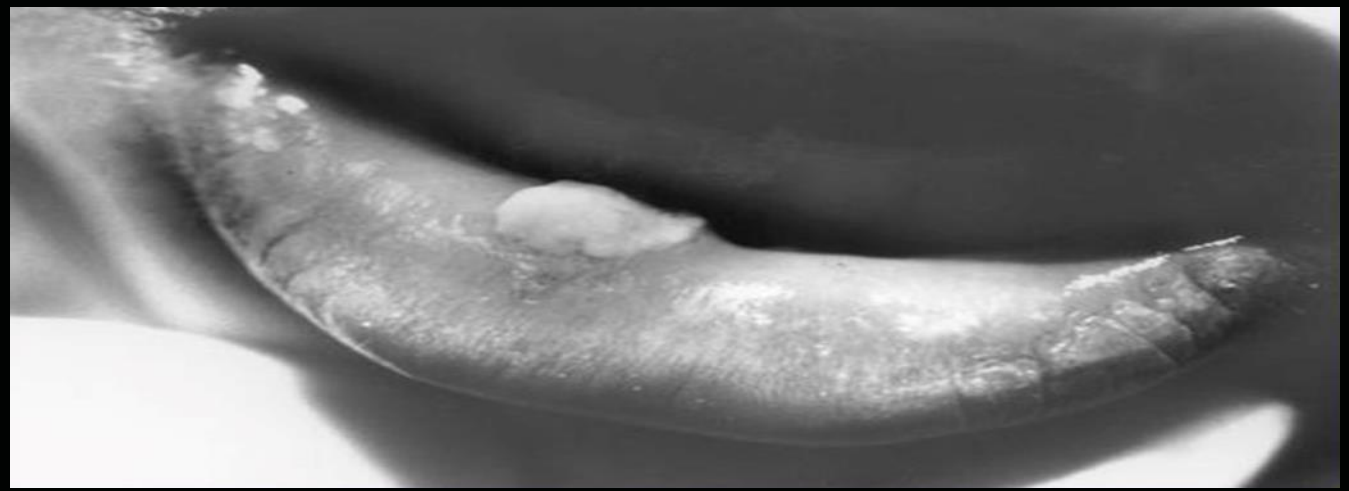
Maladie de Behçet: Maladie ou syndrome?



RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES
10 ANS

Isabelle Koné-Paut
Rhumatologie pédiatrique et CEREMAIA
Hôpital de Bicêtre, APHP
Université de Paris Saclay

28 et **29** SEPTEMBRE 2021
UIC-P - Espaces Congrès - 16, rue Jean Rey - 75015 Paris

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

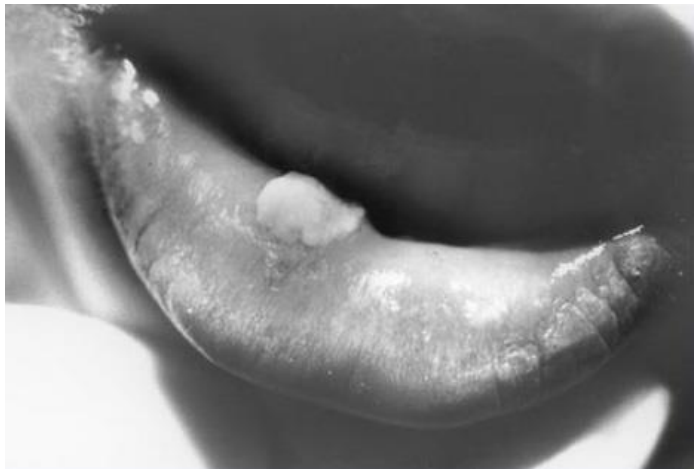
Sous l'égide de :

