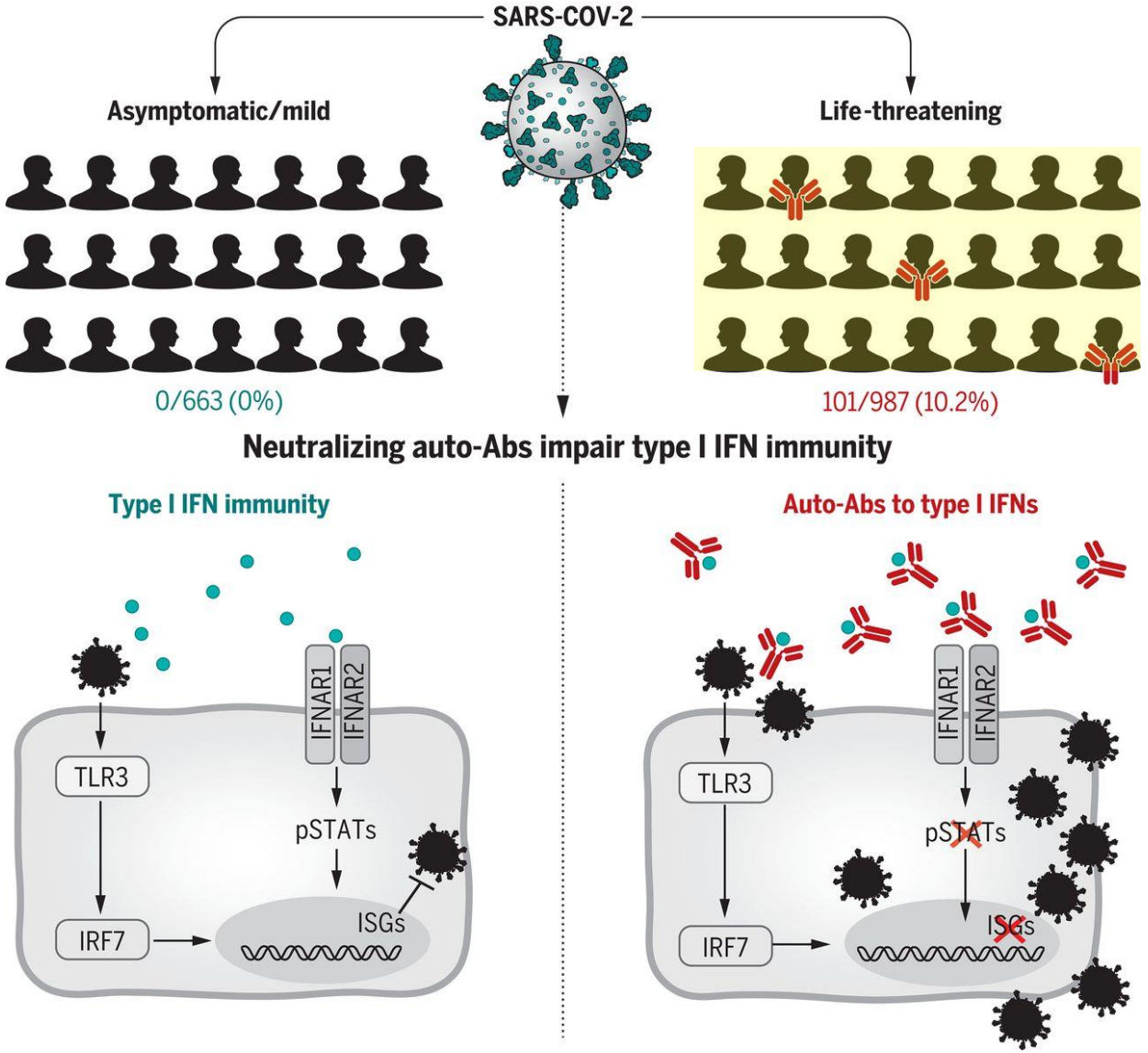

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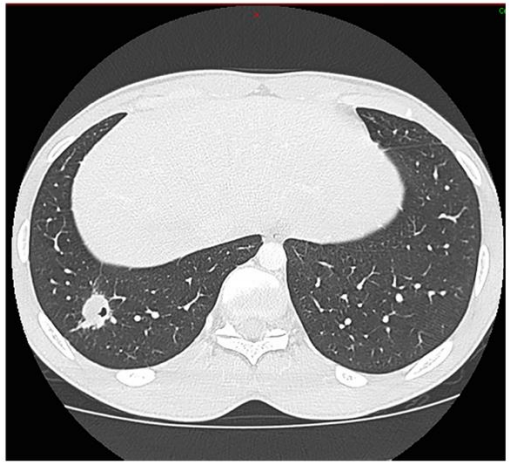
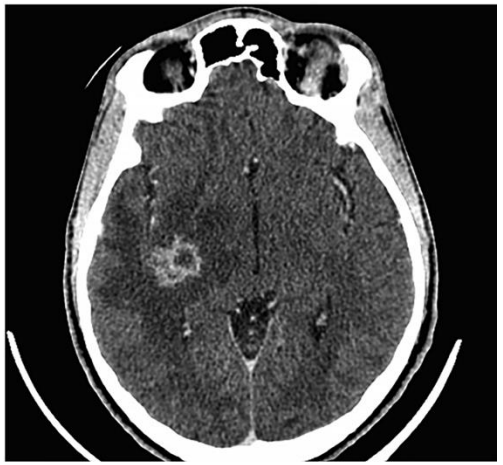
Cryptococcose





