İZMİR KATİP ÇELEBİ ÜNİVERSİTESİ

ROMATOLOJİ

2014

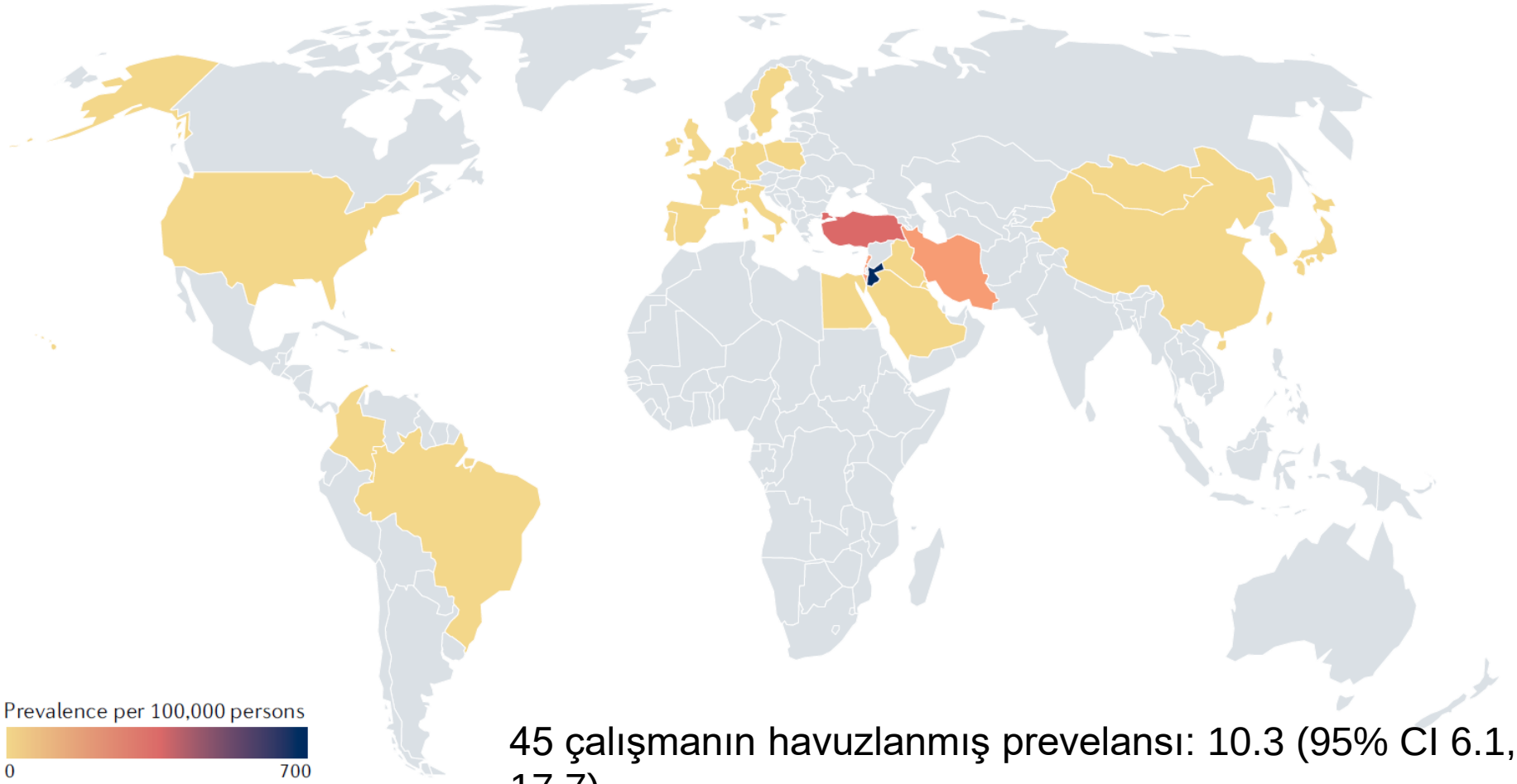
# Epidemiyoloji ve Genetik

Dr. Dilek Solmaz

- Epidemiyoloji
  - Global
  - Türkiye
- Genetik
  - HLA B51
  - ERAP

- BH sıklığı ülkeler arasında büyük farklılıklar göstermekte
  - Tarihi ipek yolu
  - Başlangıç yaşı
  - Cinsiyet dağılımları
  - Klinik domainlerin sıklıkları da farklılıklar gösterebilmekte

- Kullanılan kriterler
  - 1990 International Study Group
    - %85 se; %96 sp
  - 2014 Revize International Criteria for BD
    - %94.8 se; %90 sp




45 çalışmanın havuzlanmış prevelansı: 10.3 (95% CI 6.1, 17.7)

Fig. 4 | **Global prevalence of Behçet syndrome.** Behçet syndrome occurs most commonly along the ancient silk road between the Mediterranean and China. See Supplementary Table 4 for data used. Grey indicates no data available.

Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol. 2022 Jan;18(1):22-34
Maldini C, et.al. Rheumatology 2018;57:185195

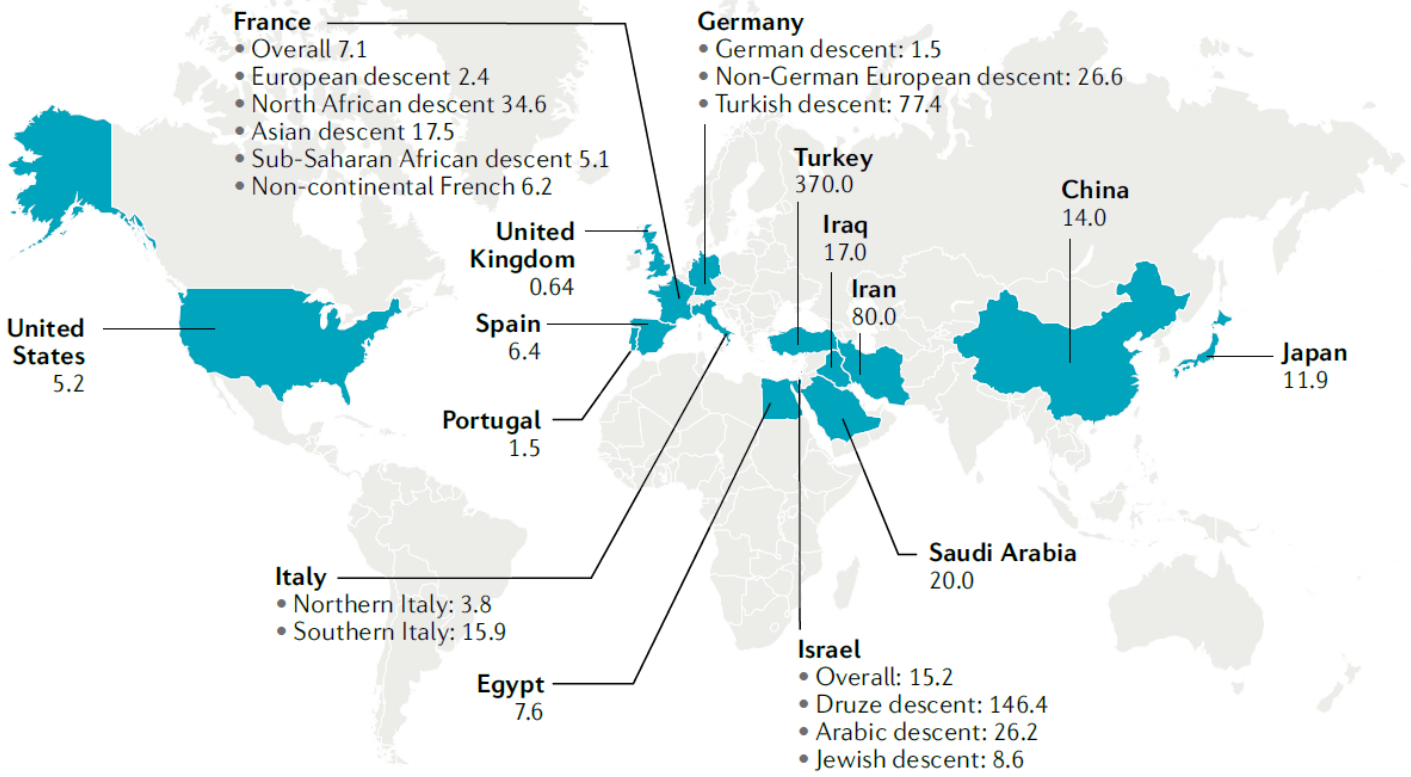



Fig. 1 | **Prevalence of Behçet syndrome.** The prevalence of Behçet syndrome is uniquely distributed across the globe with increased patient numbers in the Middle East and far-East Asia (patients per 100,000 population). Adapted from REF.[1], Springer Nature Limited.

Yazici Y, Hatemi G, Bodaghi B, Cheon JH, Suzuki N, Ambrose N, Yazici H. Behçet syndrome. Nat Rev Dis Primers. 2021 Sep 16;7(1):67

| Region | Study period | Prevalence (cases per 100,000 population) | Case definition | Study type | Reference |
|---|---|---|---|---|---|
| *Europe* | | | | | |
| Paris, France | 2003 | 7.1 | ISG 1990 | Population | 71 |
| Germany | 2012 | 1.5 | ISG 2014 | Analysis national registry | 72 |
| Mid-west, Ireland | 2017 | 6.2 | ISG 2014 | Cohort study | 73 |
| Italy | 2010 | 15.9 | ISG 1990 | Cross sectional | 74 |
| Rotterdam, Netherlands | 2012 | 7.6 | ISG 1990 | Analysis hospital database | 75 |
| Poland | 2014 | 0.34 | ICD-10 | Analysis national administrative database | 76 |
| Portugal | 1997 | 2.4 | NA | Cohort study | 77 |
| Spain | 1988-1997 | 0.66 | ISG 1990 | Cohort study | 78 |
| Southern Sweden | 2011 | 4.9 | ISG 1990 | Population | 79 |
| Switzerland | Not stated | 4.0 | ISGBD 2014 | Cohort study | 80 |
| United Kingdom | 1995-2017 | 14.6 | Read codes | National clinical database primary care | 81 |

3.3/100.000

| | | | | | |
|---|---|---|---|---|---|
| *Middle East* | | | | | |
| Egypt | 2017 | 3.6 | ISGBD 2014 | Cross sectional | 82 |
| Iraq | 1999-2000 | 17 | ISG 1990 | Cross sectional survey | 83 |
| Kurdistan, Iran | 2011-2012 | 100 | ISG 1990 | Cross sectional population survey | 84 |
| Israel | Not stated | 120 | ISG 1990 | Population | 85 |
| Jordan | Not stated | 660 | ISG | Cross sectional hospital workers | 86 |
| Kuwait | N/A | 2.1 | N/A | Cohort study | 87 |
| Lebanon | 2007 | 100 | ISG 1990 | Cross sectional population survey | 88 |
| Saudi Arabia | 1979-1992 | 20 | ISG 1990 | Cohort study | 89 |
| Istanbul, Turkey | Not stated | 421 | ISG 1990 | Cross sectional population | 90 |