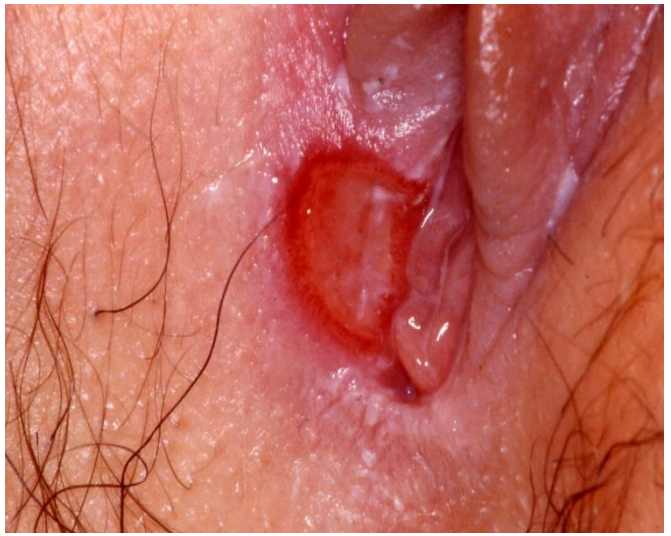
université PARIS-SACLAY

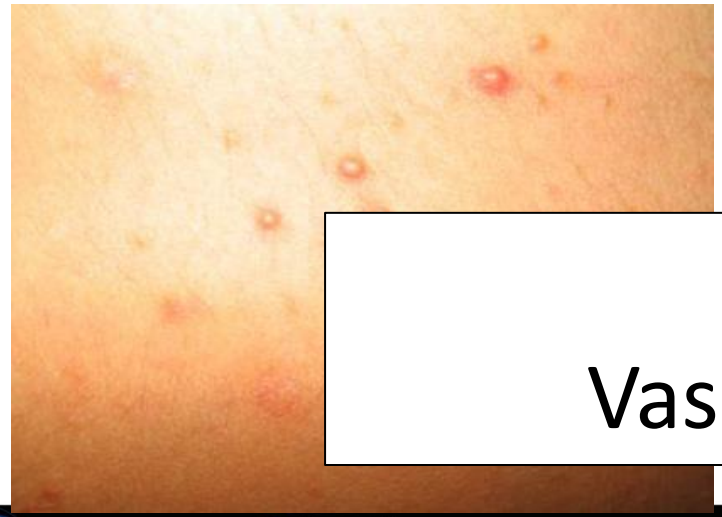
Maladie de Behçet

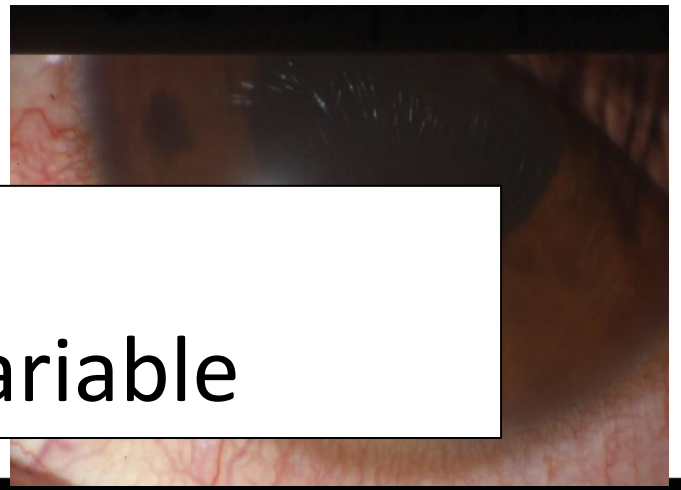
1937

4 signes sont au cœur du phénotype qui est clinique









In memoriam
Hippocrate
Adamantiades

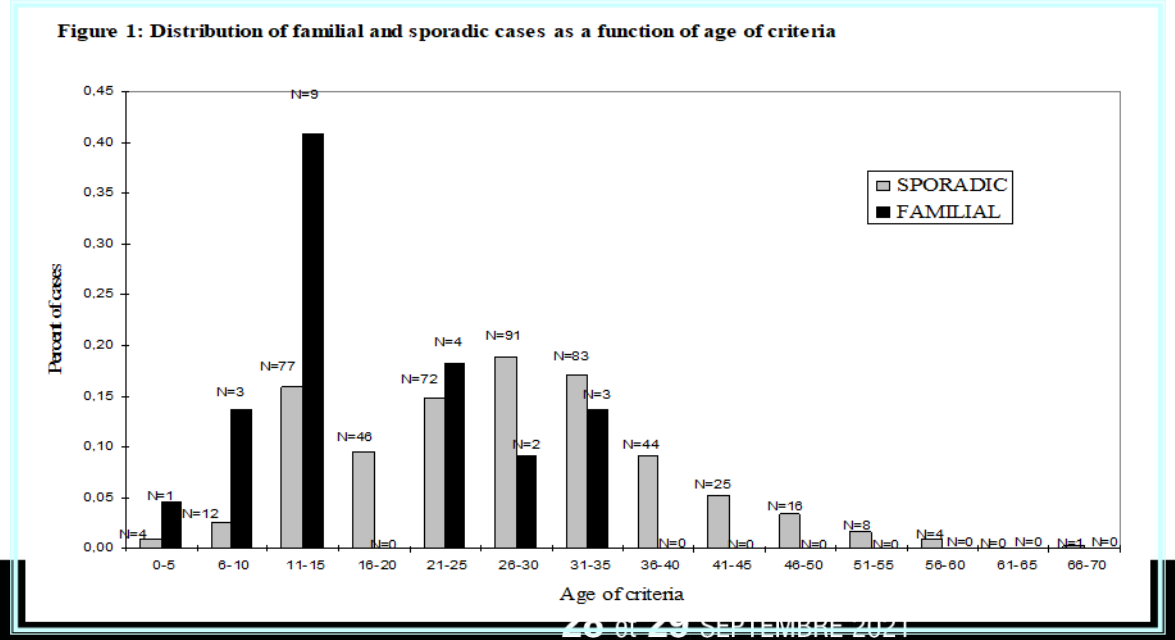
\+

Vascularite variable

Débats sur l'origine de la maladie de Behçet

Hypothèses chronologiques

1. Infectieuse: streptocoque, virus..
2. Auto-immune: adultes, HLA B51 (19% de la susceptibilité), présence d'autoanticorps (rare)
3. Génétique: Intérêt pour les formes pédiatriques et familiales
4. Auto inflammatoire: sur la base du phénotype clinique, du lien avec *MEFV*, et histopathologique >> immunologique



Koné-Paut et al. J Pediatrics 1999; 135: 89-93

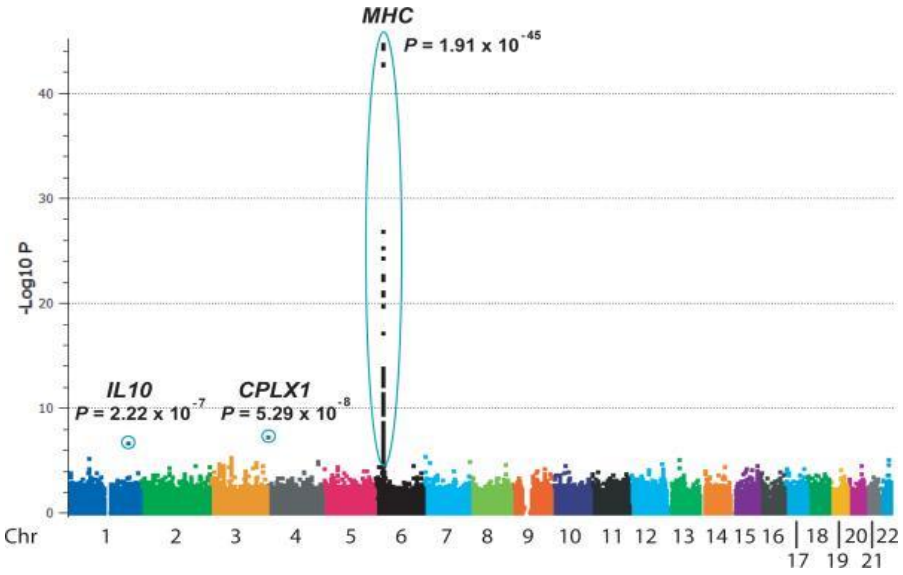
Genome-wide associations

Liaison génétique entre chaque marqueur microsatellite et la maladie "complexe"

Forte association avec HLA Classe I

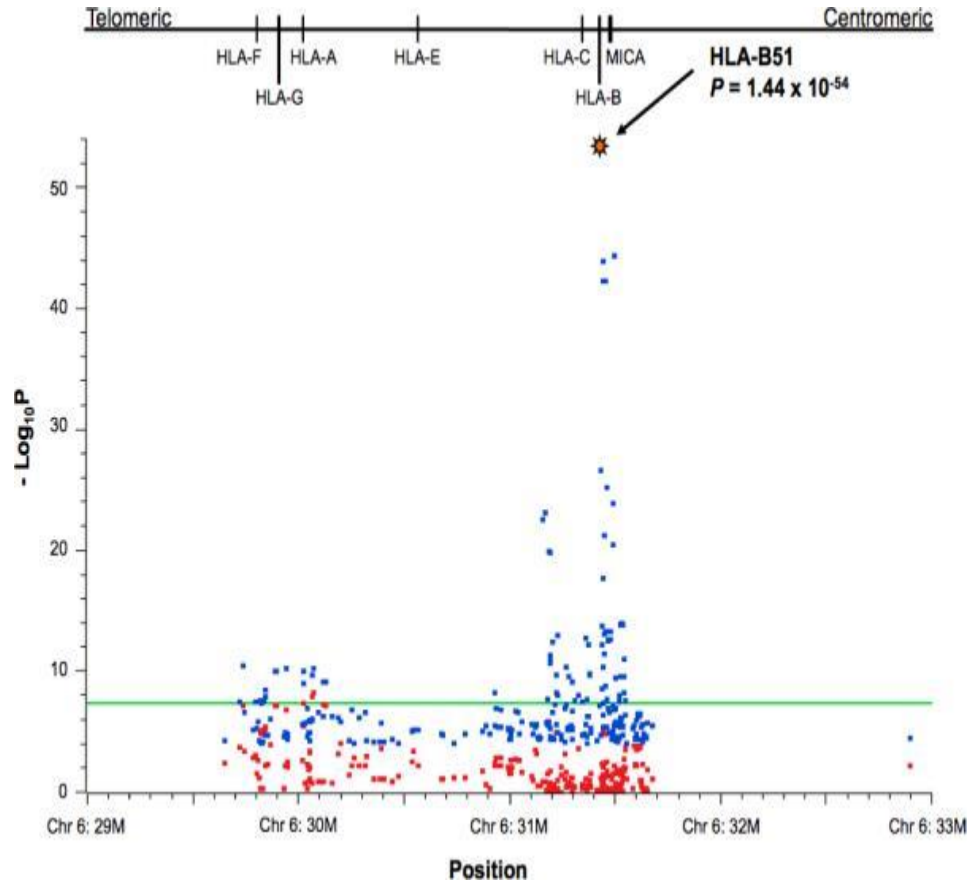
*Meguro, A. *et al*. *Ann. Rheum. Dis.* 69, 747–754 (2010)