Case Report: Invasive Cryptococcosis in French Guiana: Immune and Genetic Investigation in Six Non-HIV Patients

Jeanne Goupil de Bouillé[1,2], Loïc Epelboin[3,4], Fanny Henaff[3], Mélanie Migaud[5], Philippe Abboud[3], Denis Blanchet[3,4], Christine Aznar[3,4], Felix Djossou[3,4], Olivier Lortholary[6], Narcisse Elenga[3,4], Anne Puel[5,6,7], Fanny Lanternier[5,6,8] and Magalie Demar[3,4]*

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Pathogens: *C. neoformans var. grubii* (n=3), *C. gattii* (n=2), *Cryptococcus Sp.* (n=1)

Front Immunol. 2022 Apr 26;13:881352.

Investigation to be performed in a patient with cryptococcosis

Underlying condition	No underlying condition

HIV infection +++

Immunosuppressive therapy

Autoimmune disease

Solid organ transplant

Haematologic disease

Diabet

Cirrhosis

Chronic renal failure

Splenectomy

Malignancies

1. Family history of fungal, bacterial, viral infections ?

> Family tree ☺

2. Standard immuno assay

> Lymphocyte immunophenotyping

> Antinuclear factors

> C3, C4, CH50

> Immunoglobulins

> HTLV serology

3. Not routinely but relevant

> IL12/INFγ production

> Anti GM-CSF antibodies

> *STAT1* gene

4. Research team

NGS…

Adapted from Front Immunol. 2022 Apr 26;13:881352.

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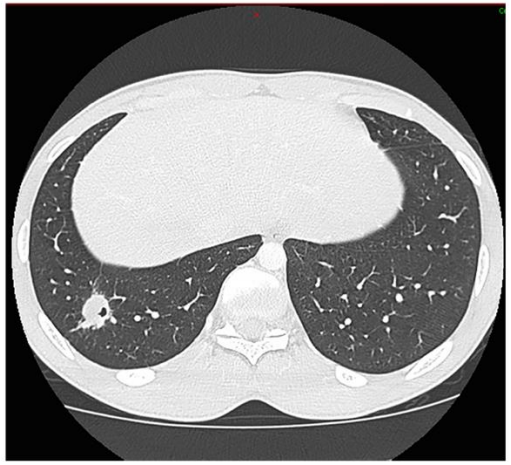
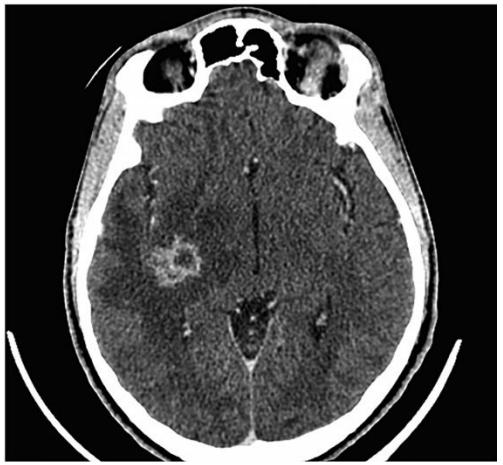
Cryptococcose





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Pathogens: *C. neoformans var. grubii* (n=3), *C. gattii* (n=2), *Cryptococcus Sp.* (n=1)

TABLE 2 | Immune exploration of the *Cryptococcosis* cases.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
HTLV1 serology	Negative	Negative	Negative	Negative	Negative	Negative
Lymphocyte immunophenotyping (CD4/CD8/B/NK)	Normal	NK lymphopenia Re-controlled Normal	Normal	Normal	Normal	Normal
Immunoglobulin (g/g/L)	Normal	Normal	Normal	Normal	Normal	Normal
Study of IL12/Interferon gamma production (in comparison with a healthy individual)	Normal	Normal	Normal	Not done	Not done	Normal
Anti-GM-CSF antibodies	Positive with positive neutralizing activity	Negative	Negative	Positive with positive neutralizing activity	Not done	Negative
Anti-IFN γ antibodies	Negative	Negative	Negative	Not done	Not done	Negative
STAT1 gene	Not done	Wild type	Wild type	Wild type	Not done	Wild type

Front Immunol. 2022 Apr 26;13:881352.

