Genetics of autoinflammation (including Behçet's)

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Cell, Vol. 97, 133–144, April 2, 1999, Copyright ©1999 by Cell Press

Germline Mutations in the Extracellular Domains of the 55 kDa TNF Receptor, TNFR1, Define a Family of Dominantly Inherited Autoinflammatory Syndromes

The autosomal dominant periodic fevers therefore represent a class of human disease shown to be caused by mutations in TNF receptors. Autoantibodies are not a general feature of these illnesses or the recessively inherited FMF, and for this reason the term *autoinflammatory* is preferable to *autoimmune* in describing these disorders. Variation in ethnic background, pattern of cutaneous involvement, and presence of systemic amyloidosis have created uncertainty about the etiology and classification of the dominantly inherited periodic fevers.

Autoinflammatory Disorders

- An emerging family of clinical disorders characterized by
  - episodes of seemingly unprovoked inflammation
  - without high-titer autoantibodies or antigen-specific T lymphocytes
  - inborn errors of the innate immune system

Autoimmunity vs Autoinflammation

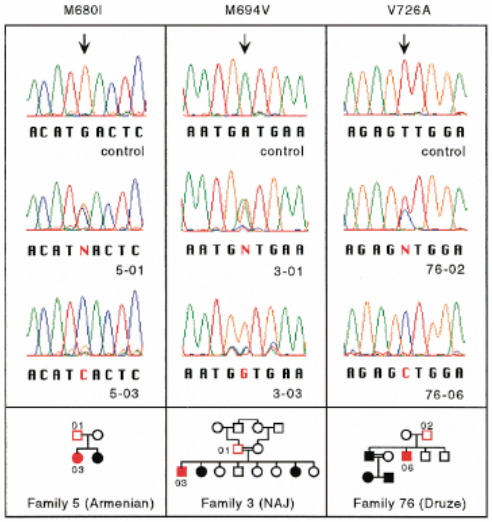
Autoinflammatory Disorders

- Autosomal recessive
  - Familial Mediterranean fever
  - Hyper-IgD and periodic fever syndrome (HIDS)

- Autosomal dominant
  - TNF receptor-associated periodic syndrome (TRAPS)
  - Muckle-Wells syndrome
  - Familial cold urticaria syndrome (FCAS)
  - Neonatal onset multisystem inflammatory disorder (NOMID or CINCA)

Familial Mediterranean Fever

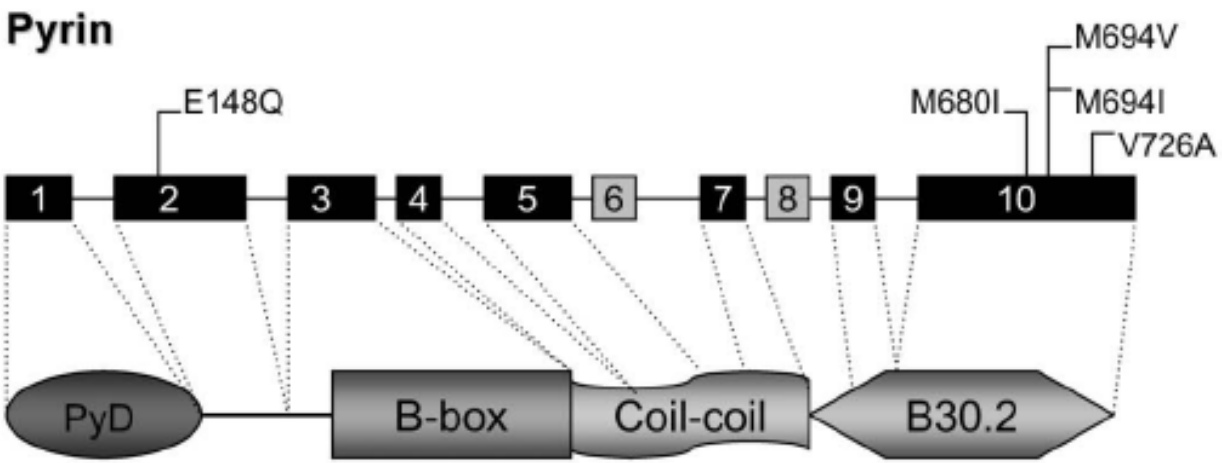
- Associated with the MEFV gene
  - MEFV gene was positionally cloned in 1997
    - French FMF Consortium, Nature Genet 1997; 17: 25-31
    - International FMF Consortium, Cell 1997; 90: 797-807



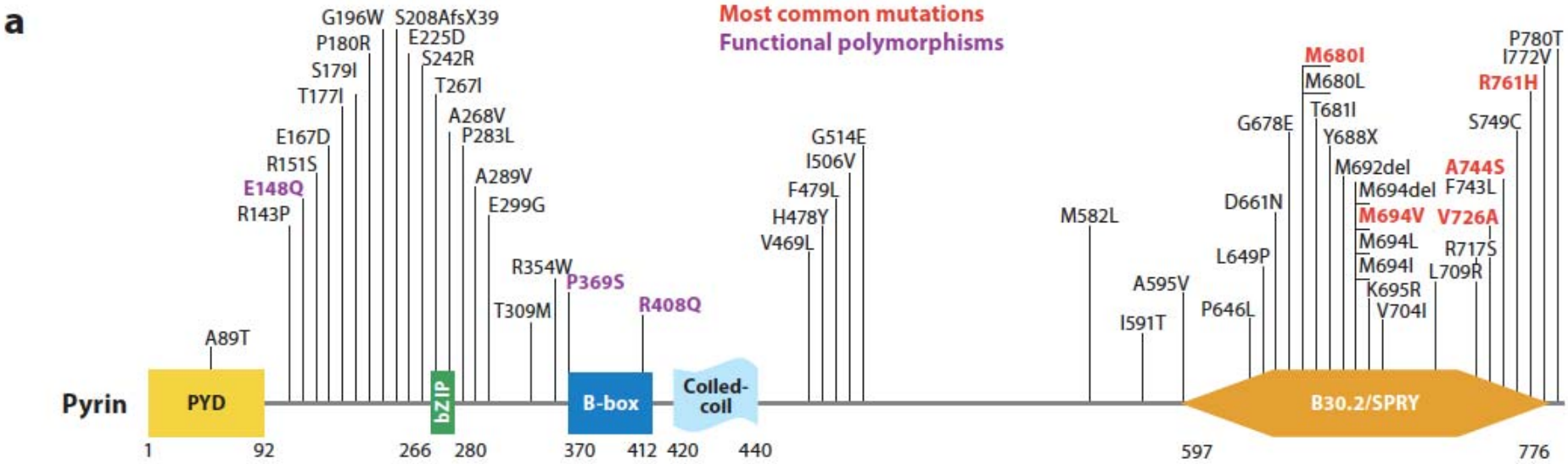
Cell 1997; 90: 797-807

- Pyrin (marenostrin) protein
    - 781 aminoacid
    - Expressed in granulocytes, activated monocytes, fibroblasts (skin, synovium, peritoneum)

Familial Mediterranean Fever



Stojanov and Kastner. Curr Opin Rheumatol 2005; 17: 586-99



Masters et al. Annu Rev Immunol 2009; 27:621–68

Molecular Cell, Vol. 10, 417–426, August, 2002, Copyright ©2002 by Cell Press

The Inflammasome: A Molecular Platform Triggering Activation of Inflammatory Caspases and Processing of proIL-β

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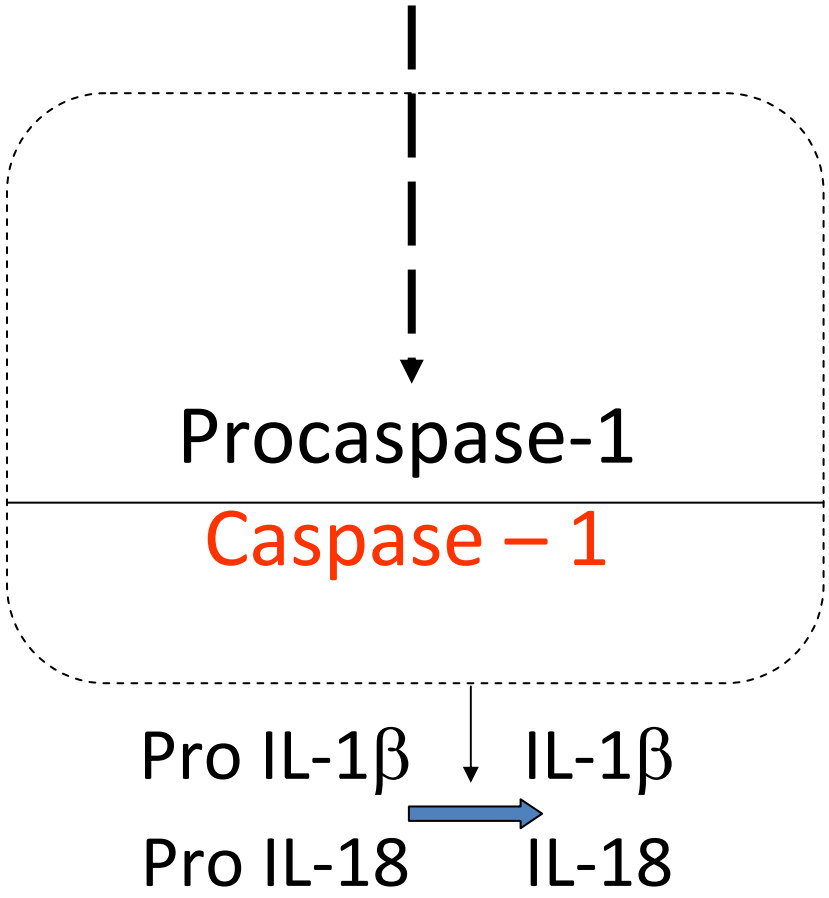
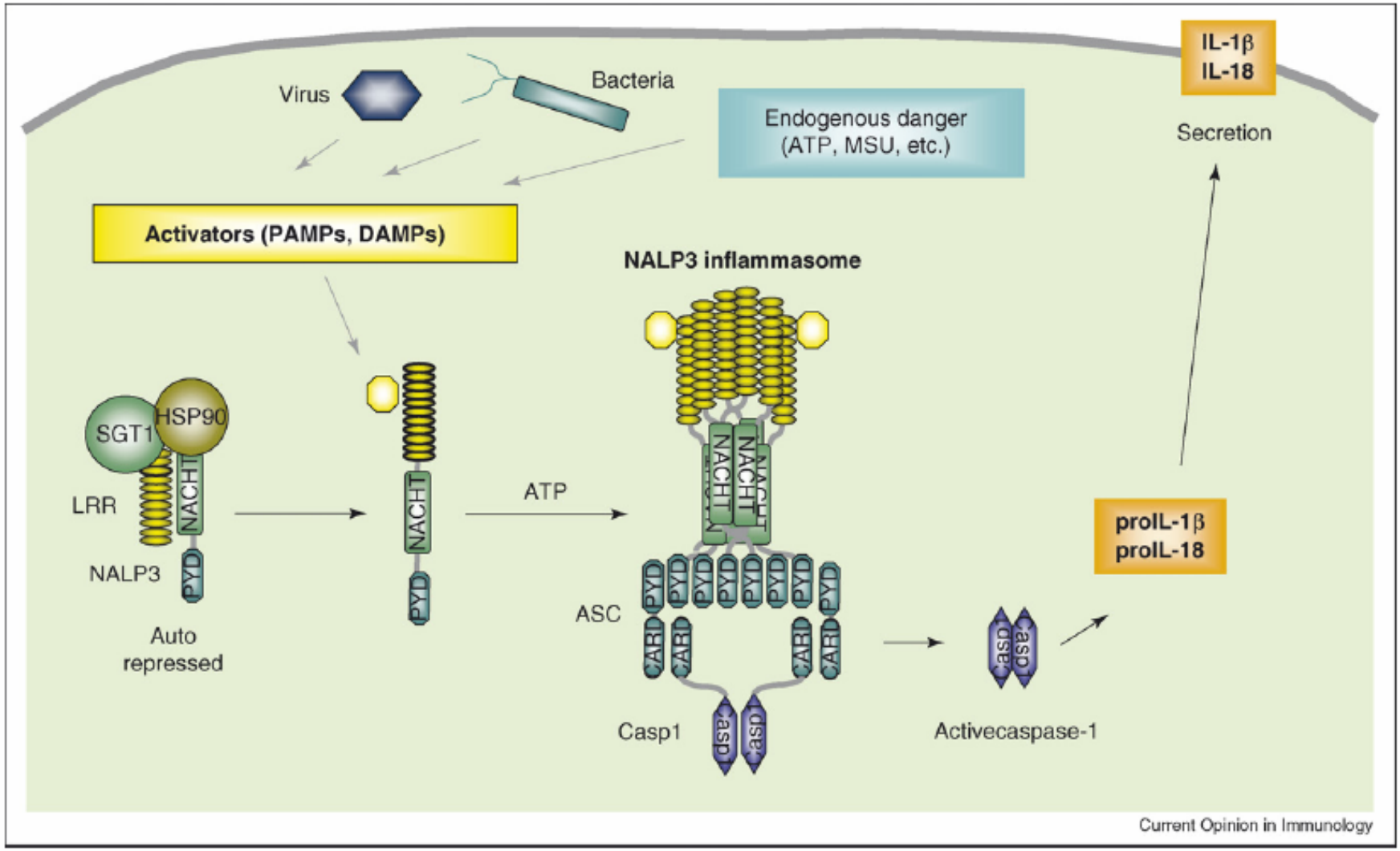
University of Lausanne
BIL Biomedical Research Center
Chemin des Boveresses 155
CH-1066 Epalinges
Switzerland