P < 5.0 × 10−8 as the threshold for genome wide significance



The –log10 P values (allelic Chi-squared test) for association of 311,459 autosomal SNPs in 1215 BD cases and 1278 controls from Turkey are shown segregated by chromosome and sorted by genomic position.

Remmers HL et al, Nat Genetics 2010; July 11



292 SNPs from the MHC region with allelic Chi-squared P < 0.0001, in blue en red (après avoir sorti le B51).

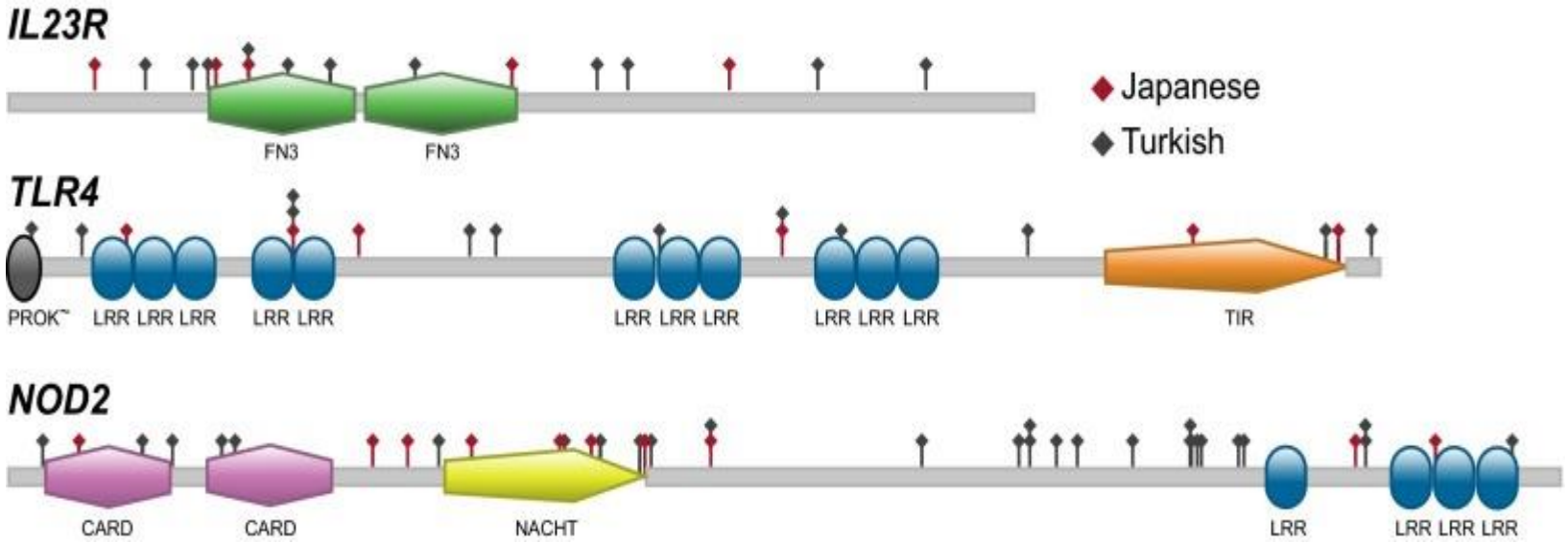
MEFV and TLR4 in Behçet's disease

Texte de la présentation

Kirino Y et al. PNAS, 2013 May 14

Resequencing of with known associations

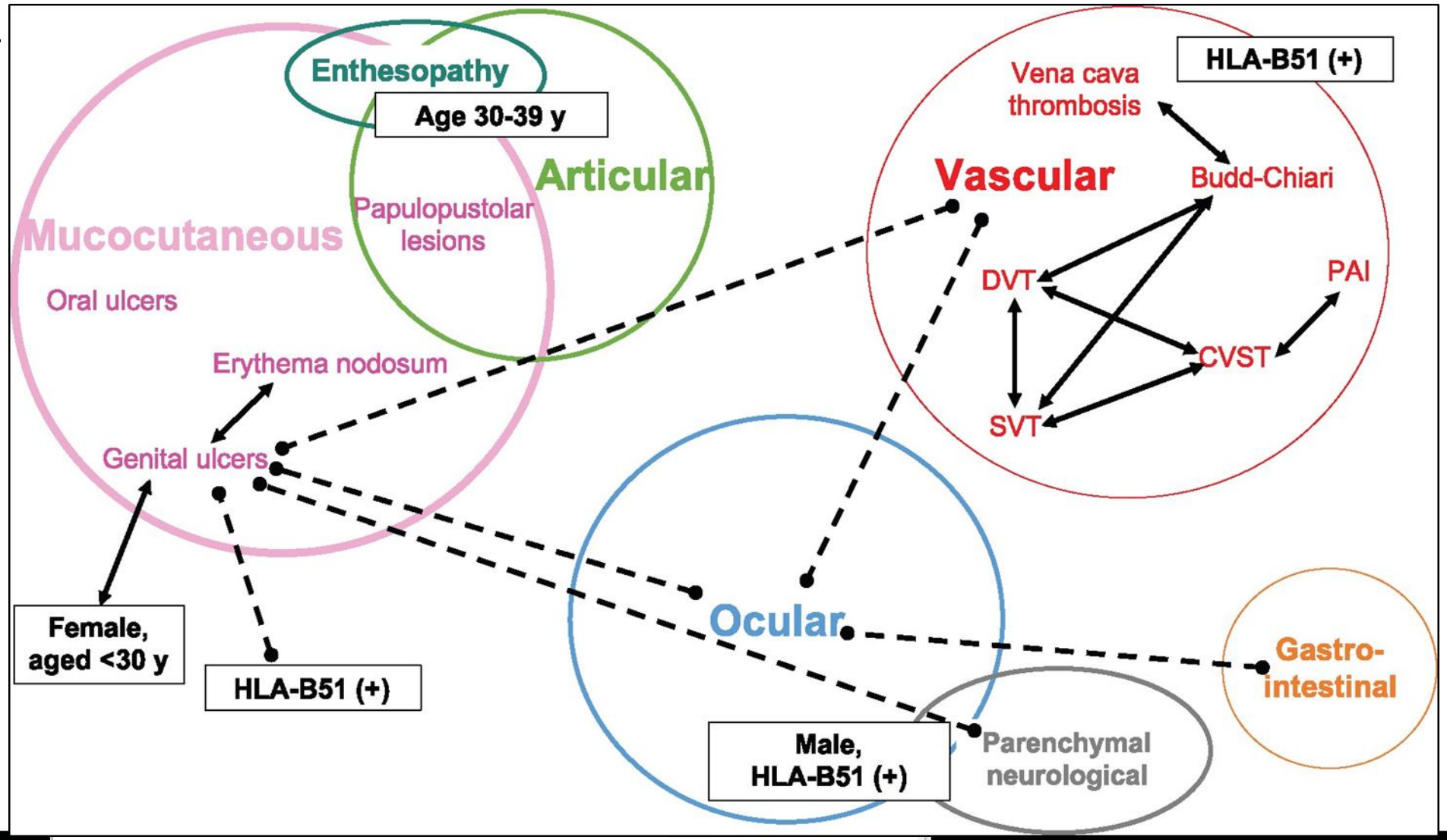
- **BD**
  - IL10, IL23R, CCR1, STAT4, KLRK1, KLRC1, KLRC2, KLRC3, KLRC4, and ERAP1