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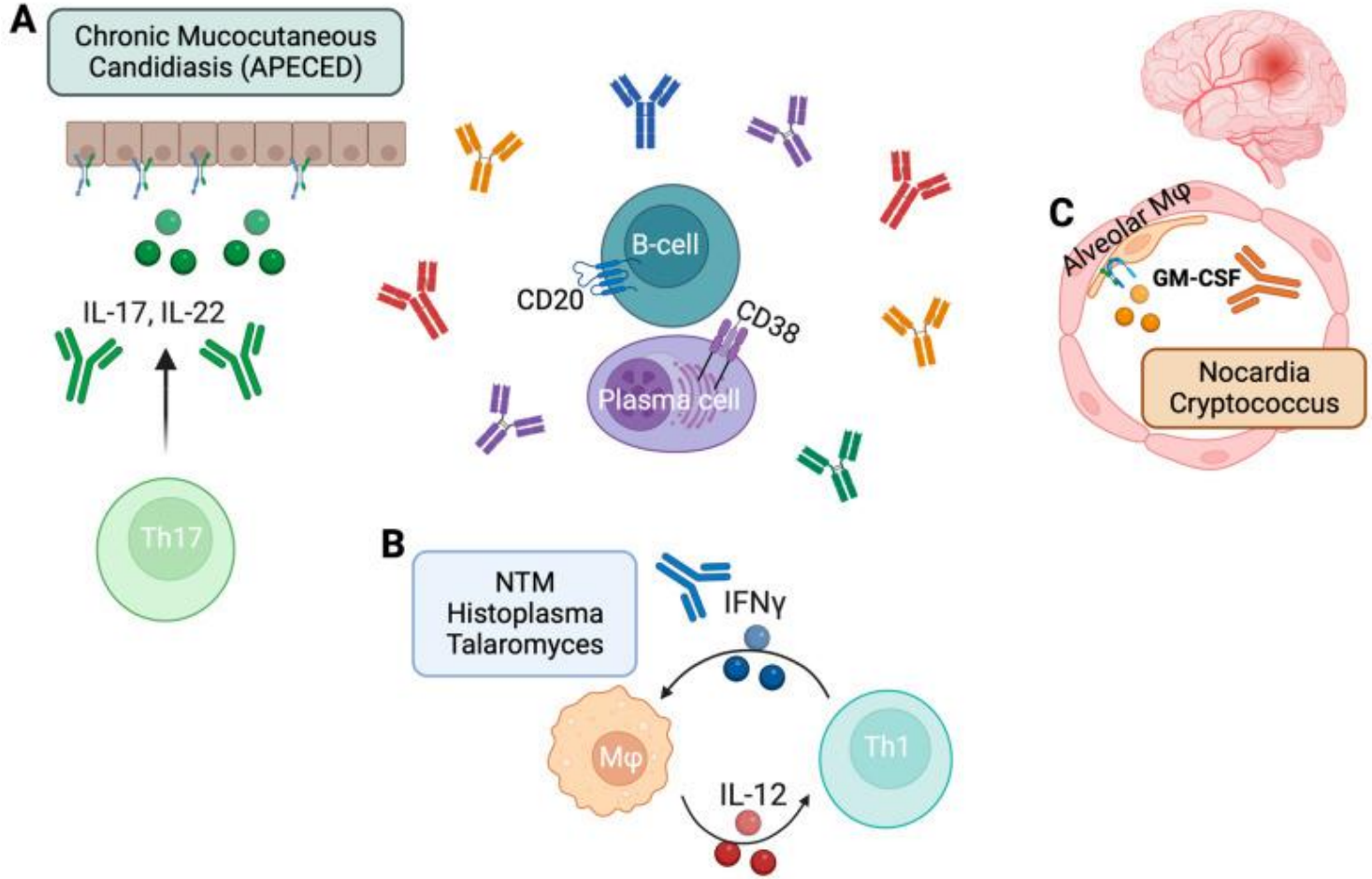
Suggested mode of action of auto-antibobies



Int J Mol Sci. 2023 Dec 30;25(1):515

Overview of most important ACAAs and their suggested mode of action. **Central to the process of auto-antibody production are B lymphocytes and plasma cells**, which can be targeted with host-directed therapies, such as rituximab (anti-CD20). (A) The cytokines IL-17 and IL-22 are essential in the interaction between epithelial barrier and Candida. IL-17 induces production of antimicrobial peptides and IL-22 enforces epithelial cell proliferation and repair, both through the IL-17-receptor and IL-22-receptor present in epithelial cells. This process is disrupted by anti-IL-17 and anti-IL-22 auto-antibodies. (B) IFNγ produced by Th1-cells is an essential activator of macrophages. It improves killing of intracellular pathogens, such as NTMs and several fungi, and induces IL-12 production, which in turn stimulates IFNγ production by Th1-cells. Anti-IFNγ auto-antibodies disrupt this proinflammatory loop. (C) **GM-CSF is essential in the activation of**, among others, **alveolar macrophages**, and the induction of production of reactive oxygen species. **Anti-GM-CSF auto-antibodies** therefore **increase the risk for specific pulmonary infections with Nocardia and cryptococcal species and apart from local infection also increase the risk for disseminated disease such as Nocardia brain abscesses and cryptococcal meningitis**. APECED, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFN, Interferon; IL, Interleukin; Mϕ, macrophage; NTM, Non-tuberculous mycobacteria; Th, T-helper cell.