31.8/100.0000

| | | | | | |
|---|---|---|---|---|---|
| *Americas* | | | | | |
| Brazil | 2006-2007 | 0.3 | ISG 1990 | Cross sectional hospital | [91] |
| Colombia | 2012-2016 | 1.1 | ICD-10 code: M352 | Analysis administrative database | [92] |
| South western, USA | Not stated | 10.6 | ISG 1990 | Cross sectional hospital database | [93] |

| | | | | | |
|---|---|---|---|---|---|
| *Asia* | | | | | |
| China | Not stated | 10 | ISG 1990 | Cross sectional population survey | [94] |
| Japan | Not stated | 13.5 | Not stated | Not stated | [95] |
| Mongolia | 2015-2019 | 2.4 | ISG 1990 | Cross sectional | [96] |
| Korea | 2011-2017 | 15.1 | Korean Disease Classification | Analysis insurance database | [97] |
| Taiwan | 2000 | 1.4 | ICD-9-CM 136.1 | Analysis national insurance database | [98] |

4.5/100.000

- İnsidans çalışmaları daha da az ….

| Ülke | n/100.000 |
|---|---|
| Kore | 3.97 |
| Japonya | 0.75 |
| Almanya* | 1.0 |
| İspanya | 0.66 |
| İsviçre | 0.65 |
| İsveç | 0.20 |
| İtalya | 0.24 |
| Polanya | 0.05 |
| US | 0.38 |
| Fransa* | 0.72 |

| Yazar | Yılı | Bölge | Sıklık | Taranan popülasyon | BH n (K/E) | Kriter |
|---|---|---|---|---|---|---|
| Demirhindi, O | 1981 | İstanbul | 80/100.000 | 4960 | 4 (N/A) | O'Duffy |
| Yurdakul, S | 1988 | Çamaş | 370/100.000 | 5131 | 19 (13/6) | O'Duffy |
| Idil, A | 2001 | Ankara | 110/100.000 | 13894 | 16 (11/5) | ISG |
| Azizlerli, G | 2003 | İstanbul | 420/100.000 | 23896 | 101 (52/49) | ISG |
| Çakır, N | 2004 | Havsa | 20/100.000 | 4861 | 1 (N/A) | ISG |
| Cosgun, S | 2004 | İstanbul | 50/100.000 | 1996 | 10 (4/6) | ISG |
| Seyahi, E | 2010 | İstanbul | 90/100.000 | 4462 | 4 (0/4) | ISG |
| Çakır, N | 2012 | Havsa | 19/100.000 | 17835 | 3 (1/2) | ISG |
| Çölgeçen, E | 2015 | Kayseri | 172/100.000 | 5218 | 9 (4/5) | ISG |

Havuzlanmış prevalansı: 119.8/100.000

Maldini C, et.al. Rheumatology 2018;57:185195

- Yaş
  - Ortalama başlangıç yaşı
    - Kadın:28.4
    - Erkek:26.7
  - 15 yaş öncesi ve 50-55 yaş sonrası başlangıç nadir
    - Juvenil başlangıç %2-5
    - Kore çalışmasında >70 yaş üstü başlangıç <%3

N. Akkoç . Best Practice & Research Clinical Rheumatology 32 (2018)

- Cinsiyet
  - Erken çalışmalarda erkek dominansı
  - 33 ülkenin dahil edildiği bir metaanalizde
    - 19 M>F
    - 6 M=F
    - 7 M<F

Göz

Vasküler

Pozitif paterji

Papülopüstüler lezyonlar

Genital ülser

Eritema nodozum

Artrit

Bonitsis NG, et al. Gender-specific differences in AdamantiadeseBehçet's disease manifestations: an analysis of the German registry and meta-analysis of data from the literature. Rheumatology 2015;54(1):121e33.

Davatchi F, et al.. Behcet's disease: epidemiology, clinical manifestations, and diagnosis. Expert Rev Clin Immunol. 2017 Jan;13(1):57-65.

Table 2: Comparison of symptoms (in percentage) from different parts of the world