Summary

Generation of Interleukin (IL)-1β via cleavage of its proform requires the activity of caspase-1 (and caspase-11 in mice), but the mechanism involved in the activation of the proinflammatory caspases remains elusive. Here we report the identification of a caspase-activating complex that we call the inflammasome. The inflammasome comprises caspase-1, caspase-5, Pycard/Asc, and NALP1, a Pyrin domain-containing protein sharing structural homology with NODs. Using a cell-free system, we show that proinflammatory caspase activation and proIL-1β processing is lost upon prior immunodepletion of Pycard. Moreover, expression of a dominant-negative form of Pycard in differentiated THP-1 cells blocks proIL-1β maturation and activation of inflammatory caspases induced by LPS in vivo. Thus, the inflammasome constitutes an important arm of the innate immunity.

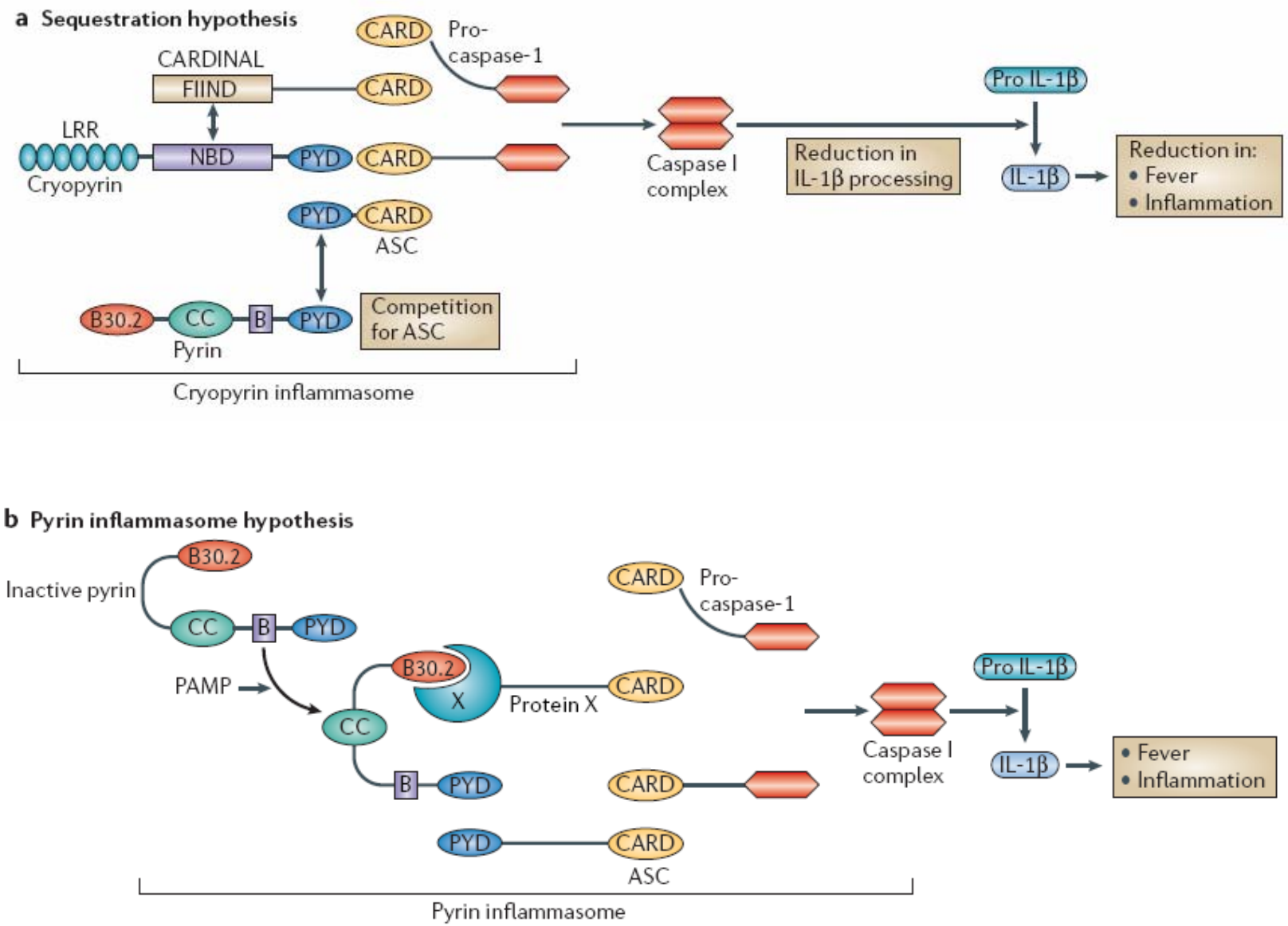


Inflammasome



Petrilli et al. Curr Opin Immunol 2007; 19: 615-22.

Familial Mediterranean Fever



Nature Rev Immunol 2006; 6: 183-195

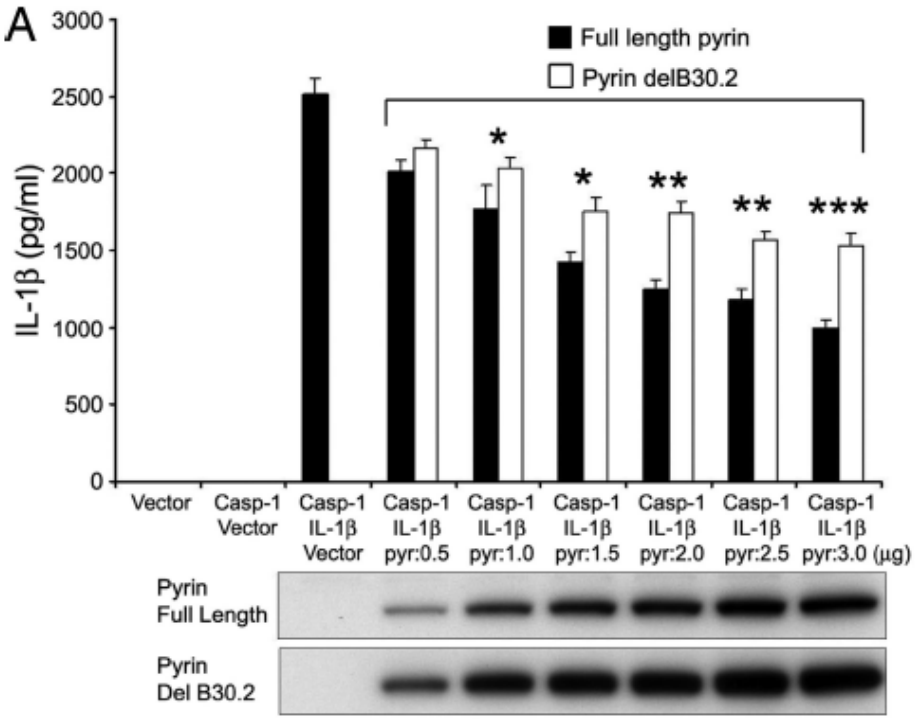
PNAS

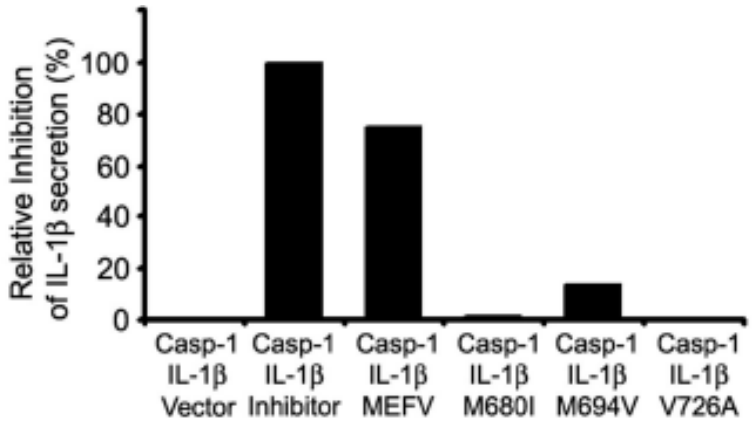
The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1β production

Jae Jin Chae*†, Geryl Wood*, Seth L. Masters‡, Katharina Richard*§, Grace Park¶, Brian J. Smith‡, and Daniel L. Kastner*

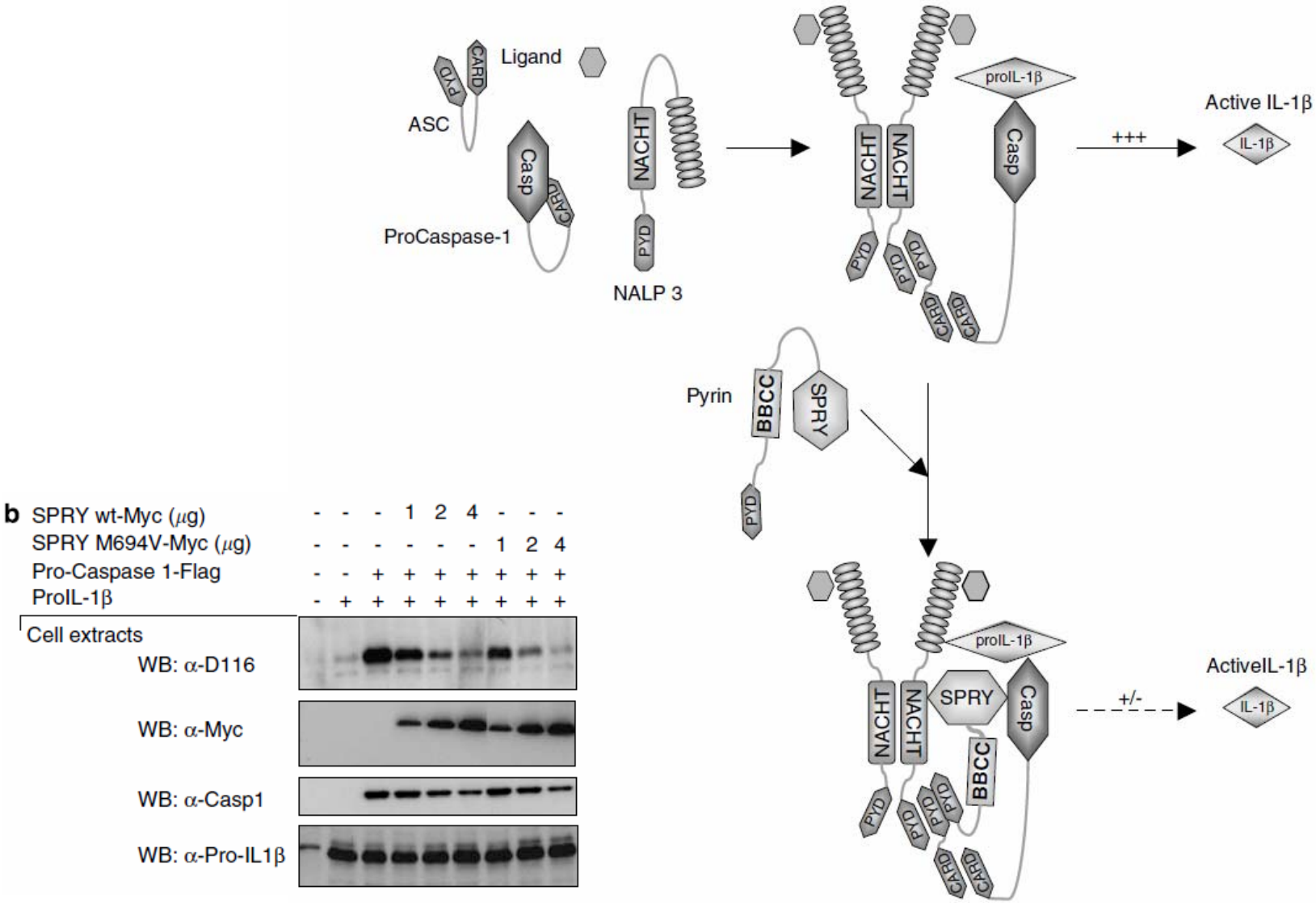
*Genetics and Genomics Branch and ¶Office of the Clinical Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892; and ‡The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Victoria 3050, Australia