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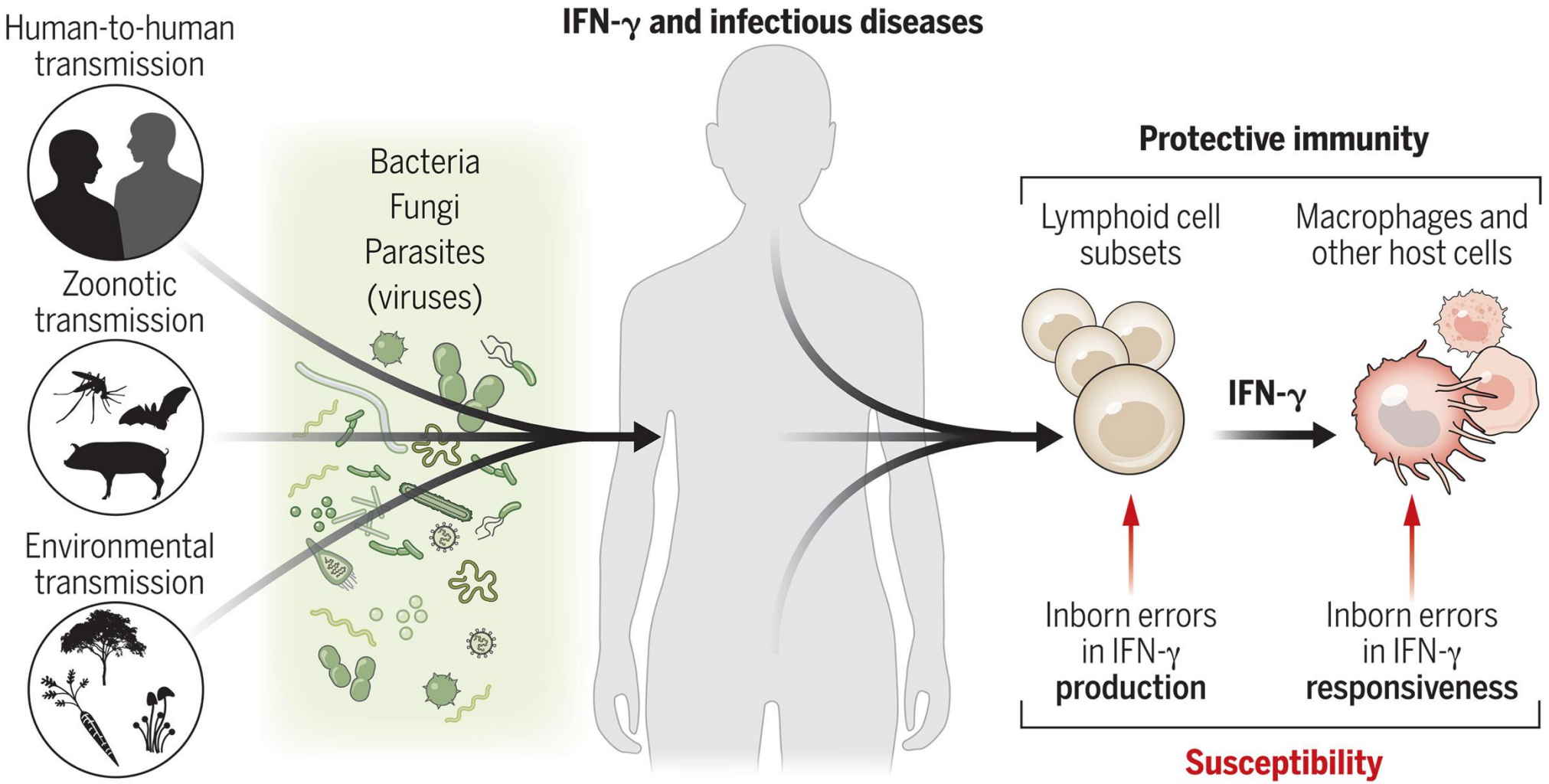
IFN-γ et maladies infectieuses



Science Review, vol 384,Issue 6693

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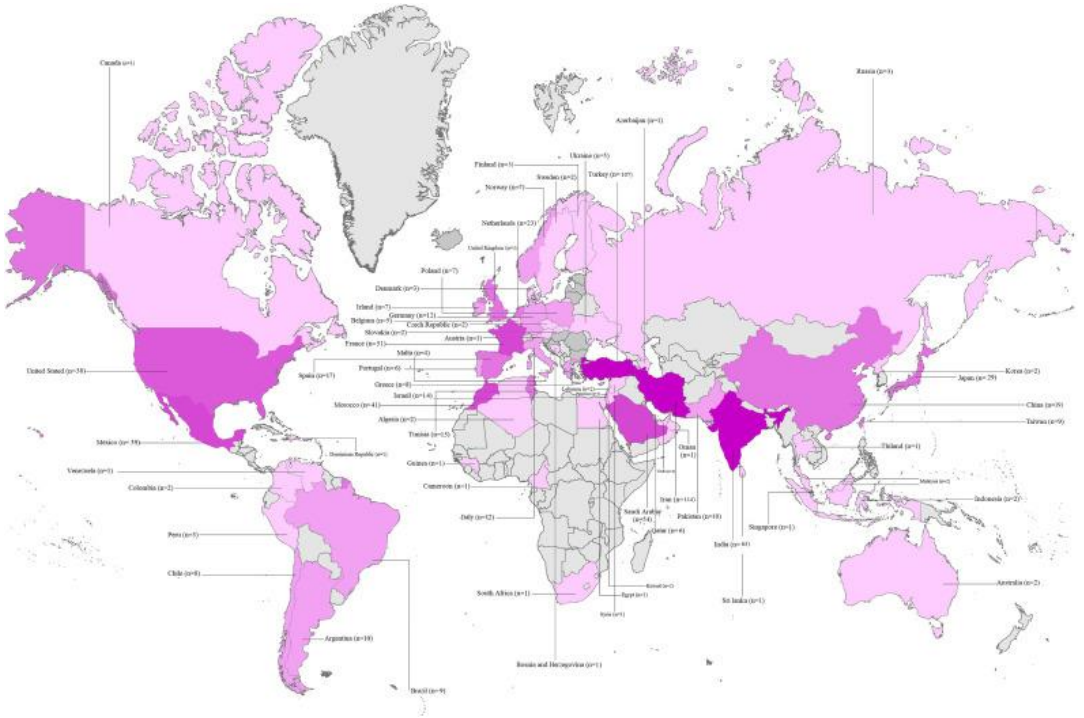
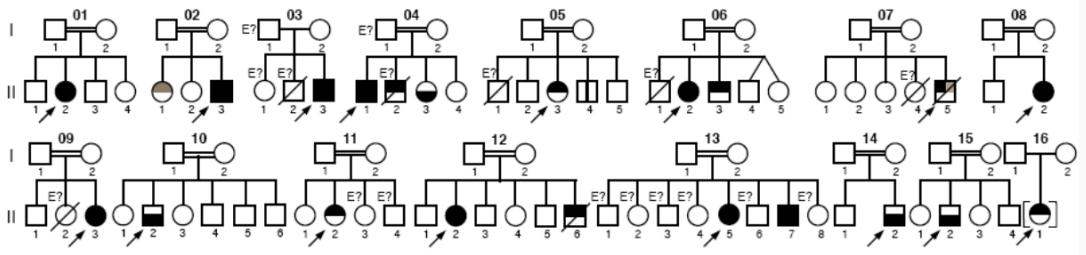
Prédisposition mendélienne aux infections mycobactériennes (MSMD)