- **Innate immunity**
  - IL1B, IL1R1, IL1RN, NLRP3, MEFV, TNFRSF1A, PSTPIP1, CASP1, PYCARD, NOD2, and TLR4



The *MEFV* Met694Val mutation, increases the risk of BD in the Turkish population (OR, 2.65; P = 1.8 × 10−12).

Classer la maladie de Behçet: Le défi impossible?

Texte de la



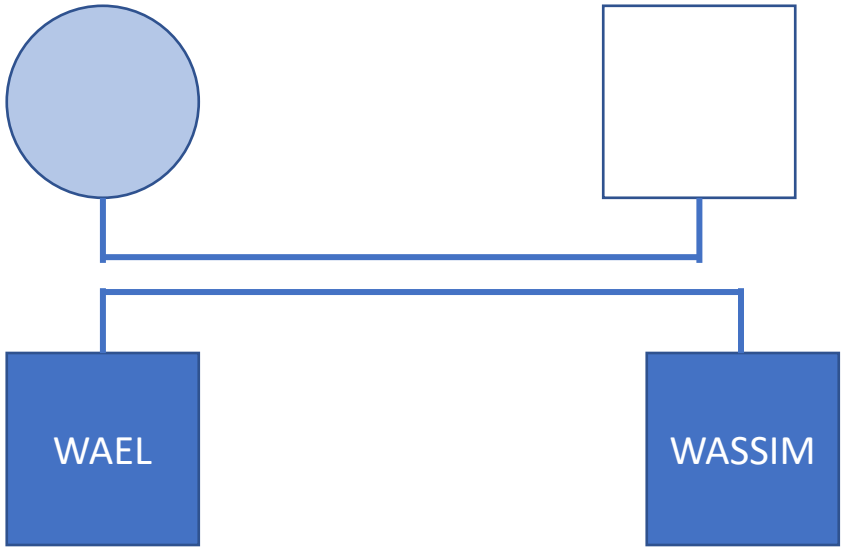
The saga of diagnostic/classification criteria in Behcet's disease

Fereydoun Davatchi, Bahar Sadeghi Abdollahi, Cheyda Chams-Davatchi, Farhad Shahram, Hormoz Shams, Tahereh Faezi, Massoomeh Akhlaghi, Zahra Ghodsi, Negin Mohtasham

upplement_3, 2020,

WAEL: Unrelated parents of Algerian ancestry

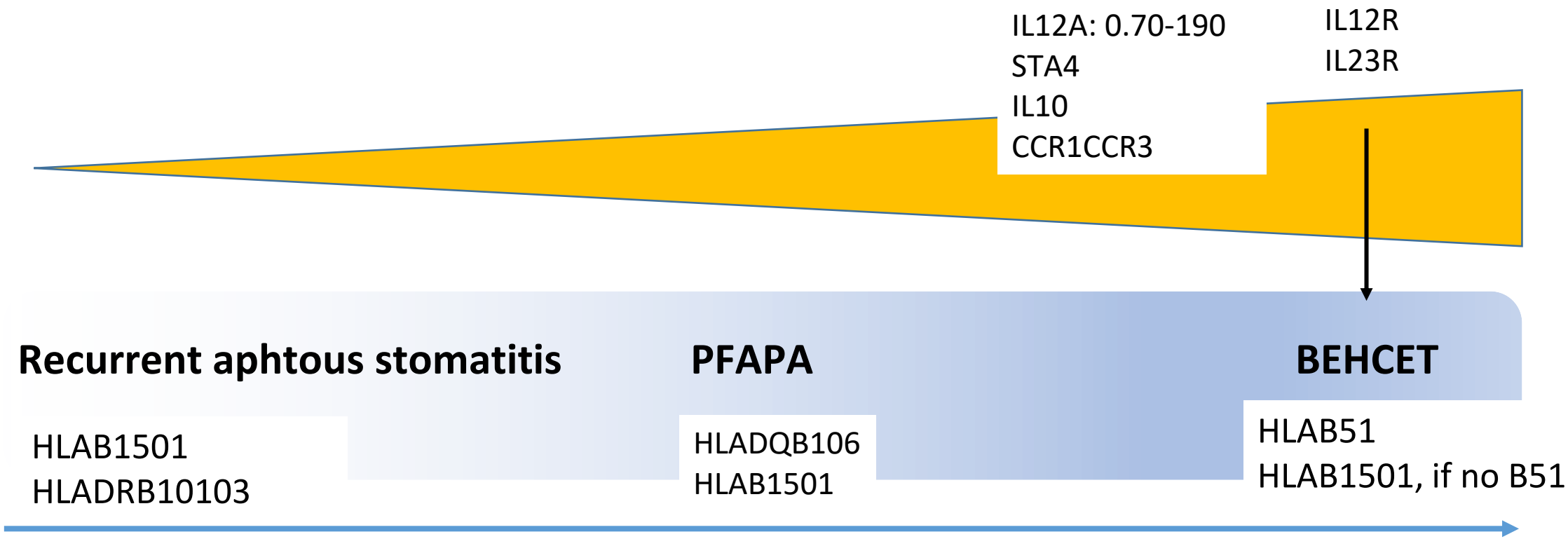
Recurrent oral ulcers
M694I/M694I
HLA B51