| | Year | Cases No. | OA | GA | Skin PF* | Eye | Joint | CNS | GI | Vasc Phl* | Epid |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Iran[27] | 2010 | 6500 | 97.3 | 64.6 | 64.9 | 56.8 | 37.4 | 3.7 | 7.4 | 8.3 | 4.7 |
| Korea[31] | 2001 | 1527 | 98.8 | 83.2 | 84.3 | 50.9 | 38.4 | 4.6 | 7.3 | 1.8 | 0.6 |
| Korea[32] | 2014 | 3674 | 99.7 | 88.4 | 85.3 | 36 | 45.3 | 2.9 | 8 | 2.2 | 1.1 |
| Japan[16] | 1993 | 3316 | 98.2 | 73.2 | 87.1 | 69.1 | 56.9 | 11 | 15.5 | 8.9 | 6 |
| Turkey[29] | 2003 | 2313 | 100 | 88.1 | 54* | 29.1 | 11.6 | 2.3 | 1.4 | 7 | - |
| China[30] | 2006 | 1996 | 98.4 | 76.3 | 69 | 34.8 | 30 | 6.5 | 8.8 | 7.7 | - |
| Morocco[33] | 2006 | 1034 | 100 | 85.6 | - | 64.7 | 51.8 | 17.2 | 11.1 | 19.8 | 3.1 |
| Germany[22] | 2014 | 861 | 98 | 63.4 | 78.6 | 45.3 | 54.3 | 3.5 | 12.6 | 13 | 10 |
| Tunisia[40] | 2009 | 674 | 100 | 85.8 | 69.3* | 32.8 | 56.5 | 12.8 | - | 26.7 | - |
| Algeria[40] | 2009 | 552 | 100 | 75 | 69.2* | 45.8 | 51.6 | 10.9 | - | 27.2 | - |
| England[25] | 1997 | 419 | 100 | 89 | 86 | 68 | 93 | 31 | 7 | 22* | - |
| Iraq[43] | 2008 | 330 | 100 | 83 | - | 42 | - | - | - | - | - |
| Egypt[17] | 1997 | 274 | 92 | 75.9 | 39.4 | 75.9 | 49.6 | 25.9 | 10.2 | 23.4 | 15.7 |
| Russia[36] | 2015 | 250 | 100 | 81.2 | 88.8 | 54 | 73.2 | 8 | 25.2 | 25.2* | 10 |
| Jordan[45] | 2000 | 200 | 99.5 | 86.5 | 90.5 | 42 | 47 | 38.5 | 17 | 24 | 27 |
| USA[46] | 2000 | 164 | 98 | 80 | 66 | #50 | 41 | 23 | 8 | - | 2 |
| Italy[55] | 1991 | 155 | 98 | 73 | 86 | 93 | 77 | 17 | 34 | 18 | 19 |
| Portugal[48] | 1991 | 154 | 100 | 93 | 60 | 50 | 64 | 5 | 20 | 18* | - |
| Saudi Arabia[48] | 1994 | 119 | 100 | 87 | 57 | 65 | 37 | 44 | 4 | 25 | 4 |
| Israel[14] | 2007 | 112 | 100 | 67.9 | 41.1 | 52.7 | 69.6 | 11.6 | - | 15.2* | - |
| Brazil[38] | 2009 | 106 | 100 | 92.5 | 59.4* | 47.2 | 35.8 | 17.9 | 6.6 | 16 | - |
| Greece[42] | 2000 | 101 | 100 | 78 | 75 | 73 | 54 | 20 | 4 | 11 | 13 |
| Lebanon[49] | 2006 | 90 | 100 | 72.2 | 83.3 | 53.9 | 59.1 | 24.1 | 6.9 | 36.8 | - |
| France[19] | 2008 | 79 | 100 | 80 | 90 | 51 | 59 | 10 | - | 30 | 15.6 |
| Spain[35] | 2006 | 74 | 98.5 | 82.4 | 64.2 | 42.5 | | 16.7 | 18.2 | 21.6 | - |
| Taiwan[56] | 2006 | 67 | 100 | 67.2 | 74.6 | 35.8 | 50.7 | 19.4 | 17.9 | 7.5 | 3.2 |
| India[50] | 1995 | 58 | 89.7 | 77.6 | 63.8 | 43 | 70.7 | 1.7 | 5.2 | 10.3* | 0 |
| Romania[52] | 2004 | 56 | 96.4 | 51.7 | - | 26.8 | 5.3 | 17.8 | 28.5 | 50 | - |
| Sweden[23] | 2013 | 40 | 100 | 80 | 88 | 53 | 40 | 0 | - | 20 | - |
| Hong Kong[53] | 2004 | 37 | 100 | 81 | 73 | 35 | 54 | 5 | 14 | 11 | - |
| Singapore[53] | 2004 | 37 | 100 | 73 | 73 | 41 | 62 | 5 | 35 | 5 | - |
| Tadjikistan[54] | 2000 | 36 | 100 | 71 | 79 | 49 | 44 | 14 | - | 14* | - |
| Australia[53] | 2004 | 31 | 90 | 68 | 84 | 66 | 87 | 29 | 38 | 19 | 0 |
| Thailand[51] | 2006 | 23 | 100 | 69.6 | 60.9 | 52.2 | 34.8 | 8.7 | 8.7 | 8.7 | - |

Decimals were rounded to the nearest integer for figures superior to 9

No.: Number of cases. OA: Oral aphthosis. GA: Genital aphthosis.

CNS: Central nervous system involvement. GI: Gastrointestinal manifestations.

Vasc: Vasculitis. Epid: Epididymitis. PF : Pseudofolliculitis. Phl : Phlebitis



Davatchi F, et al. Behcet's disease: epidemiology, clinical manifestations, and diagnosis. Expert Rev Clin Immunol. 2017 Jan;13(1):57-65.

# Genetik

- Geografik dağılımı
- MHC I ile olan ilişkisi
- Ailesel olguların varlığı patogenezdeki genetik yükü destekler kanıtlar olarak karşımıza geliyor

Gül A, et al. Familial aggregation of Behçet's disease in Turkey. Ann Rheum Dis. 2000 Aug;59(8):622-5.

- Ailesel vakalar
  - **Türkiye ..%18.2**
  - **Kore …%15.4**
  - **İsrail… %13.2**
  - Çin …%2.6
  - Japon… %2.2
  - Avrupa… %0-4.5
- Pediatrik vakalarda oran erişkinlerden daha yüksek olarak bildirilmiş (%12 vs %2)

N. Akkoç . Best Practice & Research Clinical Rheumatology 32 (2018)

*Ann Rheum Dis* 2000;**59**:622–625

# Familial aggregation of Behçet's disease in Turkey

Ahmet Gül, Murat Inanç, Lale Öcal, Orhan Aral, Meral Koniçe

- 170 BH indeks
  - 31 (%18) indeks hastanın 51 hasta yakınında BH
  - Juvenil başlangıçlı olan 12 hastanın 4 de aile öyküsü (%33)
  - Kardeşlerdeki tekrar oranı
    - BH **%4.2** (95% CI 1.2 to 7.2%)
    - RAS %13.3 (95% CI 8.1 to 18.5%)
    - «sibling recurrence risk ratio» (λs): (8-37/10.000)
      - 11.4-52.5

## A twin study in Behçet's syndrome

S. Masatlioglu[1], E. Seyahi[2], E. Tahir Turanli[3], I. Fresko[2], F. Gogus[4], E. Senates[5], F. Oguz Savran[6], H. Yazici[2]

