Behçet Hastalığı'nın İmmünopatogenezi

Ahmet Gül

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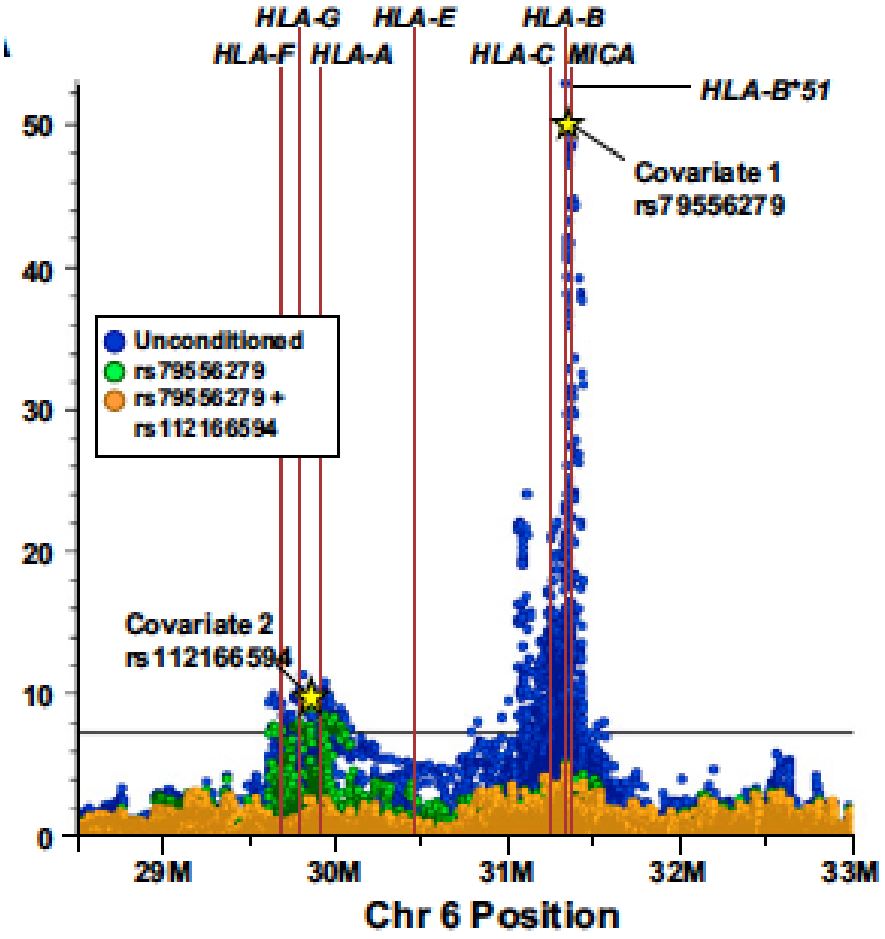


Konuşma Planı - İmmünopatogenez

- Behçet hastalığı kompleks (multifaktoriyal) bir hastalıktır
  - *Değişken damar vasküliti*
    Tromboz yatkınlığı
  - *Nötrofilik dermatoz*

Genetik /Epigenetik

→ HLA

→ HLA-dışı

Çevresel

→ Tetikleyici mikroplar

Bu konuşmayla ilgili herhangi bir çıkar çatışması bildirimi yoktur.

Environmental Triggers
Streptoccocal antigens, viruses, trauma

Genetic Susceptibility
*HLA-B*51, other HLA alleles, non-HLA polymorphisms*

Hyper-Inflammatory Response

Innate Immunity

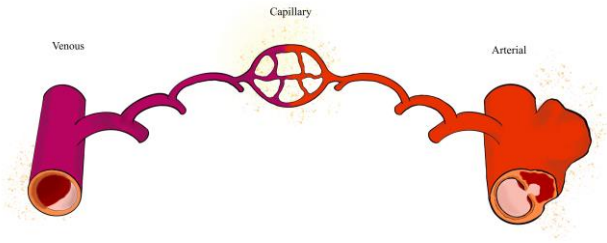
Activation of neutrophils, monocytes, NK cells and innate lymphocytes

Adaptive Immunity

Th1 polarization
Th17 polarization

Endothelial Activation

Thrombosis
Vasa vasorum vasculitis



Clinical Manifestations

Mucocutaneous
Aphthous ulcers
Papulopustular lesions
Nodular lesions

Ocular
Posterior/ Panuveitis

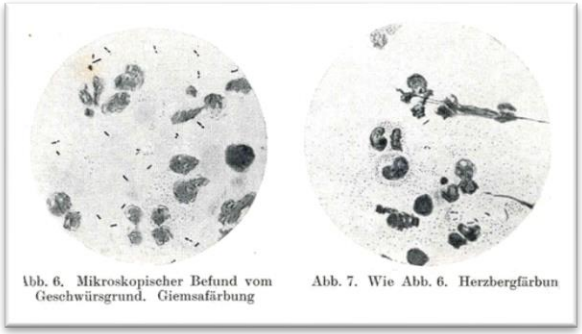
Vascular
Superficial thrombophlebitis
Deep vein thrombosis
Arterial aneurysms and occlusions

Neurologic
Parenchymal
Vascular

Musculoskeletal
Arthritis

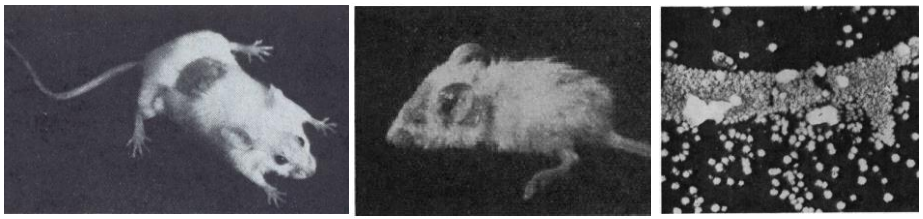
Gastrointestinal
Aphthous ulcers

Virütik olması muhtemel…



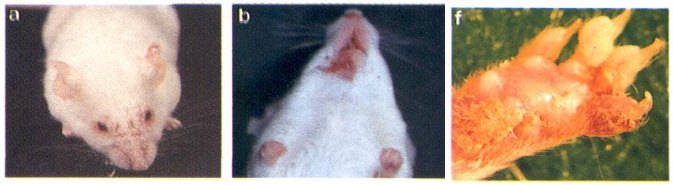
Dermatologische Wochenschrift 1937; 105:1152-7

- Spesifik bir virus hastalığı ?



Sezer FN. Am J Ophthalmol 1953; 36: 301-15.

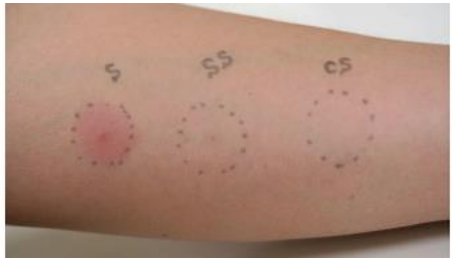
- Herpes simplex virusu
  - İmmün yanıt farklılıkları
  - ICR hayvan modeli



Sohn S, et al. Eur J Dermatol 1998; 8: 21-3.

Mikraki intan…

- Streptokok infeksiyonları
  - Ağız içi infeksiyonlar ve kolonizasyon
    - *S. sanguis, S. oralis, S. mitis, S. salivarius, …*
  - Diş çekimleri sonrasında hastalık bulgularında alevlenme
  - Deri injeksiyonu sonrasında alevlenme
  - Tükürük ile deri reaksiyonu



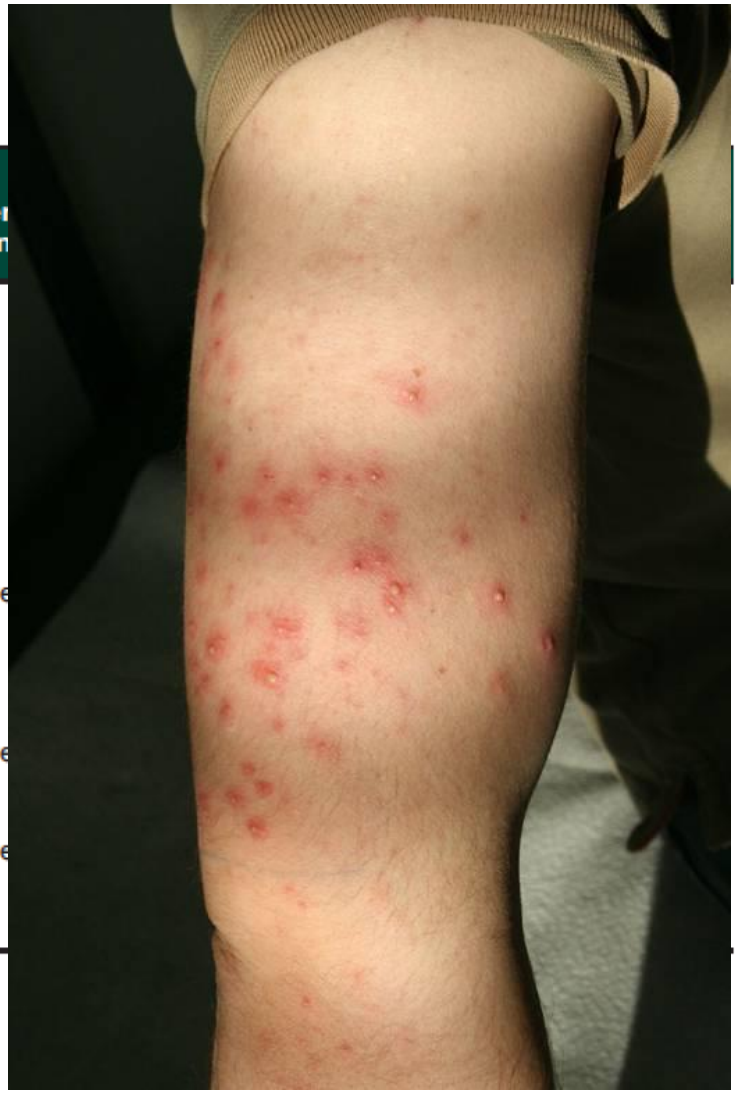
Kaneko et al. Eur J Dermatol. 2008;18:489-98.

Behçet Hastalığı – Çevresel Tetikleyiciler

- Bakteriler
  - Steptokoklar (S. sanguis KTH-1, tükürükteki diğer suşlar), pnömok, mikobakteri, diğerleri

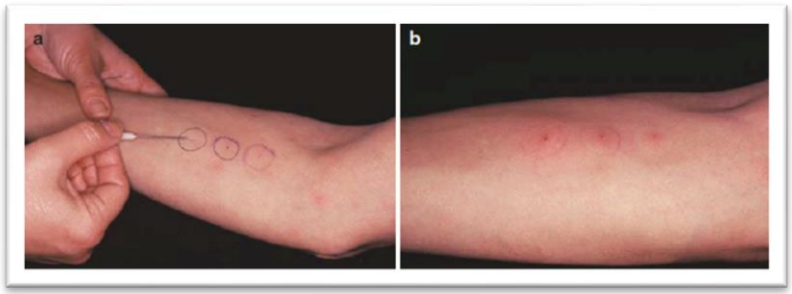
Age, years/ gender	Origin	Clinical presentation of BD	Disease duration, years	HLA allele	Pather testin
32/male	Swiss	Recurrent aphthous oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum, arthralgia, thrombophlebitis, cerebral venous thrombosis, retinochoroiditis	11	B51+	ND
41/male	Turkish	Recurrent aphthous oral ulcers, genital ulcers, arthritis, erythema nodosum, pseudofolliculitis	6	ND	Negative
41/female	Turkish	Recurrent aphthous oral ulcers, oligoarthritis	6	B51+	Negative
46/male	Turkish	Recurrent aphthous oral ulcers, pseudofolliculitis, thrombophlebitis, uveitis	15	B51+	Negative

Hügle T, et al. Rheumatology 2012;51:762764

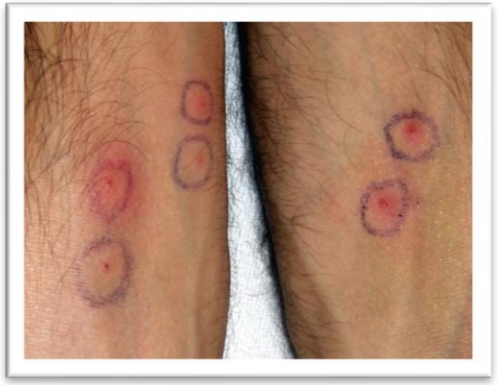


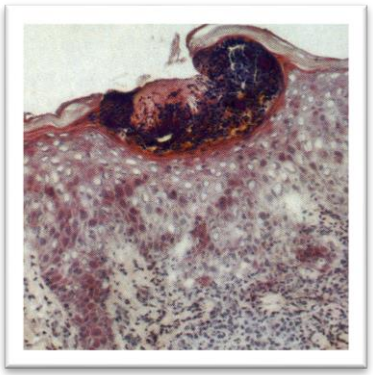
Behçet Hastalığı – Çevresel Tetikleyiciler (Paterji Reaksiyonu)

- 20G iğne travmasının yapıldığı yerde indürasyon ve eritem (48. saat)



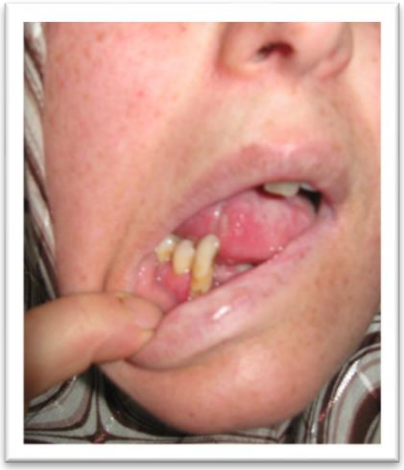
48. saat

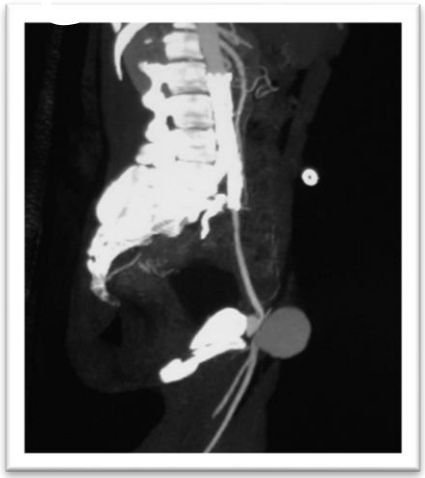




Gül et al. Br J Dermatol 1995; 132: 901-7.

