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Maladies auto-inflammatoires & poumon

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Qu'allons-nous aborder ?

- Concept d'auto-inflammation
  - Médiée par l'interféron
- Deux maladies auto-inflammatoires monogéniques
  - Dont la principale atteinte est une pneumopathie interstitielle diffuse
  - Qui partagent des mécanismes physiopathologiques communs
- Aspects cliniques
- Perspectives thérapeutiques

Auto-inflammation : nouvelles entités

≈ 50 gènes

Définition initiale

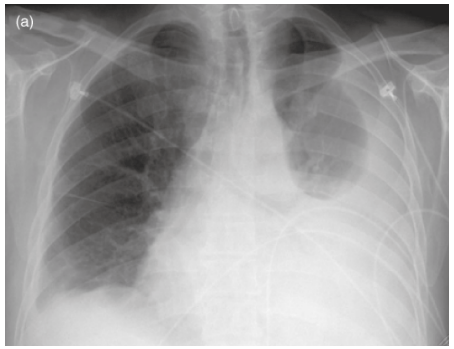
Fièvres récurrentes, stériles (non infectieuses)

De cause héréditaire

Définition actuelle

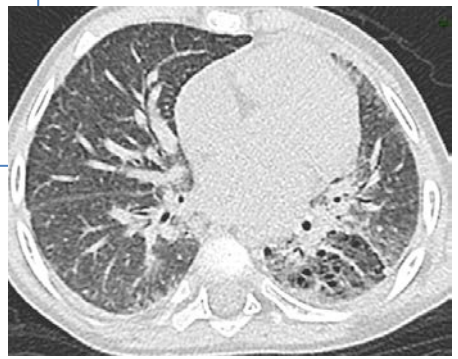
Inflammation stérile, non infectieuse, avec ou sans fièvre, nécessité de périodicité ?

De cause héréditaire



Pleurésie

… PID



Hannan et al, Int Med J 2012
Jeremiah et al, JCI 2014

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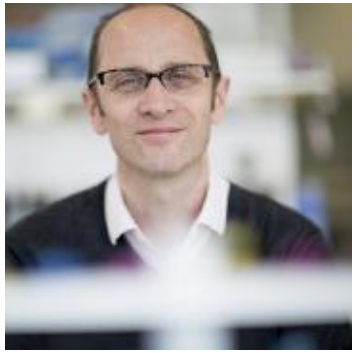
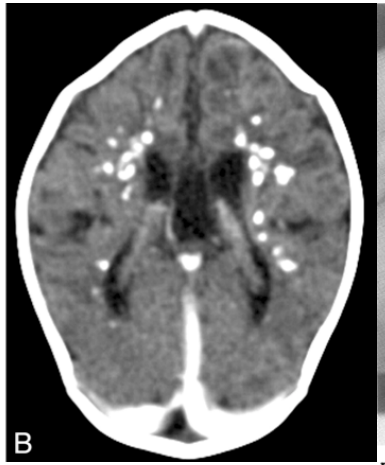
Interféronopathies
Concept de 2011

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *The Year in Human and Medical Genetics: Inborn Errors of Immunity*

Type I interferonopathies: a novel set of inborn errors of immunity

Yanick J. Crow





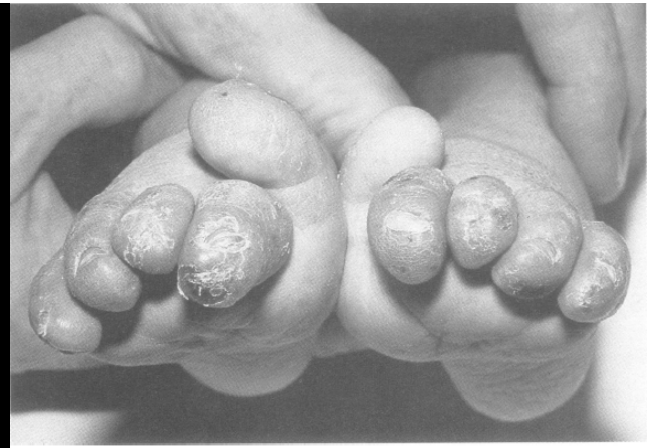


Figure 2 Severe, unexplained chilblains which developed after the second birthday of the infant depicted in fig 1.