- 14 BH…8 hasta DZ, 6 hasta MZ
- 120 kontrol
- Concordance rate
  - 2/6 MZ (%33)
  - 1/8 DZ (%12.5)
  - BH için genetik geçiş %42 olarak tahmin edilmiş

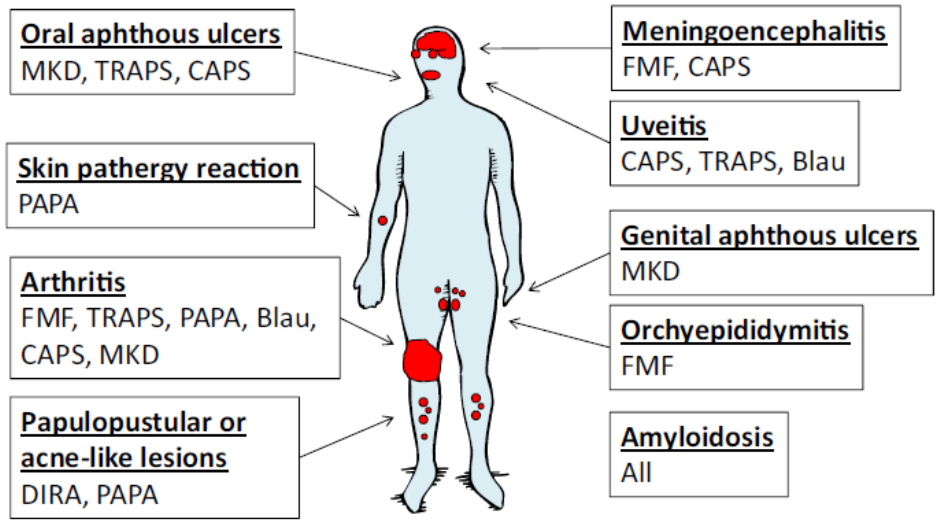



**Fig. 1** Clinical features of Behçet's disease overlapping with monogenic autoinflammatory disorders. *Abbreviations*: *MKD* mevalonate kinase deficiency, *TRAPS* tumour necrosis factor receptor-associated periodic syndrome, *CAPS* cryopyrin-associated periodic syndrome, *FMF* familial Mediterranean fever, *PAPA* pyogenic arthritis, pyoderma gangrenosum and acne syndrome, *DIRA* deficiency of interleukin-1 receptor antagonist

Gül A. Pathogenesis of Behçet's disease: autoinflammatory features and beyond. Semin Immunopathol. 2015 Jul;37(4):413-8.

**Table 1** Summary of tissue involvement per MHC-I-opathy, organised per clinical specialty (references underlying the summarised data and scores can be found in online supplemental table 1

| | Disease | PsO* | PsA† | SpA | B*27 AU | BD | BU |
|---|---|---|---|---|---|---|---|
| Medical specialty | Primary risk MHC-I-allele(s) | C*06 | C*06/B*27 | B*27 | B*27 | B*51 | A*29 |
| | Prognosis worse when primary MHC-I allele present | 3 | 0 | 3 | n.a | 3 | 0 |
| Ophthalmology | Uveitis‡ | 1 | 1 | 3 | 3 | 3 | 3 |
| Dermatology | Oral ulcerations | 0 | 1 | 1 | 0 | 3 | 0 |
| Dermatology | Genital ulcerations | 0 | 0 | 0 | 0 | 3 | 0 |
| Dermatology | Psoriasiform dermatitis§ | 3 | 3 | 2 | 2 | 1 | 1 |
| Dermatology | Pustular lesions¶ | 2 | 2 | 1 | 0 | 3 | 0 |
| Dermatology | Erythema nodosum-like lesions | 0 | 0 | 0 | 0 | 3 | 0 |
| Rheumatology | Spondylitis | 1 | 3 | 3 | 3 | 1 | 0 |
| Rheumatology | Arthritis | 2 | 3 | 3 | 2 | 3 | 0 |
| Rheumatology | Enthesitis | 2 | 3 | 3 | 3 | 1 | 0 |
| Rheumatol/immunol | Vasculitis** | 1 | 1 | 1 | 0 | 3 | 0 |
| Gastroenterology | Inflammatory bowel disease | 1 | 1 | 2 | 1 | 2 | 0 |
| Internal medicine | Comorbid hypertension | 1 | 2 | 2 | 0 | 0 | 2 |
| Neurol/Int Med/cardiol | Comorbid cardiovasc disease | 2 | 2 | 2 | 0 | 1 | 0 |
| | Legend: | 3 | part of the disease ectrum | | | | |
| | | 2 | regularly reported | | | | |
| | | 1 | infrequently reported | | | | |
| | | 0 | | | | | |

3 part of the disease spectrum.
2 regularly report.
1 infrequently reported.
0 either unknown / no reports / not present.