2 y: Periodic fever, odynophagy, adenitis: PFAPA?
6y: Recurrent oral ulcers
11y: Bilateral panuveitis + retinal vasculitis
13 years: Acneiform lesions
HLAB51. M694I/-

13 months: Periodic fevers, odynophagy, adenitis
18 months: Kawasaki disease
4 years: Henoch shonlein purpura
7 years: Recurrent oral ulcers, acneiform lesions
Acute myocarditis without COVID 19
HLA B51. M694I/-

Behçet's spectrum disorders



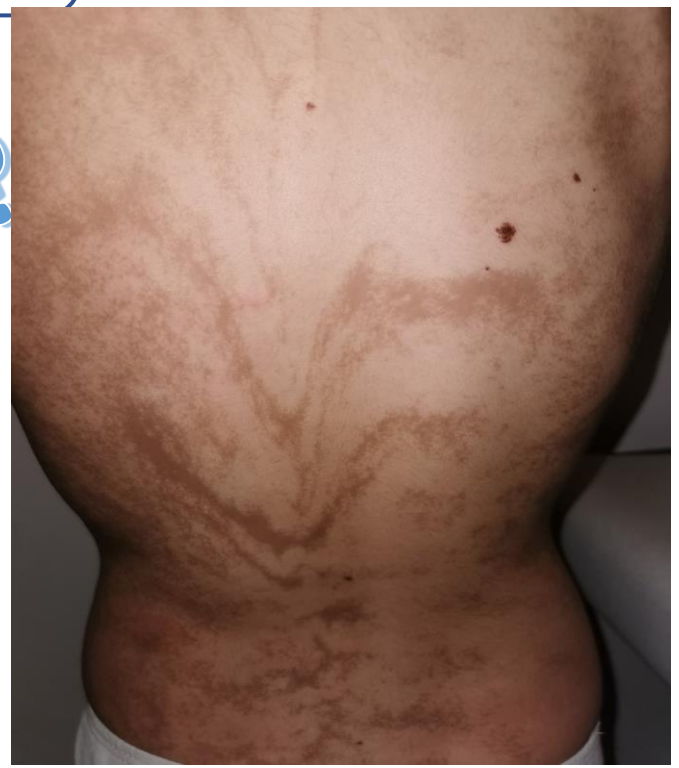
Increased disease severity higher HLA associations

Mathiram K et al, Proc Natl Acad Sci U S A. 2020 Jun 23;117(25):14405-14411

Ava (2008)

- Fille unique, parents non consanguins
- 6 mois: Taches mélanodermiques suivant les lignes de Blashko, agénésie dentaire, dents coniques
- Retard statural: Déficit complet en GH, traitement par hormone de croissance. TSH élevée, T4 normale.
- 9 ans : Aphtes buccaux récurrents
- 10 ans: cytolyse hépatique (découverte fortuite) ; BH: granulomatose hépatique portale et lobulaire non nécrosante (phlébite granulomateuse)
- 12 ans: Aphtes vulvaires
- Pas de fièvre: inflammation modérée (CRP 9 mg/L; VS 41mm/h)