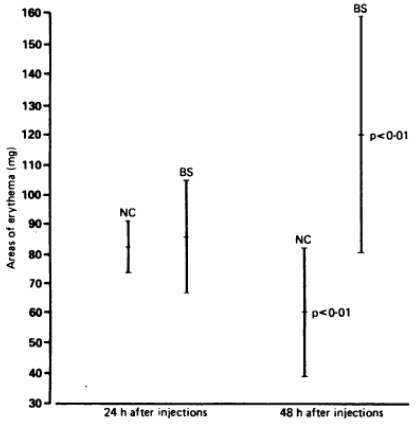
Lokal travma sonrası hastalık belirtilerinin gelişmesi





Sahutoglu et al. Rheumatol Int 2019

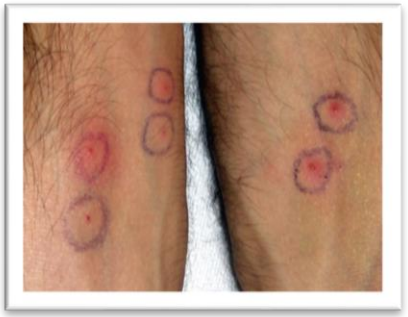
Ürik asit kristallerine karşı artmış reaksiyon



Cakir et al. ARD 1991; 50: 634-6

Behçet Hastalığı – Paterji Reaksiyonu

- Deri mikrobiyomu paterji reaksiyonunda rol oynuyor mu?
  - Pozitif test sonuçlarında azalma
    - %65-80%'lerden %20-40'a



- Künt ve kalın iğneler daha kuvvetli reaksiyon uyarır

  Dilsen et al. Ann Rheum Dis 1993; 52: 823-5

- Derinin cerrahi temizliği paterji reaksiyonuna olumsuz tesir eder

Pathergy reaction under different conditions

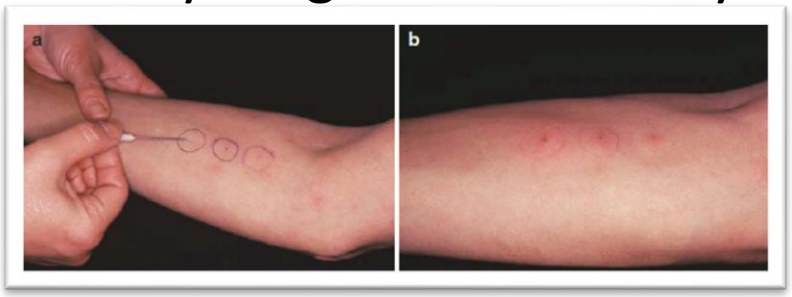
Povidone iodine (10%) (n=93)*				*Chlorhexidine (100%)† (n=47)*				*Chlorhexidine (4%)‡ (n=42)*			
Surgically cleaned forearm	*Conventionally cleaned forearm*	*First observer*	*Second observer*	*Surgically cleaned forearm*	*Conventionally cleaned forearm*	*First observer*	*Second observer*	*Surgically cleaned forearm*	*Conventionally cleaned forearm*	*First observer*	*Second observer*
–	+	23§	19§	–	+	14¶	13§	–	+	5‖	9‖
+	–	3§	3§	+	–	3¶	1§	+	–	2‖	3‖
+	+	22	22	+	+	14	14	+	+	22	11
–	–	45	49	–	–	16	19	–	–	13	19

*Interobserver agreement, 89·8%; κ value, 0·74. †Interobserver agreement, 88·3%; κ value, 0·743. ‡Interobserer agreement 79·2%; κ value, 0·58.
§Significant at p=0·01. ¶Significant at p=0·05. ‖Significant at p=0·25.

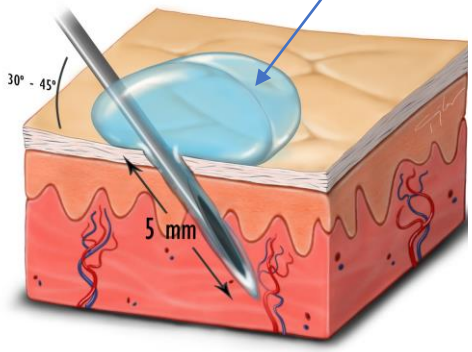
Fresko I, et al. Ann Rheum Dis 1993;52:619-20

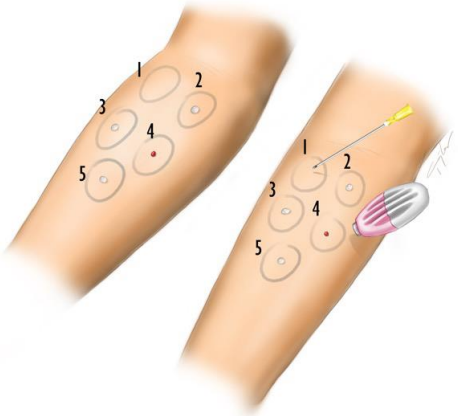
Behçet Hastalığı – Paterji Reaksiyonu

- İğne travmasının uyardığı inflamatuvar yanıt

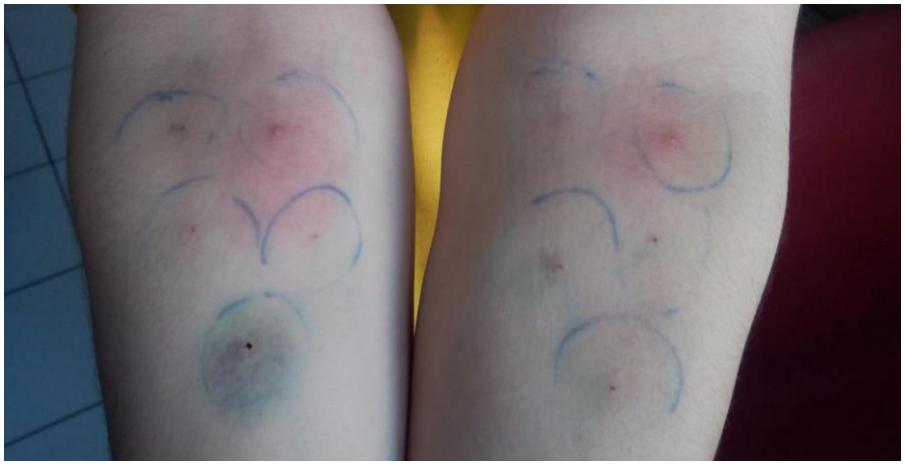


+ farklı ek uyarılar
(Alum, ATP, Pnömokok aşısı polisakkaritleri, …)





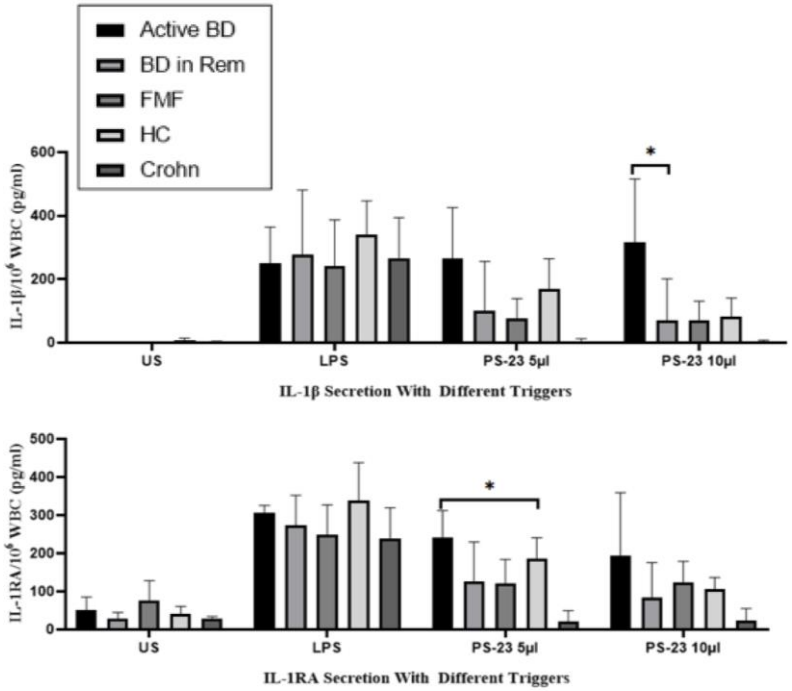
- ***Streptococcus pneumonia* polisakkarid antijenleriyle test duyarlılığında belirgin artış**
  - Peptid yapısında antijen ve adjuvan yok
  - Streptokok PS antijenleri için standart kaynak



Behçet Hastalığı – Paterji Reaksiyonu

- Streptococcus pneumonia polisakkarid antijenleriyle test duyarlılığında belirgin artış, özgüllük ise korunmuş durumda
- Aktif hastalarda daha yüksek pozitiflik
  - *Epigenetik değişiklikler?*

Methods / Groups	20G	20G + PS-23	21G lancet	21G lancet+ PS-23	20G + Alum	20G + ATP
Active BD (n, %)	4/66 (6,1)	**53/66 (80,3)**	3/64 (4,7)	**15/50 (30,0)**	1/20 (5,0)	0/16
BD in Remission (n, %)	0/18	1/18 (5,6)	0/18	0/8	0/10	0/10
BD all (n, %)	4/84, (4,8)	**54/84 (64,3)**	3/82 (3,7)	**15/58 (25,9)**	1/30 (3,3)	0/26
Healthy controls (n, %)	0/24	0/24	0/23	0/6	0/21	0/18
ROU (n, %)	0/65	0/65	0/63	0/30	0/45	0/35
Rheumatic disorders n, (%)	0/28	0/28	0/27	0/12	0/21	0/16
No criteria (n, %)	0/61	0/61	0/59	0/31	0/39	0/30
IBD (n, %)	0/11	0/11	0/11	0/2	0/11	0/9



Çalışmada kullanılan değişik uyarıcılarla Tam Kan Çalışması (Whole Blood Assay) kullanılarak sitokin üretimlerinin incelenmesi

Behçet Hastalığı – Çevresel Tetikleyiciler

- Mikrobiyota değişiklikleri ve disbiyozis bulguları

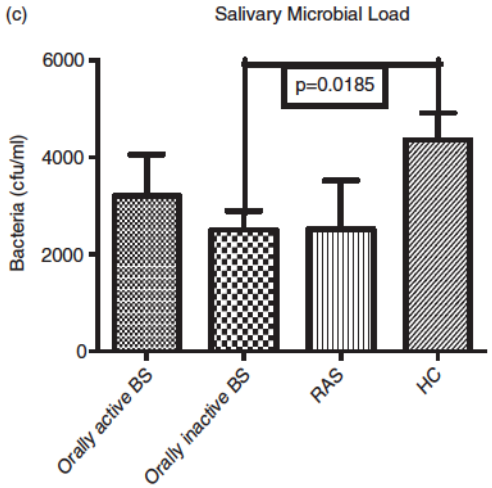
Journal of Oral Microbiology

ORIGINAL ARTICLE

The oral mucosal and salivary microbial community of Behçet's syndrome and recurrent aphthous stomatitis

Noha Seoudi[1], Lesley A. Bergmeier[1], Francis Drobniewski[2,3], Bruce Paster[4,5] and Farida Fortune[1]*

[1]Centre for Clinical and Diagnostic Oral Sciences, Institute of Dentistry, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [2]Centre for Immunology and Infectious Diseases, Blizard Institute of Cell and Molecular Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [3]Department of Infectious Diseases, Imperial College, London, UK; [4]Department of Microbiology, The Forsyth Institute, Boston, MA, USA; [5]Department of Microbiology, Harvard School of Dental Medicine, Boston, MA, USA



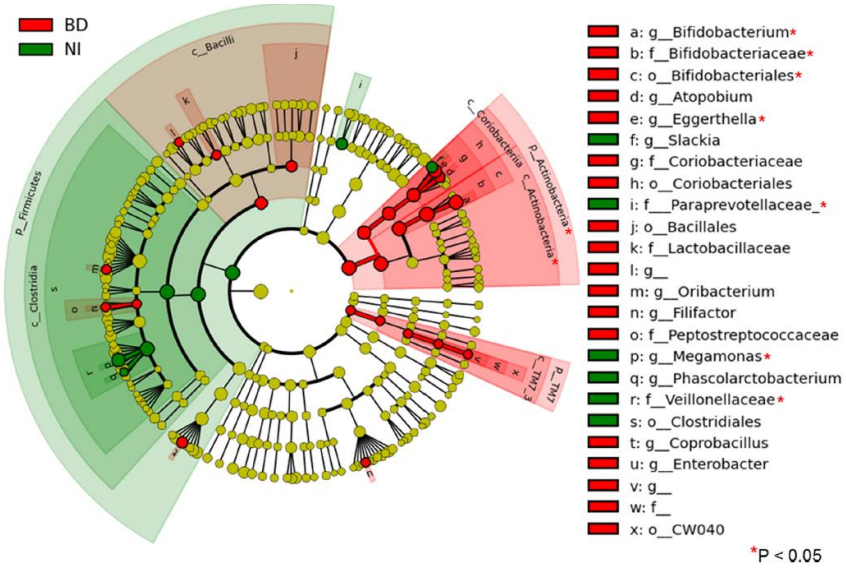
J Oral Microbiol 2015, 7: 27150

RESEARCH ARTICLE

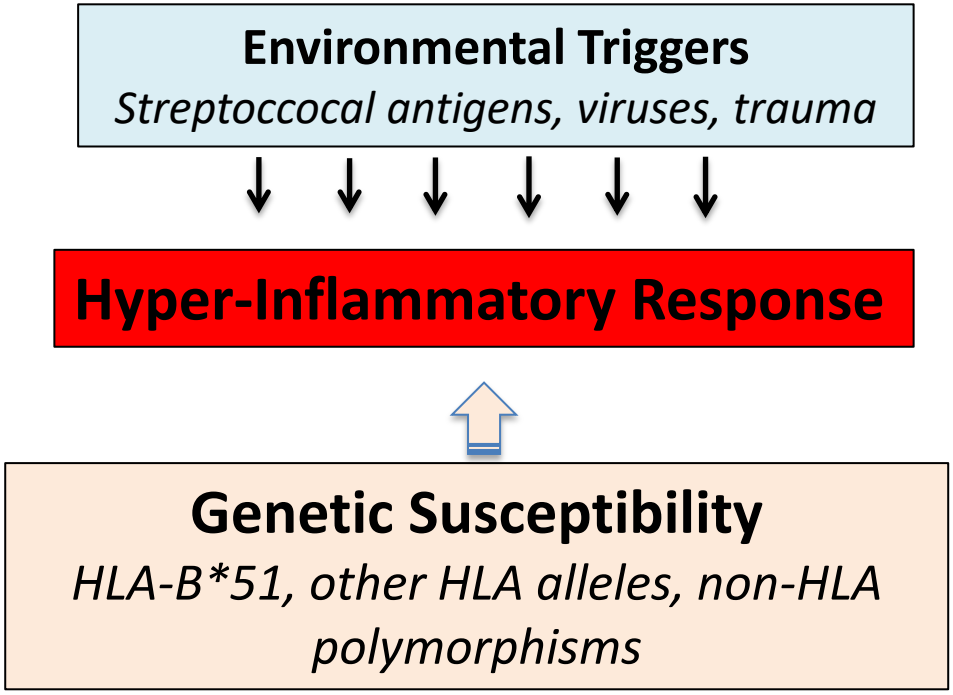
Bifidobacteria Abundance-Featured Gut Microbiota Compositional Change in Patients with Behcet's Disease

Jun Shimizu[1], Takao Kubota[2], Erika Takada[1], Kenji Takai[1], Naruyoshi Fujiwara[1], Nagisa Arimitsu[1], Yuji Ueda[1], Sueshige Wakisaka[1], Tomoko Suzuki[1], Noboru Suzuki[1]*

1 Department of Immunology and Medicine, St. Marianna University School of Medicine, Kawasaki, Japan,
2 Department of Medicine, the Japan Self Defense Forces Central Hospital, Tokyo, Japan

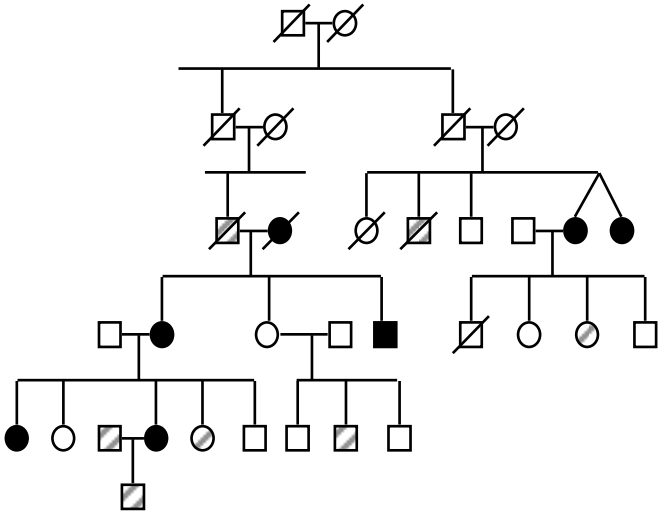


PLoS ONE 11(4): e0153746.


