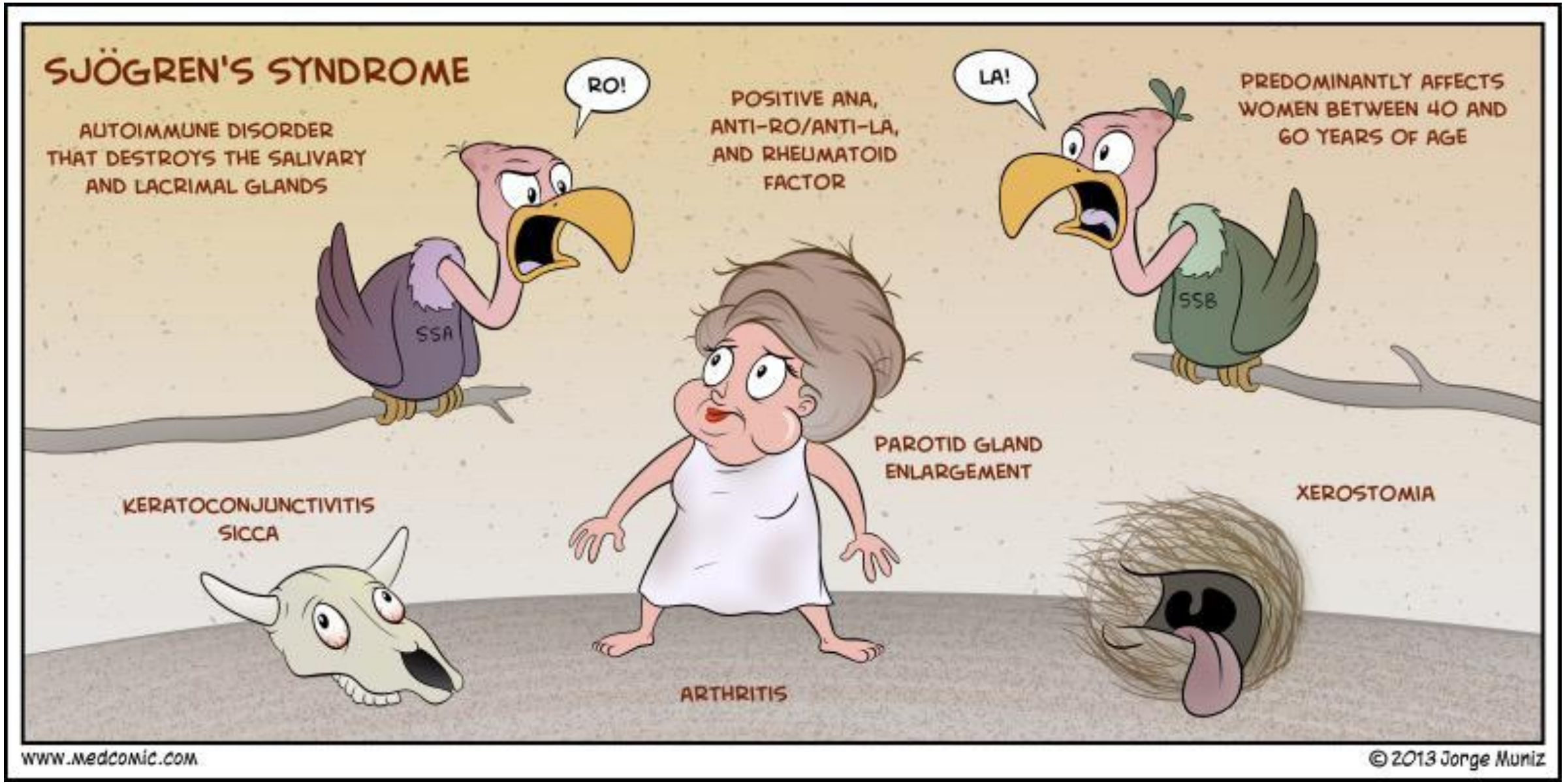
Sjögren Sendromu; Epidemiyoloji ve Genetik

Prof. Dr. Fatoş Önen

DEÜTF Romatoloji BD


SJÖGREN'S SYNDROME
AUTOIMMUNE DISORDER THAT DESTROYS THE SALIVARY AND LACRIMAL GLANDS
RO!
SSA
POSITIVE ANA, ANTI-RO/ANTI-LA, AND RHEUMATOID FACTOR
LA!
SSB
PREDOMINANTLY AFFECTS WOMEN BETWEEN 40 AND 60 YEARS OF AGE
KERATOCONJUNCTIVITIS SICCA
PAROTID GLAND ENLARGEMENT
XEROSTOMIA
ARTHRITIS
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Tarihçe

1882 Theodor Karl Gustav von Leber

- Gözde kuruluk ve inflamasyon “keratitis filamentosa”

1892 Jan Mikulicz-Radecki

- Tükürük ve gözyaşı bezlerinde inflamasyon “Mikulicz syndrome ”
- W. B. Hadden → Pilokarpin ile göz kuruluğunda düzelme

1925 Henri Gougerot

- Generalize muköz kuruluk (göz, ağız, burun, trakea ve vajina) ve tükürük bezlerinde atrofi

1933 Henrik Samuel Conrad Sjögren

- Keratokonjunktivitis sikka (Rose Bengal ve methylene blue)
- PhD tezi, 19 KKS’lı kadın hasta (13’ünde artrit) → “Sjögren sendromu”
- 1957 Gothenburg Üniversitesi “Doktor”
- 1961 İsveç Hükümeti onursal “Profesör”