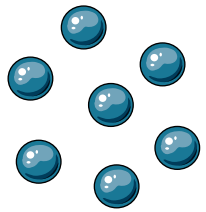
1984
Sd d'Aicardi-Goutières

Maladies Mendéliennes

Sécrétion accrue & inappropriée d'IFN de type I

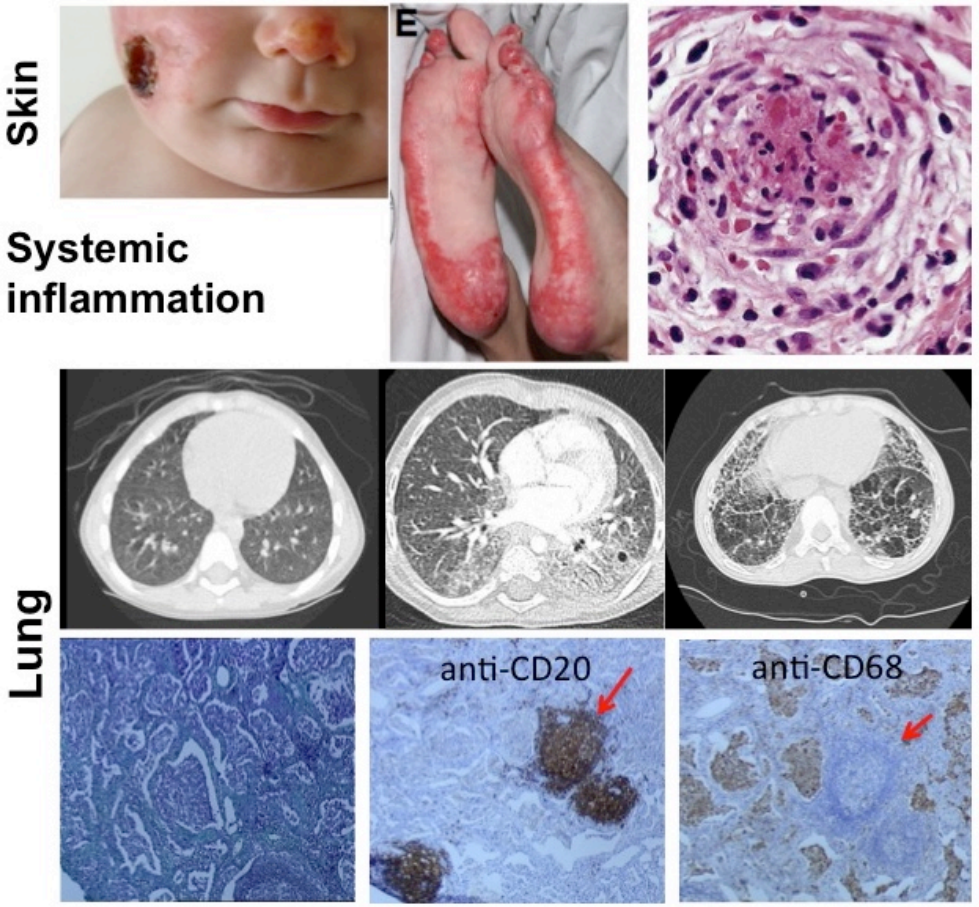
>25 génotypes

"Tous" organes

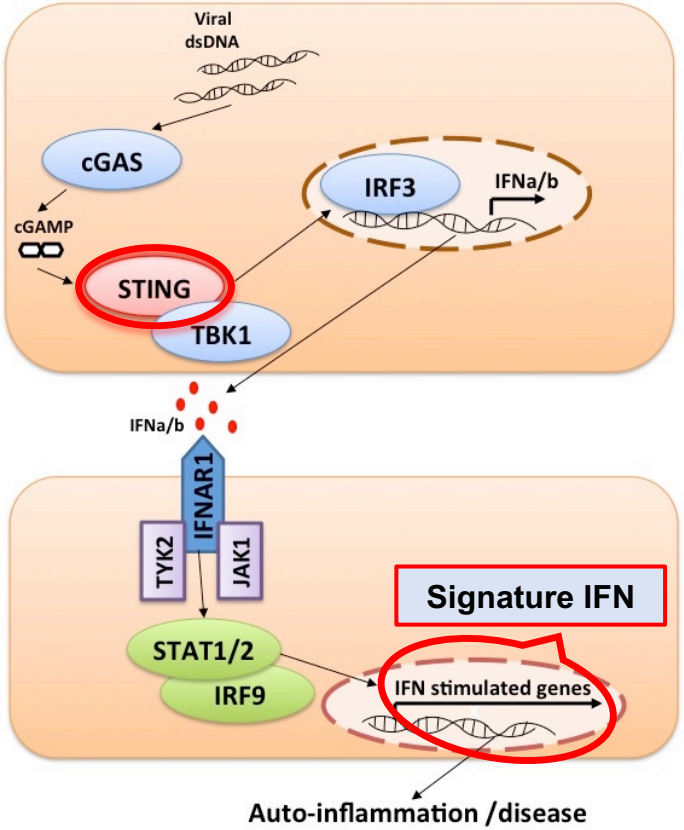


SAVI : mutations activatrices de *STING1* codant pour STING

Une triade classique



Liu et al, NEJM 2014
Jeremiah et al, JCI 2014



Adapté de Rodero et al, PNAS 2016

SAVI révélé par une PID

Interstitial Lung Disease Caused by STING-associated Vasculopathy with Onset in Infancy

American Journal of Respiratory and Critical Care Medicine Volume 194 Number 5 | September 1 2016

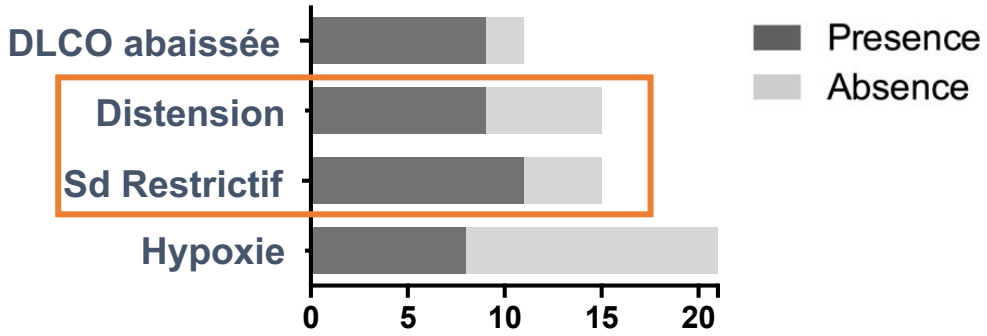
Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (*TMEM173* Mutation)

Cécile Picard, MD; Guillaume Thouvenin, MD; Caroline Kannengiesser, MD, PhD; Jean-Christophe Dubus, MD, PhD; Nadia Jeremiah, PhD; Frédéric Rieux-Laucat, PhD; Bruno Crestani, MD, PhD; Alexandre Belot, MD, PhD; Françoise Thivolet-Béjui, MD, PhD; Véronique Secq, MD, PhD; Christelle Ménard; Martine Reynaud-Gaubert, MD, PhD; and Philippe Reix, MD, PhD

Chest, Sept 2016

Littérature : 67 patients
- PID # 80%
- Fibrose # 50%
- HIA : n = 4 (dont extériorisée n = 2)

- Atteinte isolée possible
- Début insidieux +++
- Profil particulier des EFR



Alice Hadchouel

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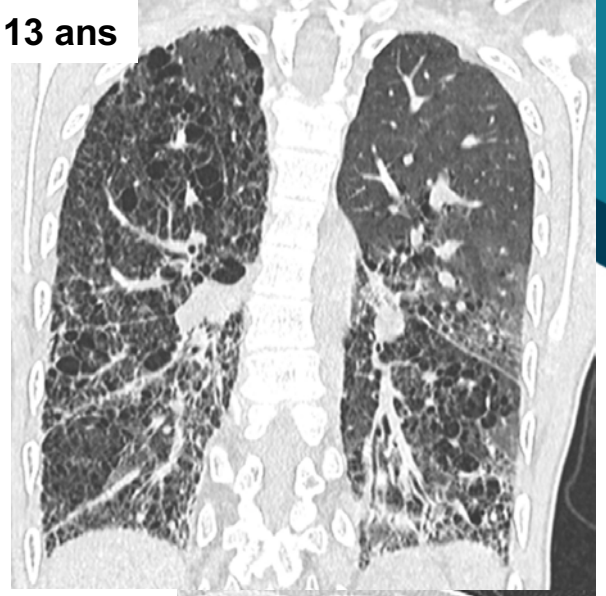
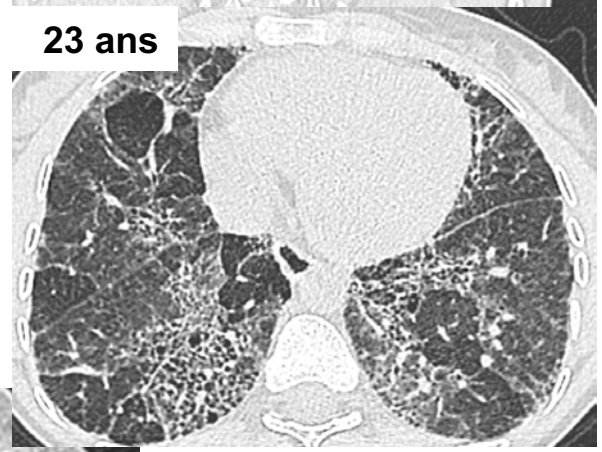
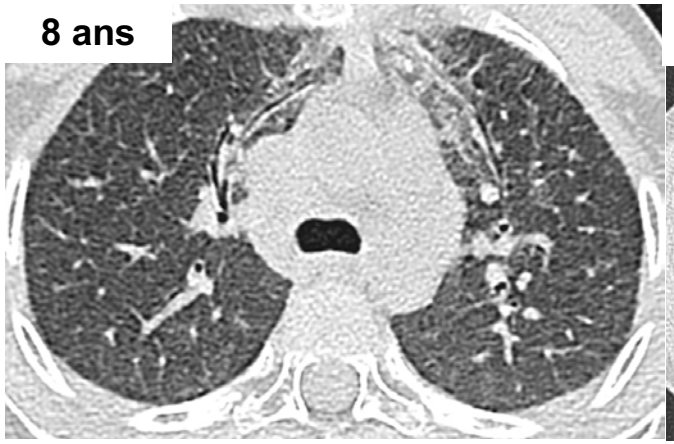
SAVI & Poumon
aspects radiologiques

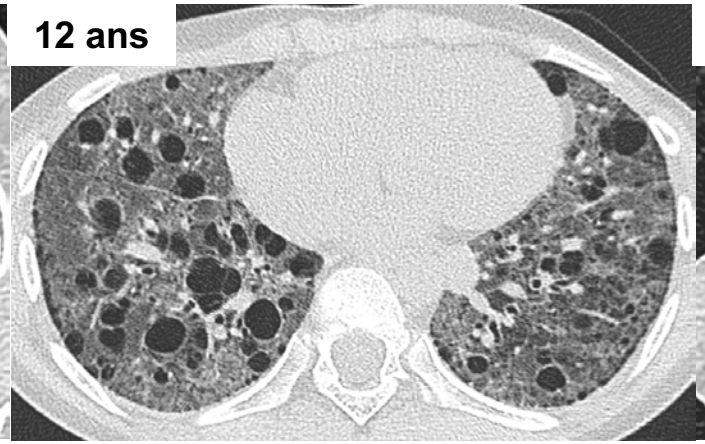


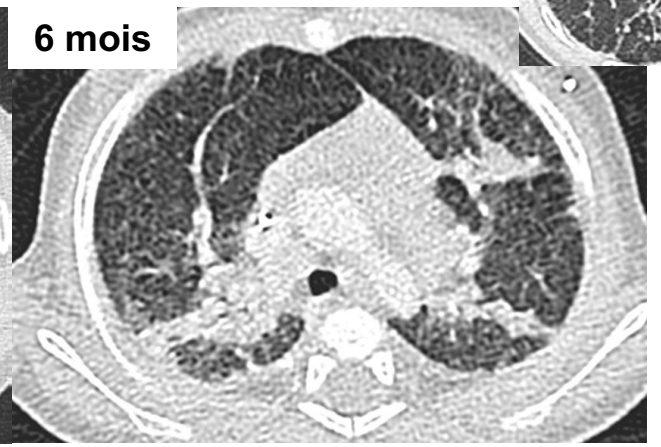


- Lésions élémentaires clés
  - Verre dépoli +/- en mosaïque (*crazy paving*)
  - Kystes micro / macro
  - Asymétrie des lésions