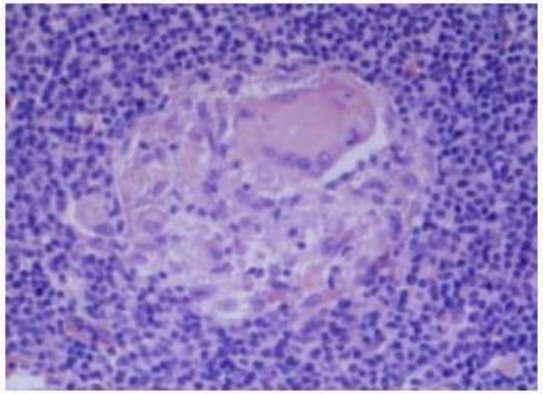
158 articles, 68 pays

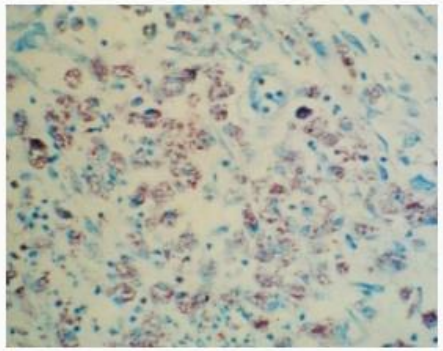


Cas familiaux (consanguinité)



Très rare $\sim 10^{-5}$
Infection par le BCG (BCGite) et par des mycobactéries de l'environnement
Enfants jeunes
Infection localisée, voire disséminée





Casanova et al

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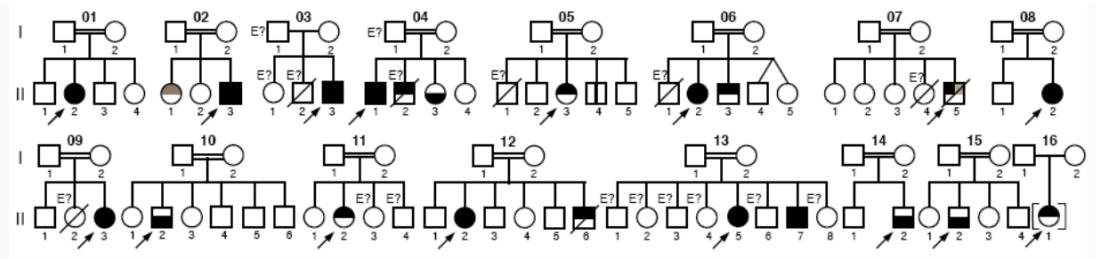