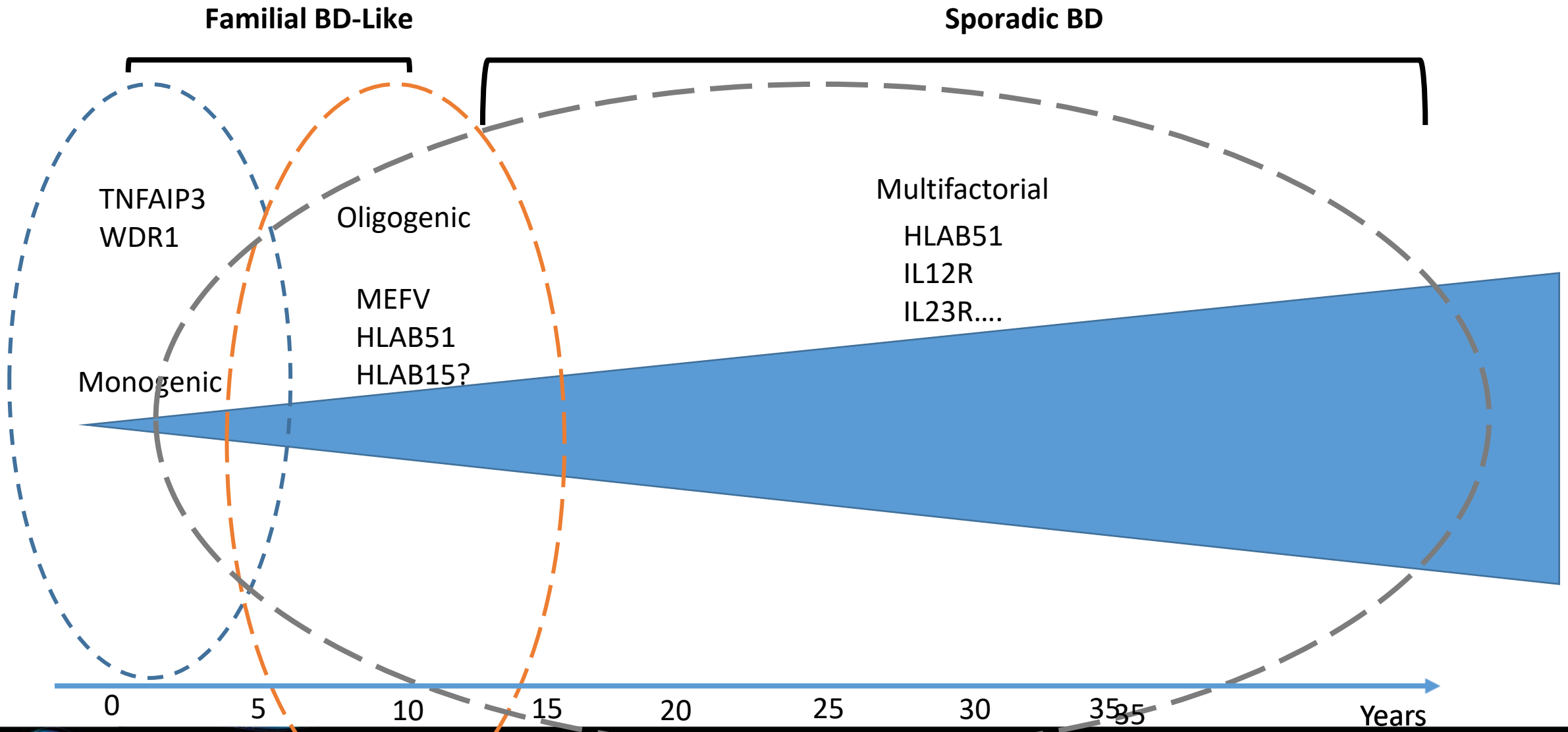
Incontinentia pigmenti



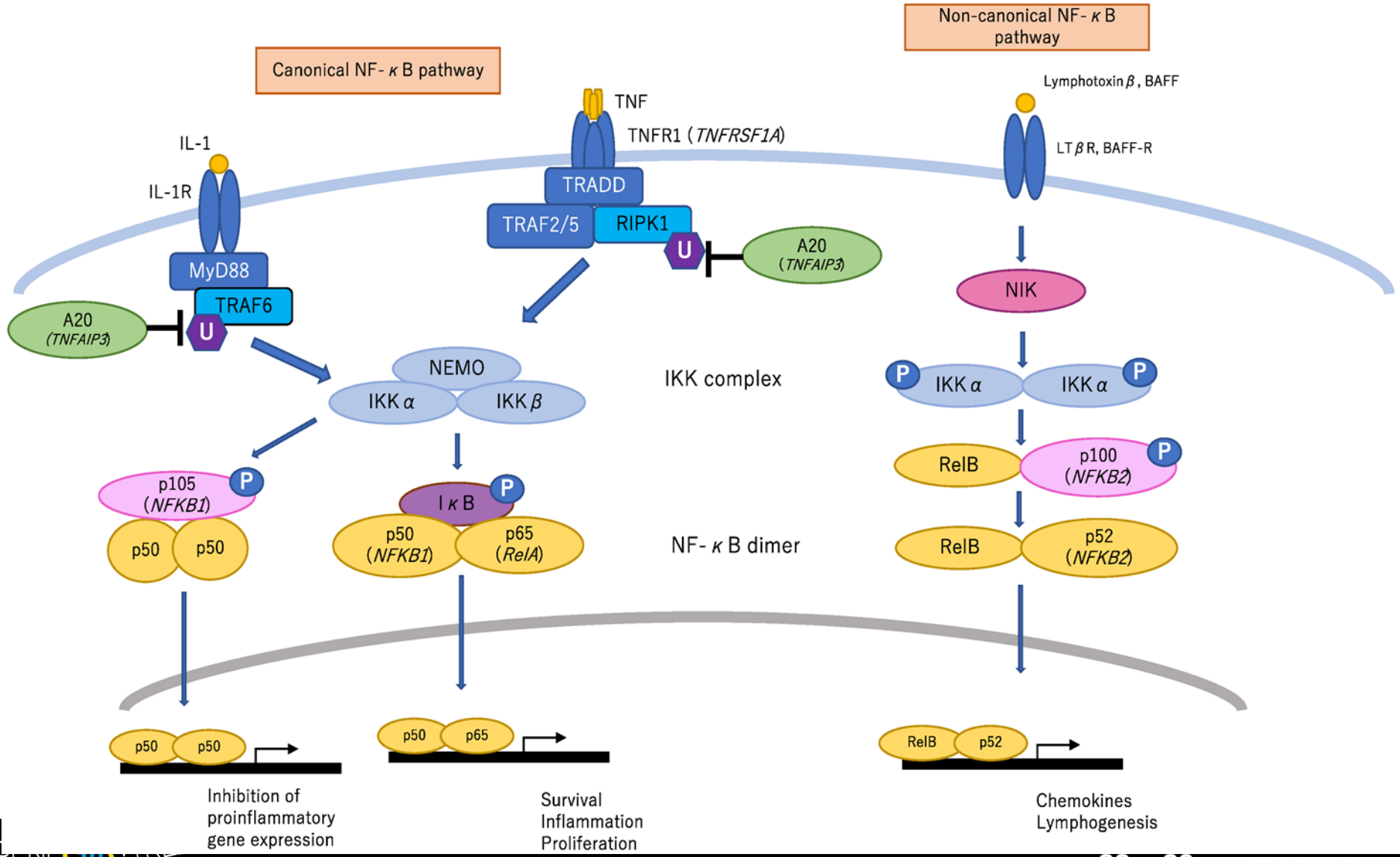
Behçet ou pas Behçet?

Mutation hétérozygote, p.His413Tyr, exon 10 du gène IKBKG (NEMO)

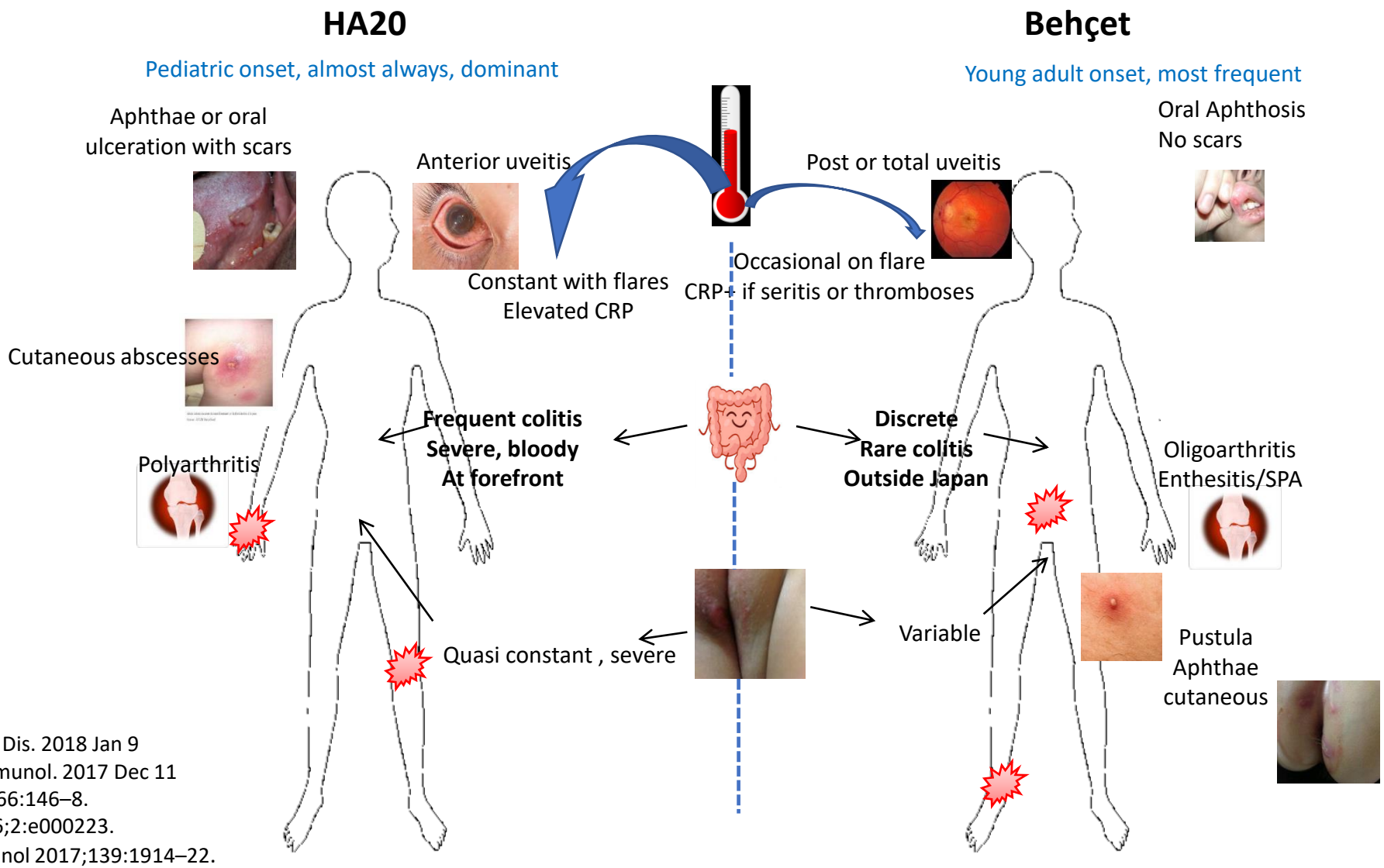
Mécanismes liés à l'âge et phénotype de la MB