Epidemiyoloji

İnsidans ve Prevalans

- Bir hastalığın epidemiyolojisini anlatan en önemli 2 gösterge;
  - İnsidans, spesifik bir periyodda yeni pSJS olgusu gelişim riskini ölçer
  - Prevalans, pSJS bulunan nüfus oranıdır
  - Hastalığın yükünü tanımlamada ve etiyolojisini anlamada insidans ve prevalans çalışmaları önemli ipuçları verir

- Çalışma yöntemleri, kullanılan sınıflandırma kriterleri, çalışılan nüfusun özelliklerindeki farklılıklar vb nedenlerle sonuçlar arasında tutarsızlıklar gözlenmektedir

Sistematik Derleme; 2007

Clinical and Experimental Rheumatology 2007; 25: 1-4

EDITORIAL

Epidemiology of Sjögren's syndrome: where are we now?

A. Binard[1], V. Devauchelle-Pensec[1], B. Fautrel[3], S. Jousse[1], P. Youinou[2], A. Saraux[1]

[1]Rheumatology Unit and [2]Laboratory of immunology, Brest Teaching Hospital, Brest, France; [3]Rheumatology Unit, Pitié-Salpétrière Teaching Hospital, Paris, France.

Primary Sjögren's syndrome (pSS) is an autoimunne disease characterized by lymphocytic infiltration of the exocrine glands. Keratoconjunctivitis sicca and xerostomia related to lachrymal and salivary gland infiltration, respectively, are the main clinical manifestations. Asthenia may be present also. However, symptoms vary widely across patients in their nature and severity, a fact that hinders case ascertainment. Diagnostic criteria for pSS are required by both physicians and patients in order to

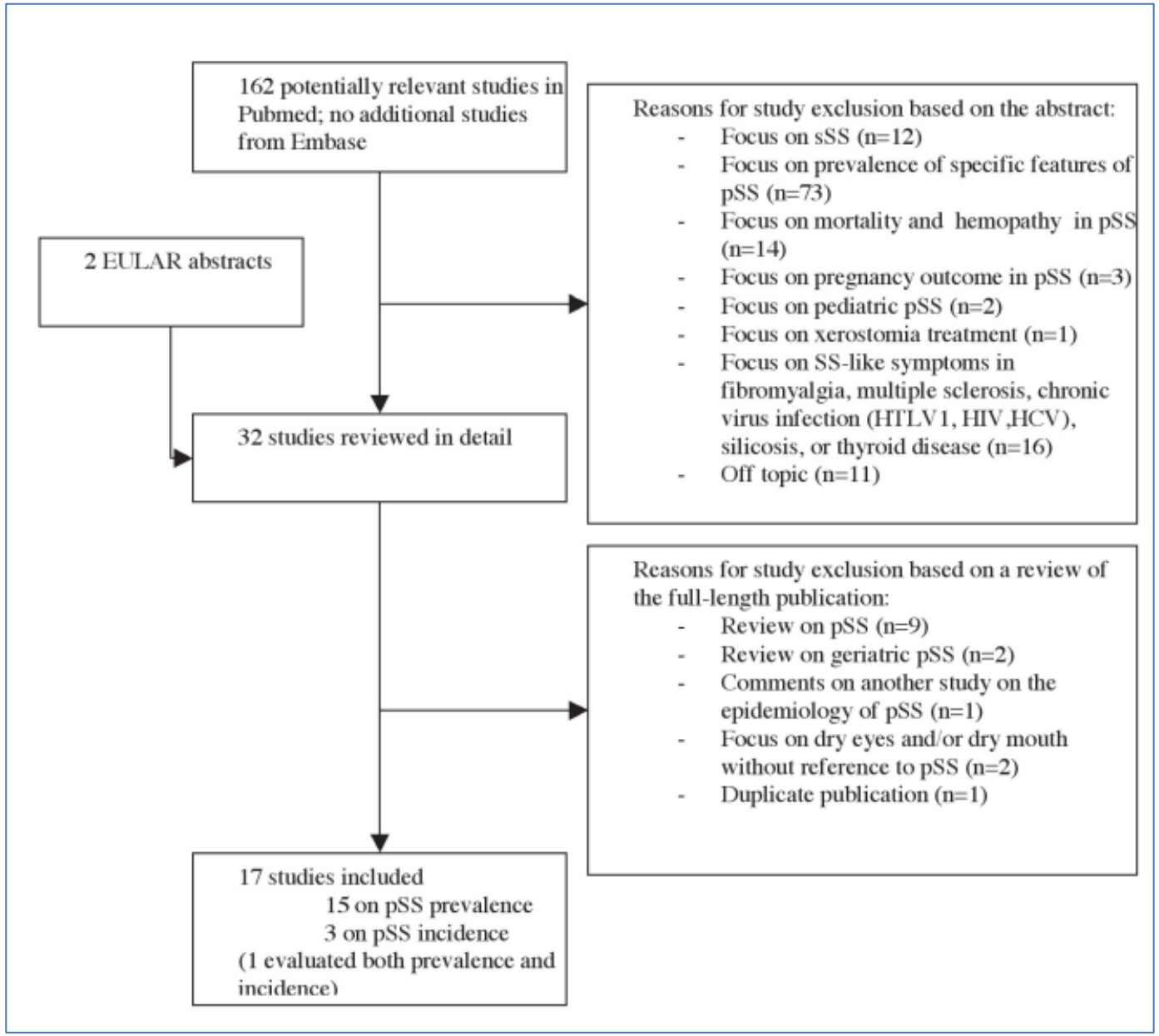
studies. The abstract databases of the American College of Rheumatology and European League against Rheumatism meetings held in 2004 and 2005 were searched.