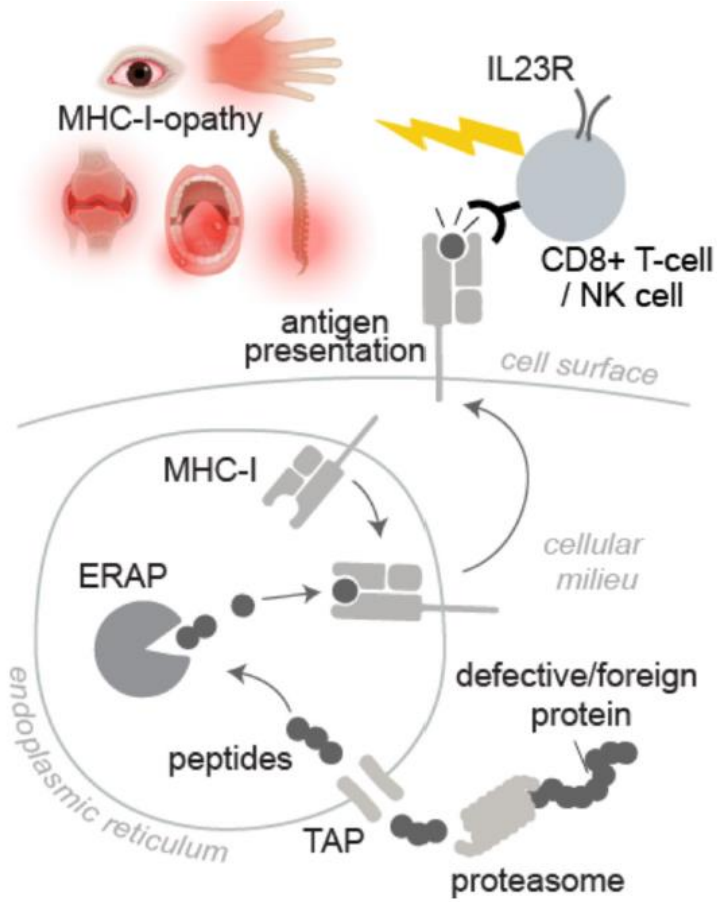



**Figure 1** An overview of the role of the MHC-I pathway in MHC-I-opathies. The proteasome produces peptide fragments that are transported into the endoplasmic reticulum by the transporter associated with antigen processing (TAP) and trimmed by ERAP1 and ERAP2 (ERAP) to a length of 8-11 amino acids before binding to MHC-I molecules. After trafficking to the cell surface the MHC-I-peptide complex is "read out" by surveying immune cells, triggering antigen-specific CD8+ T cell responses or natural killer (NK) cell activation. MHC-I-opathies are genetically associated with functionally distinct variants of MHC-I and ERAP which alter the peptide repertoire presented by MHC-I. Autoreactive T cells in the periphery that escape tolerance mechanisms and promote inflammation against self-peptide epitopes. Biorender software was used to create elements from this figure under an academic license.

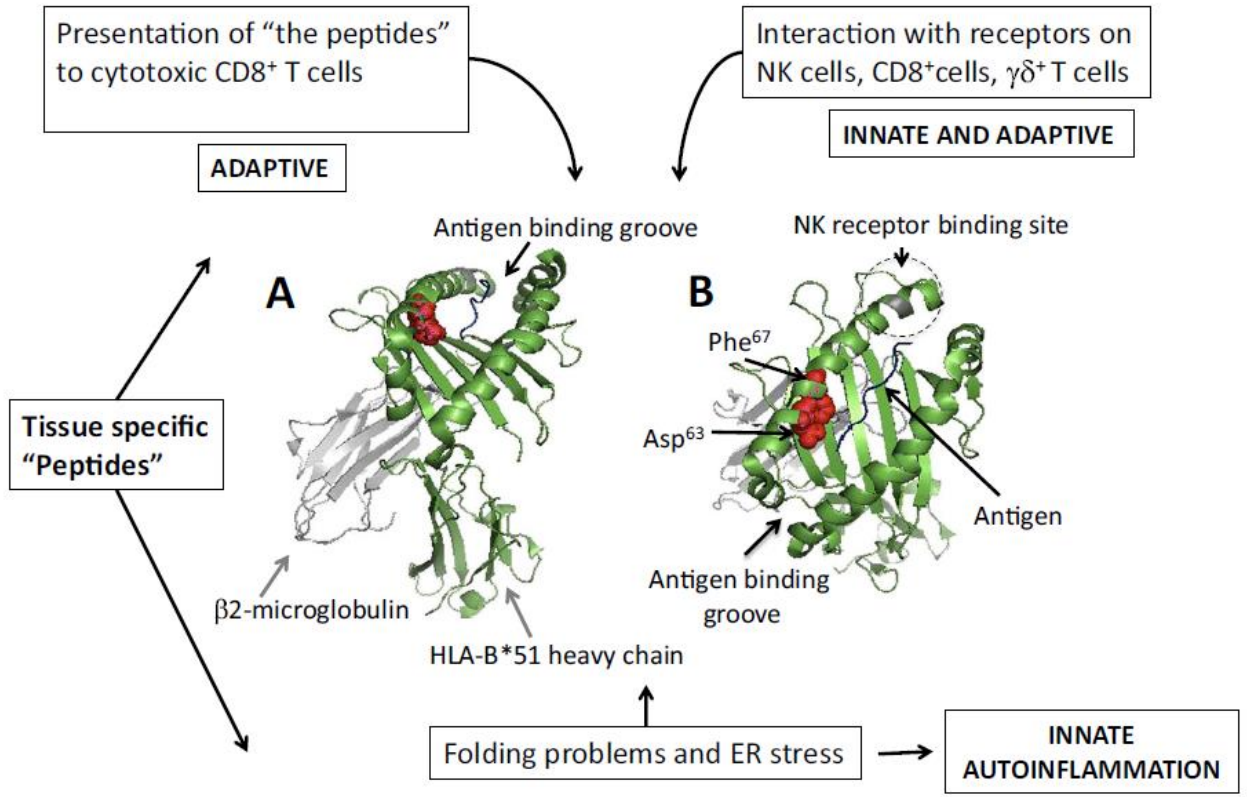
- HLA dışı genler
  - intercellular adhesion molecule (ICAM) 1
  - endothelial nitric oxide synthase
  - TNF
  - vascular endothelial growth factor (VEGF)
  - manganese superoxide dismutase
  - cytochrome P450
  - interleukin (IL) 10
  - IL-23 receptor

# HLA B51

- HLA B51 ile olan ilişki uzun zamandır bilinmekte
  - 1974
- HLA B51 allel taşıyıcılarında BH için OR: 5.78 (95% CI, 5.00-6.67)
- Sıklık
  - Hastalarda: %34-65
  - Kontrollerde: %11-22

de Menthon M, et al. HLA-B51/B5 and the risk of behcet's disease: a systematic review and meta-analysis of case-control genetic association studies. Arthritis Care Res 2009;61(10):1287e96.