- Progression précoce vers la fibrose (dès l'âge de 7 mois)
  (bronchectasies de traction, rayon de miel, diminution des volumes)







Laureline Berteloot

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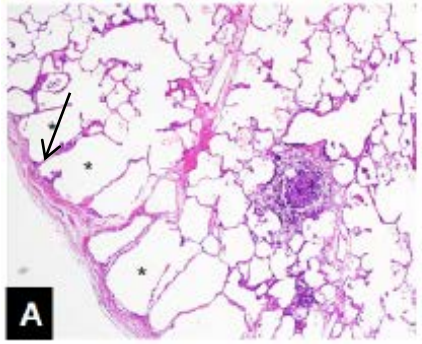
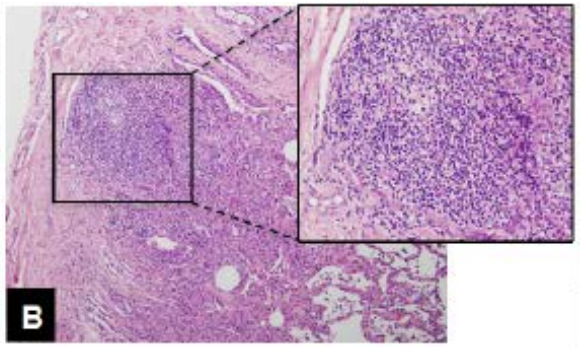
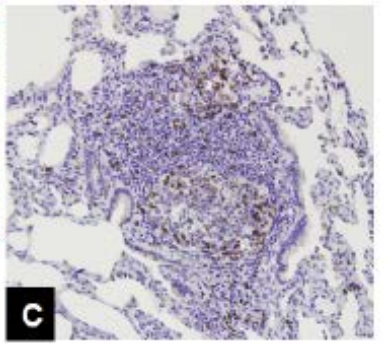
SAVI & Poumon
aspects histologiques

Emphysème

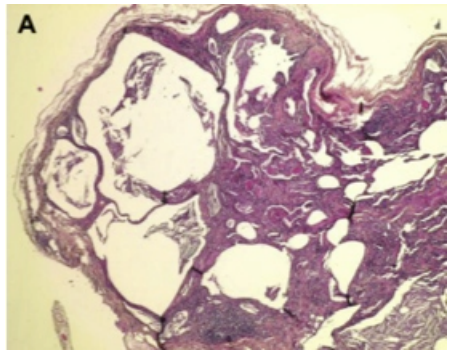


Infiltrat interstitiel lymphoïde

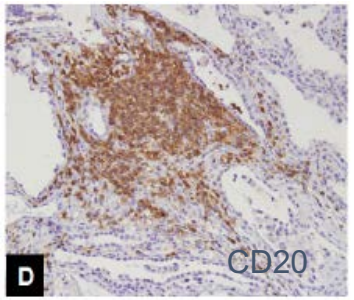


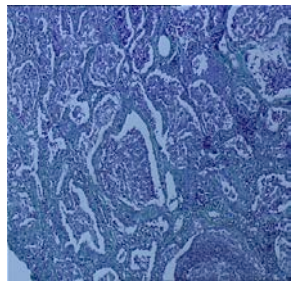


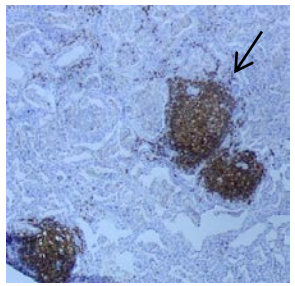
Fibrose

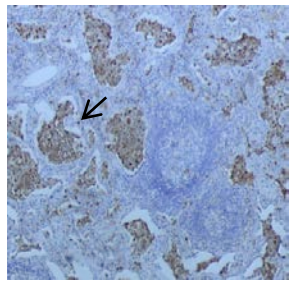


Infiltration macrophagique alvéolaire + hyperplasie folliculaire

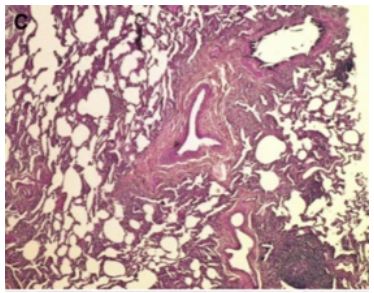


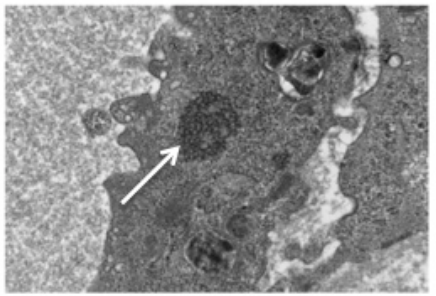






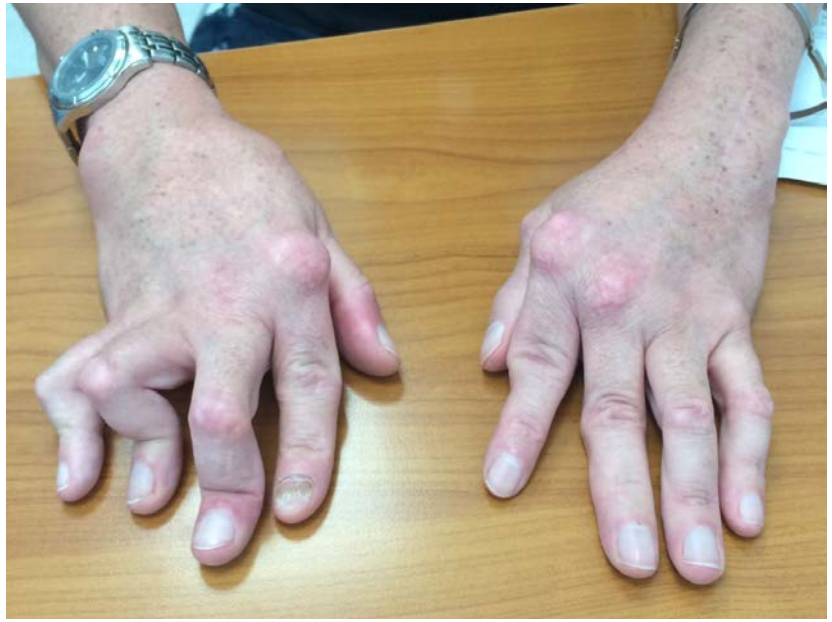
. ø d'atteinte vasculaire sauf 1 cas (MO)
. Inclusions tuboréticulaires endothéliales (ME)