The abstracts of the publications retrieved by the search strategy were used to select publications relevant to the study. The full-length versions of these publications were printed out and reviewed in detail. We did not use validated instruments to assess the quality of the selected studies. For

Seçilen çalışmaların kalitesi değerlendirilmemiş

Yöntem; Akış Şeması

Binard A, et al. CER 2007



Genel Populasyonda pSjS Prevalansı/İnsidansı; 13 Çalışma

Binard A, et al. CER 2007

Year, country (reference no)	Diagnostic criteria	Population size (n)	Prevalence % (95% CI)	Incidence per 10^5 (95% CI)
2006, Greece (2)	AECC	488 435	0.092 (0.08-0.10)	5.3 (4.5-6.1)
2004, UK (3)	AECC	548	0.4 (0.04-1.32)	-
2005, Greece (4)	AECC	8740	0.15 (0.09-0.21)	-
1997, Denmark (5)	Copenhagen	499	0.2 to 0.8	-
2004, Turkey (6)	AECC	2835	0.21 (0.08-0.46)	-
1995, China (7)	San Diego	2066	0.34 (0.44-1.25)	-
2004, Turkey (6)	European	2835	0.35 (0.17-0.65)	-
1997, Denmark (5)	European	499	0.6 up to 2.1	-
1999, Slovenia (8)	European (definite pSS)	339	0.6 (0.07-2.16)	-
1997, Greece (9)	European (definite pSS)	837	0.6 (0.19-1.39)	-
2004, Turkey (10)	AECC	939	0.6 (0.24-1.39)	-
1995, China (7)	Copenhagen	2066	0.77 (0.44-1.25)	-
2004, Turkey (10)	Revised Japanese criteria	939	1.4 (0.74-2.37)	-
2004, Turkey (10)	European	939	1.5 (0.85-2.57)	-
1998, UK (11)	European	616	2.1 (1.13-2.58)	-
1989, Sweden (12)	Copenhagen	705	2.7 (1.0-4.5)	
1997, Greece (9)	European (definite/probable pSS)	837	3.59 (2.43-5.08)	-
2001, USA (13)	Physician diagnosis from 1976 to 1992	~100 000	-	3.9 (2.8-4.9)
2004, Slovenia (14)	European	241	-	3.9 (1.1-10.2)

95%CI: 95% confidence interval; AECC: American European Consensus Criteria; pSS: primary Sjögren's syndrome.

İlk Tarama Fazında Uygulanan Ankete Göre Çalışmaların Pozitif Prediktif Değeri

Binard A, et al. CER 2007

Ref (n°)	Diagnostic criteria	Population size (n)	Question-naire+ (n)	FP (n)	TP (n)	PPV (%)
(5)	Copenhagen	499	189	188	1	0.53
(5)	European	499	189	186	3	1.59
(10)	AECC	939	186	180	6	3.23
(6)	AECC	2835	159	153	6	3.77
(11)	European	616	341	328	13	3.81
(6)	European	2835	159	149	10	6.29
(10)	Revised Japanese criteria	939	186	173	13	6.99
(10)	European	939	186	172	14	7.53
(9)	European (definite SS)	837	45*	30	5	11.11
(3)	AECC	548	4	2	2	50.00
(9)	European (definite/probable SS)	837	45*	5	30	66.67

FP: False positive; TP: True positive, PPV: positive predictive value.
*In this study, 10 of 45 women refused further testing; in order to obtain a conservative (lower) PPV estimate for this study, we considered that all 45 women had false-positive questionnaires.

Sistematik Derleme ve Metaanaliz; 2015

EXTENDED REPORT

Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis

Baodong Qin,[1] Jiaqi Wang,[2] Zaixing Yang,[1] Min Yang,[1] Ning Ma,[1,3] Fenglou Huang,[1,4] Renqian Zhong[1]

Handling editor Tore K Kvien

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ABSTRACT

Objective Epidemiological studies of primary Sjögren's syndrome (pSS) are crucial for describing the burden to society and the public medical system and for shedding light on aetiology. Previous reports of the epidemiology of pSS show variable outcomes. We conducted a systematic review of the epidemiology of pSS to assess the prevalence rates (PRs) and incidence rates (IRs), and to investigate possible geographic variations in pSS.

Methods A systematic literature search of PubMed and Embase (updated to 22 October 2013) was performed to identify all published reports on the epidemiology of pSS. The incidence and prevalence rates of pSS were summarised with IRs or PRs and 95% CIs.

Results The literature search yielded 1880 related citations. Only 21 fulfilled the inclusion criteria. According to a random-effects model, the pooled IR for pSS was 6.92 (95% CI 4.98 to 8.86) per 100 000 person-years. The overall PR was 60.82 (95% CI 43.69 pSS. Insight into the incidence and prevalence of pSS would be advantageous to describe the burden of the disease and to better understand its aetiology. Several studies have investigated the incidence and prevalence of pSS, but there were inconsistencies owing to different case-finding, case-ascertainment and populations under study. Until now, epidemiological studies of pSS have not been systematically summarised. In the present study, we systematically reviewed the literature regarding incidence and prevalence rates and conducted a meta-analysis to provide recommendations for future studies describing the epidemiology of pSS.