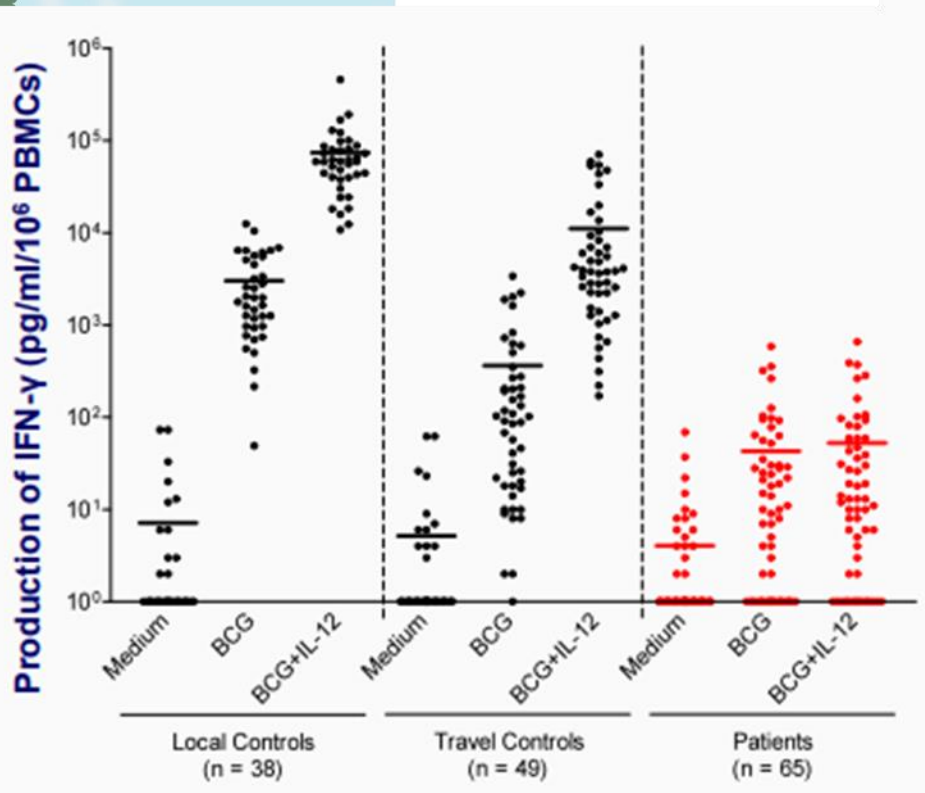

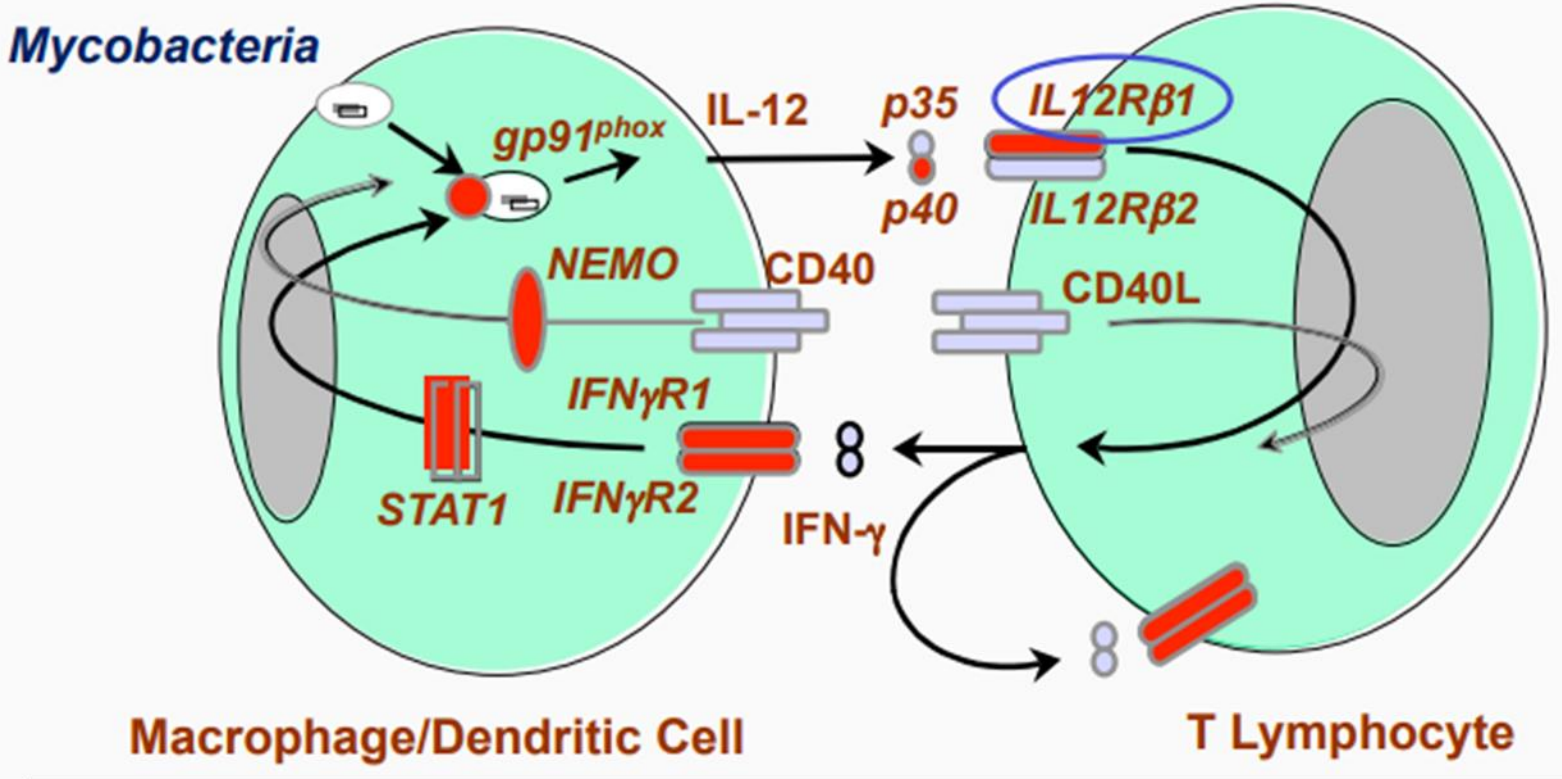

Casanova et al

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