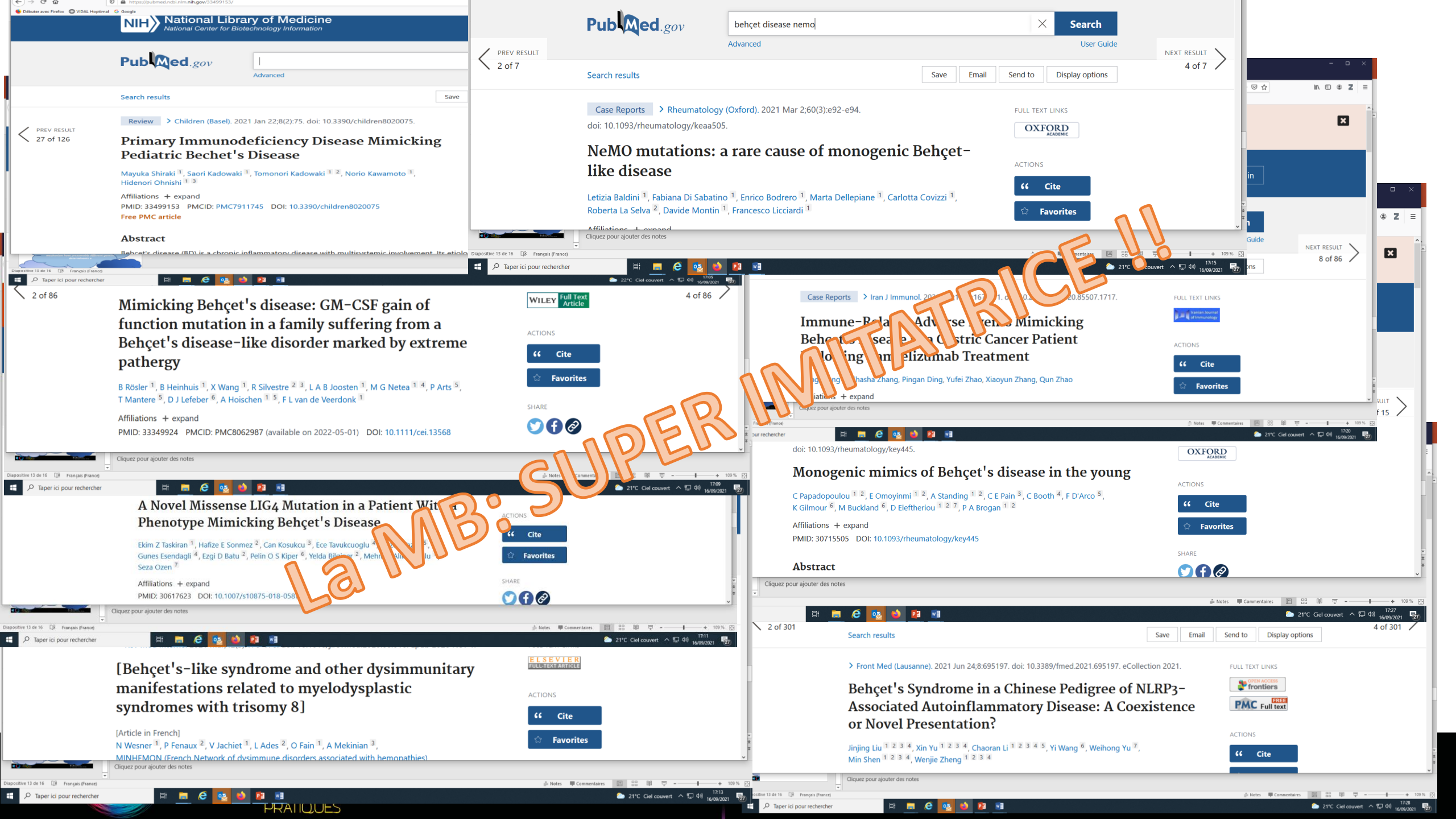
Voie NFKB et phénotypes Behçet-like



HA20 « Behçet-like » versus polyfactorial Behçet's disease



Aeschlimann FA,. Ann Rheum Dis. 2018 Jan 9
Kadowaki T,. J Allergy Clin Immunol. 2017 Dec 11
Ohnishi H,. Allergol Int 2017;66:146–8.
Shigemura T. RMD Open 2016;2:e000223.
Takagi M,. J Allergy Clin Immunol 2017;139:1914–22.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Review
Children (Basel). 2021 Jan 22;8(2):75. doi: 10.3390/children8020075.
Primary Immunodeficiency Disease Mimicking Pediatric Bechet's Disease
Mayuka Shiraki, Saori Kadowaki, Tomonori Kadowaki, Norio Kawamoto, Hidenori Ohnishi
Affiliations + expand
PMID: 33499153 PMCID: PMC7911745 DOI: 10.3390/children8020075
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Case Reports
Rheumatology (Oxford). 2021 Mar 2;60(3):e92-e94.
doi: 10.1093/rheumatology/keaa505.
NeMO mutations: a rare cause of monogenic Behçet-like disease
Letizia Baldini, Fabiana Di Sabatino, Enrico Bodrero, Marta Dellepiane, Carlotta Covizzi, Roberta La Selva, Davide Montin, Francesco Licciardi
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Mimicking Behçet's disease: GM-CSF gain of function mutation in a family suffering from a Behçet's disease-like disorder marked by extreme pathergy
B Rösler, B Heinhuis, X Wang, R Silvestre, L A B Joosten, M G Netea, P Arts, T Mantere, D J Lefeber, A Hoischen, F L van de Veerdonk
Affiliations + expand
PMID: 33349924 PMCID: PMC8062987 (available on 2022-05-01) DOI: 10.1111/cei.13568
WILEY Full Text Article
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Case Reports
Iran J Immunol.
Immune-Related Adverse Events Mimicking Behçet's Disease in Gastric Cancer Patient Following Camrelizumab Treatment
Zhasha Zhang, Pingan Ding, Yufei Zhao, Xiaoyun Zhang, Qun Zhao
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Iranian Journal of Immunology
A Novel Missense LIG4 Mutation in a Patient With Phenotype Mimicking Behçet's Disease