METHODS

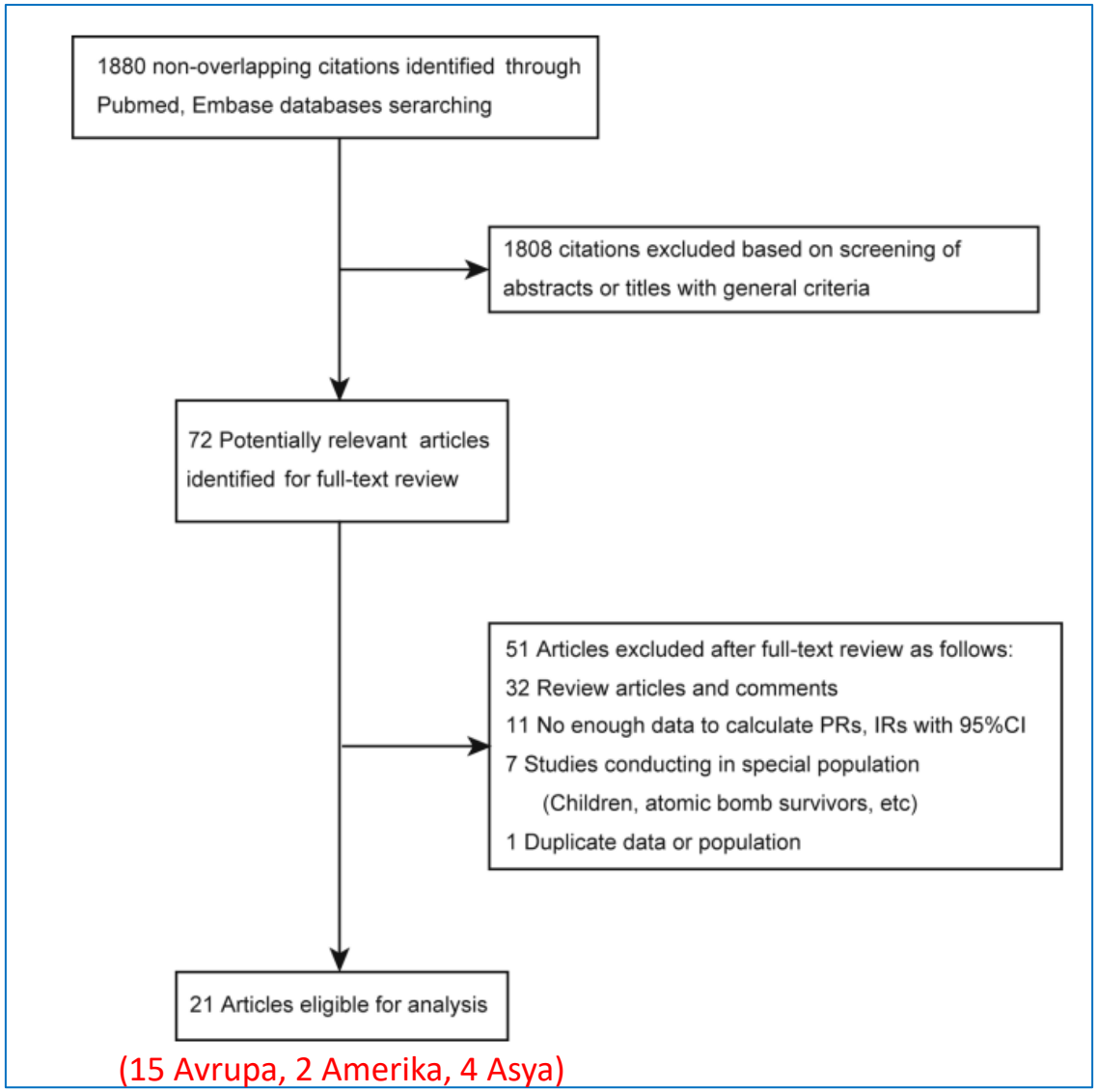
Search strategy

We conducted a systematic literature search with a predetermined protocol according to guidelines set by Meta-analysis of Observational Studies in

Ann Rheum Dis 2015;74:1983–1989

Yöntem; Akış Şeması

Qin B, et al. ARD 2015



(15 Avrupa, 2 Amerika, 4 Asya)

Qin B, et al. ARD 2015

Primer SjS İnsidansı (/100 000); 6 Çalışma

Table 1 Summary of studies including the incidence of primary Sjogren's syndrome

Author	Year	Country	Study period	Cases finding	Study design	Case ascertainment	Age of patients with pSS*	pSS cases (n)	Person- years	Female/male (n)	IR (95% CI)/100 000	Quality
Pillemer *et al*[31]	2001	USA (Minnesota)	1976–1992	Medical record search	Population based	NS	59.0±15.8	53	1 358 994	51/2	6.90 (5.01 to 8.79)	Good
Plesivcnik Novljan *et al*[32]	2004	Slovenia (Ljubljana)	2000–2002	Medical record search	Population based	EC-1996†	51.3±14.5	71	1 799 685	65/6‡	7.22 (5.47 to 8.98)	Good
Alamanos *et al*[14]§	2006	Greece (north-west Greece)	1982–2003	Medical record search, personal registry physicians	Population based	AECG-2002¶	55.4±12.5	422	7 962 264	402/20	10.10 (9.11 to 11.08)	Good
Weng *et al*[33]	2011	China (Taiwan)	2005–2007	NHI Research Database	Population based	NS	53.5±14.2	3352	55 866 666	3040/312	11.00 (10.61 to 11.39)	Good
Yu *et al*[13]§	2013	China (Taiwan)	2000–2008	NHI Research Database	Population based	ICD codes System	NS	855	8 066 037	736/119	18.50 (17.16 to 19.84)	Good
See *et al*[19]§	2013	China (Taiwan)	2005–2009	NHI Research Database	Population based	ICD codes system	NS	583	4 953 660	501/83	20.05 (18.29 to 21.80)	Good