Environmental Triggers
Streptoccocal antigens, viruses, trauma
Hyper-Inflammatory Response
Genetic Susceptibility
HLA-B*51, other HLA alleles, non-HLA polymorphisms

Behçet Hastalığı – Genetik Yatkınlık

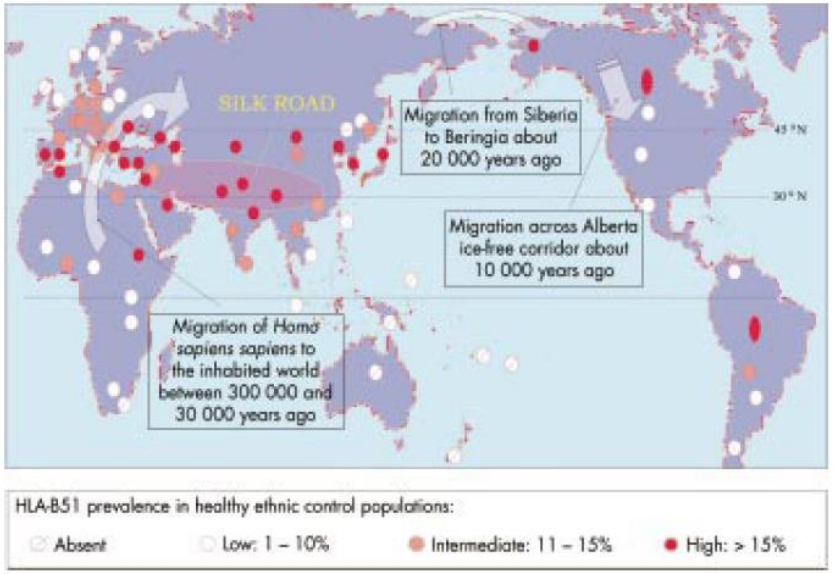
Ailevi Birikim



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

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

Coğrafi Dağılım



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

HLA-B*51 ile İlişki

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.

TABLE I—FREQUENCY OF HL-A ANTIGENS IN BEHÇET'S DISEASE

HL-A antigen	Controls (n = 78)	Behçet's disease (n = 21)	χ^2	P
1	0 (0%)	0 (0%)	..	
2	30 (38·5%)	12 (57·1%)	2.36	0·1 < P < 0·2
3	3 (3·8%)	0 (0%)	0·04	
9	41 (52·6%)	8 (38·1%)	1·39	
10	16 (20·5%)	7 (33·3%)	1·52	
11	11 (14·1%)	2 (9·5%)	0·04	
5	24 (30·8%)	15 (71·4%)	11·46	P < 0·0007
4c	32 (41·0%)	19 (90·5%)	14·30	P < 0·0002
7	8 (10·3%)	2 (9·5%)	0·10	
8	1 (1·3%)	1 (4·8%)	0·10	
12	7 (9·0%)	0 (0%)	0·89	
13	1 (1·3%)	0 (0%)	0·50	
w10	14 (17·9%)	3 (14·3%)	0·00	

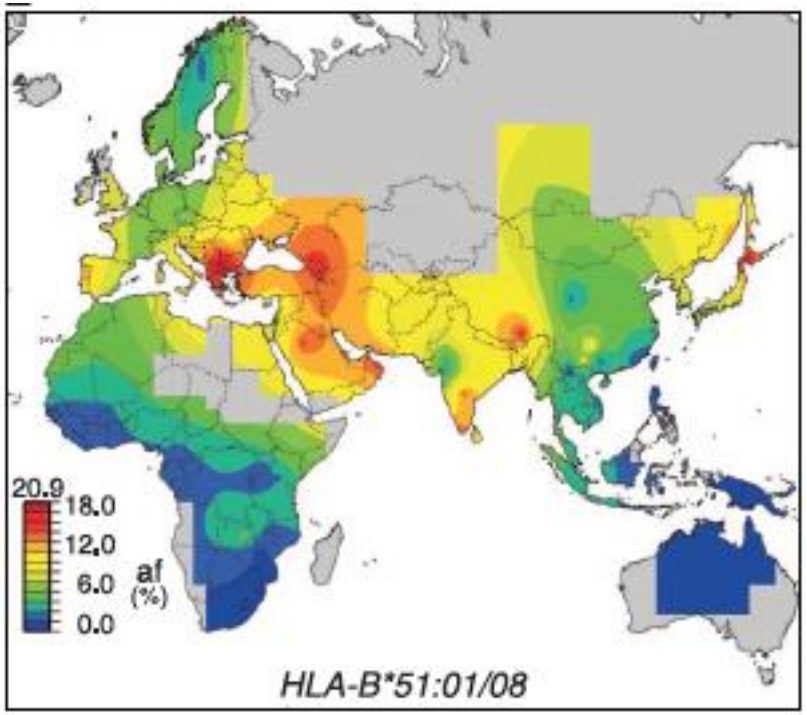
The Shaping of Modern Human Immune Systems by Multiregional Admixture with Archaic Humans

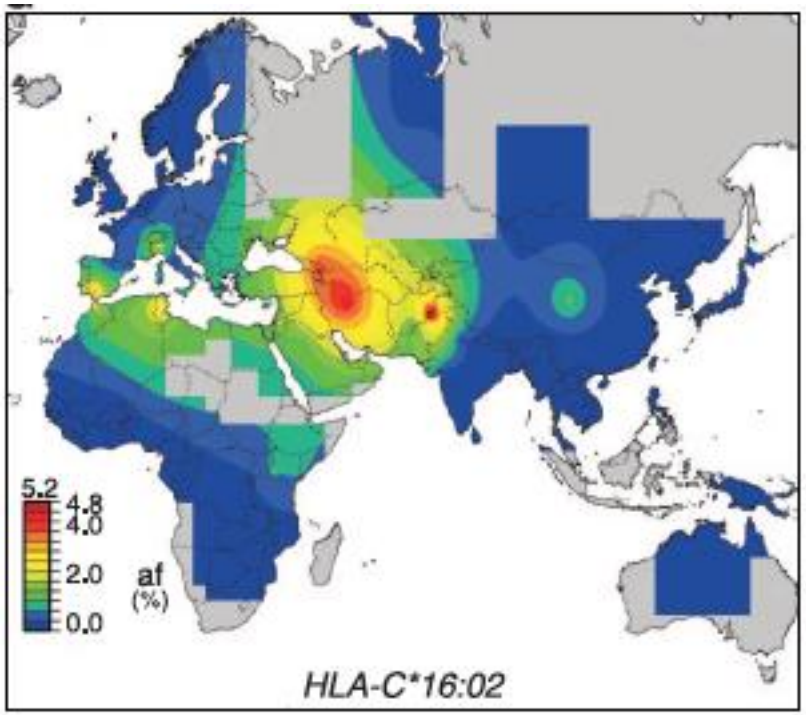
Laurent Abi-Rached *et al.*

Science **334**, 89 (2011);

A

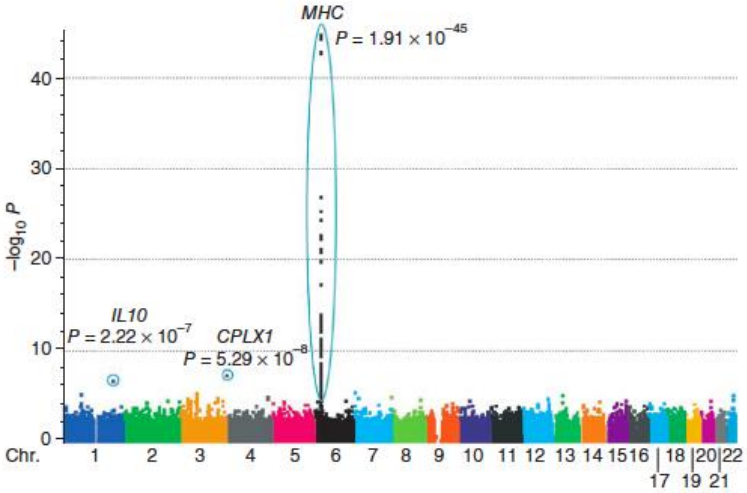
Neandertal *HLA class I*							
Allele				Closest modern type		Next best type	
Locus	#	Coverage	Reads (#)	Name	Differences	Name	Differences
HLA-A	1	30%	40	A*02 [not :05]	0	A*68	14
	2	16%	16	A*26/*66	0	A*34	2
HLA-B	1	28%	34	B*07:02/03/06[§]	0	B*48	2
	2	32%	43	B*51:01/08	0	B*52/*78	2
HLA-C	1	35%	52	C*07:02[§]	0	C*08/*18	46
	2	25%	31	C*16:02[§]	0	C*05	9



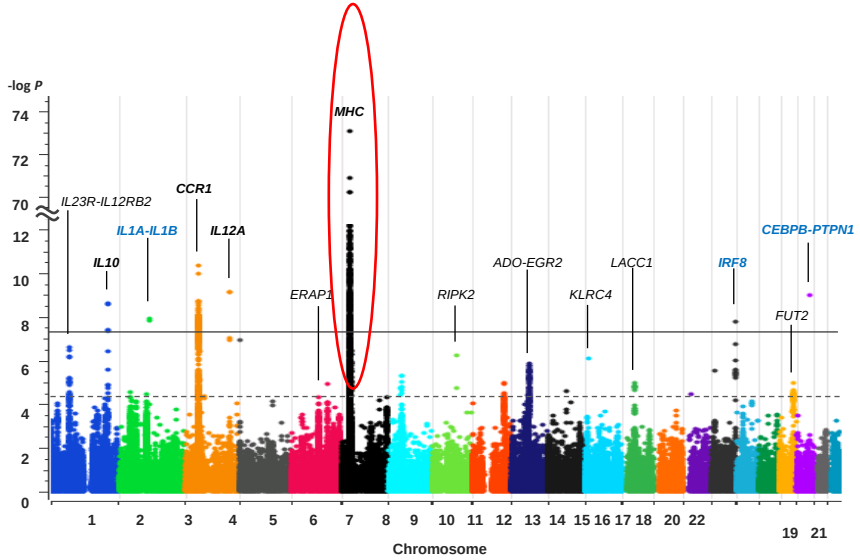


Behçet Hastalığı – Genetik Yatkınlık

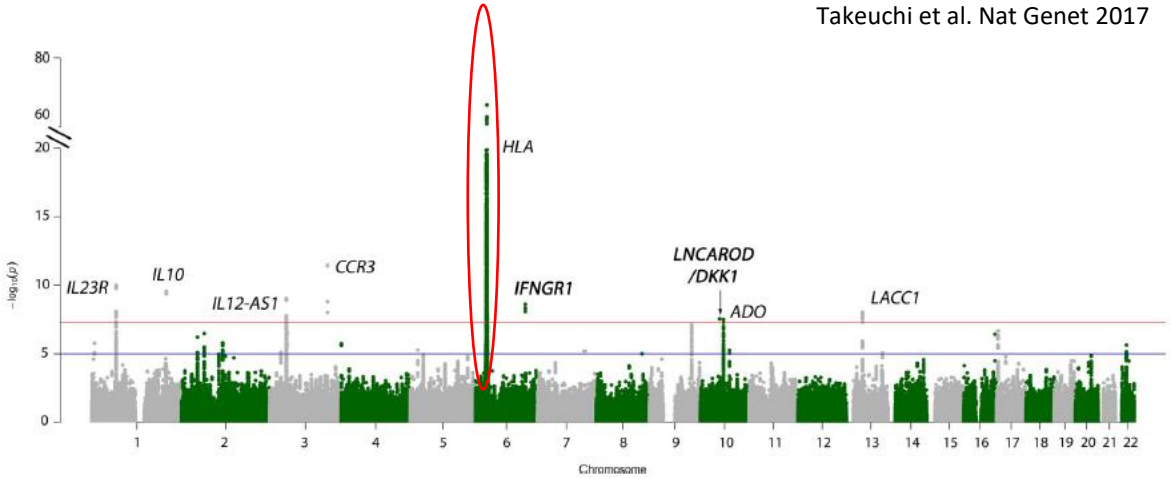
- Behçet hastalığına genetik yatkınlık oluşturan en güçlü neden HLA-B*51 allelidir



Remmers et al. Nat Genet 2010; 42: 698-702



Takeuchi et al. Nat Genet 2017



Ortiz Fernández L, et al. Arthritis Rheumatol 2021;73:1244-52

Behçet Hastalığı – HLA-B*51

CURRENT OPINION

The association of Behçet's syndrome with HLA-B51 as understood in 2021

Mitsuhiro Takeno

Curr Opin Rheumatol 2022;34:4-9

Table 1. Prevalence of Behçet's syndrome and frequency of HLA-B*51 in various countries

	Prevalence (/100000)	HLA-B*51 (%)	
		Patients with Behçet's syndrome	Control
Japan	7.0–14.6	58.9	13.8
Iran	16.7–80.0	61.9	28.7
Saudi-Arabia	19.5	76.9	22.2
Turkey	80.0–421.0	75.0	24.7
Italy	3.8	57.4	19.2
Spain	5.6–7.5	36.2	19.6
German	0.6–1.47	57.6	12.3

- HLA-B*51 tanı testi olarak kullanılmamalıdır

Table 2. Clinical clusters in Japanese patients with Behçet's syndrome

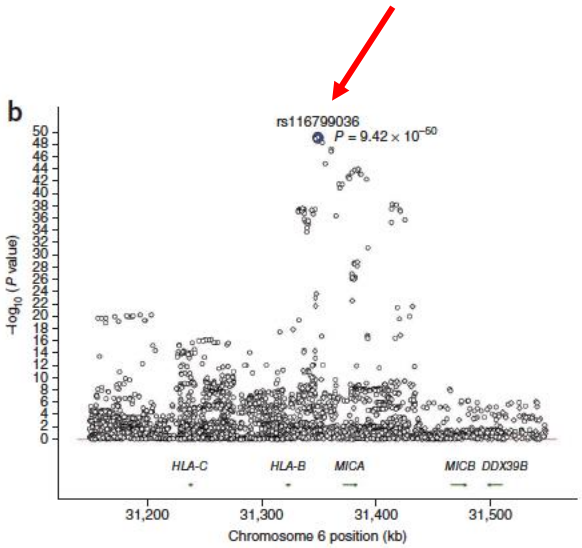
Characteristic clinical presentation	Cluster 1 Mucocutaneous dominant	Cluster 2 Mucocutaneous with arthritis	Cluster 3 Ocular involvement	Cluster 4 Neurological involvement	Cluster 5 Gastrointestinal involvement
Age at onset (years, mean ± SD)	33.6 ± 10.3	37.4 ± 12.3	40.5 ± 12.8	34.8 ± 10.4	37.4 ± 12.3
Sex (ratio of female) (%)	64.3	75.6	31.5	47.8	57.1
HLA-B*51 (%)	52.1	50.9	50.0	52,7	33.0

SD, standard deviation.