Edited by Charles A. Dinarello, University of Colorado Health Sciences Center, Denver, CO, and approved May 19, 2006 (received for review March 14, 2006)



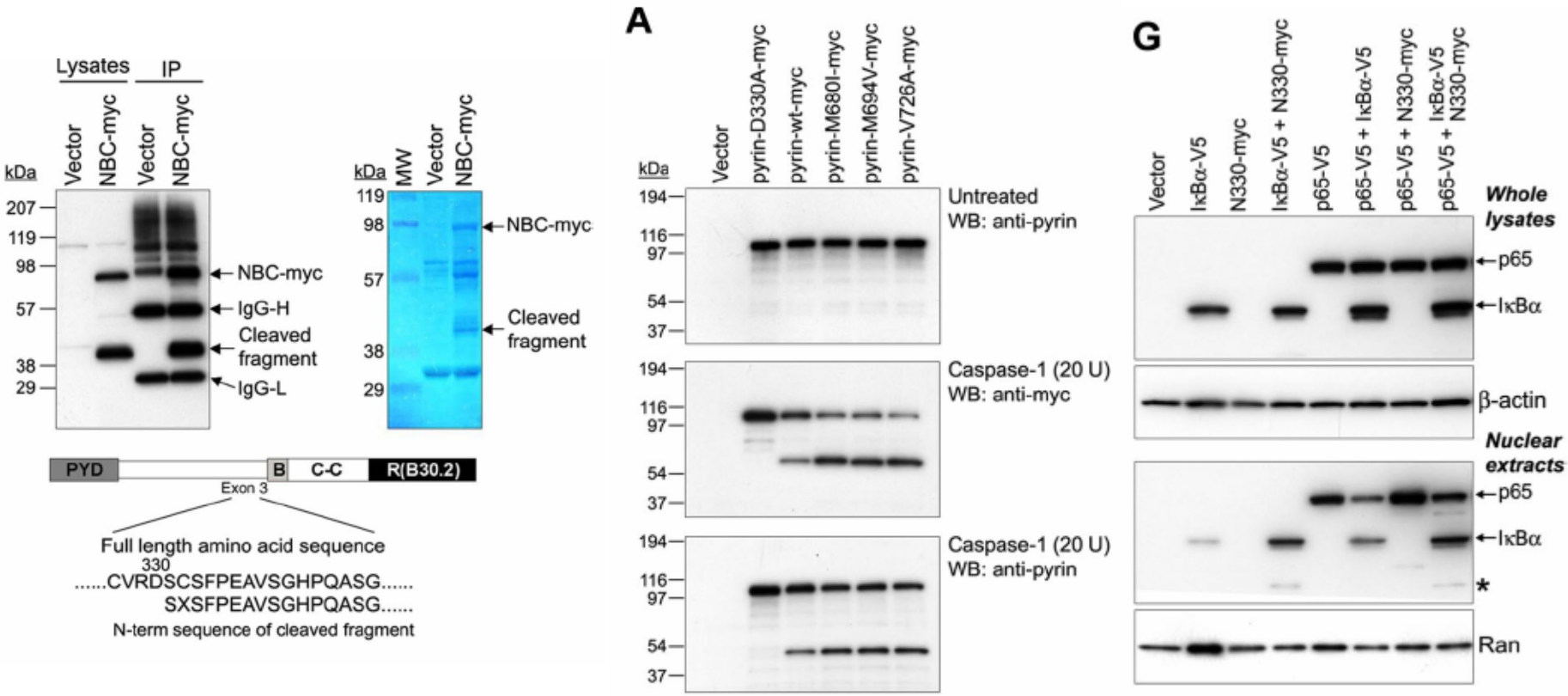


Pyrin interacts with caspase 1



Papin et al. Cell Death Differ 2007; 14: 1457-66

Caspase 1 interacts with pyrin



Chae et al. Blood 2008; 112: 1794-1803

High Carrier Rate of the MEFV Mutations

- Heterozygote advantage ?
- Increased susceptibility to develop inflammatory disorders ?
  - Behçet's disease
    - Increased frequency of vascular involvement
  - Ankylosing spondylitis
    - More frequent recurrent oral aphthous ulcers, peripheral arthritis, higher acute phase response

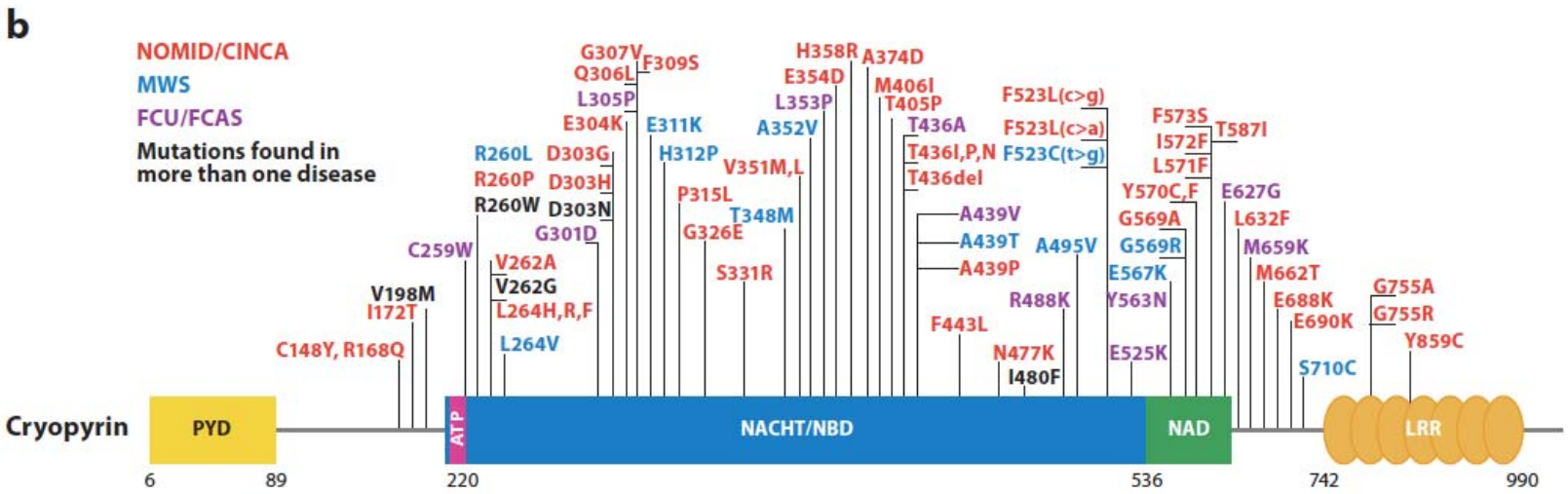
Cosan et al. Arthritis Rheum 2010

  - Rheumatoid arthritis
    - More severe disease course ?
  - Multiple sclerosis
    - More severe disease course ?
  - Systemic lupus erythematosus
    - Higher frequency of pleuritis/pericarditis in carriers

Erer et al. Unpublished data

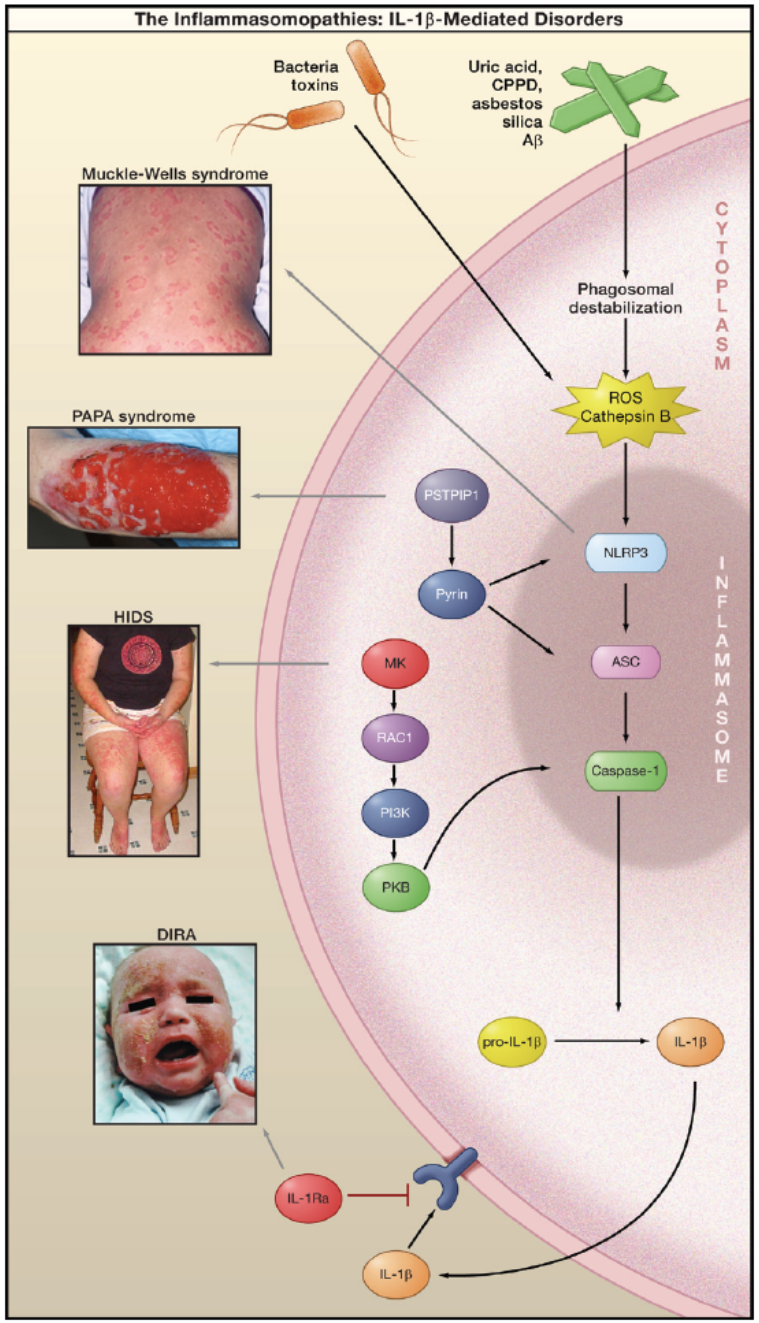
NLRP3 Associated Disorders

- Familial cold urticaria / familial cold autoinflammatory syndrome (FCU/FCAS)
- Muckle-Wells Syndrome
- Neonatal-onset multisystem inflammatory disease (NOMID) [or chronic infantile neurologic cutaneous articular (CINCA) syndrome]