**Fig. 2** Possible HLA-B*51-related pathogenic mechanisms in Behçet's disease




HLA B51 NK hücreleri ile α1 heliksinin 77-83 aa aracılığı ile etkileşime geçiyor (Bw4 motif)

Semin Immunopathol (2015) 37:413–418

- HLA B51 pozitif bireylerde
  - ERAP-1 polimorfiziminin tanımlanması
  - HLA B51’in peptid bağlayan kısmına yüklenmesindeki önemi ortaya koymuştur.

Gül A. Pathogenesis of Behçet's disease: autoinflammatory features and beyond. Semin Immunopathol. 2015 Jul;37(4):413-8.

- ERAP-1 polimorfizmleri
  - Enzimatik aktiviteyi
  - Peptid spesivitesini
  - Organ spesifik peptidome üretimini
  - Diğer peptidazlarla birlikte BH duyarlılığını etkilemektedir

ERAP-1 allotiplerinin belirlenmesi ve hastalığa katkısının değerlendirildiği

1900 BH

1779 HC

Bu çalışmada Türk popülasyonunda >%1 sıklıklarda 8 tane allotip tanımlanmış.

Sadece Hap 10 hastalıkla ilişki göstermekte

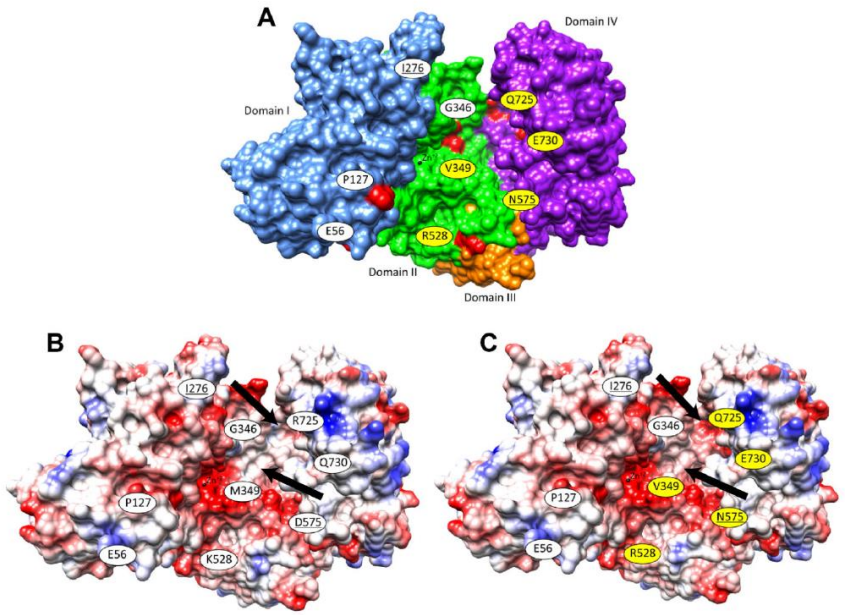



**Figure 1.**
Behçet's disease-associated form of ERAP1. (A) Surface representation of ERAP1, colored by domain, shows the locations and identities of the common variant amino acid residues (red spheres) in the ERAP1 allotypes, and their proximity to the catalytic $Zn^{2+}$ atom (black sphere). Models displaying the electrostatic surface potential of Hap1 (B) and the Behçet's disease-associated Hap10 (C) demonstrate changes in surface potential near to the catalytic site (black arrows). Ancestral alleles are marked with white labels, non-ancestral alleles are marked with yellow labels; labels of residues not visible are underlined. This model was created using 3MDJ and UCSF Chimera software. In (B) and (C), red coloration indicates positive surface charge, blue indicates negative surface charge, and white indicates neutrality.

Hipoaktif ERAP-1 allotipleri HLA B51'in peptid bağlamasında değişikliklere yol açarak BH riskine katkıda bulunabilmektedir.

HLA B51- ERAP-1/Hap 10 varlığı tek başına HLA B51 varlığına göre hastalık riskini 11 kat artırmakta

**A single endoplasmic reticulum aminopeptidase-1 protein allotype is a strong risk factor for Behçet's disease in HLA-B*51 carriers**

*Ann Rheum Dis.* 2016 December ; 75(12): 2208–2211. doi:10.1136/annrheumdis-2015-209059.

*Ann Rheum Dis*. 2022 November ; 81(11): 1603–1611. doi:10.1136/ard-2022-222277.

# The Behçet's disease risk variant HLA-B51/ ERAP1-Hap10 alters human CD8 T cell immunity

**Ann Cavers**[1,*], **Matthias C. Kugler**[2,*], **Yesim Ozguler**[1,4,3,*], **Arshed F. Al-Obeidi**[5], **Gulen Hatemi**[3,4], **Beatrix M. Ueberheide**[6], **Didar Ucar**[4,7], **Olivier Manches**[8,9], **Johannes Nowatzky**[1,10]

- ERAP-1 Hap10 diğer varyantlara göre düşük enzim aktivitesine sahip
- Hipoaktif ERAP-1 yetersiz kesilmiş uzun peptidleri Class I e sunuyor
- Bunun sonucunda da anormal bir CD8 T hücre yanıtı ortaya çıkıyor
- Bu ilişkinin biyolojik ve fonksiyonel etkisini göstermeyi planlamışlar
- Bu amaçla
  - 26 tedavi almayan aktif BH
  - 22 HC genotipini belirliyorlar
- CRISPR-Cas 9 genom düzenlemesini kullanarak bir in vitro model sistemi oluşturuyorlar ve CD8 T hücresi efektör fonksiyonu aracılığıyla immünojenisite üzerindeki etkisi değerlendiriliyor.