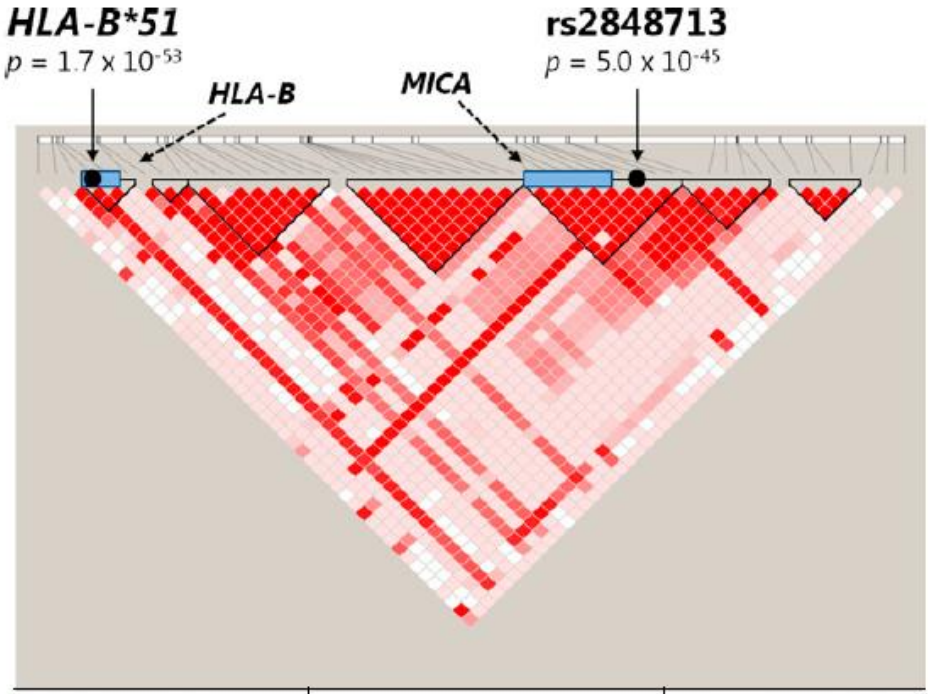
- Klinik fenotiplerin belirlenmesinde rolü olabilir

Behçet Hastalığı – MHC Sınıf I Bölgesi ile İlişki

- HLA-B*51 BH ile ilişkili uzun LD gösteren HLA-B/MICA haplotipinin en önemli parçasıdır



Hughes T, et al. Nat Genet 2013;45:319-24



Extended haplotype	OR (95%CI)	p	Case f	Control f
*HLA-B*51* positive	2.81 (2.44, 3.25)	9.4E-47	0.321	0.144
*HLA-B*51* negative	0.96 (0.72, 1.27)	0.764	0.042	0.044

Ombrello MJ, et al. PNAS 2014

HLA-B*51 – İlişkili Olası Patogez Mekanizmaları

Received: 16 August 2019 | Revised: 6 November 2019 | Accepted: 7 December 2019

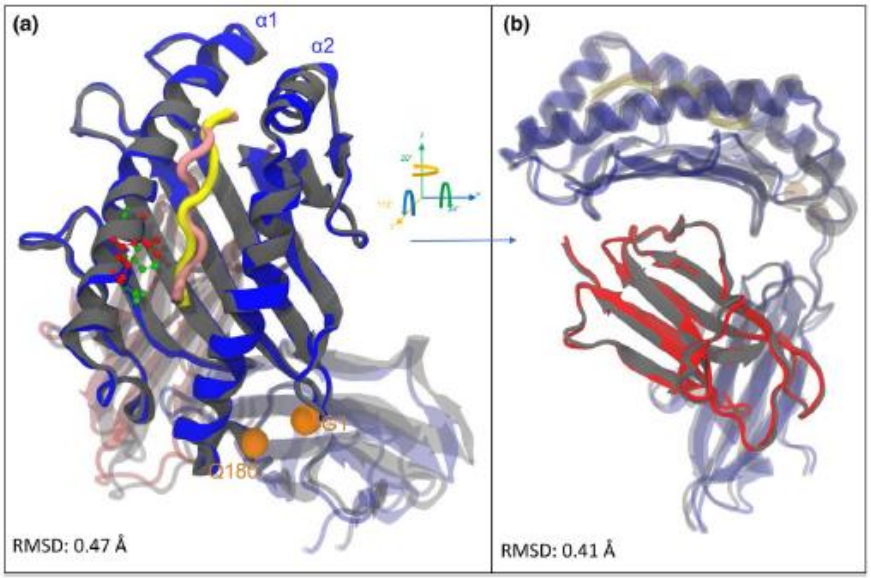
DOI: 10.1111/cbdd.13658

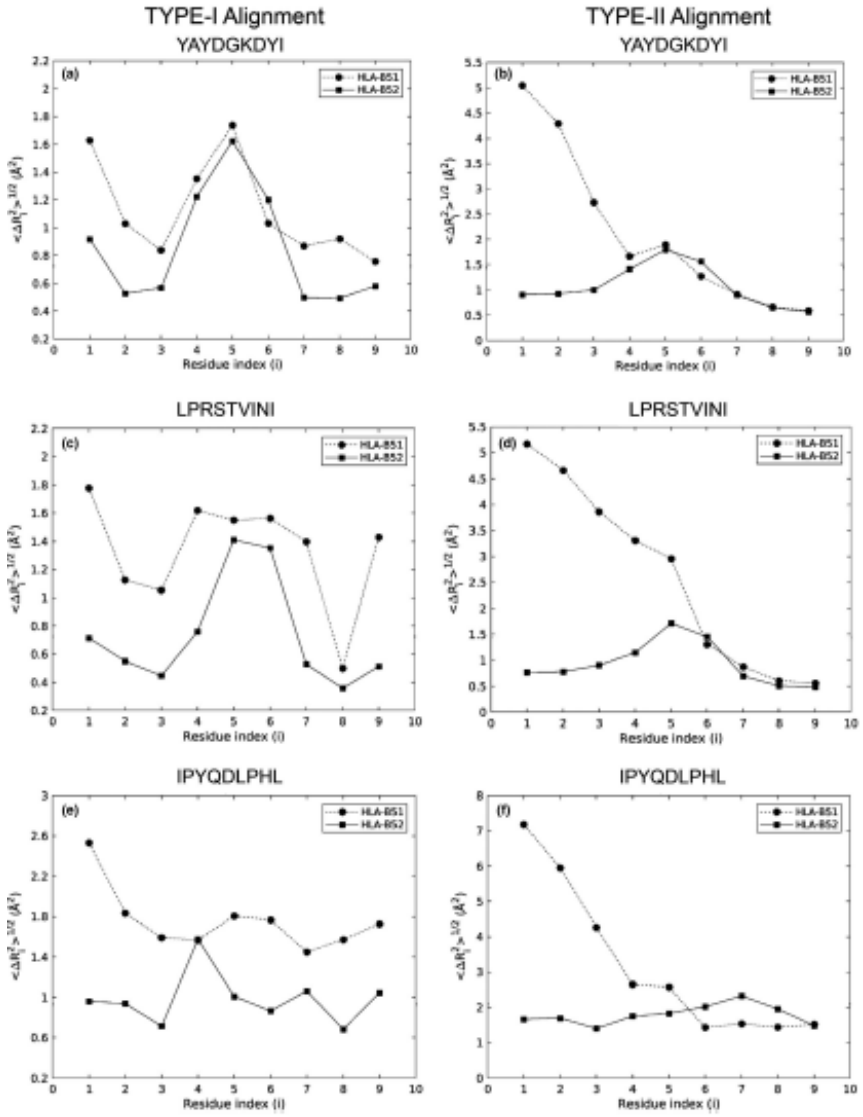
SPECIAL ISSUE - BAUDD CONFERENCE

WILEY

Molecular dynamics simulations provide molecular insights into the role of HLA-B51 in Behçet's disease pathogenesis

Mert Gur[1] | Mert Golcuk[1] | Ahmet Gul[2] | Burak Erman[3]





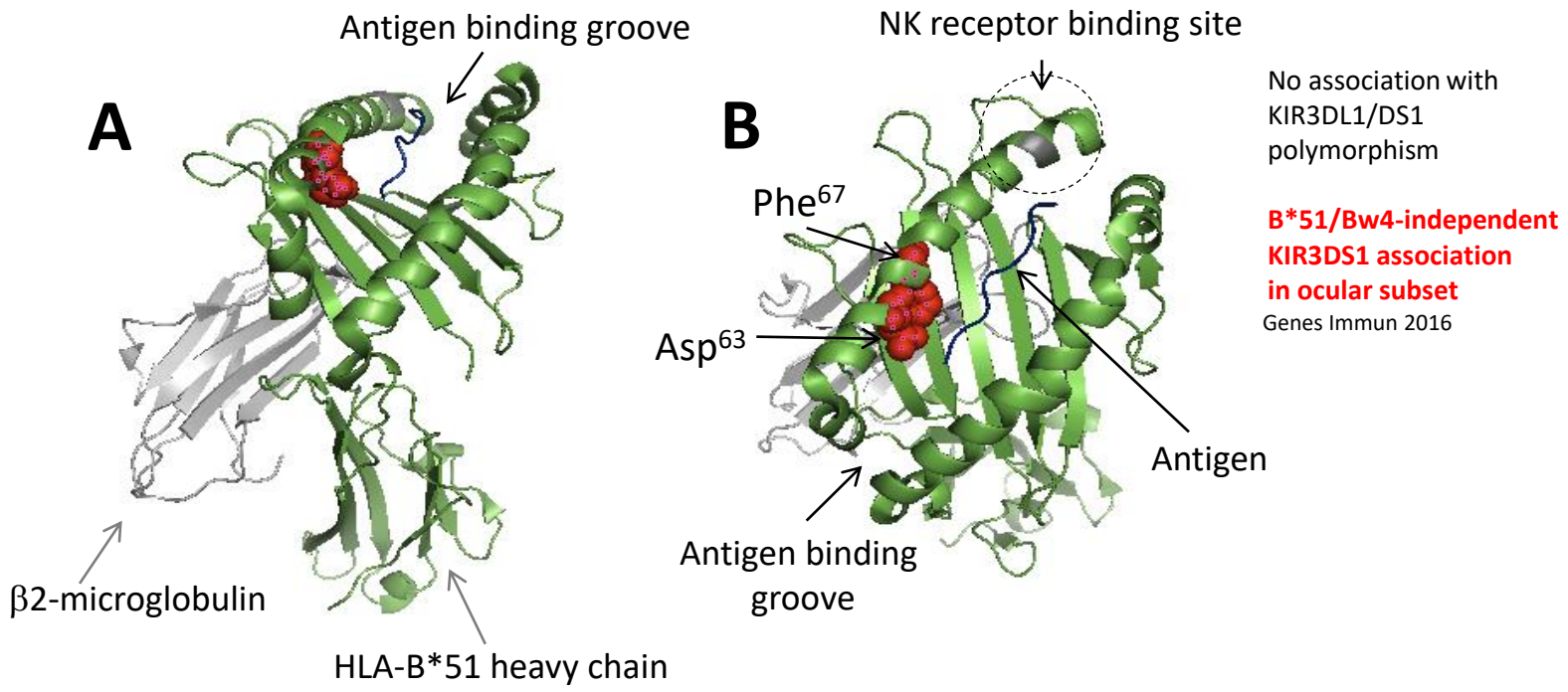
HLA-B*51 – İlişkili Olası Patogez Mekanizmaları

Belirli “peptid”lerin sitotoksik CD8⁺ T hücrelerine sunulması

EDİNSEL

NK hücleri, CD8⁺ hücreler, γδ⁺ T hücreleri üzerindeki reseptörlere bağlanma

DOĞAL ve EDİNSEL



No association with KIR3DL1/DS1 polymorphism

B*51/Bw4-independent KIR3DS1 association in ocular subset

Genes Immun 2016

Gul A. Semin Immunopathol 2015;37:413-8.

HLA-B*51 – İlişkili Olası Patogez Mekanizmaları

KIR3DL1/S1 Allotypes Contribute Differentially to the Development of Behçet Disease

Harry Petrushkin,*,† Paul J. Norman,‡ Emma Lougee,§ Peter Parham,¶ Graham R. Wallace,‖ Miles R. Stanford,# and Farida Fortune†

Table III. The effects of the functional genotype *KIR3DL1/S1* combinations

KIR3DL/S1 allele		HC n=433, BD n=256							
Allele 1	**Allele 2**	**HC (n)**	**HC (%)**	**BD (n)**	**BD (%)**	***P***	***Pc***	**OR**	**95% CI**
3DL1^{HIGH}	*3DL1*^{HIGH}	85	19.63	60	23.44	NS	NS	1.19	0.82-1.74
3DL1^{HIGH}	*3DL1*^{LOW}	71	16.40	36	14.06	NS	NS	0.86	0.56-1.32
3DL1^{HIGH}	*3DL1*^{NULL}	76	17.55	24	9.38	**0.0035**	**0.0350**	0.53	0.33-0.87
3DL1^{HIGH}	*3DS1*	83	19.17	39	15.23	NS	NS	0.79	0.52-1.21
3DL1^{LOW}	*3DL1*^{LOW}	17	3.93	7	2.73	NS	NS	0.70	0.28-1.7
3DL1^{LOW}	*3DL1*^{NULL}	23	5.31	16	6.26	NS	NS	1.18	0.61-2.27
3DL1^{LOW}	*3DS1*	24	5.54	35	13.67	**0.0004**	**0.0040**	2.47	1.43-4.25
3DL1^{NULL}	*3DL1*^{NULL}	10	2.31	7	2.73	NS	NS	1.18	0.45-3.15
3DL1^{NULL}	*3DS1*	30	6.93	23	8.98	NS	NS	1.30	0.74-2.29
3DS1	*3DS1*	14	3.23	9	3.52	NS	NS	1.09	0.46-2.55

J Immunol 2019; 203:1629-1635

- Artmış NK hücre aktivitesiyle ilişki?

HLA-B*51 – İlişkili Olası Patogez Mekanizmaları

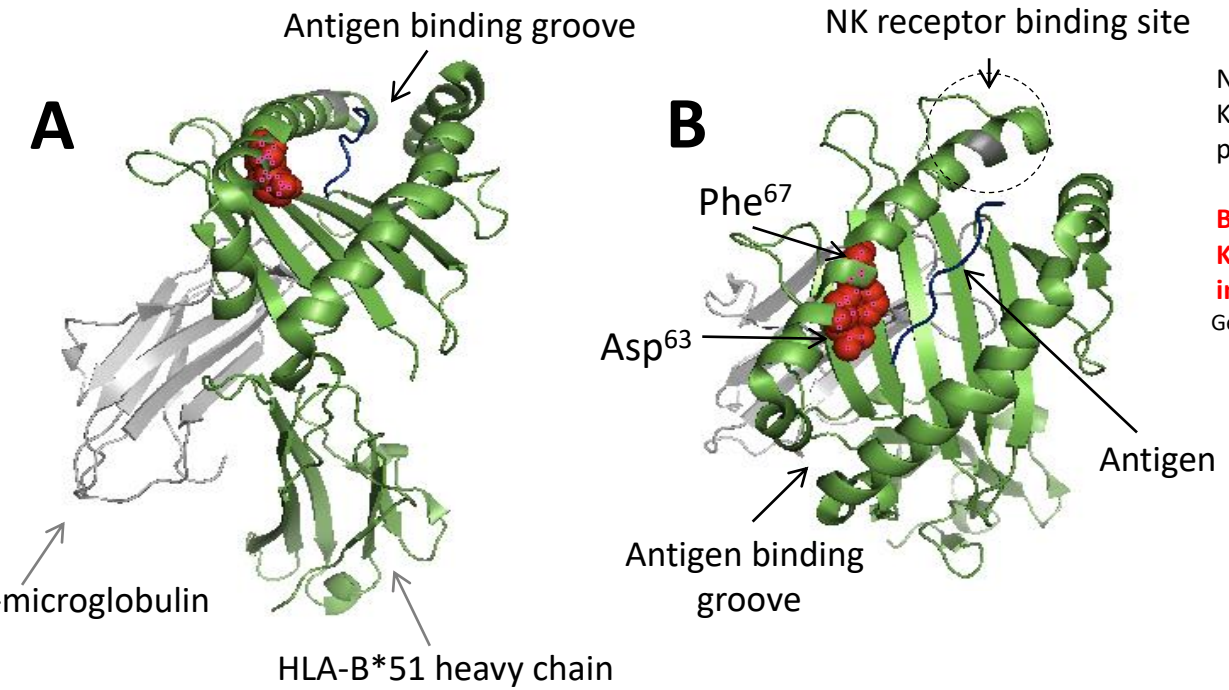
Belirli “peptid”lerin sitotoksik CD8⁺ T hücrelerine sunulması

EDİNSEL

NK hücleri, CD8⁺ hücreler, γδ⁺ T hücreleri üzerindeki reseptörlere bağlanma

DOĞAL ve EDİNSEL

Dokuya özgü “Peptid”ler



No association with KIR3DL1/DS1 polymorphism

B*51/Bw4-independent KIR3DS1 association in ocular subset
Genes Immun 2016

Protein katlanma sorunları ve ER stresi → **DOĞAL OTOİNFLAMASYON**

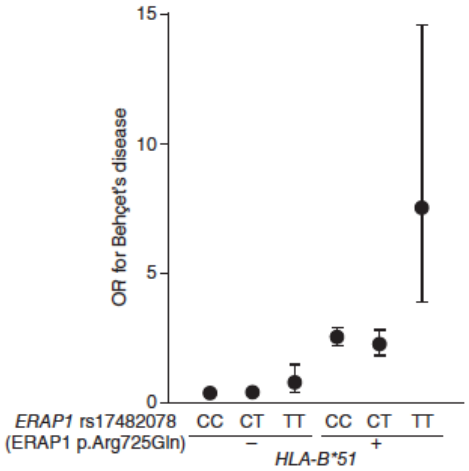
Gul A. Semin Immunopathol 2015;37:413-8.