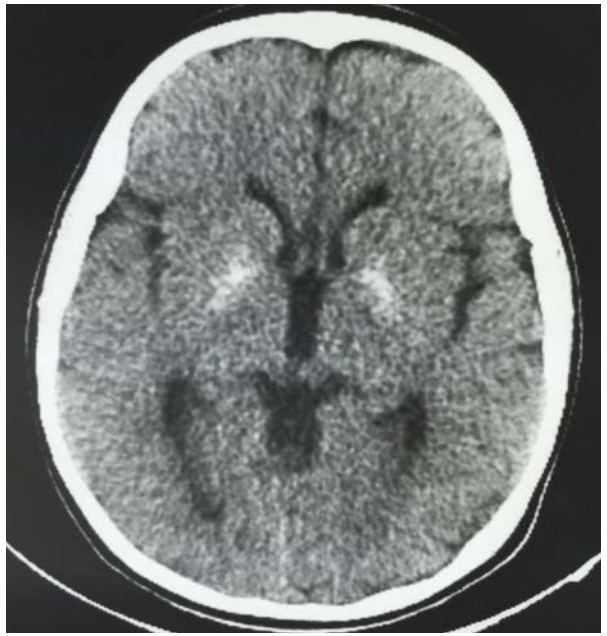


Liu et al NEJM, 2014
Jeremiah et al JCI, 2014
Picard et al Chest, 2016
Dr Molina et Fabre, Necker

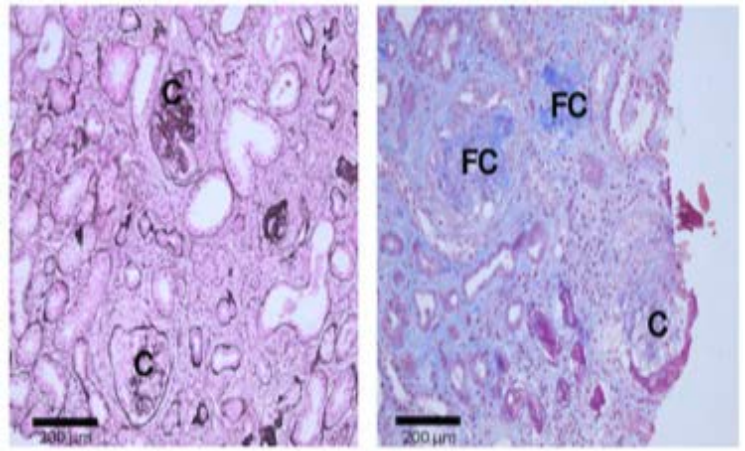
SAVI : extension du phénotype



- Atteinte articulaire
  - Arthropathie Jaccoud-like
  - Arthrite juvénile idiopathique RF+



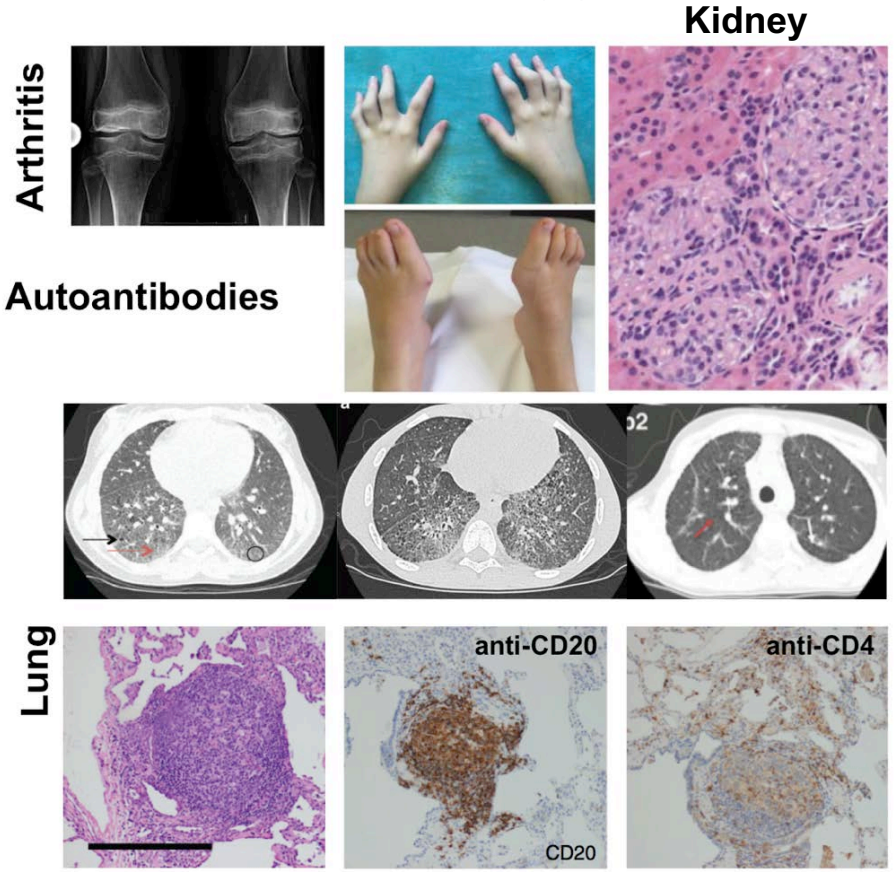
- Atteinte rénale
  - Vascularite à ANCA
- Atteinte neurologique ?



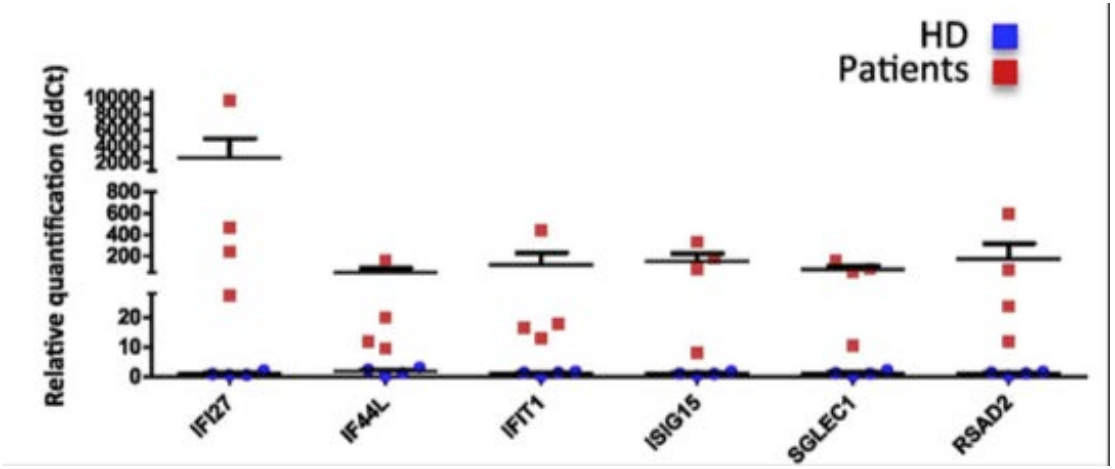
Frémond et al, accepté dans JACI in practice
Staehls et al, Frontiers Immunol I2020

Syndrome COPA

2015 : Mutations hétérozygotes de *COPA* (AD)