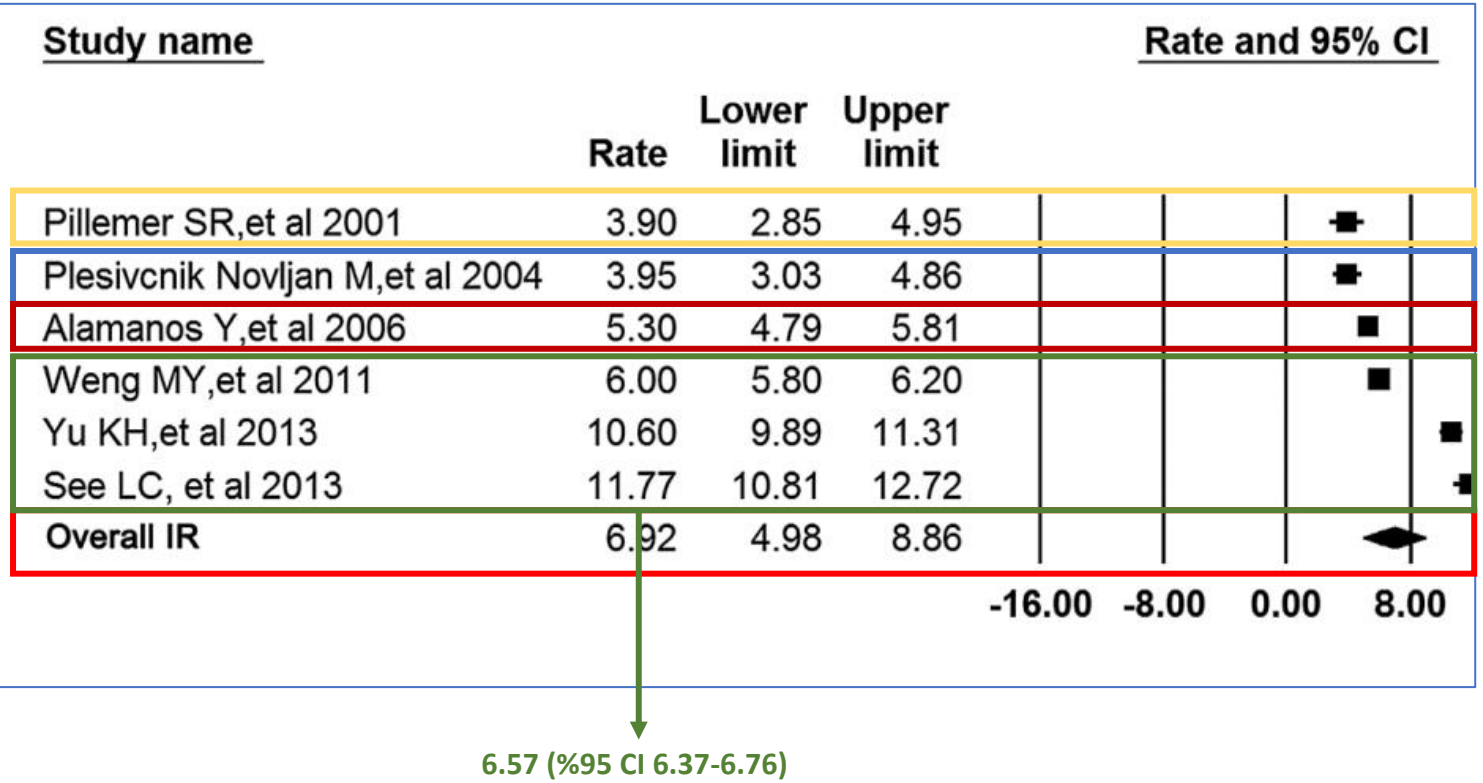
*Ages shown as mean±SD.
†EC-1996 is European classification criteria for Sjogren's syndrome published in 1996.
‡Fifty per cent of the study population was assumed to be female.
§The study reported the prevalence and incidence rate of pSS.¶AECG-2002 is a revised version of the European criteria for Sjogren's syndrome proposed by the American-European Consensus Group in 2002.
NS, no stated; pSS, primary Sjögren's syndrome.

Değerlendirme sırasındaki havuzlanmış yaş:
56.2 (%95 CI 52.5-59.8)

Tüm pSjS İnsidans Tahminleri (/100 000 kişi-yılı)

Qin B, et al. ARD 2015

Figure 2 Overall incidence rate estimates of primary Sjögren's syndrome per 100 000 person-years at risk (meta-analysis using the random-effects model).