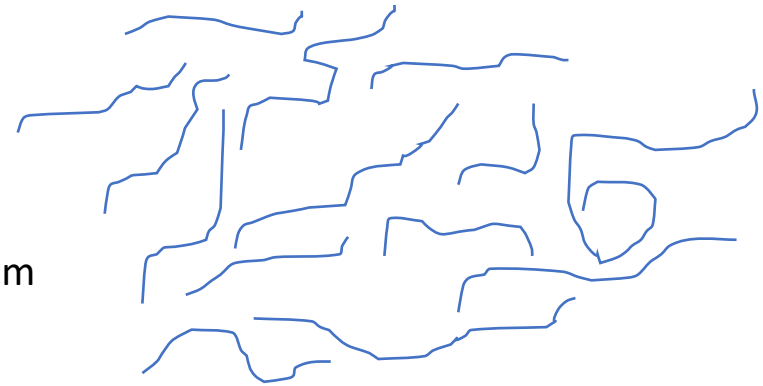
Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between *HLA-B*51* and *ERAP1*

Yohei Kirino[1,2,12], George Bertsias[1,3,12], Yoshiaki Ishigatsubo[2], Nobuhisa Mizuki[4], Ilknur Tugal-Tutkun[5], Emire Seyahi[6], Yilmaz Ozyazgan[7], F Sevgi Sacli[6], Burak Erer[8], Hidetoshi Inoko[9], Zeliha Emrence[10], Atilla Cakar[10], Neslihan Abaci[10], Duran Ustek[10], Colleen Satorius[1], Atsuhisa Ueda[2], Mitsuhiro Takeno[2], Yoonhee Kim[11], Geryl M Wood[1], Michael J Ombrello[1], Akira Meguro[4], Ahmet Gül[8,13], Elaine F Remmers[1,13] & Daniel L Kastner[1,13]

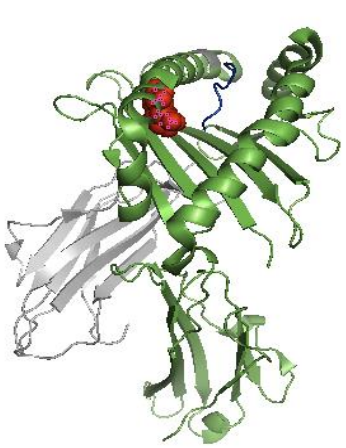
Kirino et al. Nat Genet 2013;45:202-7

Kendi proteinlerimizin yıkımlarıyla ortaya çıkan peptidler
ve diğer sitoplazmik proteinlerin yıkım ürünleri





Sitozol
Protezom
İmmünoproteazom



HLA Sınıf I

Endoplasmik Retikulum
ERAP1
ERAP2

ERAP1 Haplotipleri ve Hastalık Riski

Coding haplo-type[a]	Amino acid position 12	56	127	276	346	349	528	575	725	730	Hap freq cases n (%)	Hap freq ctrls n (%)	P-value[b]	Homozyg hap odds ratio (95% CI)
Hap1	Ile[c]	Glu	Pro	Ile	Gly	Met	Lys	Asp	Arg	Gln	388 (10.3)	383 (10.9)	4.60E-01	0.95 (0.81-1.10)
Hap2	Thr	Glu	Arg	Ile	Gly	Met	Lys	Asp	Arg	Gln	458 (12.2)	491 (13.9)	2.82E-02	0.86 (0.75-0.98)
Hap3	Thr	Glu	Arg	Ile	Gly	Met	Lys	Asp	Arg	Glu	501 (13.4)	454 (12.9)	5.59E-01	1.04 (0.91-1.19)
Hap5	Thr	Glu	Arg	Ile	Asp	Met	Arg	Asp	Arg	Glu	321 (8.6)	292 (8.3)	6.85E-01	1.03 (0.88-1.22)
Hap6	Thr	Glu	Pro	Ile	Gly	Met	Arg	Asp	Arg	Glu	513 (13.7)	431 (12.2)	6.87E-02	1.14 (0.99-1.30)
Hap7	Thr	Lys	Pro	Ile	Gly	Met	Arg	Asp	Arg	Glu	106 (2.8)	85 (2.4)	2.72E-01	1.18 (0.88-1.57)
Hap8	Thr	Glu	Pro	Met	Gly	Met	Arg	Asp	Arg	Glu	790 (21.1)	840 (23.9)	4.28E-03	0.85 (0.76-0.95)
Hap10	Thr	Glu	Pro	Ile	Gly	Val	Arg	Asn	Gln	Glu	631 (16.8)	504 (14.3)	3.23E-03	1.21 (1.07-1.38)

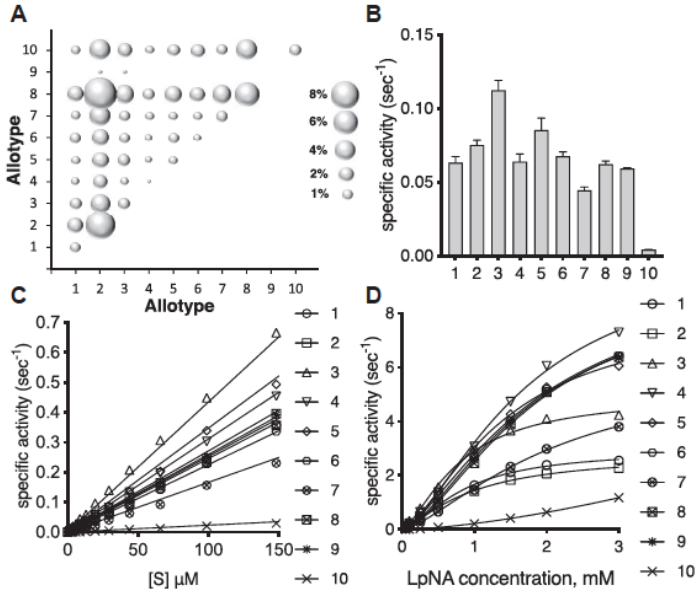
Takeuchi et al. ARD 2016 75: 2208–2211.

Table 2 Two risk factor analysis for Behçet's disease in 1876 cases and 1761 controls from Turkey

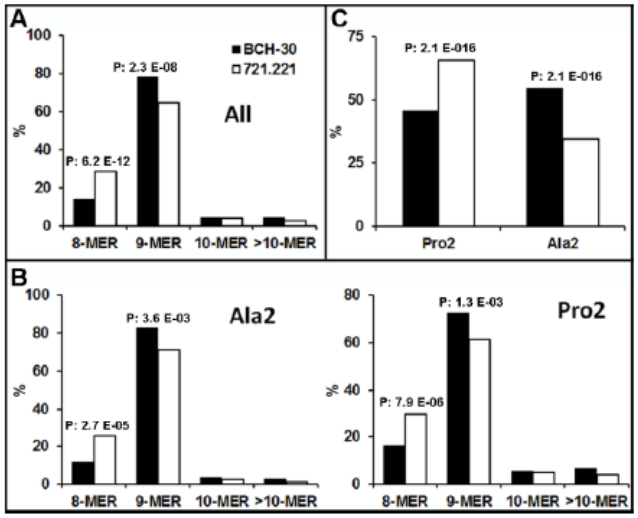
HLA-B*51/ homozygous Hap10	Number of cases, n (%)	Number of controls, n (%)	OR (95% CI)	p Value
–/–	659 (35.1)	1171 (66.5)	1.00 Reference	Reference
–/+	13 (0.7)	21 (1.2)	1.10 (0.55 to 2.21)	7.90×10^{-01}
+/–	1130 (60.2)	557 (31.6)	3.60 (3.14 to 4.14)	2.87×10^{-75}*
+/+	74 (3.9)	12 (0.7)	10.96 (5.91 to 20.32)	4.80×10^{-20}*

*Significant after Bonferroni correction, p<0.0167 (0.05/3 groups with one or more risk factors).

- Hap10 düşük enzim aktivitesine sahiptir ve HLA-B*51 için düşük afiniteli peptidom oluşturur



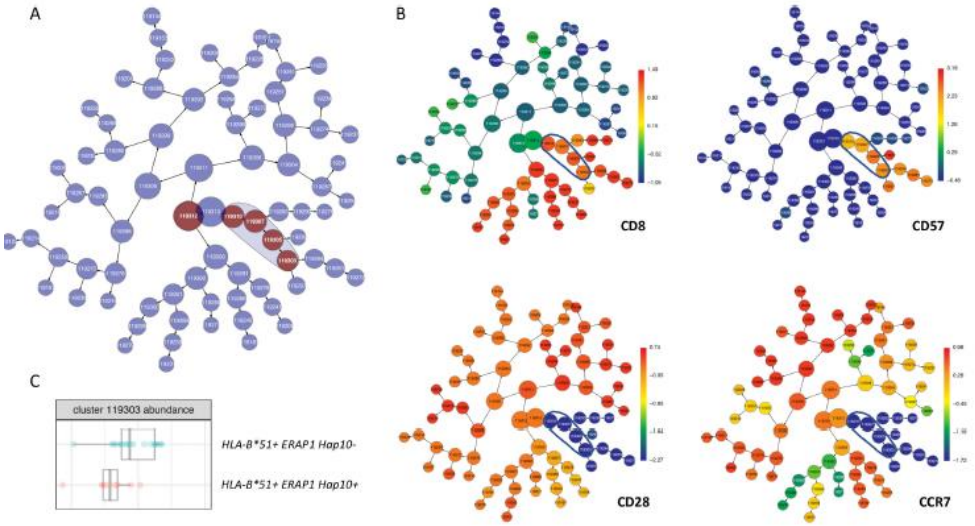
Hutchinson JP, et al. J Biol Chem 2021;296:100443

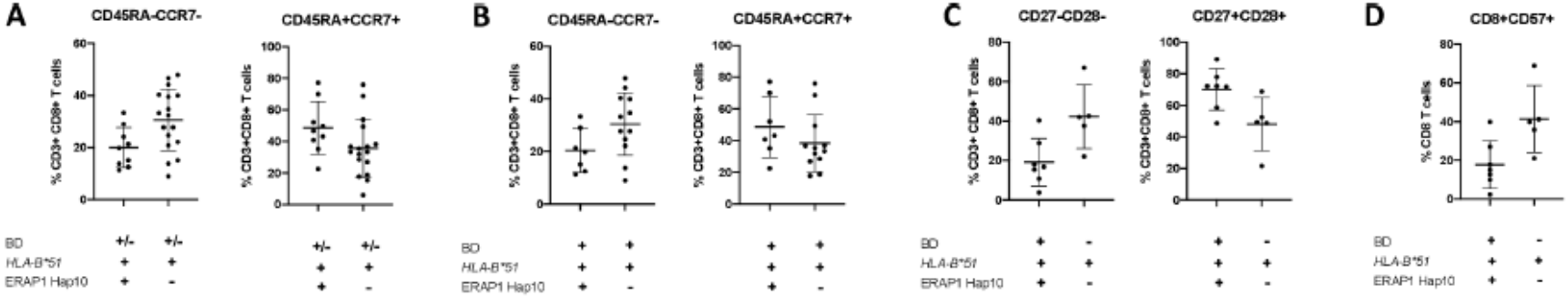


Guasp et al. JBC 2017

HLA-B*51 ve ERAP1 Hap10 Etkileşimi

- ERAP1-Hap10 ve HLA-B*51 etkileşimi sonucu CD8 sitotoksik hücrelerin özelliklerinde değişiklik olur
  - Naif hücrelere oranla antijenle karşılaşarak olgunlaşmış CD8 hücrelerde azalma (inflamasyon bölgesine göç?)

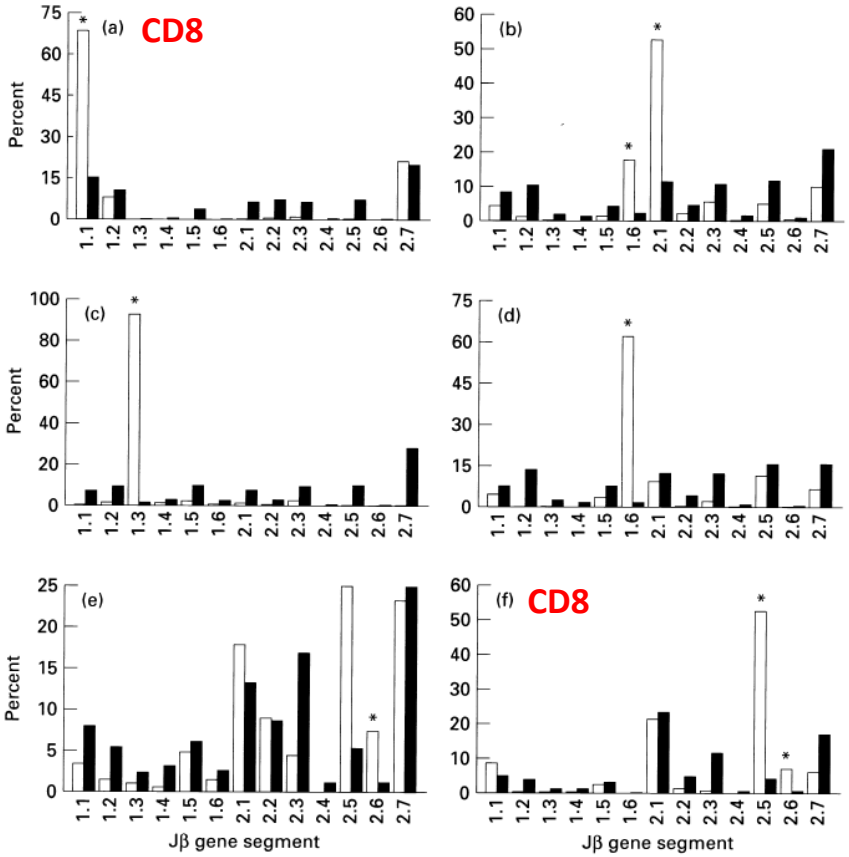




Cavers A, et al. Ann Rheum Dis 2022;81:1603–1611.

Oligoklonal T Hücre Çoğalmaları

- CD8 ve CD4 hücrelerde hastalık aktivitesiyle ilişkili oligoklonal çoğalmalar



T cell expansions in Behçet's disease

Table 4. Longitudinal analyses on T cell expansions in Behçet's disease patients

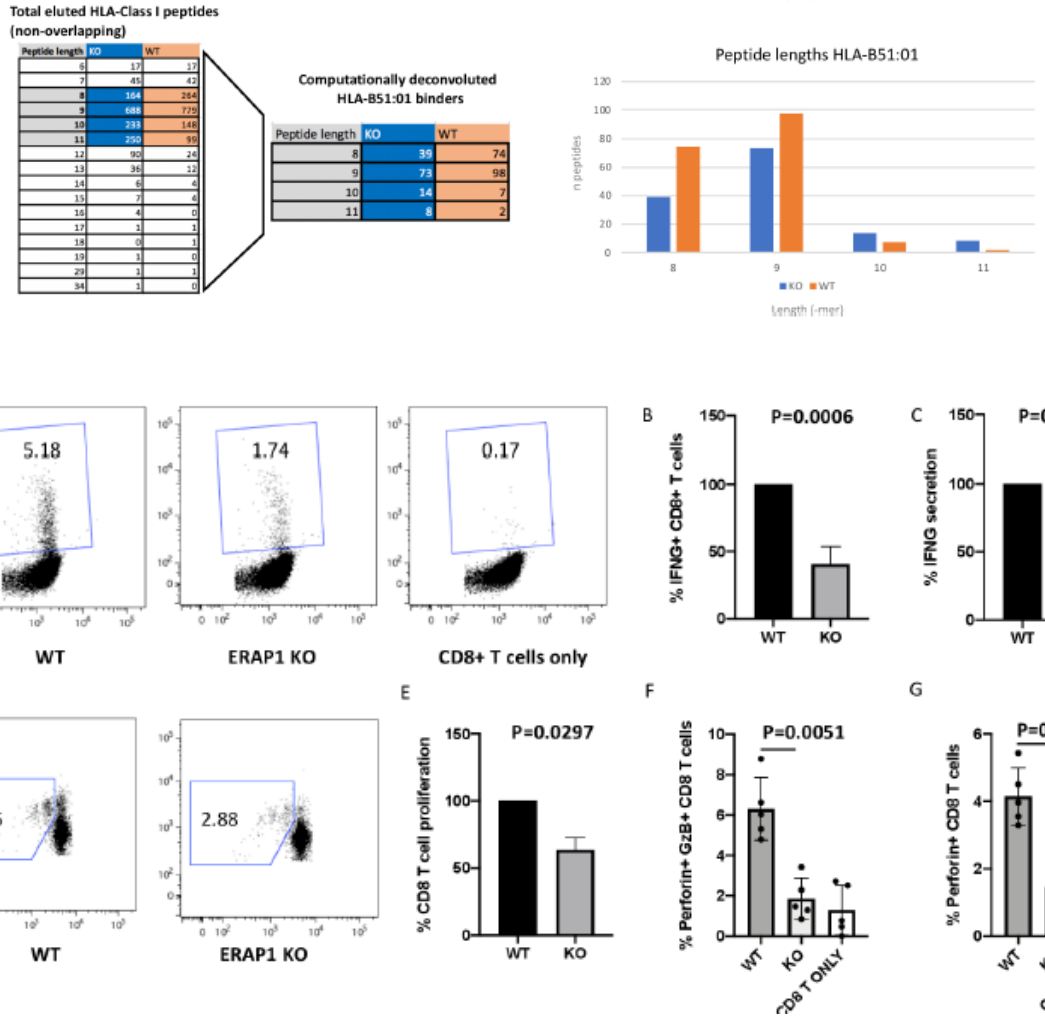
Patient	T cell subset	V segment	Time (months) 0	6	8	10	14	16	20
1	CD8	β8	**19·4***			**12·3**			
6	CD4	β6.7	**18·9**		10·0		5·0		
7	CD4	β6.7	**13·0**	4·1	3·1				
	CD8	β3	**14·2**	8·3	9·4				
	CD8	β5.3	**1·8**	0·4	**1·7**				
10	CD8	β5.1	**40·4**	**14·4**			**11·8**		
11	CD4	β3	**24·3**		9·6	9·9		7·2	
	CD4	α2.3	**9·8**		5·2	2·6		2·6	
	CD8	β5.1	5·9		**8·4**	**12·7**		**7·8**	
12	CD4	β2	**24·3**	19·2	19·2		14·4		
	CD4	β12	**8·3**	5·7	5·3		4·0		
	CD4	α12.1	**22·1**	**11·1**	**11·3**		**7·8**		
	CD8	β5.3	**10·3**	**9·5**	**9·0**		**7·9**		
16	CD8	β8	**12·4**				**14·6**		9·1
	CD8	β12	**37·7**				**11·9**		**9·4**
20	CD8	β5.1	**7·0**						**7·7**
	CD8	β5.3	**3·1**						**3·4**

*TCR V over-expressions are indicated in bold.