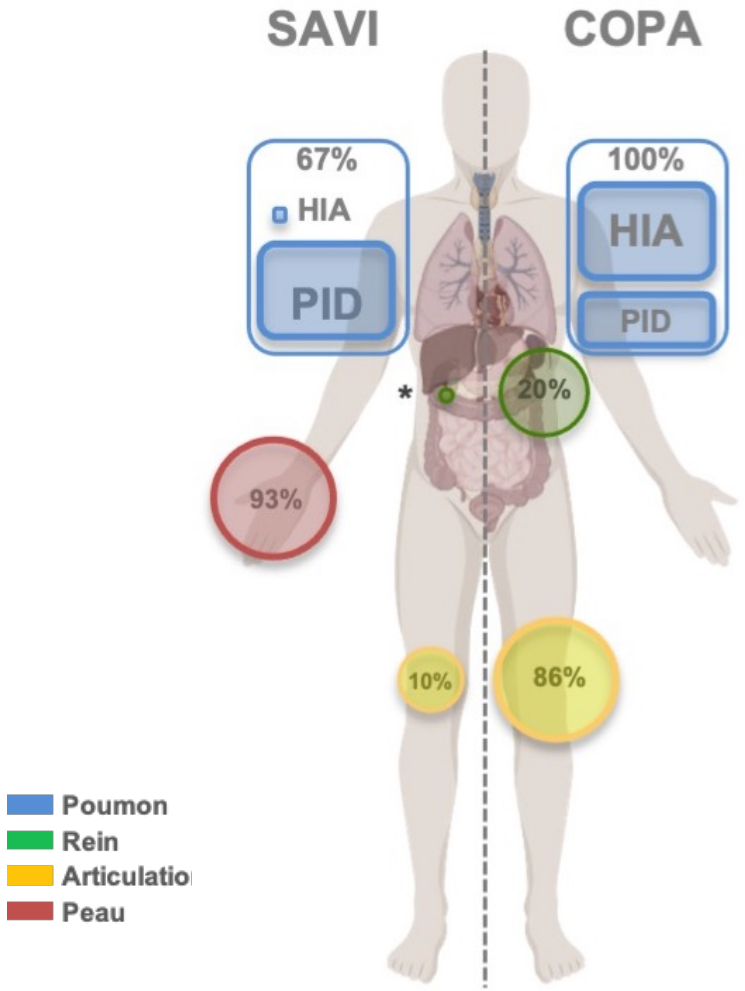
Signature IFN



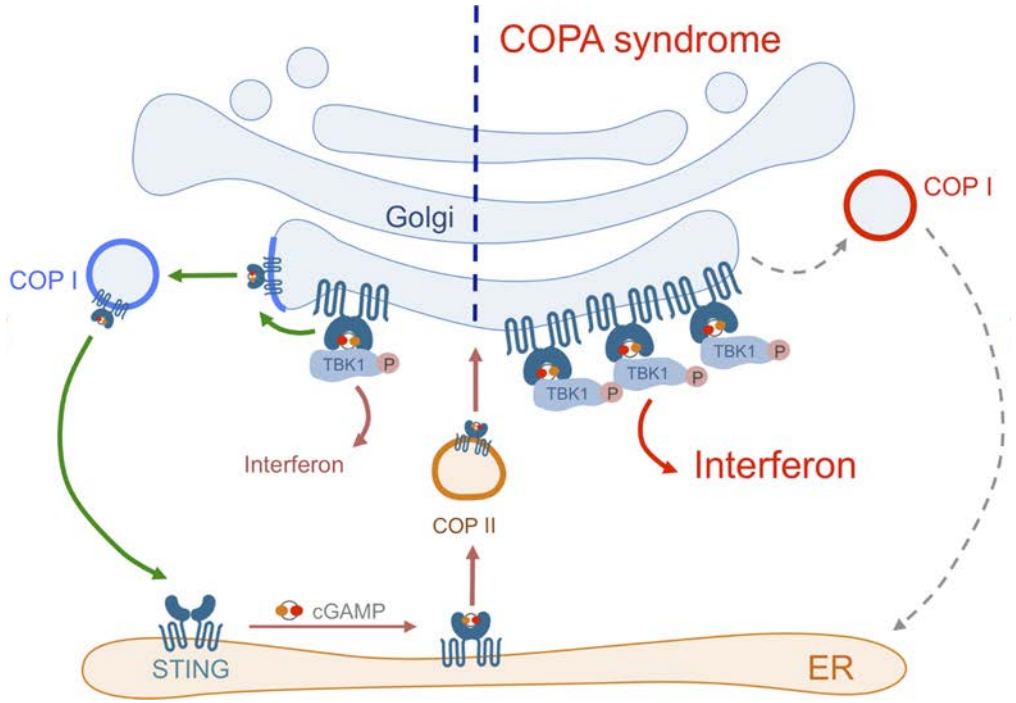
Non pénétrance clinique # 25%
64 patients (22 familles)

Watkin et al, Nat Genet 2015
Volpi et al, Clin Immunol 2017

Syndrome COPA : une nouvelle interféronopathie



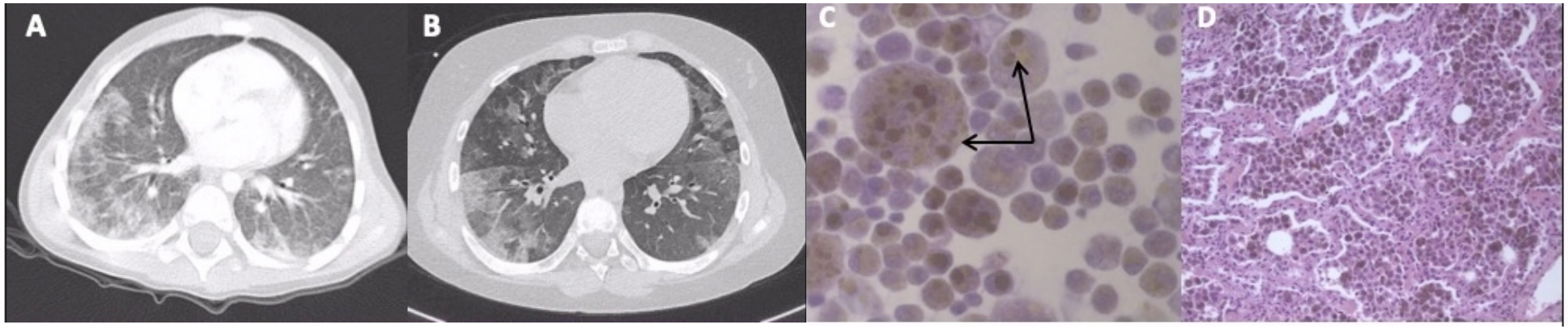
COPA silences STING



Lepelley et al, J Exp Med 2020
Deng et al, J Exp Med 2020
Rivara & Ablasser, J Exp Med 2020

COPA & Poumon

- Atteinte pulmonaire quasi-systématique
  - Présentation clinique :
    - La plus typique : Hémorragie intra-alvéolaire +++
    - PID
    - Évolution possible vers fibrose (TP : 4 pts)
  - Peut-être isolée



4 ans

10 ans

Nadia Nathan
Aurore Coulomb
Hubert Ducou le Pointe

ERJ open research

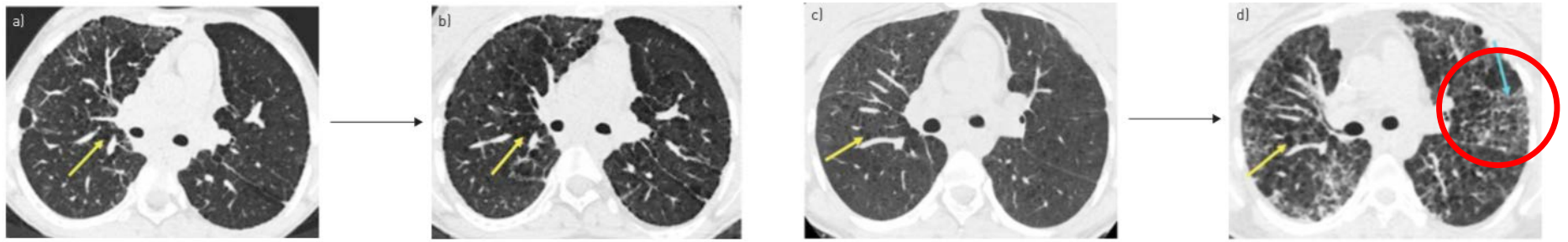
ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

Analysis of pulmonary features and treatment approaches in the COPA syndrome

Jessica L. Tsui[1], Oscar A. Estrada[2], Zimu Deng[1], Kristin M. Wang[1], Christopher S. Law[1], Brett M. Elicker[3], Kirk D. Jones[4], Sharon D. Dell[5], Gunnar Gudmundsson[6,7], Sif Hansdottir[6,7], Simon M. Helfgott[8], Stefano Volpi[9], Marco Gattorno[9], Michael R. Waterfield[10], Alice Y. Chan[10], Sharon A. Chung[11], Brett Ley[1] and Anthony K. Shum[1]