Masters et al. Annu Rev Immunol 2009; 27:621–68

IL-1b Activation Disorders (Inflammasomopathies)



Intrinsic

- FCAS, MWS, NOMID/CINCA

Extrinsic

- FMF
- PAPA
- CRMO/SAPHO Complex
- Majeed syndrome
- HIDS
- DIRA

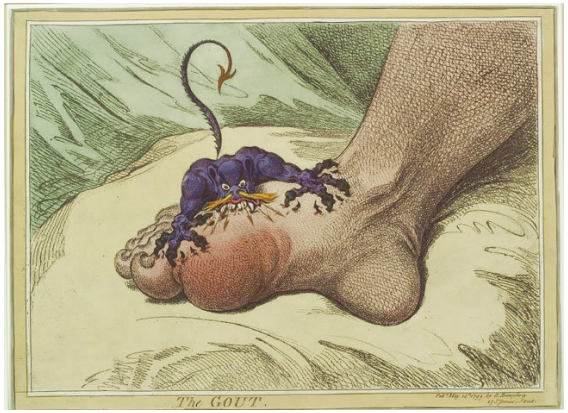
Complex/acquired

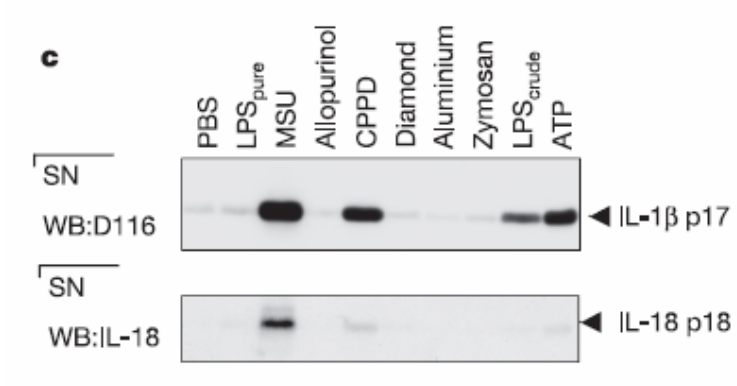
- Gout, pseudogout
- Fibrosing disorders
- Type 2 diabetes mellitus
- Schnitzler syndrome

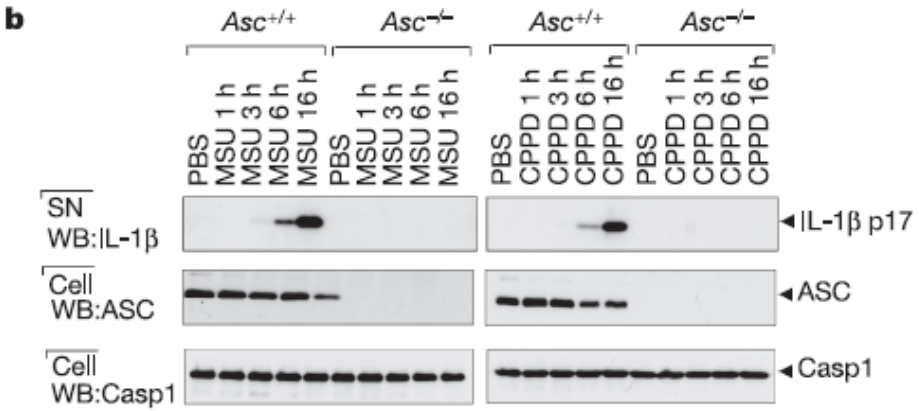
Masters et al. Annu Rev Immunol 2009; 27:621–68
Kastner et al. Cell 2010; 140: 784-90

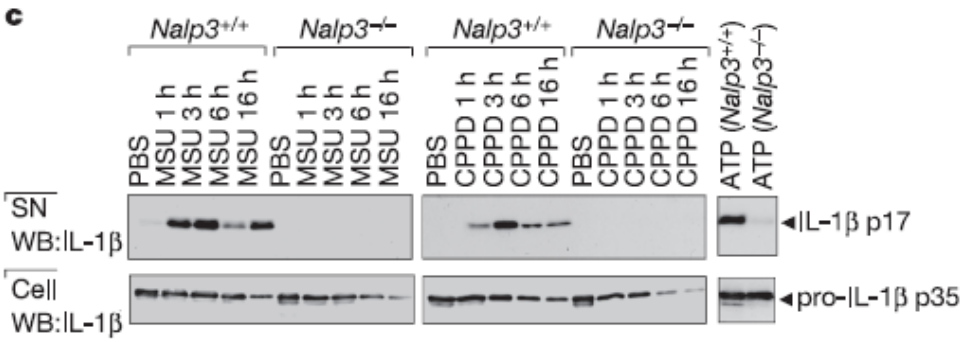
Gout-associated uric acid crystals activate the NALP3 inflammasome

Fabio Martinon[1], Virginie Pétrilli[1], Annick Mayor[1], Aubry Tardivel[1] & Jürg Tschopp[1]









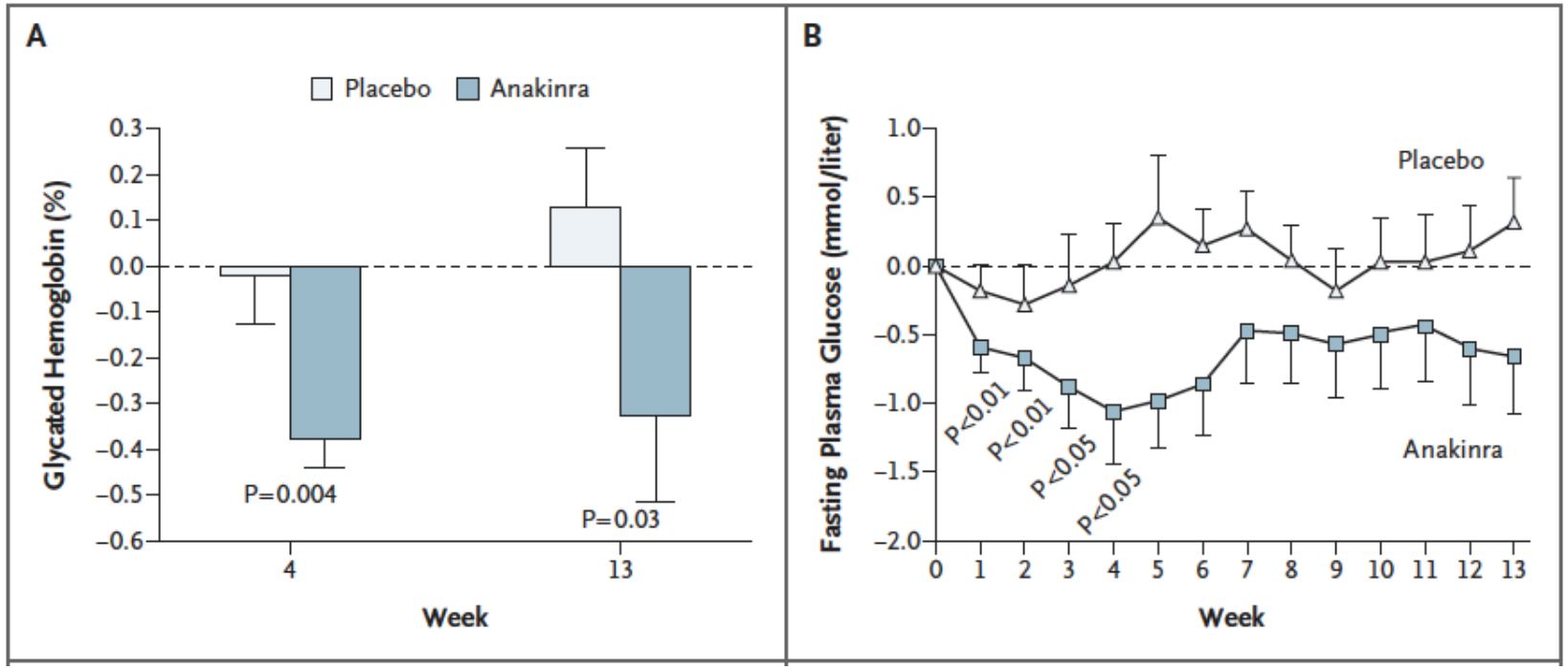
Nature 2006; 440: 237-41

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-1–Receptor Antagonist in Type 2 Diabetes Mellitus

Claus M. Larsen, M.D., Mirjam Faulenbach, M.D., Allan Vaag, M.D., Ph.D., Aage Vølund, M.Sc., Jan A. Ehses, Ph.D., Burkhardt Seifert, Ph.D., Thomas Mandrup-Poulsen, M.D., Ph.D., and Marc Y. Donath, M.D.