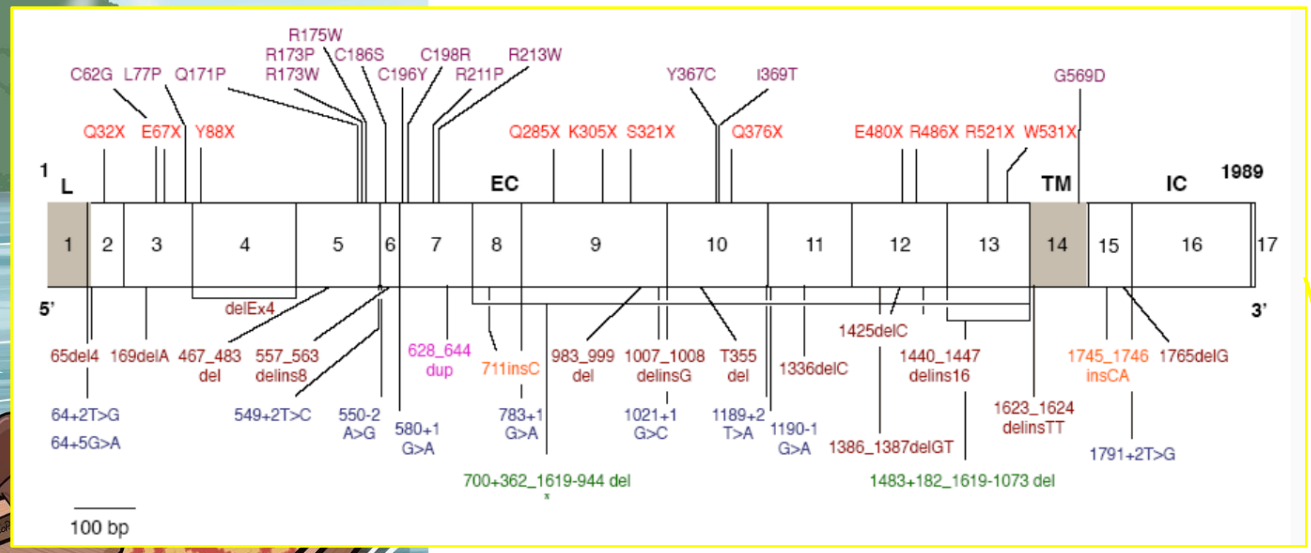

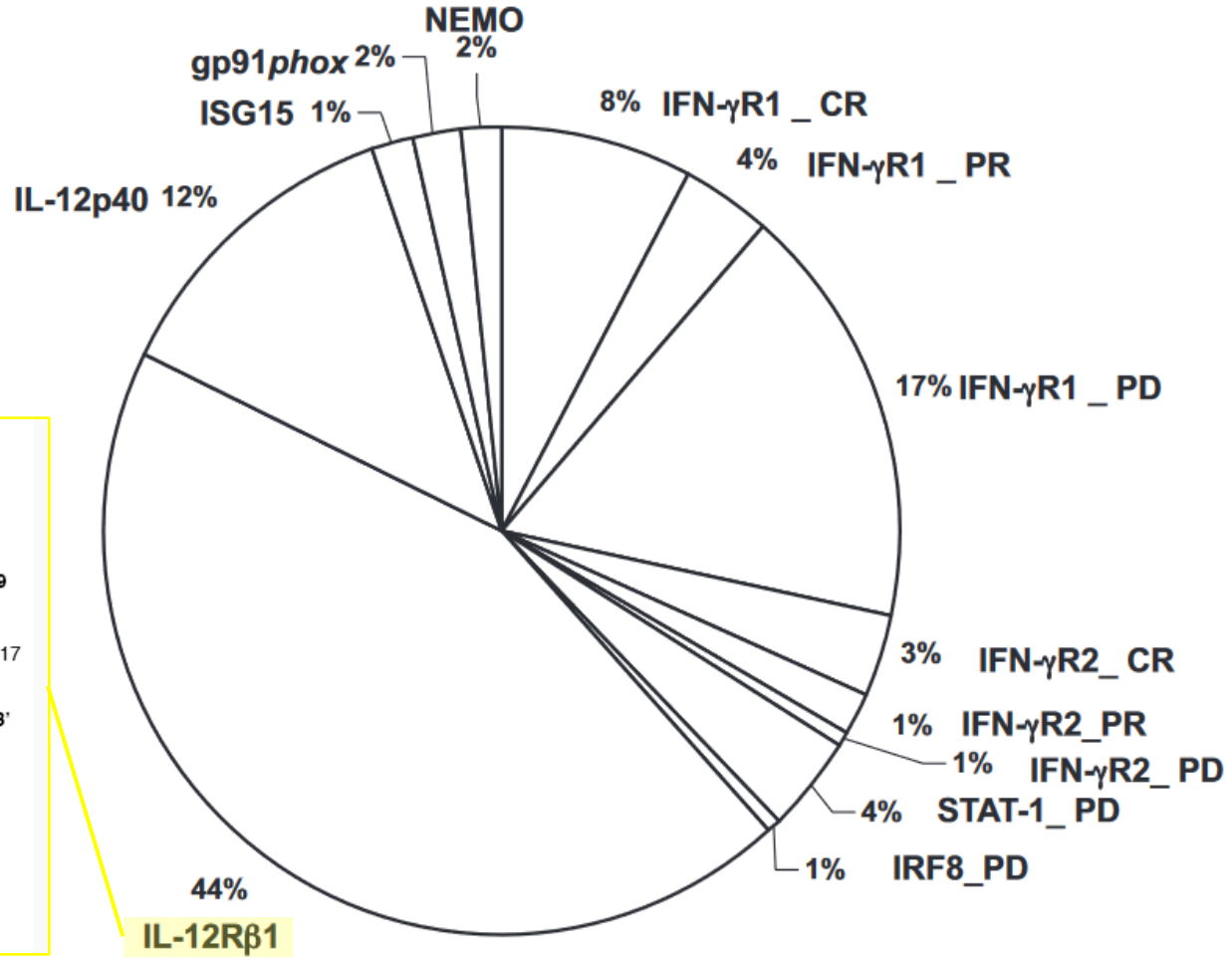

Fig. 3. Distribution of genetic disorders in MSMD patients with known etiologies.