➢ Signes radiologiques peu spécifiques

- Hémorragie alvéolaire
- PID fibrosante



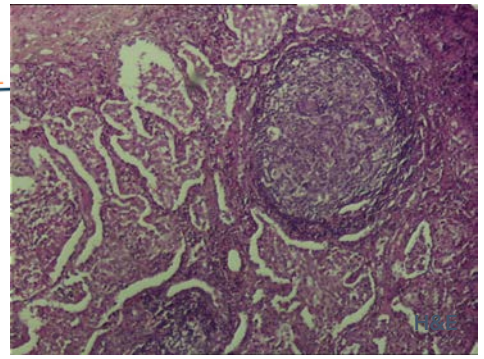
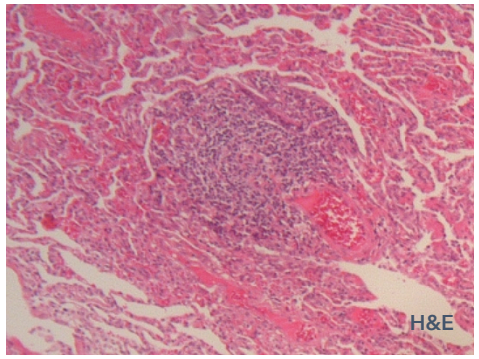
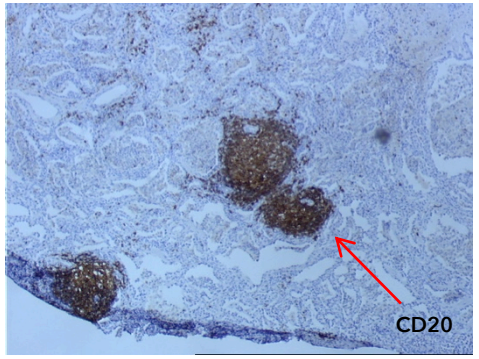
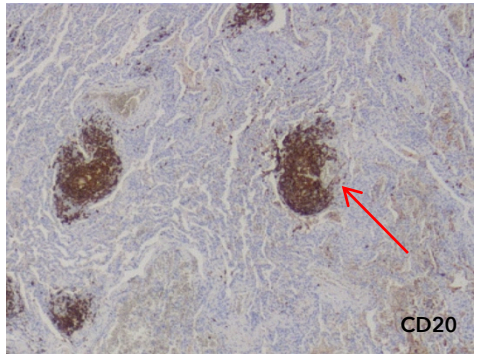
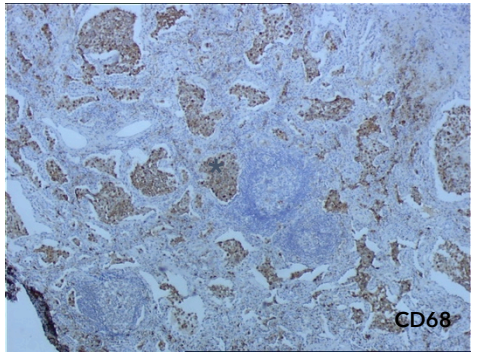
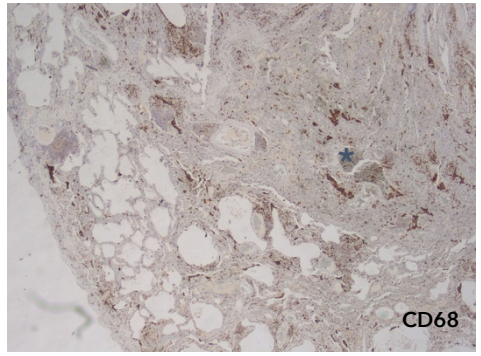
➢ Signes histologiques

TABLE 3 Lung histopathological findings

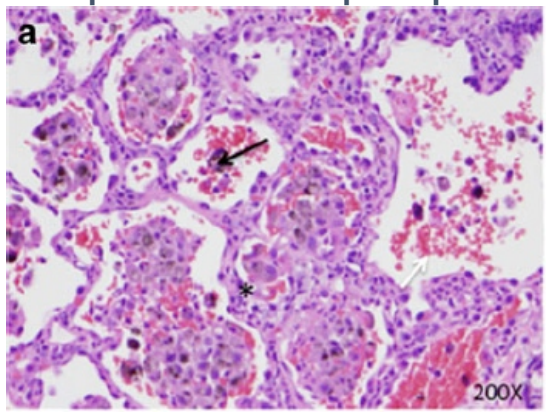
Features	Subjects (n with finding/n tested)
Number of biopsies available for review	10 (10/11)
Type of biopsy	
Open lung biopsy	8 (8/10)
Transbronchial biopsy	2 (2/10)
Follicular bronchiolitis	7 (7/10)
Alveolar haemorrhage	4 (4/10)
Airspace enlargement/cystic changes	2 (2/10)
Acute lung injury with capillaritis	2 (2/10)[#]
Interstitial fibrosis	2 (2/10)[¶]
Nondiagnostic	1 (1/10)

[#]: both subjects with this finding were related (father and daughter); [¶]: both biopsies demonstrated non-usual interstitial pneumonitis.

➢ Signes histologiques plus spécifiques

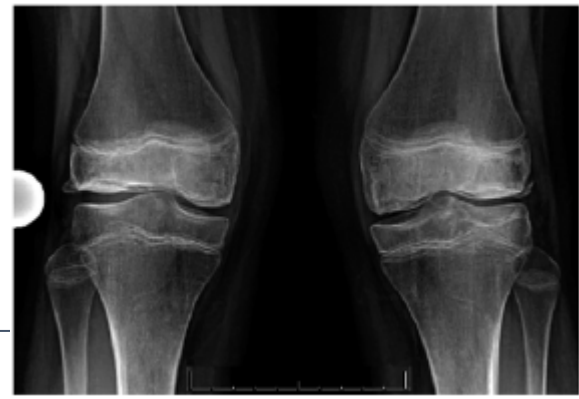
	STING	COPA
Follicules lymphoïdes		
Lymphocytes B CD20+		
Infiltrat macrophagique		

Capillarite neutrophilique

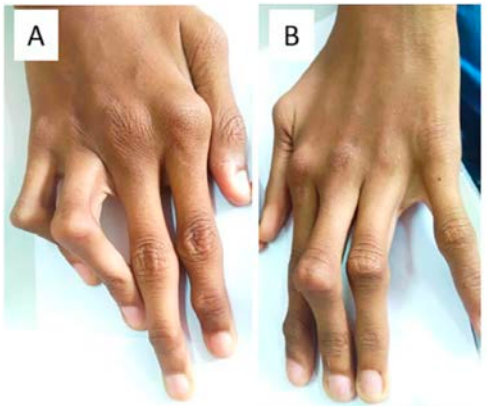


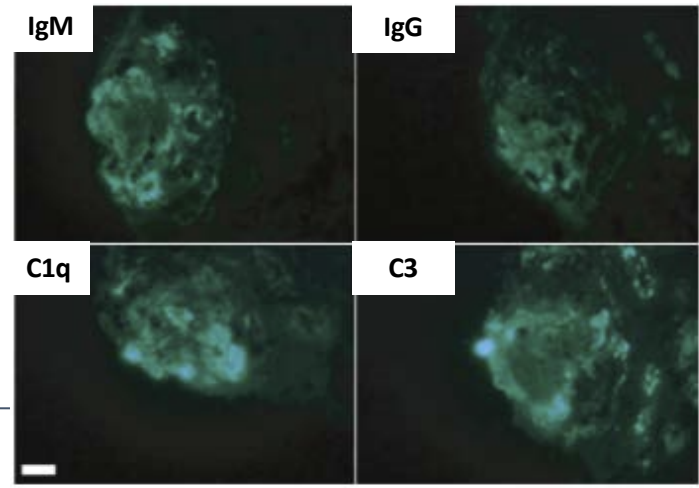
Watkin et al, Nat Genet 2015
Vece et al, J Clin Imm 2016
Lepelley et al, J Exp Med 2020

COPA & autres atteintes



- **Atteinte articulaire (70 %)**
  - Arthralgies
  - Arthrites inflammatoires nécrosantes
  - Ostéonécrose avasculaire (métaphyse, diaphyse)
  - Arthropathie Jaccoud-like
  - FR+
- **Atteinte rénale lupus-like +/- isolée & sévère** (transplantation : 2 pts)
- **Peu / pas de fièvre & retard de croissance**
- **Autres** : hépatite, thyroïdite auto-immune, atteinte neurologique…