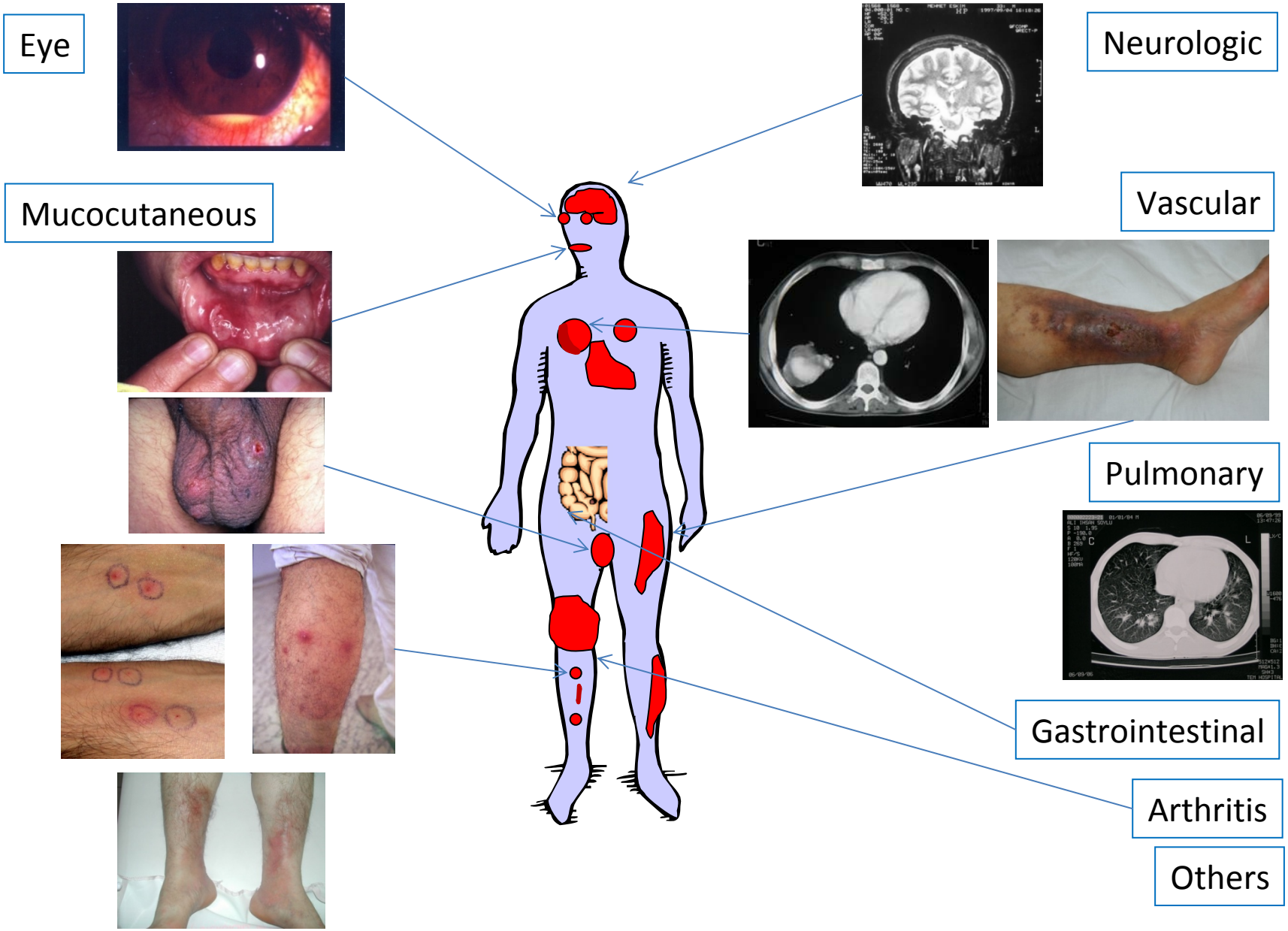


N Engl J Med 2007;356:1517-26

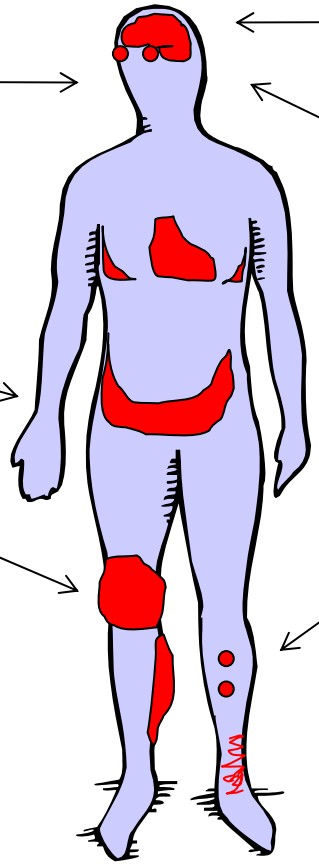
Autoinflammatory Disorders

- NF-κB activation disorders
  - Crohn disease, Blau syndrome
- Protein folding disorders of the innate immune system
  - TRAPS, SpA (Behçet's disease ?)
- Complement disorders
  - HUS, AMD
- Cytokine signaling disorders
  - Cherubism
- Macrophage activation
  - Familial HLH

Behçet's disease – A Multisystem Disorder



Behçet's disease – Overlapping features with autoinflammatory disorders



Oral aphthous ulcers
HIDS, TRAPS, MWS

Genital ulcers
HIDS

Arthritis
FMF, TRAPS, PAPA, Blau, MWS, HIDS

Amyloidosis
All

Meningoencephalitis
FMF, NOMID, MWS

Uveitis
NOMID, TRAPS, Blau

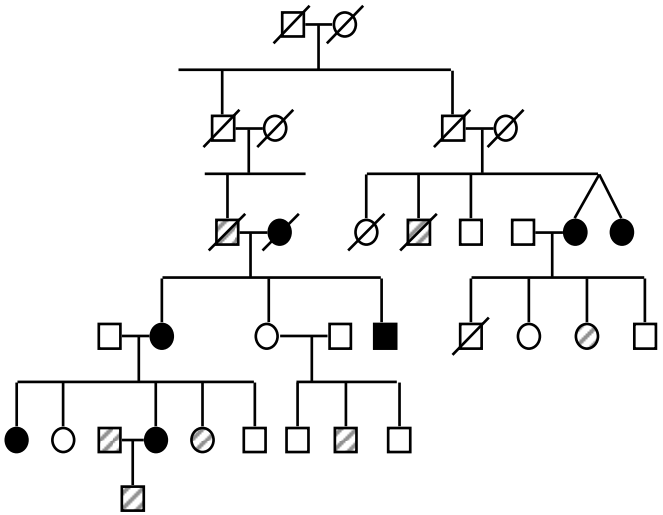
Orchyepididymitis
FMF

Acne-like lesions
PAPA

Pathergy reaction
PAPA

Behçet's disease – Complex Genetic Disorder

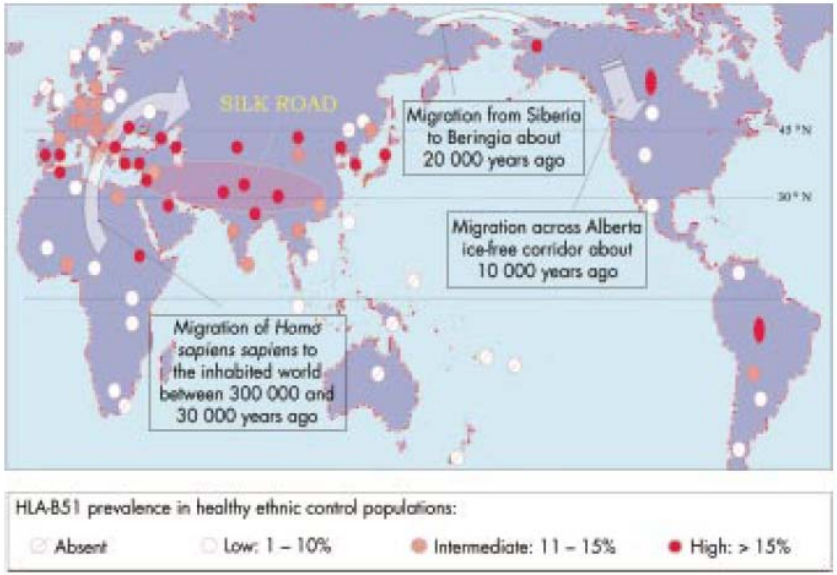
Familial Aggregation



$\lambda s = 11.4\text{-}52.5$

Gul et al. Ann Rheum Dis 2000; 59: 622-5

Geographic Distribution



Verity et al. Br J Ophthalmol 2003; 87: 1175-83.

HLA-B51 Association

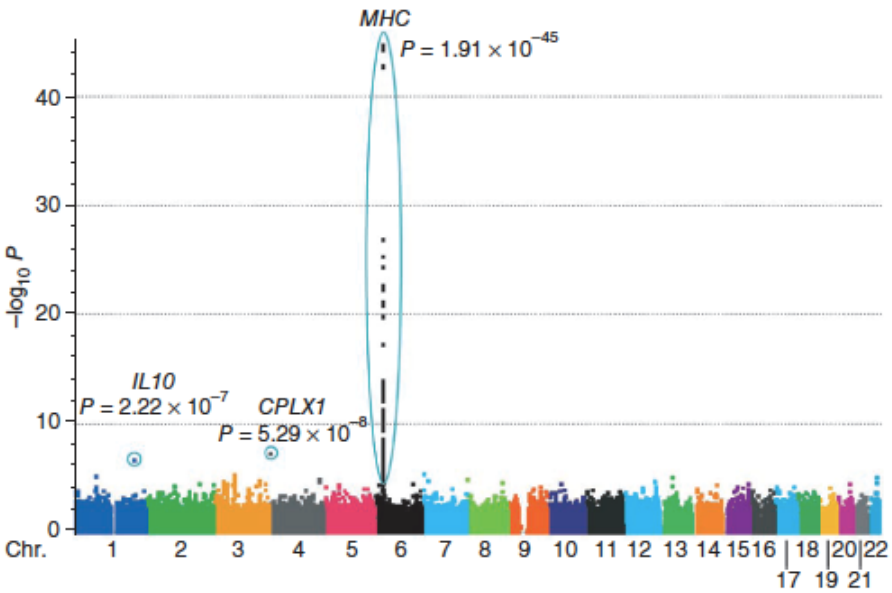
HL-A5 AND BEHÇET'S DISEASE

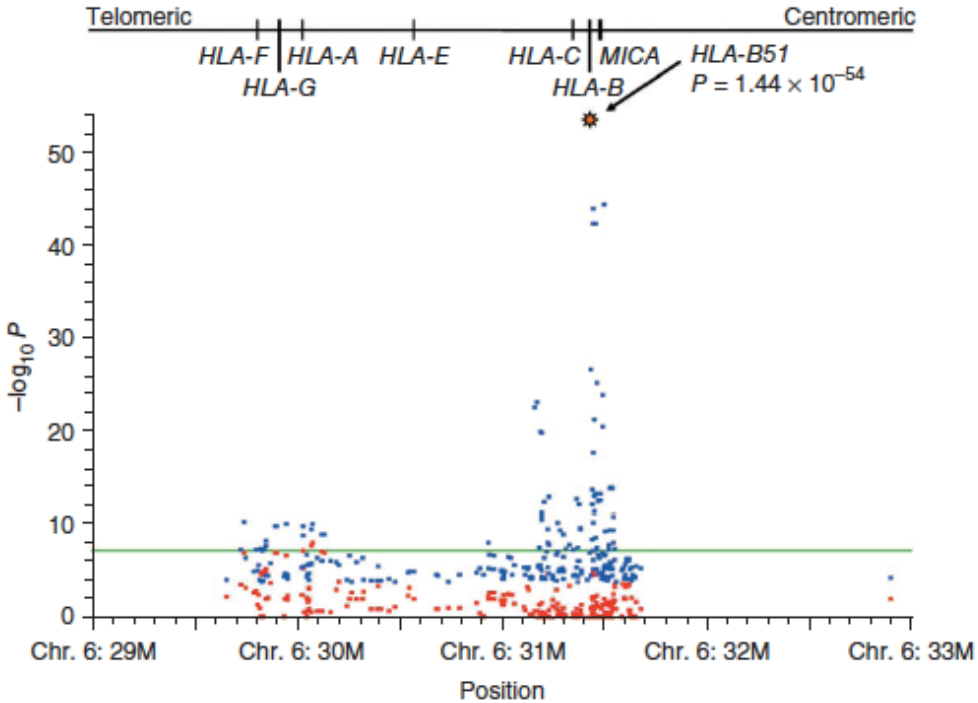
SIR,—The ætiology and nature of Behçet's disease remain obscure. Some immunological reactions seem to be at work. Recent studies have revealed possible associations between HL-A antigens and many diseases.[1] We now report our studies of HL-A antigens in Behçet's disease.

Ohno *et al*. Lancet 1973.