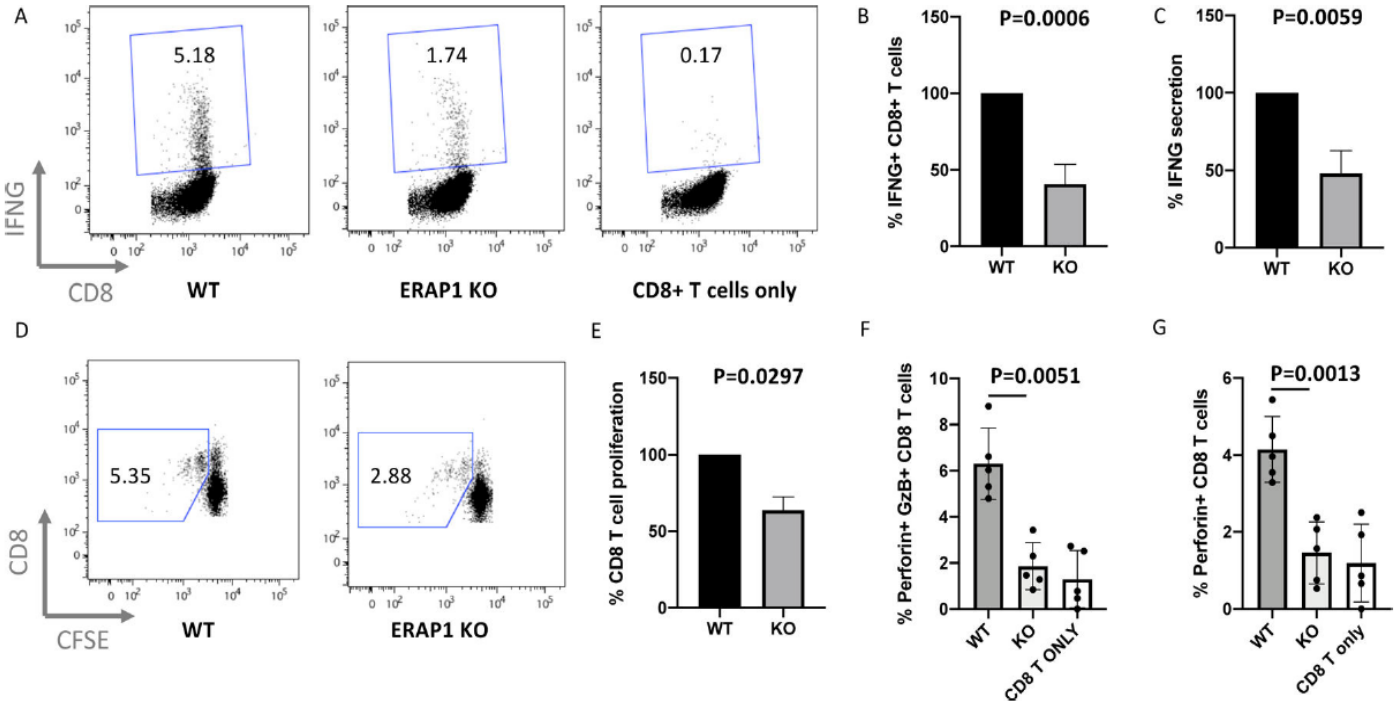



**Fig. 5. Loss of ERAP1 function shifts CD8 T cell immunodominance.**
ERAP1 KO significantly alters immunogenicity of LCL when cocultured with allogeneic human CD8 T cells, assessed here by IFN-gamma production at the single cell (ICS, **A, B**) and bulk (ELISA, **C**) levels. Other effector readouts underpin this finding: CD8 proliferation on CD3-gated PBMC (CFSE, **D, E**), perforin and granzyme B (**F, G**). CRISPR-Cas9 stable HLA-B51+ LCL were transduced with ERAP1-targeting gRNA (KO) or non-sensical gRNA (WT), and co-cultured with allogeneic human CD8 T cells in 1:4 ratio. In the long-term stimulations (**D–G**), LCL were irradiated with 6000 rad. 8 independent experiments. 6 (**A–E**) or 5 (**F,G**) different CD8 T cell donors, all in triplicates. Ratio-paired t-test. Normalized WT with gated examples (**A,B**; **D,E**). Raw data in (**F, G**) show distribution of data. See Sup. Fig. 4 for results of degranulation assays.

- ERAP-1 KO hücrelerde 9 mer den uzun peptid içeren peptidomlar gösterdiler ve wild tip kontrol hücrelerine göre alloreaktif CD8 T hücrelerini uyarmakta belirgin farklılık bulundu.
- Sonuç olarak BH da HLA-B51/ERAP Hap10 risk varyantı antijen ilişkili CD8 aktivitesini değiştirerek immun yanıtını etkileyebilir.

# Sonuç olarak;

- Epidemiyoloji
  - Karşılaştırılmalı çalışmalara ihtiyaç var
  - Endemik olmayan bölgelere göç edenler (yeni vs 2 veya 3. kuşak)
    - Çevresel faktörlerin patogenez üzerine değerlendirilmesine de olanak sağlamış olabilir
- Genetik
  - HLA B51 dışı genetik yük
  - Kompleks
  - Epigenetik çalışmalar az miktarda