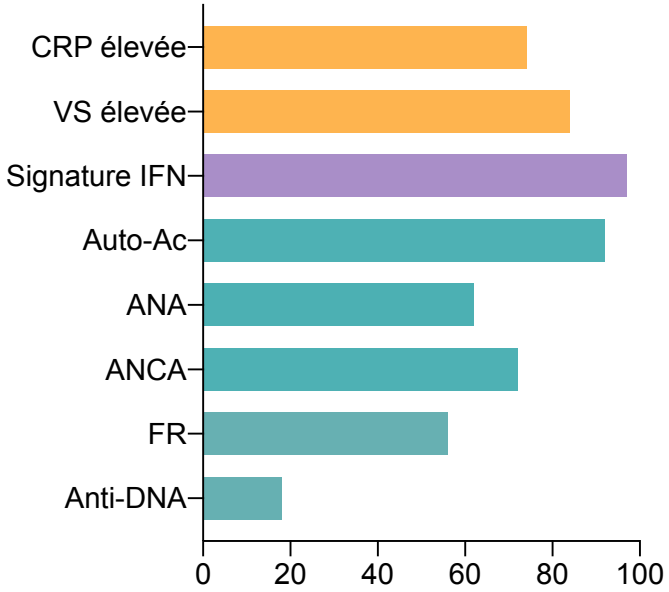




Watkin et al, Nat Genet 2015
Volpi et al, Clin Immunol 2017
Boulisfane et al, KIR 2019
Banday et al, Rheumatology 2020
Lepelley et al, J Exp Med 2020

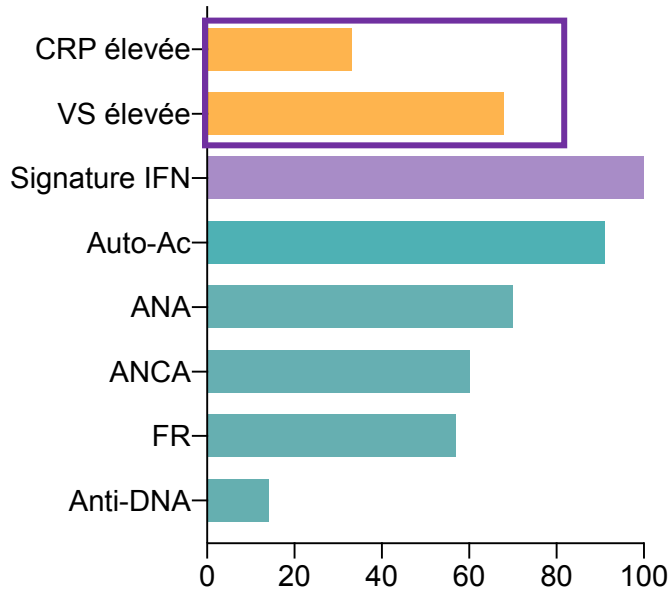
SAVI & Syndrome COPA : profil biologique

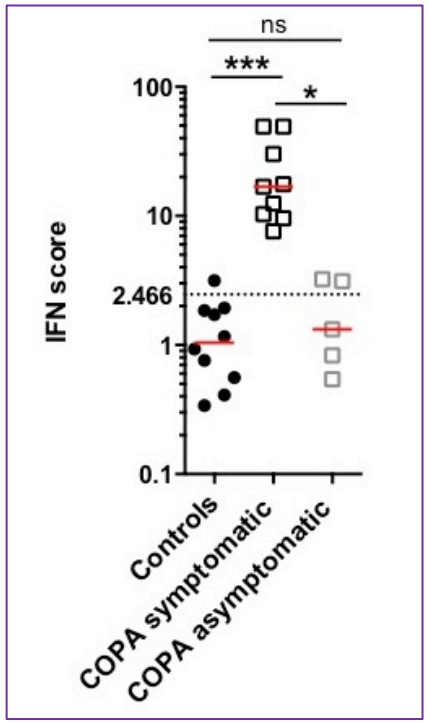
SAVI



+ HyperIgG, IgA, IgM
Lymphopénie T

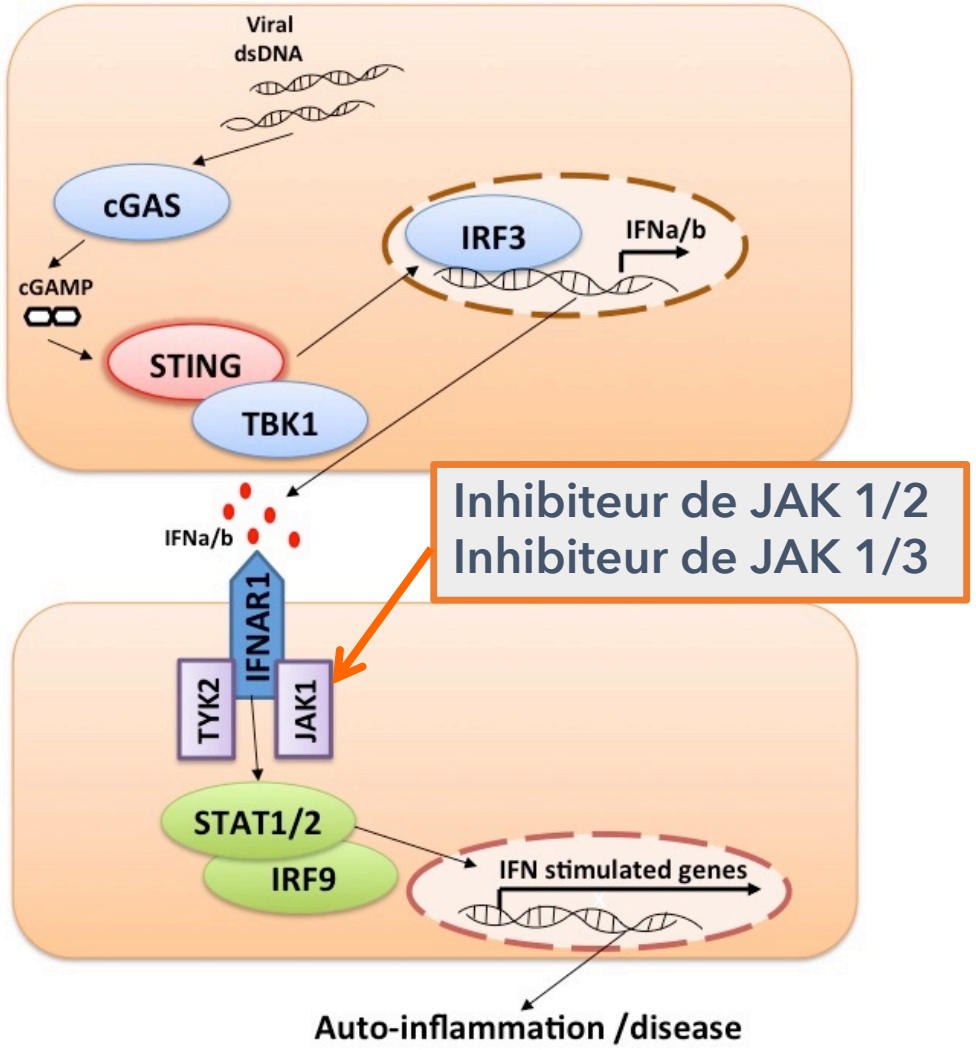
Syndrome COPA





Lepelley et al, J Exp Med 2020

Options thérapeutiques ?