Behçet's disease – GWAS

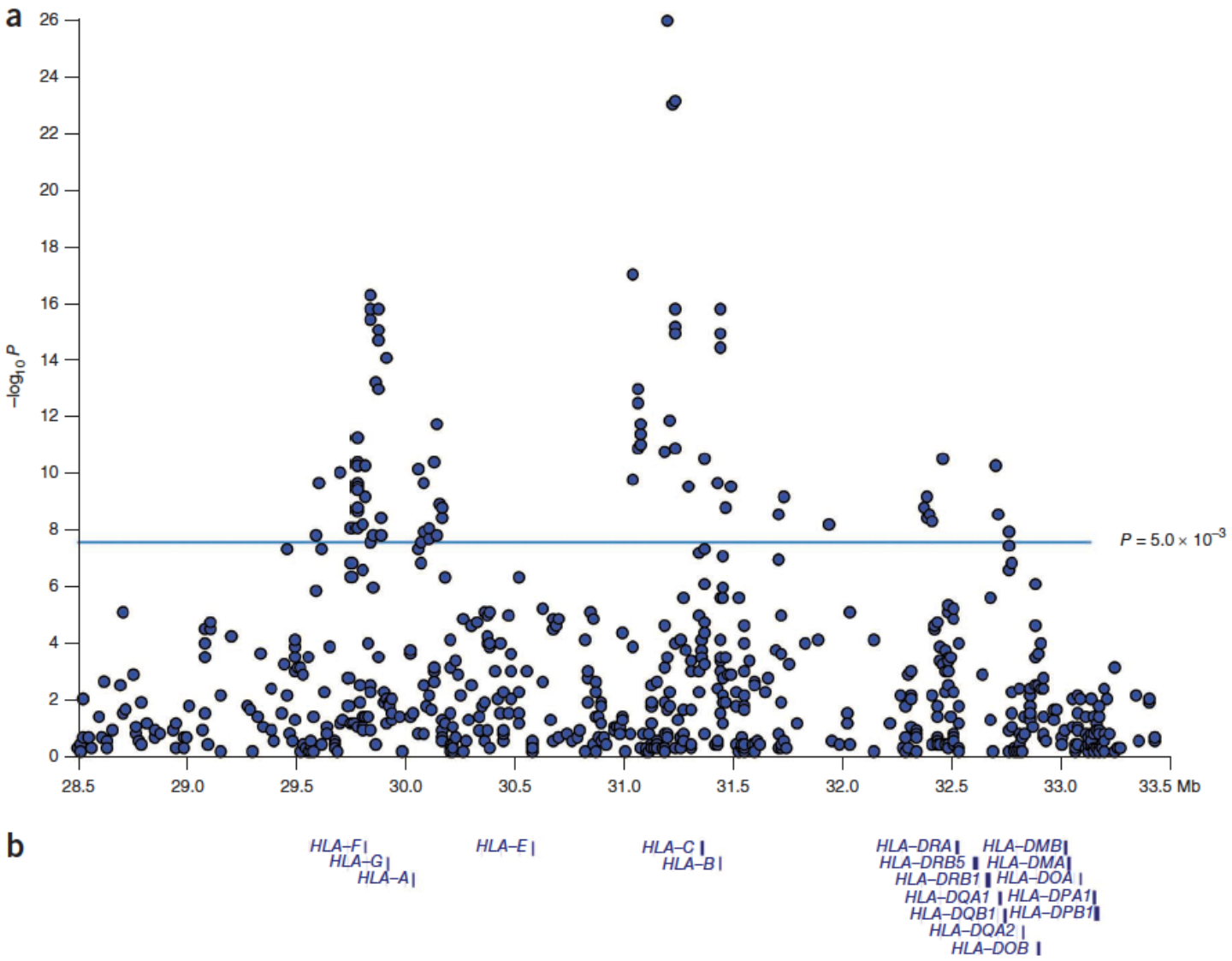
- Illumina HumanCNV370-Quad and Duo chips
  - 311,482 SNP
  - 1215 independent patients
  - 1278 independent controls
- Strong association with HLA Class I region
  - HLA-B51
  - HLA-A region



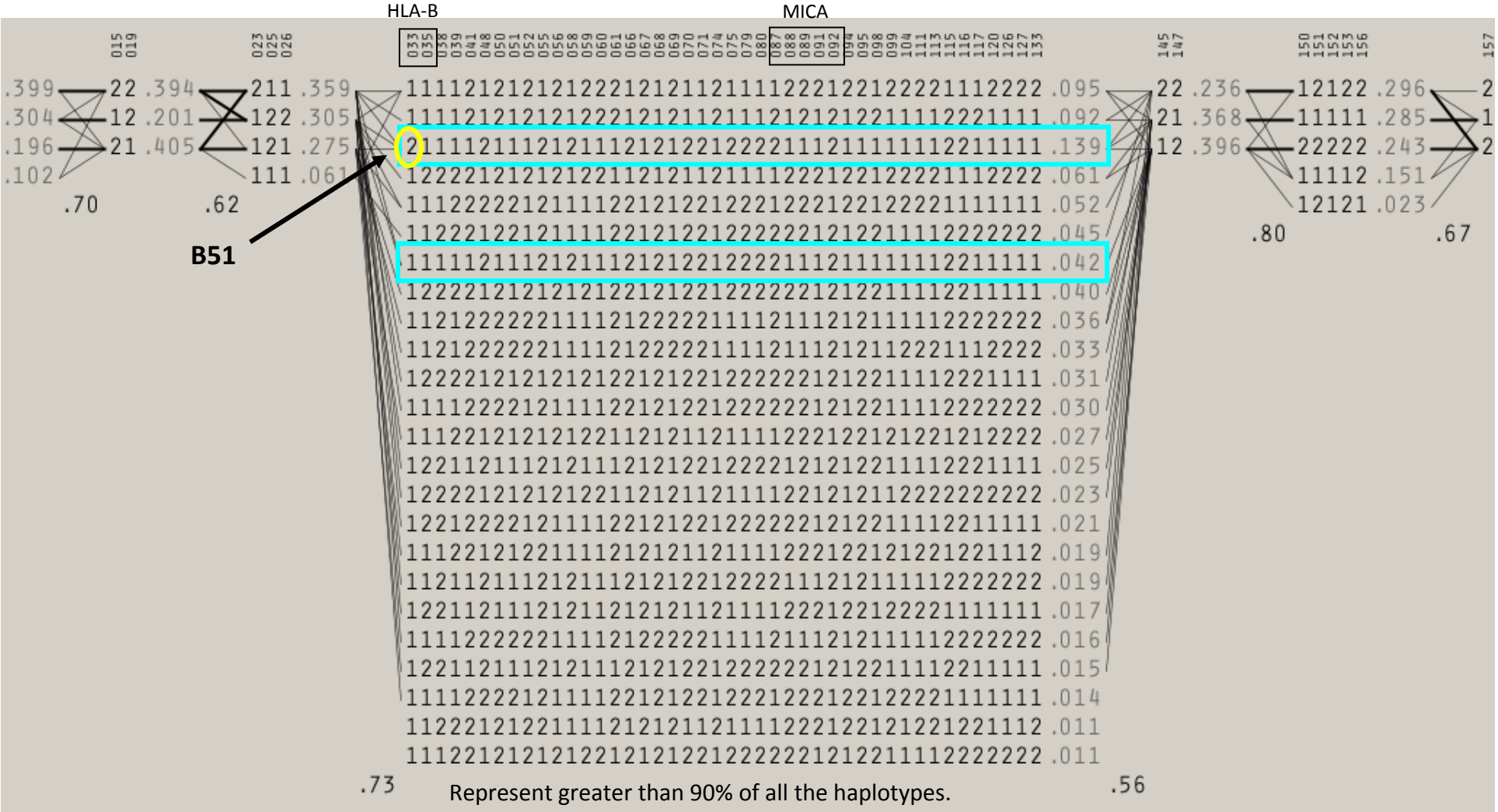


Remmers et al. Nat Genet 2010; 698-702

Behçet hastalığı – MHC Bölgesi



Mizuki et al. Nat Genet 2010; 8: 703-6

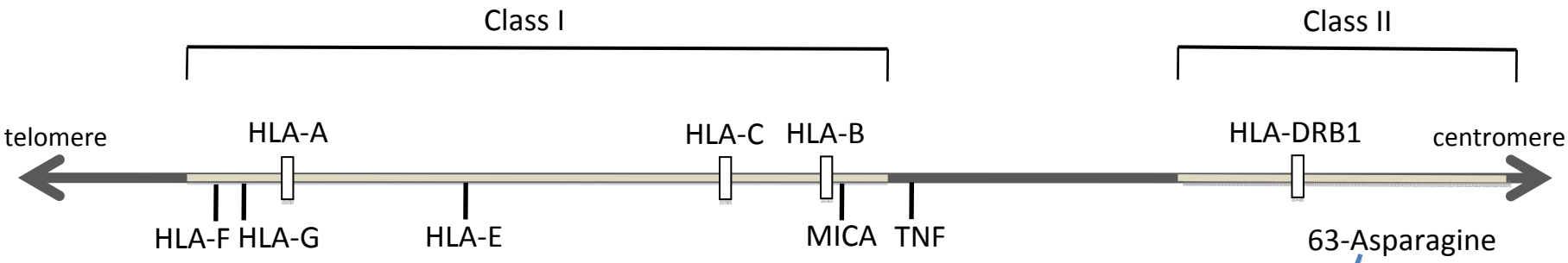


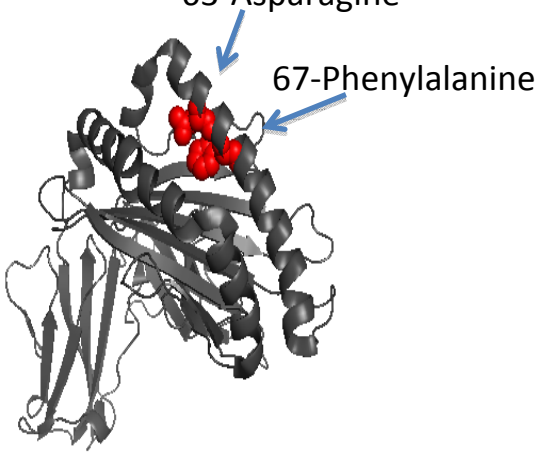
The B51 bearing haplotype frequency is found at 13.9% in controls and is found at an increased frequency, 31.4%, in cases.

A haplotype that is identical to the B51 haplotype, but that does not bear B51, is found at 4.2% frequency in controls and is not found at increased frequency in cases (4.0% frequency in cases).

The MICA alleles without (B51) do not contribute to the disease risk. Therefore B51 or the combination of B51 with MICA alleles are responsible the disease risk.

Behçet's disease – HLA-B51 Association





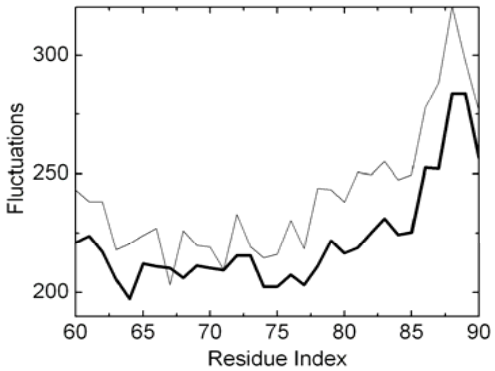
- Pathogenic role ?
  - Direct pathogenic role
  - HLA-B51 – haplotype
    - MICA-009
  - HLA-B51 – independent MHC Class I associations
    - HLA-A26
    - HLA-A*26-F*010101-G*010102 haplotype

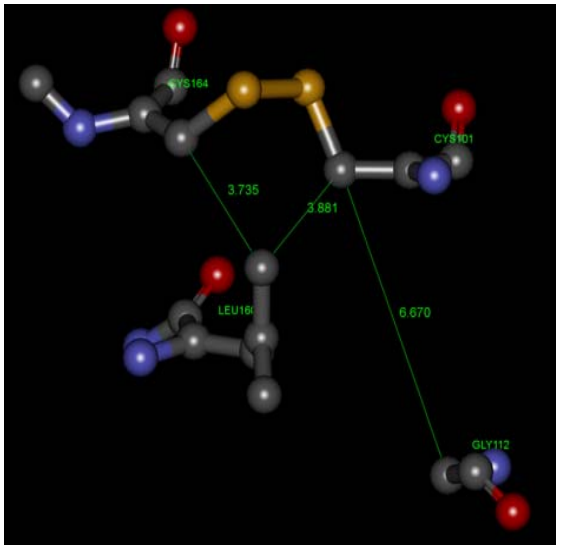
Meguro et al. Ann Rheum Dis 2009

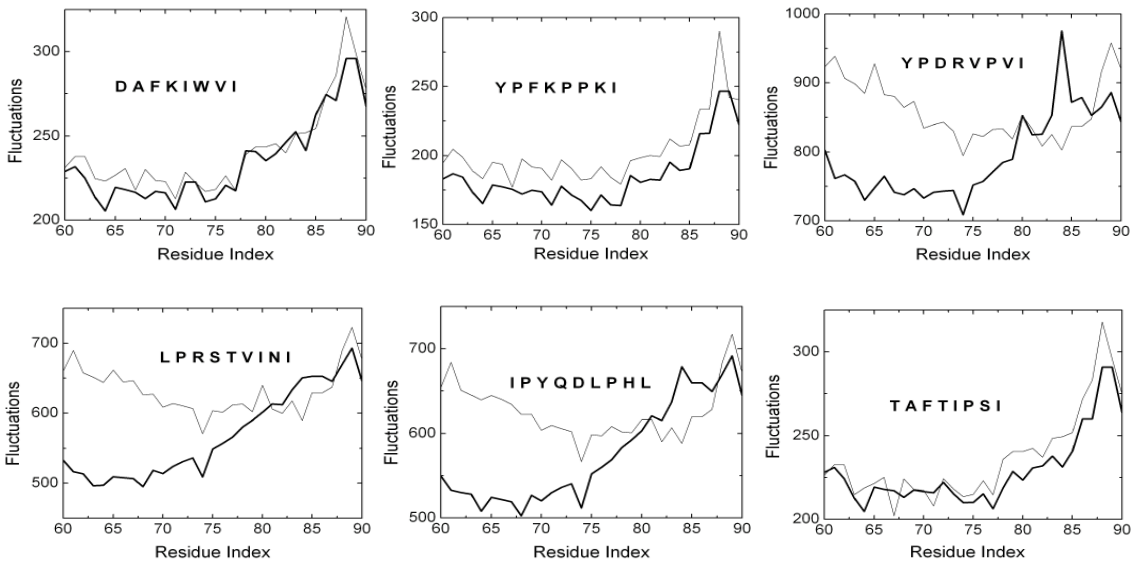
Structural comparison of HLA-B51 with HLA-B52