Esin et al. Clin Exp Immunol 1997; 107: 520-7

HLA-B*51 ve ERAP1 Hap10 Etkileşimi

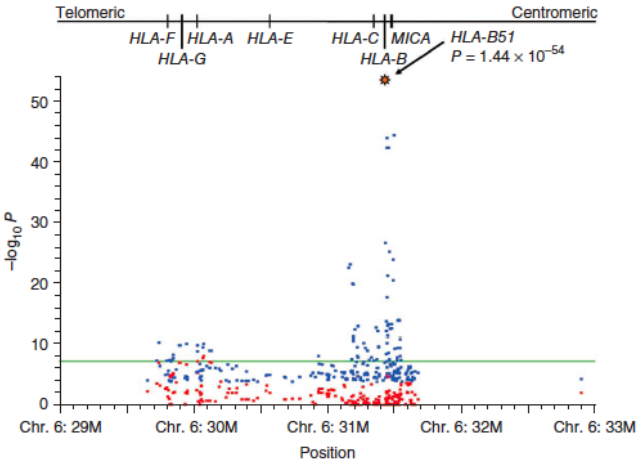
- ERAP1-Hap10 KO hücre modeliyle değişen peptidom sonucu CD8 hücrelerin aktivasyonunda değişiklik



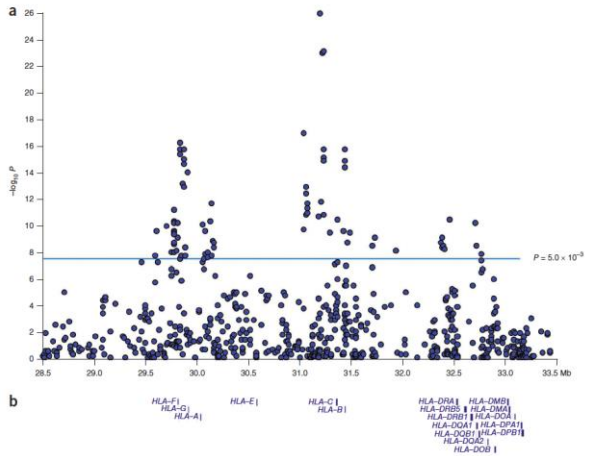
Cavers A, et al. Ann Rheum Dis 2022;81:1603–1611.

Behçet Hastalığı – MHC Sınıf I Bölgesi ile İlişki

- Diğer HLA Sınıf I alelleri ile zayıf ilişki



Remmers et al. Nat Genet 2010; 42: 698-702



Mizuki et al. Nat Genet 2010; 42: 703-6

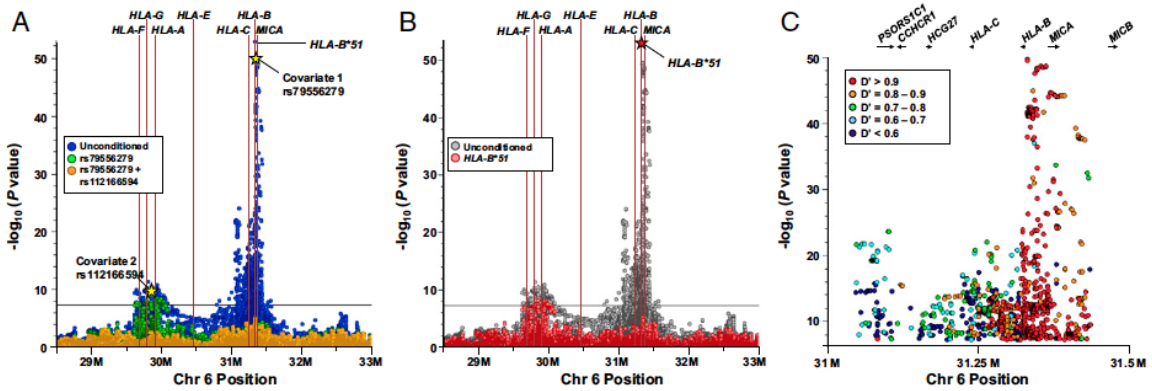


Fig. 1. *HLA-B*51* is the predominant risk allele, but variants between *HLA-F* and *HLA-A* are independently associated with BD. (*A* and *B*) The results of association testing and stepwise conditional analysis of imputed MHC region SNPs in 1,190 BD cases and 1,257 healthy control subjects from Turkey are displayed in *A*. Conditional analysis accounting for the effect of *HLA-B*51* (*B*, red dots) produced a pattern of residual association virtually identical to that seen after conditioning for rs79556279 (*A*, green dots). (*C*) Association testing results of BD-associated SNPs in proximity to *HLA-B*/*MICA* were plotted, and data points were color-coded to demonstrate D′ of each SNP with *HLA-B*51*.

Ombrello MJ, et al. PNAS 2014

Behçet Hastalığı – HLA-B*51 ve Diğer Sınıf I İlişkileri

Table 1. Additive model association testing and stepwise conditional analysis of directly ascertained HLA-B antigens in BD

Covariates	Risk allele	*P* value†	OR (95% CI)
Full collection			
None	HLA-B*51	1.3×10^{-55}	3.0 (2.6, 3.4)
HLA-B*51	HLA-B*15	1.0×10^{-5}	1.9 (1.4, 2.5)
HLA-B*51	HLA-B*27	1.0×10^{-3}	1.7 (1.2, 2.3)
+ HLA-B*15			
HLA-B*51	HLA-B*49	7.5×10^{-3}	0.6 (0.4, 0.9)
+ HLA-B*15	HLA-B*57	9.4×10^{-3}	1.7 (1.1, 2.6)
+ HLA-B*27			
HLA-B*51-negative subset			
None	HLA-B*15	3.4×10^{-5}	2.0 (1.4, 2.7)
HLA-B*15	HLA-B*49	1.1×10^{-4}	0.4 (0.2, 0.7)
HLA-B*15	HLA-B*57	5.5×10^{-3}	2.0 (1.2, 3.2)
+ HLA-B*49	HLA-B*27	6.5×10^{-3}	0.4 (0.2, 0.7)

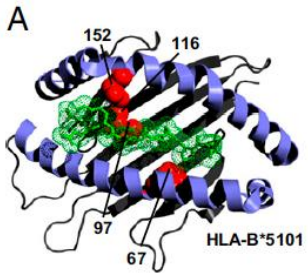
†After correcting for 31 directly ascertained HLA-B types, significance was defined as $P < 1.6 \times 10^{-3}$.

Table 2. Additive model association testing and stepwise conditional analysis of imputed two-digit classic HLA alleles in BD

Covariates	Risk allele	*P* value†	OR (95% CII)
Full collection			
None	HLA-B*51	3.4×10^{-58}	3.3 (2.8, 3.8)
HLA-B*51	HLA-A*03	4.0×10^{-8}	0.6 (0.5, 0.7)
HLA-B*51	HLA-B*15	8.7×10^{-4}	1.6 (1.2, 2.1)
+ HLA-A*03			
HLA-B*51	HLA-B*49	2.3×10^{-3}	0.6 (0.4, 0.8)
+ HLA-A*03	HLA-A*26	3.5×10^{-3}	1.5 (1.1, 2.0)
+ HLA-B*15	HLA-B*27	5.8×10^{-3}	1.6 (1.1, 2.2)
HLA-B*51–negative subset			
None	HLA-B*49	1.1×10^{-5}	0.3 (0.2, 0.6)
HLA-B*49	HLA-A*03	1.1×10^{-4}	0.6 (0.5, 0.8)
HLA-B*49	HLA-B*15	4.5×10^{-3}	1.6 (1.1, 2.1)
+ HLA-A*03	HLA-A*26	6.7×10^{-3}	1.6 (1.1, 2.2)

†After correcting for 101 imputed two-digit classical HLA alleles, significance was defined as $P < 5.0 \times 10^{-4}$.

Ombrello MJ, et al. PNAS 2014



Risk alelleri

HLA-B*15

HLA-B*27

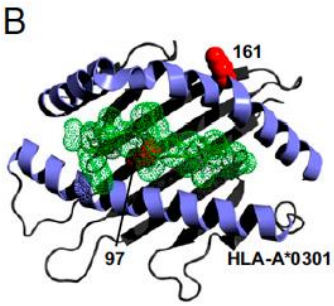
HLA-B*57

HLA-A*26

Koruyucu aleller

HLA-B*49

HLA-A*03



Behçet Hastalığı – HLA-A*26 İlişkisi

- HLA-A*26 Japon Behçet hastalarında üveitle bağımsız bir ilişki gösterir

Table 2. Comparison of ocular lesions between HLA-A26 positive and negative cases.

	HLA-A26 Positive	HLA-A26 Negative	
N	276	281	OR (95% CI), *p*
Ocular lesions	150 (54.3%)	90 (32.0%)	2.5 (1.8–3.5), <.001
Iridocyclitis	111 (40.2%)	60 (21.4%)	2.5 (1.7–3.6), <.001
Retinochorioiditis	126 (45.7%)	64 (22.8%)	2.8 (1.9–4.0), <.001
Chronic lesions	67 (24.3%)	30 (10.7%)	2.7 (1.7–4.3), <.001

OR: an odds ratio was calculated using HLA-A26 negative as reference.

Table 3. Factors affecting ocular lesions.

N = 546	OR (95%CI)	*p* value
Women	0.32 (0.22–0.47)	<.001
Age (per 10 years)	0.96 (0.84–1.10)	.572
HLA-B51 positive	1.79 (1.17–2.74)	.007
HLA-A26 positive	4.64 (3.09–6.95)	<.001

Logistic regression using general ocular lesion as depending variable and four variables on the left of the table as explanatory variables.
Eleven cases whose HLA-B51 status was unknown were excluded from this analysis.

Table 4. Comparison of ocular lesions between HLA-A26 positive and negative cases stratifying HLA-B51 status.

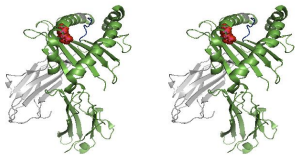
HLA-B51 positive	HLA-A26 positive	HLA-A26 negative	OR (95% CI), *p*
N	66	108	
Ocular lesions	34 (51.5%)	30 (27.8%)	2.8 (1.5–5.3), .002
Iridocyclitis	29 (43.9%)	28 (25.9%)	2.2 (1.1–4.2), .017
Retinochorioiditis	34 (51.5%)	30 (27.8%)	2.8 (1.5–5.3), .002
Chronic lesions	16 (24.2%)	13 (12.0%)	2.3 (1–5.2), .043
HLA-B51 negative	HLA-A26 positive	HLA-A26 negative	OR (95% CI), *p*
N	202	170	
Ocular lesions	109 (54.0%)	51 (30.0%)	2.7 (1.8–4.1), <.001
Iridocyclitis	80 (39.6%)	32 (18.8%)	2.8 (1.7–4.5), <.001
Retinochorioiditis	90 (44.6%)	34 (20.0%)	3.2 (2.0–5.1), <.001
Chronic lesions	49 (24.3%)	17 (10.0%)	2.9 (1.6–5.3), <.001

Eleven cases whose HLA-B51 status was unknown were excluded from this analysis.
Breslow-Day test: $p > .05$ for ocular lesions, iridocyclitis, retinochorioiditis, and chronic lesions.
OR: an odds ratio was calculated using HLA-A26 negative as reference.