Primer SjS Prevalansı; Özet

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Table 2 Summary of studies including the prevalence of primary Sjogren's syndrome

Author	Year	Country	Source					Female/ male (n)	PR (95% CI)/100 000	Quality
Zhang *et al*[20]	1995	China (Beijing)	Questio Clinical					NS	338.82 (87.82 to 589.81)	Moderate
Dafni *et al*[21]†	1997	Greece (Astakos)							597.37 (73.76 to 1120.98)	Moderate
Thomas, *et al*[22]‡	1998	UK (Manchester)						/1	3790.09 (1729.81 to 5850.36)	Moderate
Tomsic *et al*[23]‡	1999	Slovenia (Ljubljana)	Questionnaire Clinical examination	Population survey	EC-1996	2	332	NS	602.41 (−232.47 to 1437.29)	Moderate
Bowman *et al*[24]†	2004	UK (Birmingham)	Questionnaire Clinical examina					NS	236.41 (−91.23 to 564.04)	Moderate
Trontzas *et al*[25]	2005	Greece	Questionnaire Clinical examina					NS	148.74 (67.89 to 229.60)	Moderate
Kabasakal *et al*[26]†	2006	Turkey (Bornova)	Questionnaire Clinical examin					NS	722.02 (144.29 to 1299.75)	Moderate
Alamanos *et al*[14]§	2006	Greece (north-west Greece)	Medical record Personal registr					402/20	86.40 (78.16 to 94.64)	Good
Haugen *et al*[15]	2008	Norway (Hordaland)	Questionnaire Clinical examination		EC-1993¶	155	16 046	NS	430.01 (328.55 to 531.48)	Moderate
Birlik *et al*[27]	2009	Turkey (Balcova, Narlidere)	Questionnaire Clinical examinatio	Population survey	AECG-2002	6	2887	6/0	207.83 (41.53 to 374.12)	Moderate
Anagnostopoulos *et al*[28]	2010	Greece (Prefecture)	Questionnaire Clinical examinatio					NS	234.60 (4.70 to 464.51)	Moderate
Goransson *et al*[16]§	2011	Norway (Hordaland Rogaland)	Personal registry physiciansMedical					396/28	49.75 (45.01 to 54.48)	Good
Eaton *et al*[18]‡	2011	Denmark	Medical record link					NS	47.79 (45.96 to 49.62)	Good
Sardu *et al*[17]‡	2012	Italy (Sardinia)	Medical record sea					9/1	30.91 (9.49 to 52.32)	Good
See *et al*[19]	2013	China (Taiwan)	Medical record search	Population based	ICD-9	583	1 000 000	NS	58.30 (53.57 to 63.03)	Good
Maldini C, *et al*[29]	2013	France (Pairs)							11.34 (9.42 to 13.27)	Good
Yu *et al*[13]	2013	China (Taiwan)							15.99 (13.46 to 18.51)	Good
Valim *et al*[30]	2013	Brazil (Vitoria)	Questionnaire Clinical examination	Cross-sectional Population survey	AECG-2002	2	1205	NS	60.82 (43.69 to 77.94)	Moderate

Havuzlanmış Prevalans (/100 000)
Populasyon-temelli çalışmalar: 43.03 (25.74-60.31)
Örneklem surveyler: 282.35 (135.32-429.38)

Küçük çalışmalardaki prevalans büyük çalışmalardakinden daha fazla
Metaregresyon → Çalışma dizaynı heterojeniteye katkıda bulunabilir…

Havuzlanmış Prevalans (/100 000)
Avrupa (11 çalışma): 71.22 (%95 CI 48.7-93.7)
Asya (4 çalışma): 44.85 (%95 CI 3.51-86.2)

Güney Amerika (1 çalışma): %0.17

Havuzlanmış Prevalans (/100 000)
ICD kodlaması: 38.60 (%95 CI 17.21-59.99)
AECG (2002): 73.57 (%95 CI 37.51-109.63)
EC-1993: 929.32 (%95 CI 261.01-1597.62)

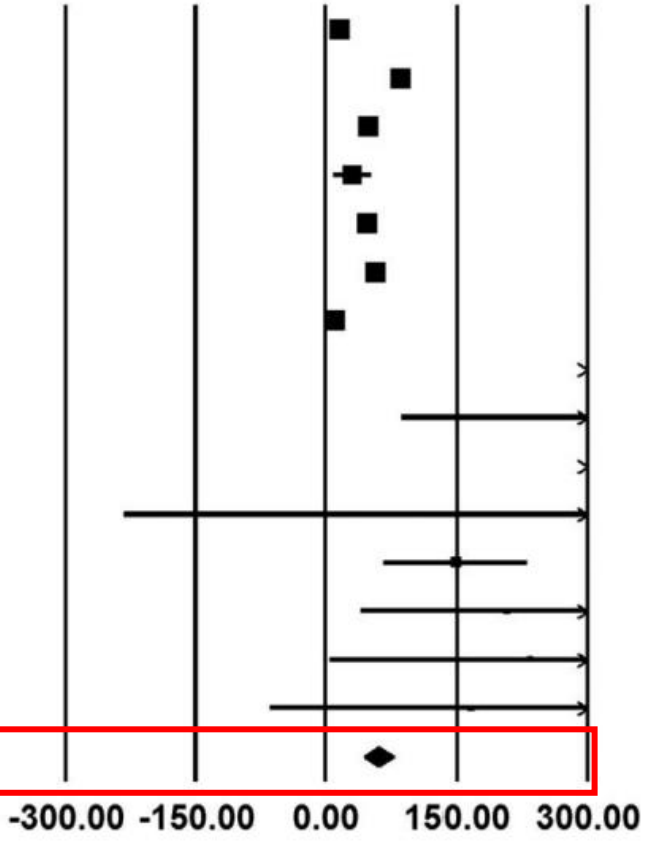
Havuzlanmış kadın/erkek (AECG /2002): 16.10 (%95 CI 12.10-21.42)

pSjS Havuzlanmış Prevalans Hızı (/100 000 kişi)

Qin B, et al. ARD 2015

Figure 4 Pooled prevalence rate for primary Sjögren's syndrome per 100 000 inhabitants across all studies.