- Thermodynamic analysis using Gauss network method

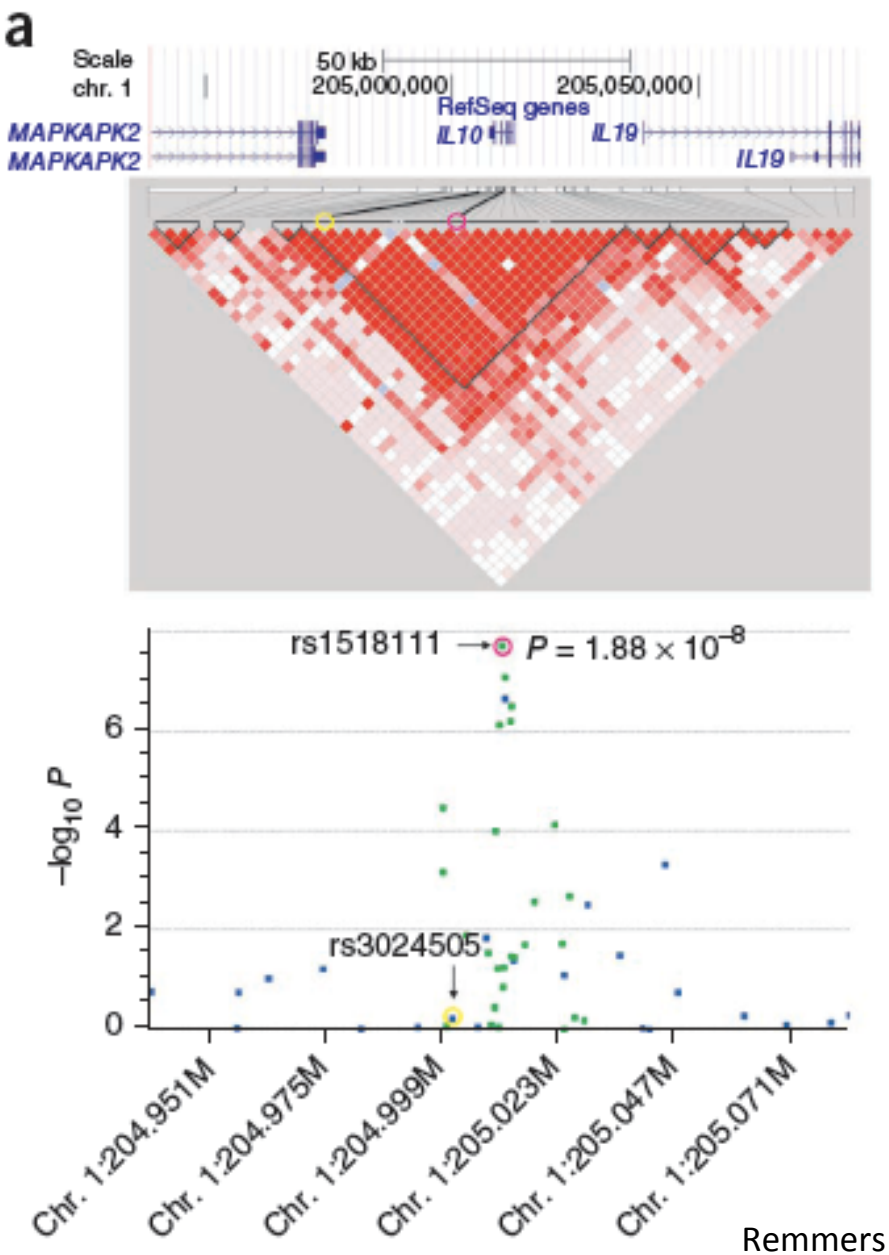
  (Gür M, Gül A, Erman B)







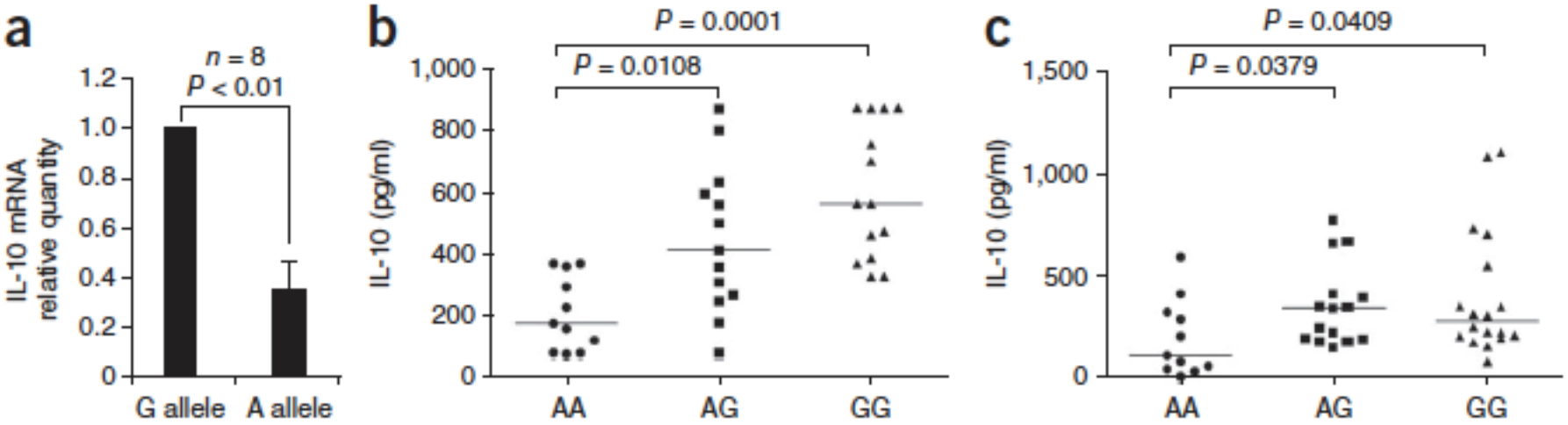
Fine Mapping for the IL10 Gene



Remmers et al. Nat Genet 2010; 698-702

Behçet's disease – The IL10 Gene Association

- Genetic predisposition for low IL-10 expression is associated with Behçet's disease

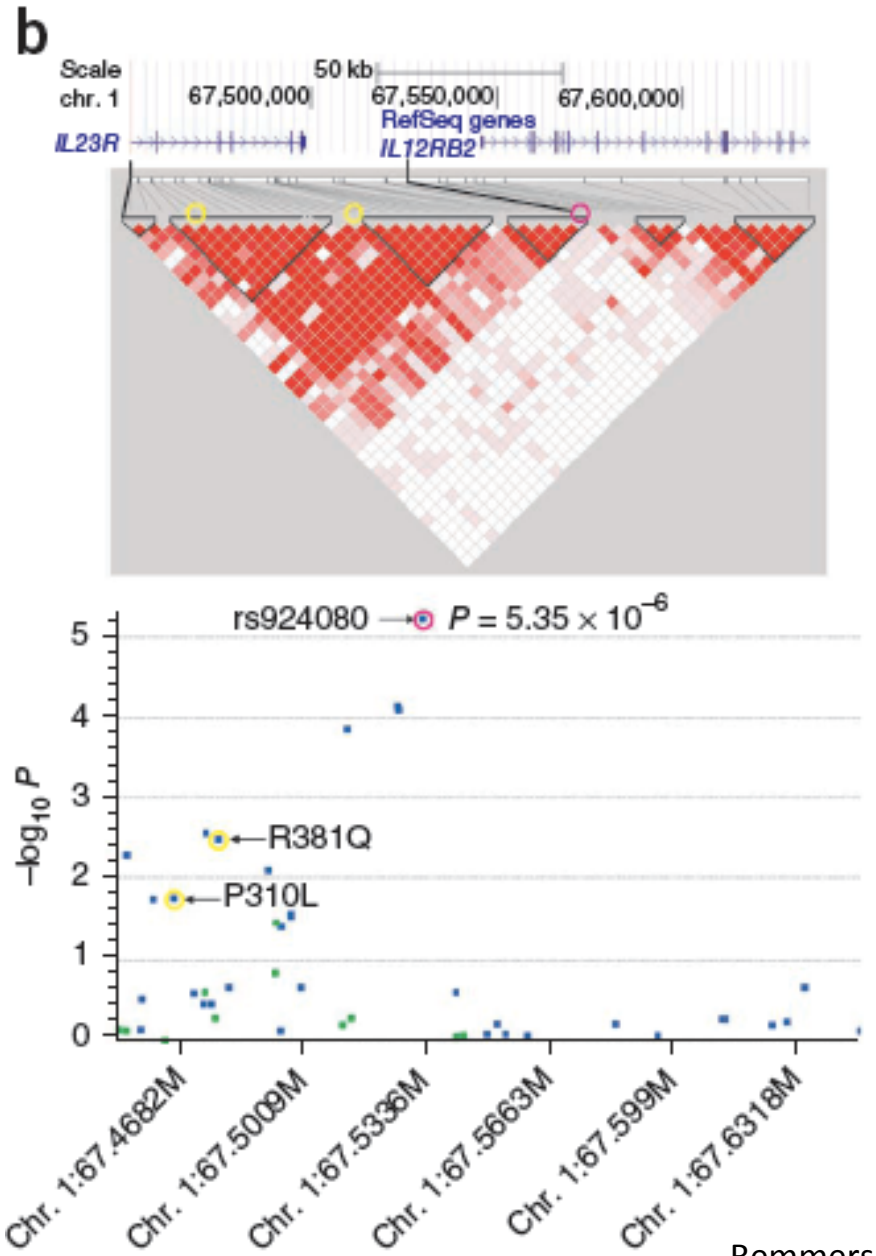


Remmers et al. Nat Genet 2010; 698-702

Behçet's disease – IL-10 association

- IL-10 is a potent regulator of innate and adaptive immune response
  - IL-10 deficiency is associated with spontaneous intestinal inflammation
  - IL-10R mutations are associated with early-onset enterocolitis
    - Glocker et al. N Engl J Med 2009; 361: 2033-45
  - In IL-10-dependent LPS model of endotoxemia, dampening of the immune response requires expression of IL-10R1 in monocytes/macrophages and/or neutrophils but not in T cells nor B cells
    - Pils et al. Eur J Immunol 2010; 40: 443–8

Behçet's Disease – IL23R – IL12RB2 Association



Remmers et al. Nat Genet 2010; 698-702

Behçet Hastalığı – Replication and Metaanalysis

Table 1 Association of three SNPs identified in the discovery GWAS in independent collections of Behçet's disease cases and controls from diverse ethnic backgrounds