Casanova et al

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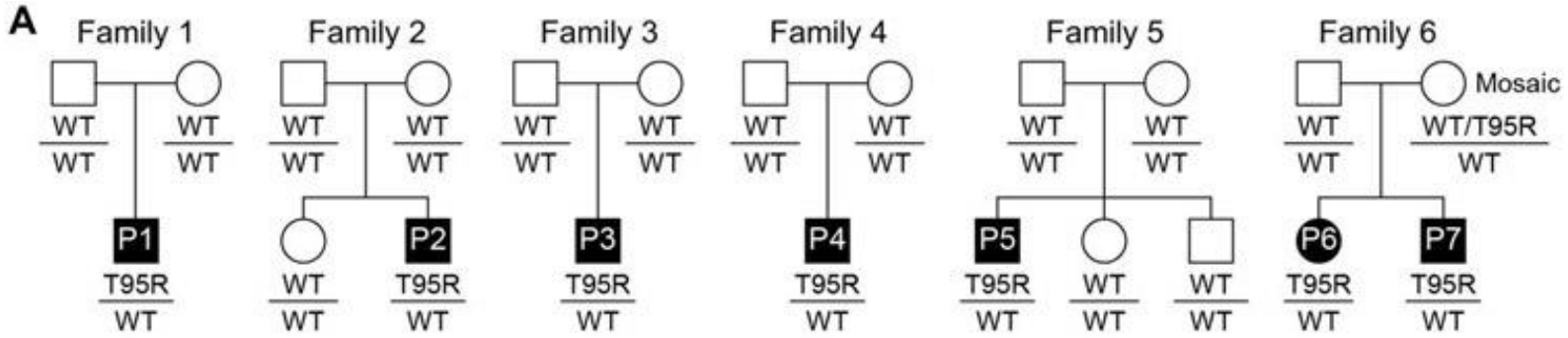
A multimorphic mutation in IRF4 causes human autosomal dominant combined immunodeficiency

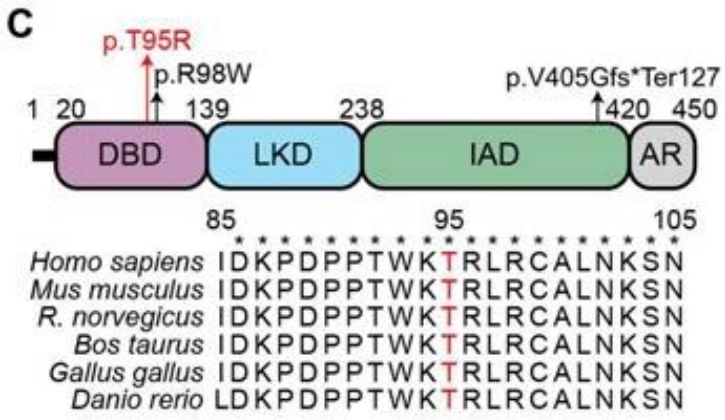
We report a recurrent heterozygous mutation in IRF4, p.T95R, causing an autosomal dominant combined immunodeficiency (CID) in seven patients from six unrelated families. The patients exhibited profound susceptibility to opportunistic infections, notably *Pneumocystis jirovecii*, and presented with agammaglobulinemia.



B

Summary of clinical features

Combined immunodeficiency (7/7)
Age of onset <12 months (7/7)
Recurrent respiratory infections (7/7)
Pneumocystis pneumonia (PCP) (6/7)
Severe viral infections (5/7)
Mycobacterial disease (2/7)



Science Immunology 20 Jan 2023, Vol 8, Issue 79

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Human genetics: from bed to bench, and bench to bed

Genetic information (genetic associations, sequencing information, -omics data)	Causal genes and pathways	Target/drug	Outcome
HCV infection (GWAS)	*IL28B*	Ribavirin and interferon treatment	Genotype-led prediction of treatment responsiveness
Primary immunodeficiency (sequencing)	*STAT1* gain-of-function mutation	JAK inhibitor, e.g. ruxolitinib	Precision therapy for chronic mucocutaneous candidiasis
Sepsis (transcriptomics)	• Endotoxin tolerance • T cell exhaustion	Corticosteroids	Differential response to treatment by endotype
HIV infection (GWAS)	*HLA-B*5701*	Abacavir	Predicting severe adverse events

Fig. 2 | **Precision medicine approaches in infectious disease informed by human genetics.** Examples of how understanding of human genetic information can be or has begun to be leveraged for improved patient care. Strategies include identifying specific molecular targets based on genetic understanding, stratifying patients to decide on use of certain drugs and using genetic knowledge to predict severe adverse reactions to medications. GWAS, genome-wide association studies; HCV, hepatitis C virus; HIV, human immunodeficiency virus; JAK, Janus kinase.

Nat Rev Genet. 2020 Dec 4;22(3):137–153

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Take home message

- Maladie**S** rare**S, <u>Y penser !</u>**
- Enquête autour d'un cas / enquête familiale / Population collective
- Traitement spécifique? (IFN, inhibiteurs de JAK,… Greffe de moelle)
- Prévention (autres infections? Risque non infectieux?)
- Dépistage d'autres cas (familiaux, phénotype similaire)
- Se rapprocher des centres de référence

Merci de votre attention

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