Inhibiteur de JAK 1/2
Inhibiteur de JAK 1/3

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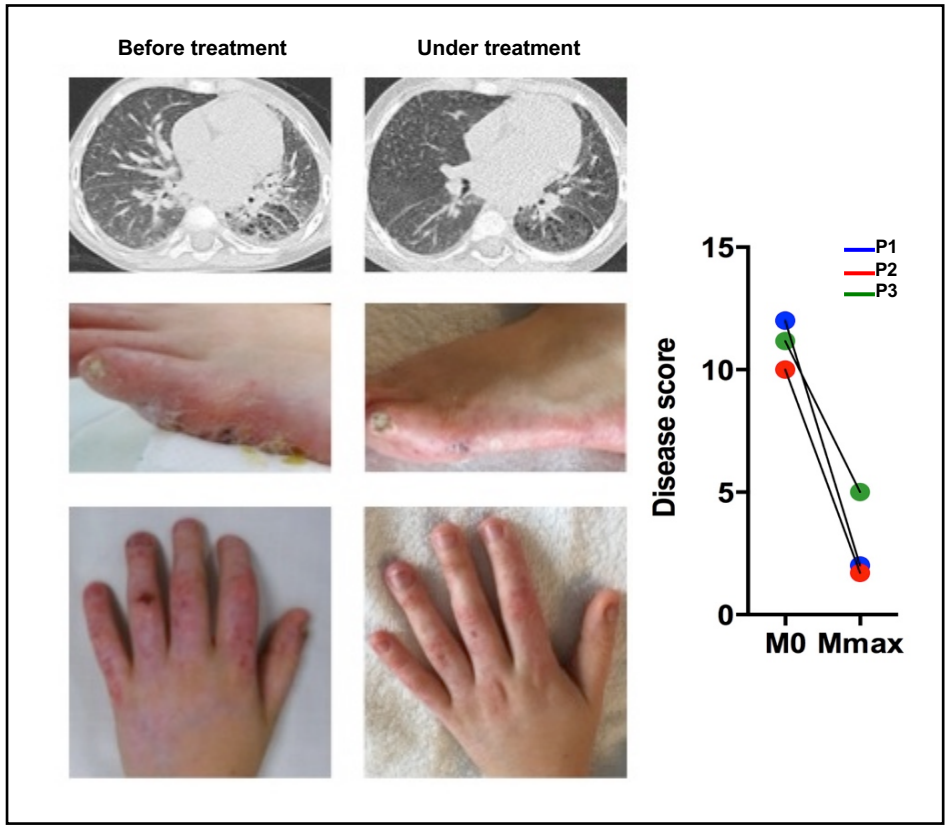
Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with *TMEM173*-activating mutations in 3 children

Frémond *et al*, JACI 2016



JCI The Journal of Clinical Investigation

JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies

Gina A. Montealegre Sanchez, … , William L. Macias, Raphaela Goldbach-Mansky

J Clin Invest. 2018;128(7):3041-3052. https://doi.org/10.1172/JCI98814.

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-019-00645-0

ORIGINAL ARTICLE

Check for updates

Efficacy and Adverse Events During Janus Kinase Inhibitor Treatment of SAVI Syndrome

Stefano Volpi[1,2,3,4] · Antonella Insalaco[5] · Roberta Caorsi[1,2] · Elettra Santori[6] · Virginia Messia[5] · Oliviero Sacco[7] · Suzanne Terheggen-Lagro[8] · Fabio Cardinale[9] · Alessia Scarselli[10] · Claudia Pastorino[2] · Gianmarco Moneta[5] · Giuliana Cangemi[11] · Chiara Passarelli[12] · Margherita Ricci[1] · Donata Girosi[7] · Maria Derchi[13] · Paola Bocca[2] · Andrea Diociaiuti[14] · May El Hachem[14] · Caterina Cancrini[10] · Paolo Tomà[15] · Claudio Granata[16] · Angelo Ravelli[1,3] · Fabio Candotti[6] · Paolo Picco[1] · Fabrizio DeBenedetti[5] · Marco Gattorno[1,2]

Received: 12 November 2018 / Accepted: 10 May 2019

- Surveillance virus (PCR)
- IgIV, Bactrim

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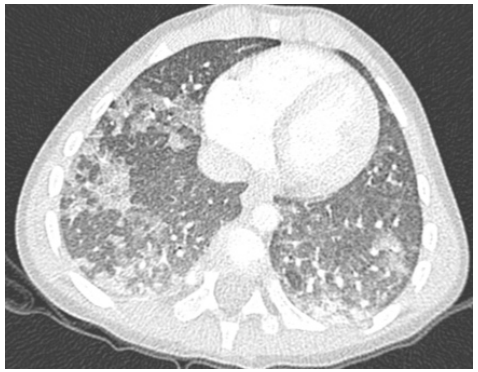
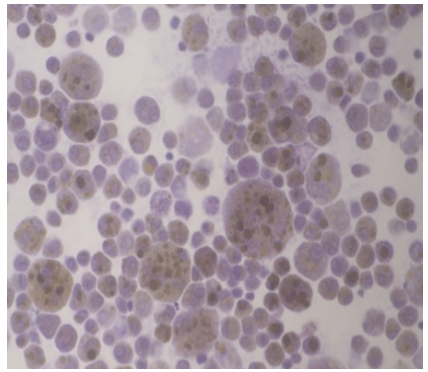
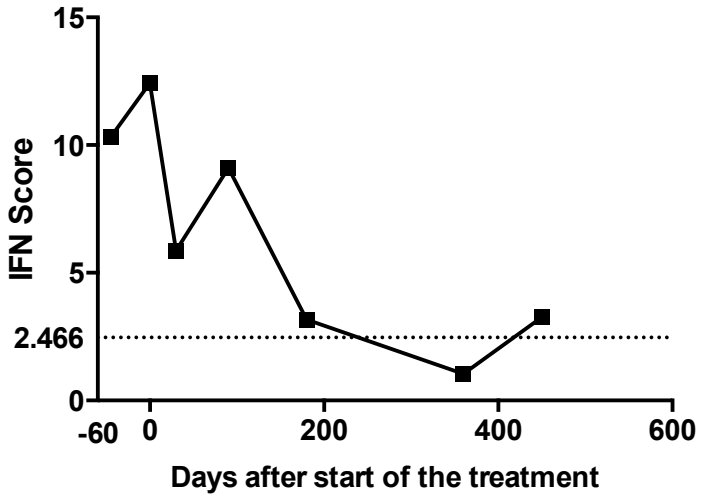
Inhibiteurs de JAK 1/2 : une option pour le syndrome COPA ?



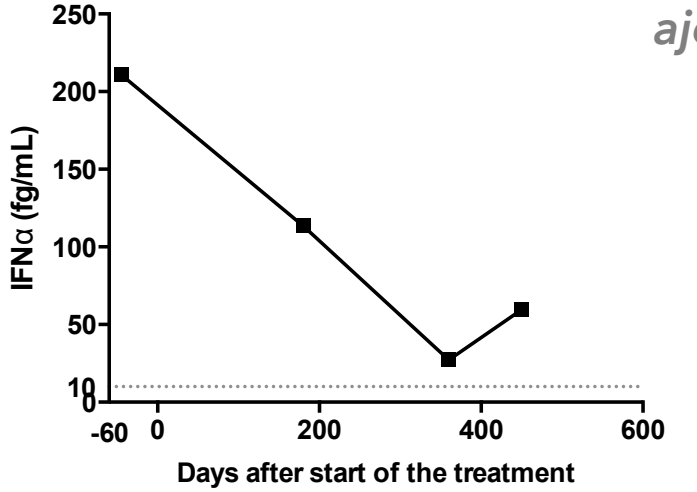


Jeune fille de 12 ans
HIA récurrentes sévères
Pas d'atteinte rénale ou articulaire
Taux modérés d'auto-anticorps

Amélioration clinique…



… mais progression vers fibrose sur TDM
et décompensation sévère récente
ajout anti-IL1 & switch JAKi



Nadia Nathan

Frémond et al, Thorax 2020

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Conclusion

- Nouvelles maladies auto-inflammatoires monogéniques avec PID et/ou HIA
- Physiopathologie encore non comprise
- Morbi-mortalité +++
  - En cas de SAVI ou Sd COPA, même en l'absence de signes cliniques pulmonaires "évidents"
    - EFR avec DLCO
    - Test de marche
    - TDM pulmonaire
- Nouvelles pistes thérapeutiques

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