Study name	Rate	Lower limit	Upper limit
Yu KH,et al 2013	15.99	13.46	18.51
Alamanos Y,et al 2006	86.40	78.16	94.64
Goransson LG,et al 2011	49.75	45.01	54.48
Sardu C,et al 2012	30.91	9.49	52.32
Eaton WW,et al 2011	47.79	45.96	49.62
See LC, et al 2013	58.30	53.57	63.03
Maldini C,et al 2013	11.34	9.42	13.27
Haugen AJ,et al 2008	430.01	328.55	531.48
Zhang,et al 1995	338.82	87.82	589.81
Thomas et al 1998	3790.09	1729.81	5850.36
Tomsic M,et al 1999	602.41	-232.47	1437.29
Trontzas PI,et al 2005	148.74	67.89	229.60
Birlik M,et al 2009	207.83	41.53	374.12
Anagnostopoulos I,et al 2010	234.60	4.70	464.51
Valim V,et al 2013	165.98	-64.05	396.00
Overall PR	60.82	43.69	77.94



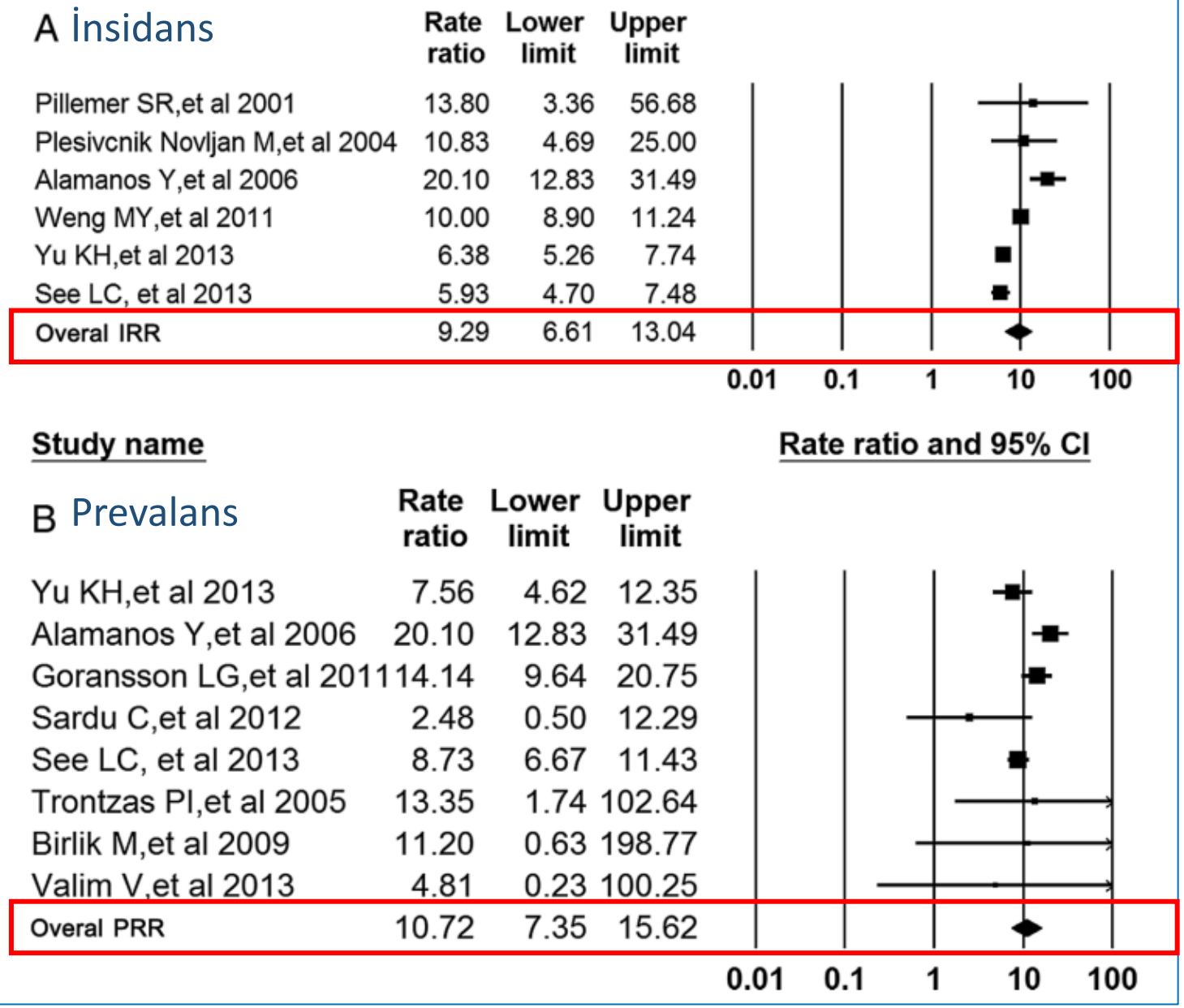
pSjS K/E Oranları

Qin B, et al. ARD 2015

Figure 3 Rate ratios of primary Sjögren's syndrome for females versus males (a, incidence; b, prevalence; meta-analyses using the random-effects model).