Sample collection	*n* cases	*n* controls	Allele frequency cases	Allele frequency controls	χ^2	χ^2 *P* value	OR	95% CI
rs1518111 (*IL10*) A/G								
Discovery, Turkish	1,161	1,221	0.38	0.30	31.62	1.88×10^{-8}[a]	1.41	1.25–1.59
Replication, Turkish	110	224	0.30	0.31	(0.02)	0.689	0.97	0.69–1.38
Replication, Middle Eastern Arab	188	163	0.35	0.26	7.15	0.007	1.56	1.12–2.16
Replication, Greek	107	84	0.40	0.27	7.21	0.007	1.41	1.26–1.59
Replication, UK European descent	120	119	0.31	0.22	4.49	0.034	1.56	1.03–2.34
Replication, Korean	77	52	0.71	0.66	0.57	0.450	1.23	0.78–2.10
Replication, Japanese	611	737	0.76	0.67	29.40	5.89×10^{-8}	1.60	1.35–1.90
CMH Meta-analysis	2,374	2,600			75.56	3.54×10^{-18}[a]	1.45[b]	1.34–1.58
rs924080 (*IL23R-IL12RB2*) A/G								
Discovery, Turkish	1,213	1,275	0.67	0.61	20.71	5.35×10^{-6}	1.31	1.17–1.47
Replication, Turkish	110	220	0.64	0.65	(0.05)	0.818	0.96	0.69–1.35
Replication, Middle Eastern Arab	165	146	0.65	0.59	2.60	0.107	1.31	0.94–1.81
Replication, Greek	102	82	0.58	0.58	0.00	0.956	1.01	0.67–1.53
Replication, UK European descent	119	118	0.55	0.53	0.30	0.585	1.11	0.77–1.59
Replication, Korean	77	54	0.79	0.74	0.72	0.397	1.28	0.72–2.28
Replication, Japanese	597	720	0.76	0.70	13.54	2.34×10^{-4}	1.39	1.17–1.65
CMH Meta-analysis	2,383	2,615			33.62	6.69×10^{-9}[a]	1.28[b]	1.18–1.39
rs11248047 (*CPLX1*) G/A								
Discovery, Turkish	1,176	1,190	0.58	0.50	27.93	1.26×10^{-7}	1.36	1.21–1.53
Replication, Turkish	111	225	0.54	0.54	0.00	0.967	0.99	0.72–1.37
Replication, Middle Eastern Arab	189	163	0.60	0.56	0.68	0.409	1.13	0.84–1.53
Replication, Greek	104	84	0.55	0.51	0.49	0.485	1.16	0.77–1.74
Replication, UK European descent	116	115	0.55	0.55	0.01	0.933	1.02	0.70–1.47
Replication, Korean	75	51	0.54	0.50	0.39	0.533	1.17	0.71–1.94
Replication, Japanese	610	726	0.46	0.47	(0.58)	0.445	0.94	0.81–1.10
CMH Meta-analysis	2,381	2,554			13.82	0.0002	1.16[b]	1.07–1.27

Parentheses in the χ^2 column denote an opposite direction of association.
[a]Genome-wide significance ($P < 5.0 \times 10^{-8}$). [b]Breslow-Day Test for homogeneity of the ORs: $P = 0.54$ for rs1518111, $P = 0.71$ for rs924080 and $P = 0.027$ for rs11248047.

Remmers et al. Nat Genet 2010; 698-702

Non-HLA Genes – Association Studies

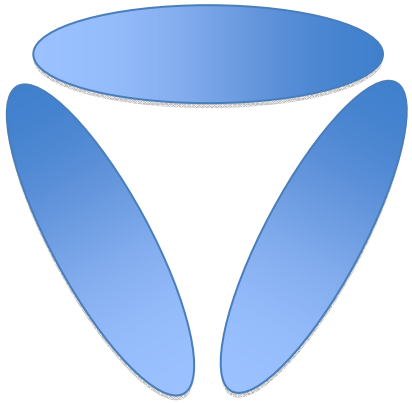
- **Cytokines, chemokines and their receptors**
  - TNF, IL-1 cluster, IL-6, IL-8, IL-10, IL-12, IL-17F, IL-18, CCR5
- **Other immune response genes**
  - NRAMP1, CTLA4, MBL, FCN2, SUMO4, FCRL3, CD94/NKG2A, *PTPN22*, CD28
- **PAMP receptors**
  - TLR4
- **Autoinflammatory polymorphisms**
  - MEFV, TNFRSF1A
- **Vascular and procoagulant polymorphisms**
  - ICAM1, eNOS, FV Leiden, Prothrombin, SOD
- **Others**
  - Cytochrome P450, NAT2

Behçet's disease – Multiple faces of inflammation

Genetic tendency

HLA-B51
  MICA, HLA-A26
IL-10
IL-23R/IL-12RB2

MEFV
eNOS
ICAM1
TNF, IL1 cluster



Environmental triggers

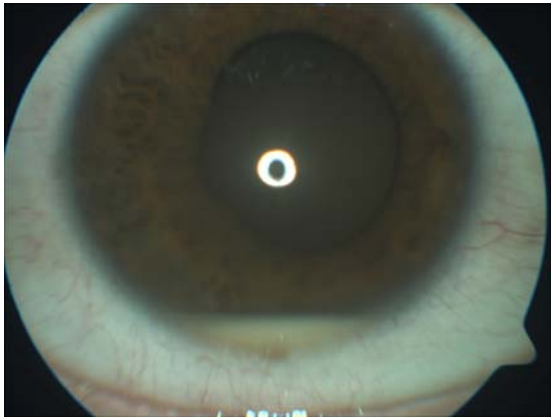
Skin and intestinal microbiome
Danger signals
Hormones
?

Increased / dysregulated inflammatory response

Defective suppression of inflammatory response
Recurrent inflammatory attacks
Neutrophils, monocyte/macrophages, $CD8^+$ T cells, $\gamma\delta$ T cells, NK cells
Dysregulated endothelial cell function / thrombotic tendency
Tissue specific differences in the regulatory mechanisms

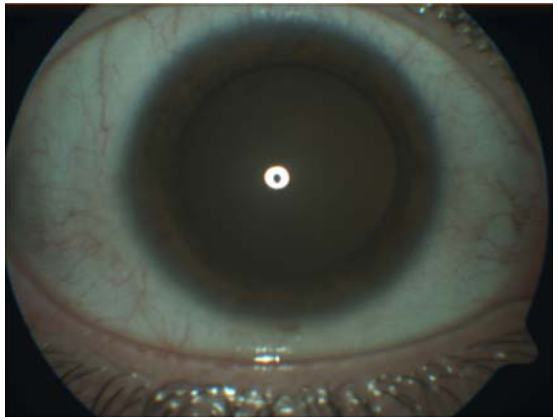
Behçet's disease – Treatment

- Administration of XOMA 052 appears safe, and regulation of IL-1β using XOMA 052 shows a rapid-onset effect for the treatment of intraocular inflammatory attack



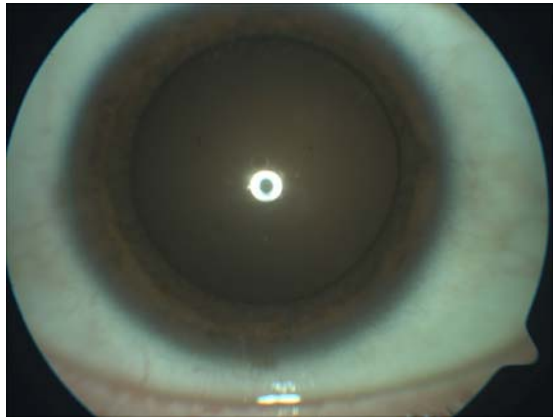
Day 0

Flare : 467 ph/msec
Anterior chmaber cell : 4+
Vitreous haze : 3+
Fundus score : 8



Day 1

Flare : 45 ph/msec
Anterior chamber cell : 4+
Vitreous haze : 3+
Fundus score : 4



Day 4

Flare : 62 ph/msec
Anterior chmaber cell : 4+
Vitreous haze : 2+
Fundus score : 4

Autoinflammatory Disorders - Reloaded

- Clinical disorders marked by
  - abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system,
  - with a significant host predisposition.

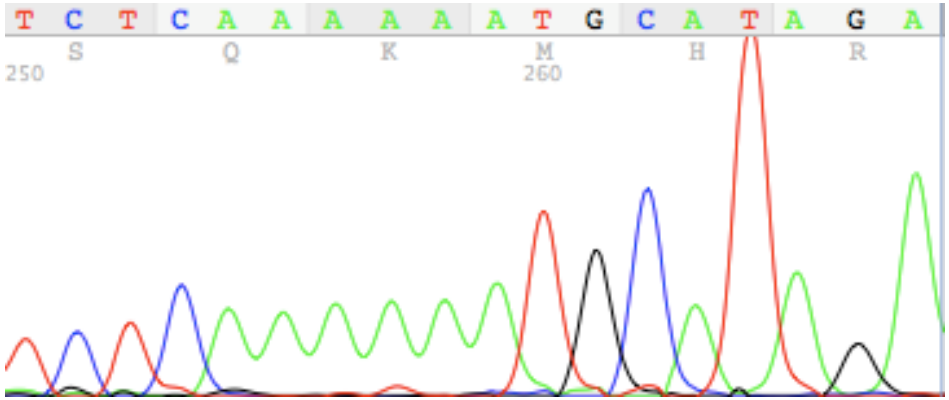
  - Mendelian diseases
  - Complex disorders

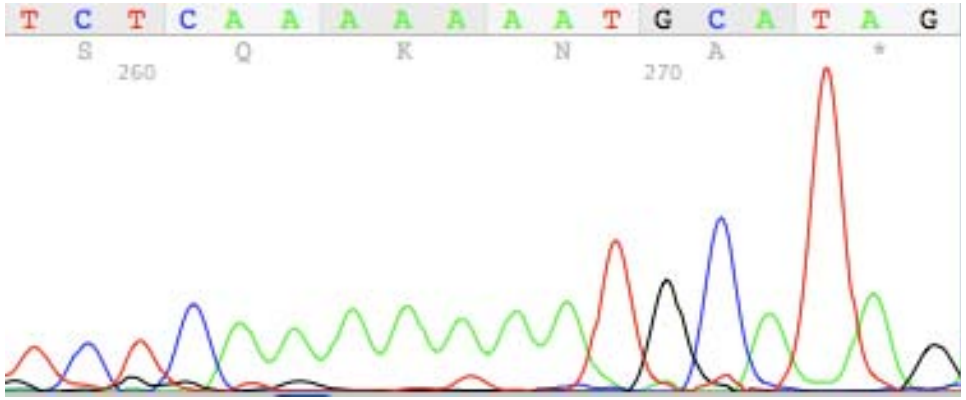
Kastner et al. Cell 2010; 140: 784-90

A New Pathway ?

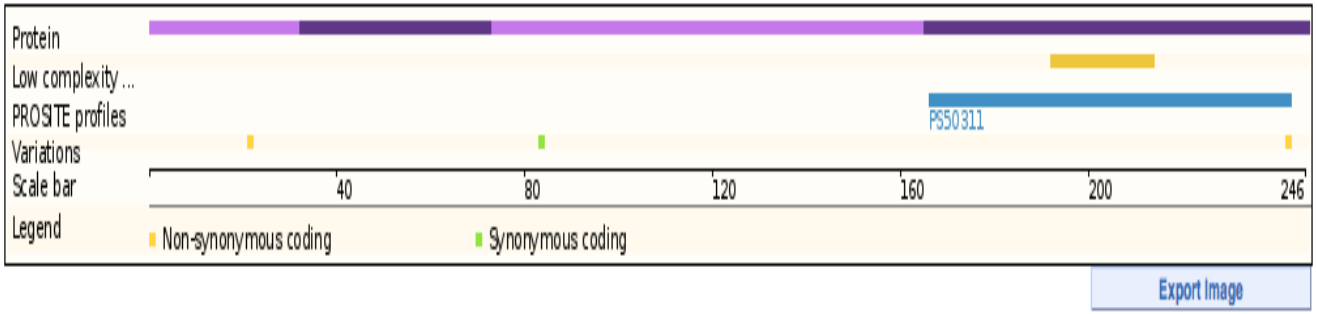
Autoinflammatory Syndrome Associated with Lymphedema

MDFIC (247 amino asid)





Exon 3

p.131 M>N

fs p.132stop