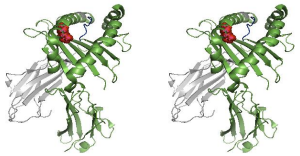
Kato H, et al. Mod Rheumatol 2020

MHC-I-opathies

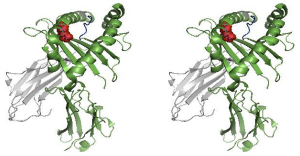
HLA-A



HLA-C



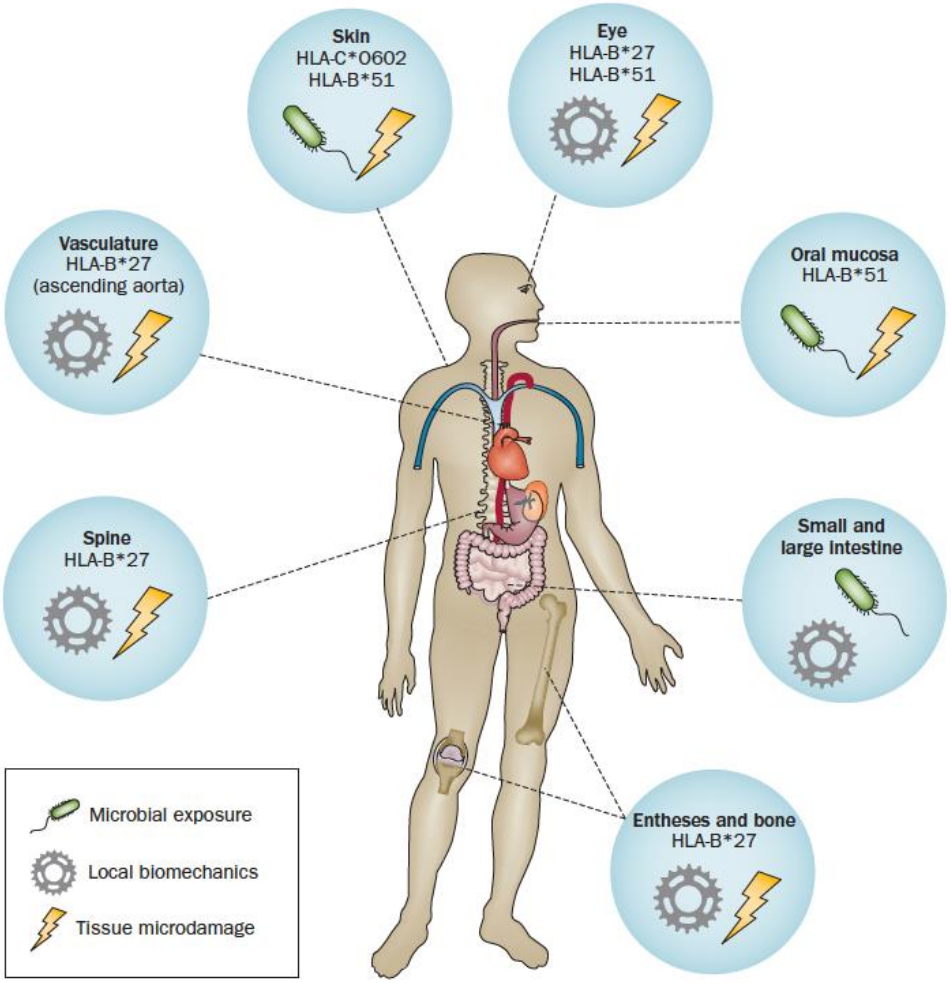
HLA-B



Dokuya özgü

<u>Peptidom</u>

ERAP1 haplotipleri ve diğerleri



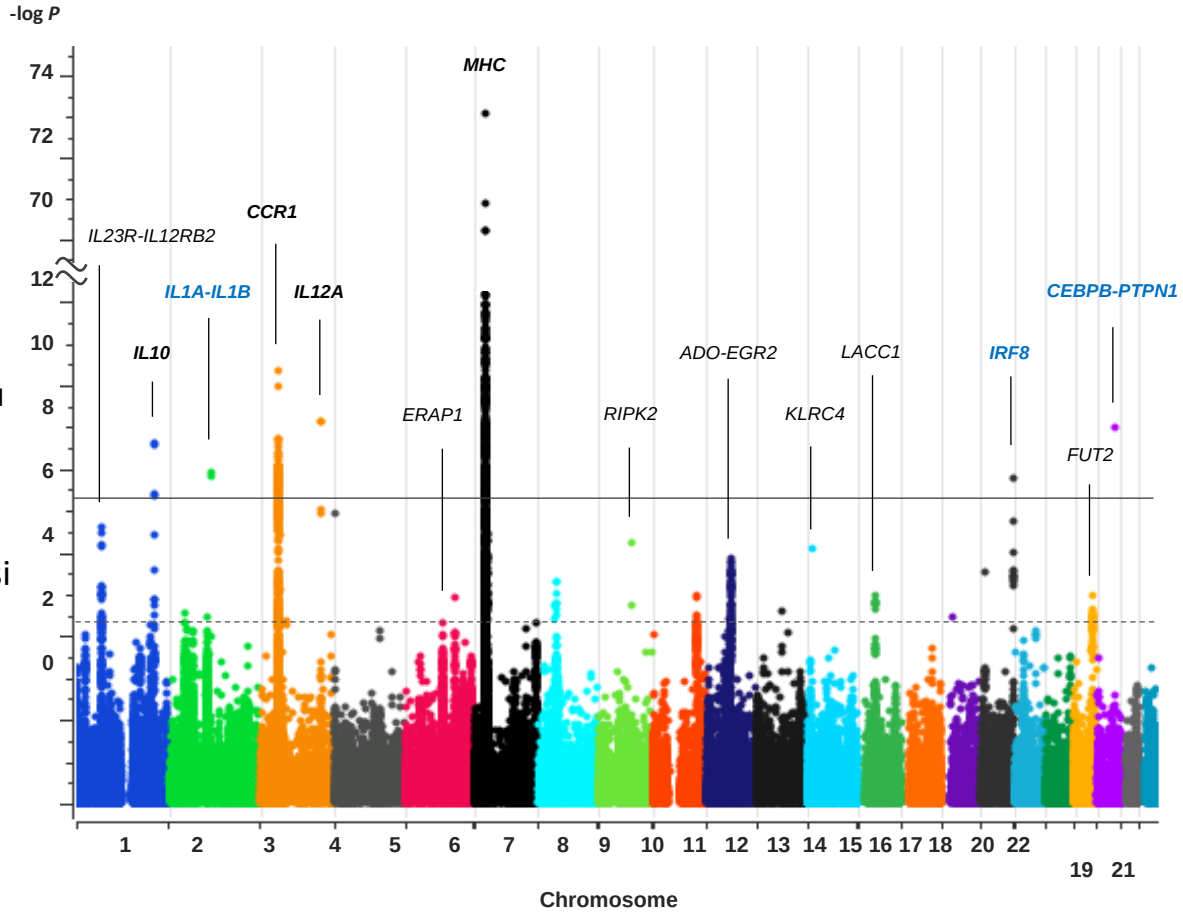
McGonagle et al. Nat Rev Rheumatol 2015;11:731-40

Behçet Hastalığı – HLA-Dışı İlişkiler

- Çok sayıda HLA-dışı gen polimorfizmi Behçet hastalığına genetik yatkınlığa katkıda bulunur
  - Farklı patojenlere immün yanıtı etkileyebilirler, doğal ve edinsel bağışıklığın şiddet ve polarizasyonunu belirlerler

Treg aktivitesi
Th1 polarizasyonu
Th17 polarizasyonu

NK hücre aktivitesi
Monosit aktivitesi
CD8 hücre aktivitesi

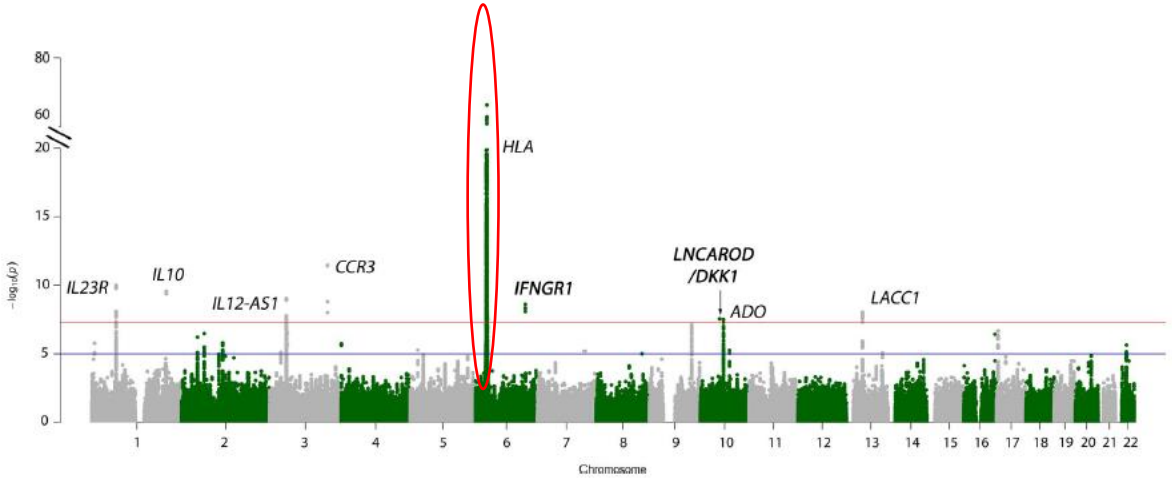


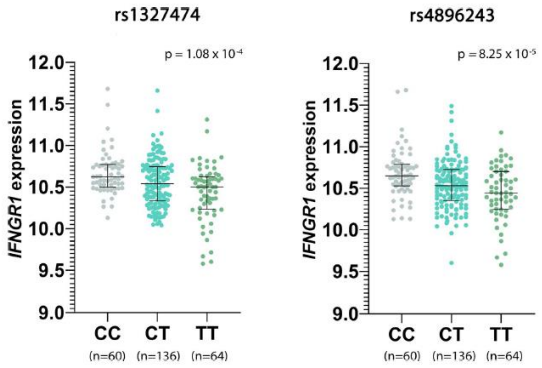
Mikroorganizmalarla etkileşim

Takeuchi et al. Nat Genet 2017

Behçet Hastalığı – HLA-Dışı İlişkiler

- Yeni GWAS çalışmaları
  - 7 farklı toplumdan (Türk, İspanyol, İtalyan, Koreli, Tunuslu, Japon, ve Batı Avrupalı) toplam 9,444 hasta ve kontrol
  - İki yeni yatkınlık lokusu: IFNGR1 (rs4896243) (odds oranı [OR] 1.25; P = 2.42×10^{-9}), ve LNCAROD/DKK1 intergenic bölgesi (rs1660760) (OR 0.78; P = 2.75×10^{-8})





Ortiz Fernández L, et al. Arthritis Rheumatol 2021;73:1244-52

Behçet Hastalığı – HLA-Dışı İlişkiler

- Immunochip Sonuçları:
  - Spondiloartritler, Crohn hastalığı, otoinflamatuvar hastalıklar ve mikrop-konak etkileşimiyle ilişkili paylaşılan inflamasyon yolları

- İnfeksiyon yatkınlığı?
- Uyarılara benzer immün yanıt?
  (EN, artrit, üveit,..)

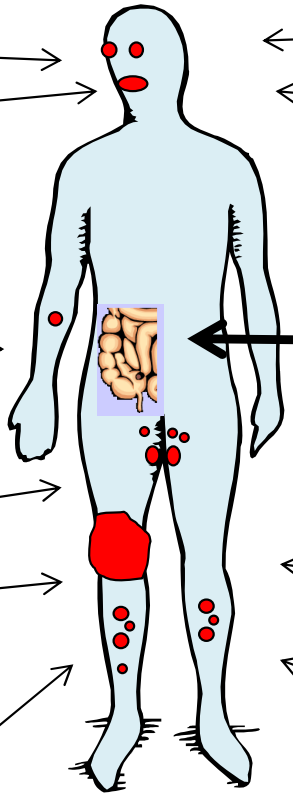
SpA – İBH (Crohn hastalığı)

Locus	Behçet's disease	IBD	Pso	CeD	MS	AS	PBC	SLE	RA	T1D	SSc	SJO	JIA	CD[a]	UC[a]	Leprosy
MHC Class I	*HLA-B*51*															
IL1A-IL1B	rs3783550/rs4402765															
MEFV	p.Met694Val															
KLRC4	rs2617170															
CEBPB-PTPN1	**rs913678**	**rs913678**														
CCR1	rs7616215/**rs13092160**			**rs13098911**												
RIPK2	rs2230801															
LACC1[b]	**rs2121033**	**rs3764147**												**rs3764147**		**rs9567307**
FUT2	**rs681343**/**rs601338**/rs1047781	**rs516246**								**rs516246**				**rs516246**		
ADO-EGR2	rs1509966/rs7075773/rs224127	rs10761659												rs10761659	rs10761659	
ERAP1	rs17482078	rs1363907	rs27432			rs30187								rs1363907		
IL10	rs1518111/rs1800871															
IRF8	**rs11117433**/rs7203487/rs142105922						**rs11117433**									
IL12A	rs76830965/**rs17810546**			**rs17810546**												
IL23R-IL12RB2	rs924080/rs1495965															
TNFAIP3	rs9494885															
STAT4	rs7574070/rs897200															

Takeuchi et al. Nat Genet 2017

Behçet Hastalığı

Crohn Hastalığı



Üveit

Oral aftöz ülserler

Intestinal tutulum

Genital aftöz ülserler

Artrit /SpA

Papülopüstüler ya da EN-benzeri

Üveit

Oral aftöz ülserler

Intestinal tutulum

Genital aftöz ülserler

Artrit /SpA

Papülopüstüler ya da EN-benzeri

Vasküler tutulum
Parenkimal nörolojik tutulum
? Paterji reaksiyonu

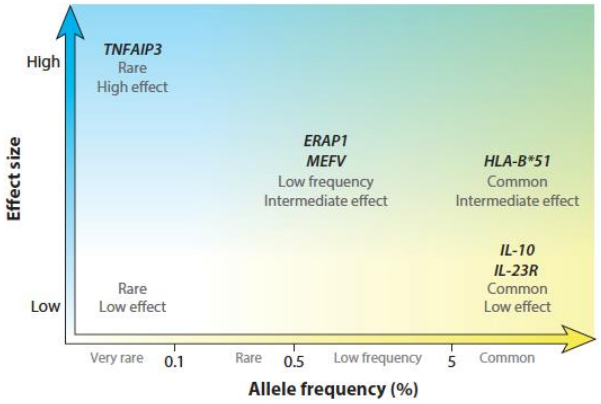
Kirino et al.
PNAS 2013

Table 2. Risk effects of the rare and low frequency nonsynonymous variants associated with Behçet disease (BD) and Crohn disease (CD)

Gene	Variant	BD	CD	Function
IL23R	G149R	Protective	Protective	Unknown
	R381Q	Protective	Protective	Reduces interleukin 23 dependent interleukin 17 production
TLR4	D299G	Protective	Risk	Reduces response to LPS
	T399I	Protective	Risk	Reduces response to LPS
NOD2	R702W	Protective	Risk	Reduces response to MDP
	G908R	Protective	Risk	Reduces response to MDP
	L1007fs	Protective	Risk	Reduces response to MDP
MEFV	M694V	Risk	Risk	Increases response to LPS

Behçet Hastalığı – Monogenik Taklitçiler

- "Behçet hastalığı benzeri" bulguları olan monogenik hastalıklar
  - A20 (TNFAIP3)



Stoffels M, **Kastner** DL. Annu Rev Genomics Hum Genet 2016;17:245-72.

Table 4 Clinical and laboratory features that are helpful to differentiate between A20 haploinsufficiency (HA20) and Behçet disease.

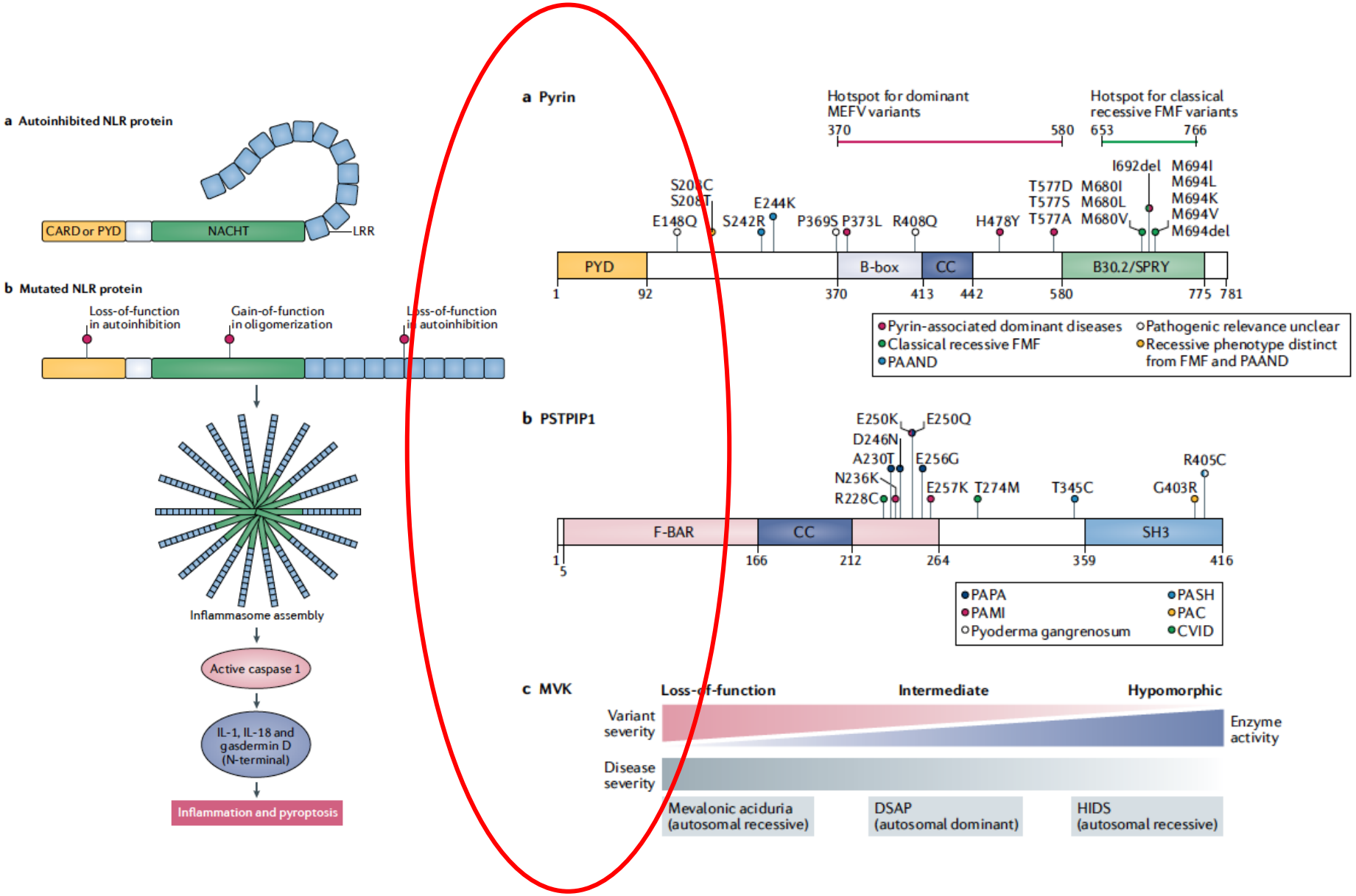
Features	HA20	Behçet disease[9 13 16–19]
Disease onset	Mostly early childhood	Early adulthood
Inheritance	Autosomal dominant	Complex inheritance pattern with familial aggregation in up to 20% of cases
Fever	Recurrent	Usually absent
Ulcers	May heal with scarring	Usually no scarring of oral ulcers
Eyes	Severe ocular disease ► Anterior uveitis ► Retinal vasculitis and choroiditis with necrotising inflammation	► Posterior or panuveitis ► Recurrent superficial retinal infiltrates resolving within days without chorioretinal scarring ► Peripheral retinal occlusive periphlebitis
Gastrointestinal	(Bloody) diarrhoea	Isolated abdominal pain*
Musculoskeletal	Mostly polyarthritis	Usually oligoarthritis
Erythrocyte sedimentation rate/C reactive protein	Elevated, especially during disease relapses	Often normal
Autoantibodies Autoimmune features	Low titre, fluctuating presence Systemic lupus erythematosus-like disease and other autoimmune features possible	Usually absent

*Gastrointestinal involvement in Behçet disease is usually mild and consists essentially of abdominal pain or discomfort except for patients from Japan and Korea.