Ekim Z Taskiran, Hafize E Sonmez, Can Kosukcu, Ece Tavukcuoglu, Gunes Esendagli, Ezgi D Batu, Pelin O S Kiper, Yelda Bilginer, Seza Ozen
Affiliations + expand
PMID: 30617623 DOI: 10.1007/s10875-018-058
[Behçet's-like syndrome and other dysimmunitary manifestations related to myelodysplastic syndromes with trisomy 8]
[Article in French]
N Wesner, P Fenaux, V Jachiet, L Ades, O Fain, A Mekinian, MINHEMON (French Network of dysimmune disorders associated with hemopathies)
ELSEVIER FULL-TEXT ARTICLE
Monogenic mimics of Behçet's disease in the young
C Papadopoulou, E Omoyinmi, A Standing, C E Pain, C Booth, F D'Arco, K Gilmour, M Buckland, D Eleftheriou, P A Brogan
Affiliations + expand
PMID: 30715505 DOI: 10.1093/rheumatology/key445
doi: 10.1093/rheumatology/key445.
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Front Med (Lausanne). 2021 Jun 24;8:695197. doi: 10.3389/fmed.2021.695197. eCollection 2021.
Behçet's Syndrome in a Chinese Pedigree of NLRP3-Associated Autoinflammatory Disease: A Coexistence or Novel Presentation?
Jinjing Liu, Xin Yu, Chaoran Li, Yi Wang, Weihong Yu, Min Shen, Wenjie Zheng
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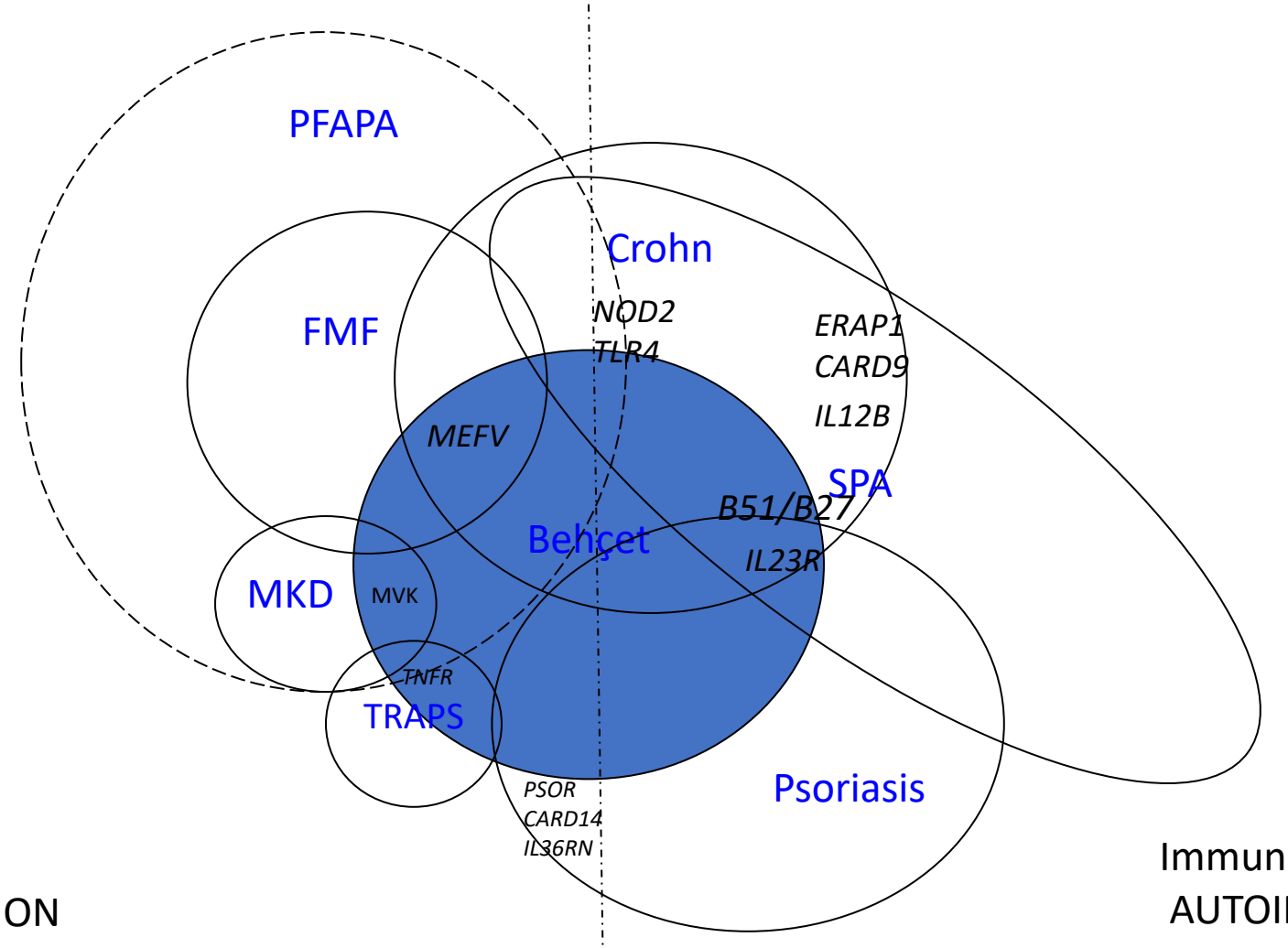
La MB: SUPER IMITATRICE !!

Quand suspecter une MB de cause génétique?

- un début précoce
- des antécédents familiaux
- une fièvre récurrente inexpliquée associée à une CRP élevée
- des symptômes digestifs au premier plan
- une dysmorphie
- une myélodysplasie (trisomie 8)

Le type de réponse immune crée un puzzle Behçet



Immunité innée
AUTOINFLAMMATION

Immunité acquise
AUTOIMMUNITE

Conclusion

Seyahi, E. Phenotypes in Behçet's syndrome. *Intern Emerg Med* **14,** 677–689 (2019).

« Behçet's SYNDROME resembles rather a construction made of several dynamic and interactive LEGO pieces of different shapes and colours. These pieces presenting phenotypes with their own disease mechanism have presumably different genetic determinants »