Aeschlimann FA et al,. Ann Rheum Dis 2018;77:728–735.

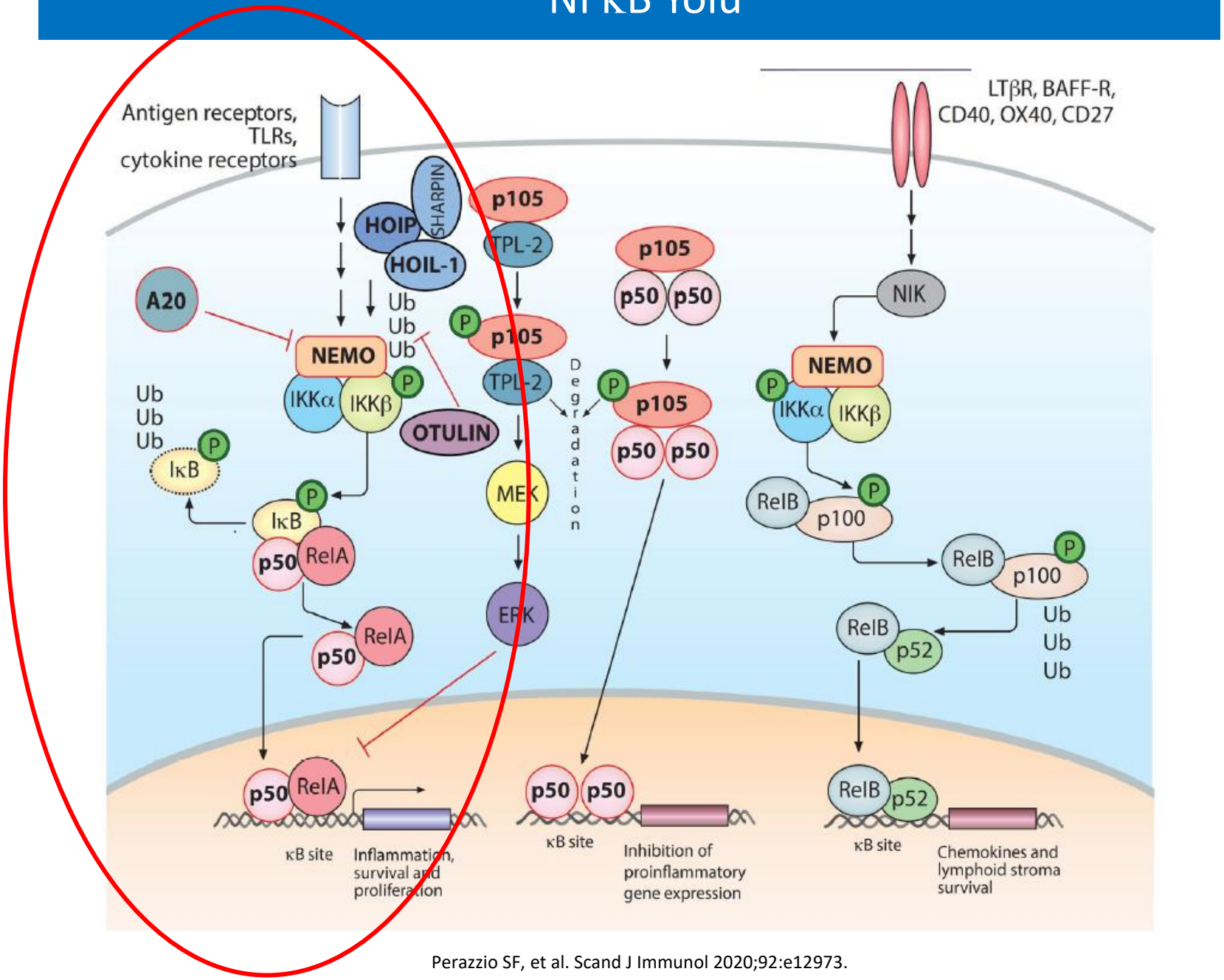
  - MKD
  - NOD2
  - WDR1, NCF1, AP1S3, LYN, GLA, STAT1, TNFRSF1A and MEFV
    - Rheumatology (Oxford) 2019;58:1227-1238
  - DADA2
  - NEMO (IKBKG), RELA, GM-CSF

Pirin Aracılı İnflamazomopatiler



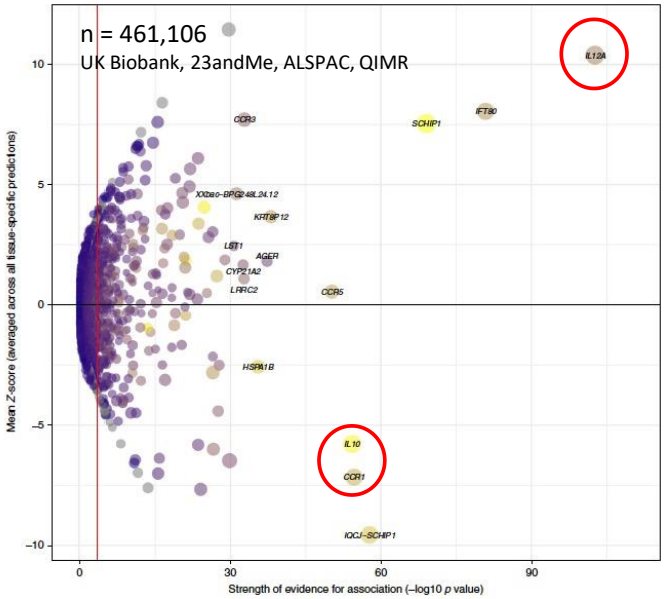
Aksentijevich I, Schnappauf O. Nat Rev Rheumatol 2021;17:405-25.

NFκB Yolu

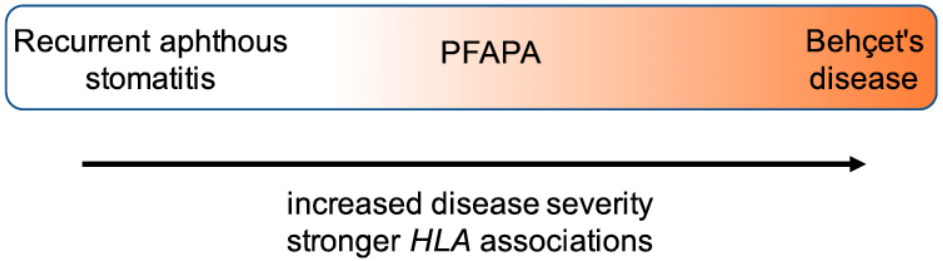


Perazzio SF, et al. Scand J Immunol 2020;92:e12973.

Behçet veya "Kompleks Aftoz" Spektrumu Hastalıklar



- Paylaşılan HLA-dışı genetik yatkınlık
  - IL12A, IL-10, CCR1



Manthiram et al. Proc Natl Acad Sci U S A 2020;117:14405-14411

HLA fenotipi belirlemede kritik öneme sahiptir

Dudding et al. Nat Commun 2019

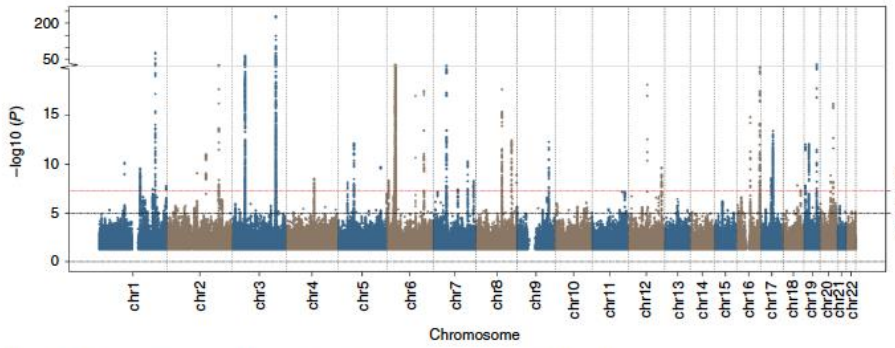
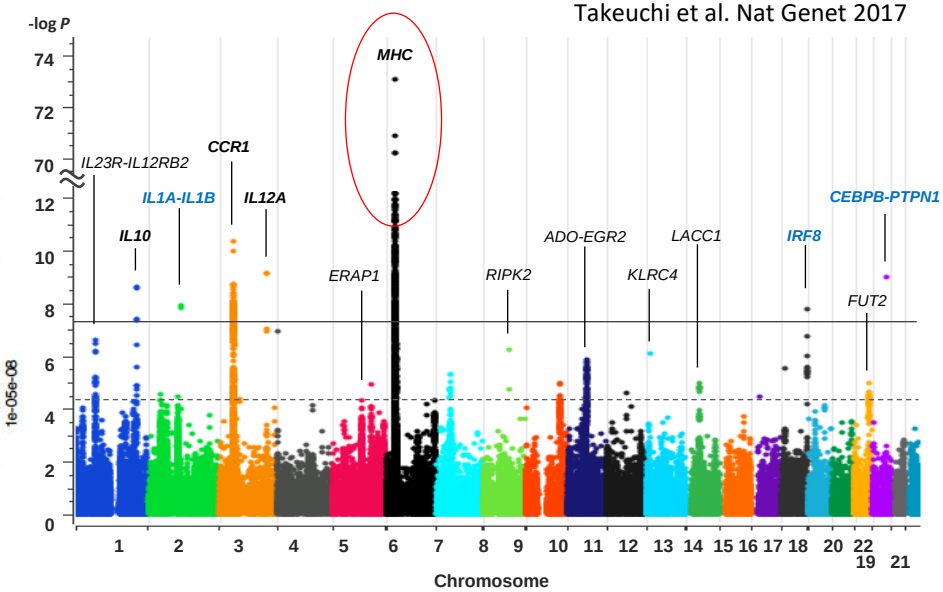


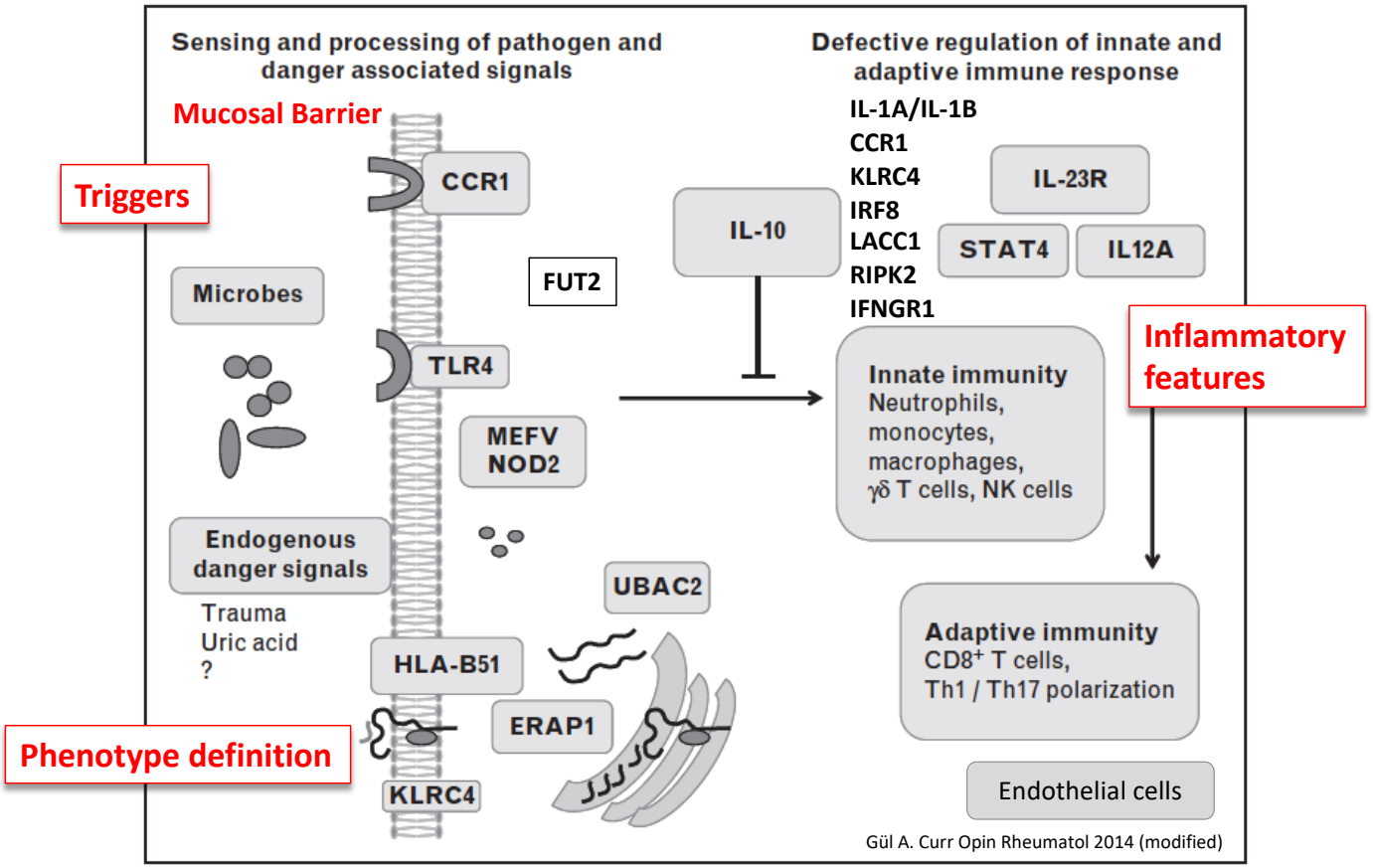
Fig. 1 Manhattan plot of genome-wide association analysis of self-reported ulcers in UK Biobank

Takeuchi et al. Nat Genet 2017



Behçet Hastalığı – Multifaktoriyal İnflamatuvar Hastalık

- Behçet hastalığı fenotipiyle ilişkili en güçlü genetik faktör HLA-B*51
  - ERAP1 allotiplerinden Hap10 ile epistatik etkileşim patogeneze katkıda bulunur
- HLA-dışı genlerdeki polimorfizmler de Behçet hastalığına genetik yatkınlığa önemli katkı sağlar
  - Farklı patojenlere immün yanıtta değişiklikler, doğal ve edinsel immün yanıtın şiddet ve polarizasyonunun etkilenmesi



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