Havuzlanmış IR (/100 000);
Kadınlarda: 12.30 (%95 CI 9.07-15.53)
Erkeklerde: 1.47 (%95 CI 0.81-2.12)

Havuzlanmış PR (/100 000);
Kadınlarda: 116.72 (%95 CI 70.39-163.05)
Erkeklerde: 5.53 (%95 CI 2.49-8.58)



Epidemiology of Sjögren Syndrome in Africa

A Scoping Review

Mickael Essouma, MD,†‡ Jean Jacques Noubiap, MD,§*
Madeleine Singwe-Ngandeu, MD,†|| and Eric Hachulla, MD, PhD¶

Background: The epidemiology of Sjögren syndrome (SS) has been extensively studied in America, Europe, and Asia.
Objective: To summarize available data on the epidemiology of SS in Africa.
Methods: MEDLINE, EMBASE, and African Journals Online were searched from inception up to May 17, 2020, to identify relevant articles. Data gleaned from these reports have been summarized narratively in this review.
Results: Twenty-one hospital-based studies were included. These studies reported 744 cases of SS. The mean age at diagnosis varied between 28 and 73.6 years, and the female proportion ranged from 83.3% to 100%. There was no population-based incidence or prevalence. Among people with autoimmune and other rheumatic conditions, the frequency of primary SS was in the range 1.9% to 47.6%, whereas that of rheumatoid arthritis–associated secondary SS was in the range 4.3% to 100%. Sicca symptoms were the commonest features, with most frequently involved organs being joints, lungs, and neurological structures. Main autoantibodies were anti-Ro/SS antigen A, anti-La/SS antigen B, and antinuclear antibodies.
Conclusions: The epidemiology of SS is poorly characterized in Africa. Available data are broadly consistent with those from other populations. Extensive and high-quality research is urgently needed.

Key Words: Africa, epidemiology, Sjögren syndrome

(*J Clin Rheumatol* 2022;28: e240–e244)

risk of pSS is overall similar to that of the general population, it is higher in older patients with parotid enlargement, systemic features including cardiovascular diseases, hypocomplementemia, cryoglobulinemia, infections, and solid as well hematological malignancies.[4]

Epidemiological data on SS in African populations are limited, and these populations are very underrepresented in global epidemiological studies[3,5–8] Recent studies from Europe and America have highlighted some ethnic differences in the phenotypic expression of SS, with earlier onset, reduced gender disparity, and high rates of risk factors for lymphoma being more common in Africans (North African Arabs, sub-Saharan Africans, Afro-Caribbeans, and African Americans) living outside Africa compared with Whites.[5,7,8] However, there is a potential for variations in disease expression, depending on the geographic location, even within the same ethnic group.[5] This raises the need to well characterize the epidemiology of SS in Africa. Accordingly, we conducted a review aiming to summarize available data on the epidemiology of SS in Africa.

METHODS

This review was conducted in accordance with the 5-step approach proposed by Arksey and O'Malley.[9]

Genetik ve Epigenetik

X Kromozomu

- En önemli tek risk faktörü: Kadın cinsiyet (K/E=14/1)
  - Klinefelter sendromlu (47,XXY) kişilerde pSS riski, 46,XX kadınlardakine benzer
  - Turner sendromu (45,X) ile pSS birlikteliği çok nadir
  - 47,XXX kadınlarda pSS prevalansı, 46,XX kadınlardakinin 2.9 katı…

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Review Article

Contribution of Genetic Factors to Sjögren's Syndrome and Sjögren's Syndrome Related Lymphomagenesis

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Table 1: Genetic associations of the HLA alleles with Sjögren's syndrome susceptibility.

Study	Year	Population	Sample size (patients/controls)	Associated HLA alleles
Chused et al. [18]	1977	American Caucasian	110 (19/91)	HLA-Dw3
Fye et al. [22]	1978	American Caucasian	115 (19/96)	HLA-Dw3-HLA-B8
Moutsopoulos et al. [23]	1978	American Caucasian	208 (24/184)	B lymphocytes immune response associated (Ia) antigens
Moutsopoulos et al. [24]	1979	American Caucasian	206 (22/184)	HLA-DRw3-HLA-B8
Manthorpe et al. [27]	1981	Danish	32 (32/—)	HLA-Dw2
Mann and Moutsopoulos [25]	1983	American Caucasian	52 (25/27)	HLA-DRw3-HLA-B8
Molina et al. [28]	1986	American Caucasian	694 (68/626)	HLA-B8 HLA-DR3 DRw52
Moriuchi et al. [29]	1986	Japanese	135 (21/114)	DRw53
Vitali et al. [30]	1986	Italian	90 (28/62)	DR3
Papasteriades et al. [26]	1988	Greek	218 (46/172)	DR-5
Pease et al. [31]	1989	British Caucasian	141 (41/100)	DR-3 DRw52

Morling et al. [41]	1991	Danish	19 (19/—)	DQA1*0501-DQB1*0201-DQA1*0301
Kang et al. [36]	1993	American Caucasian	210 (75/135)	DRB1*03-DRB3*0101-DQB1*0201-DQA1*0501
Kang et al. [36]	1993	Chinese	87 (45/42)	DRB1*0803-DQA1*0103-DQB1*0601
Kang et al. [36]	1993	Japanese	82 (33/49)	DRB1*0405-DRB4*0101-DQA1*0301-DQB1*0401
Roitberg-Tambur et al. [43]	1993	Jews (Israel)	275 (17/258)	DQA1*001-DQA1*0201-DQB1*0501
Roitberg-Tambur et al. [43]	1993	Greek	76 (22/54)	DQA1*0501 HLA-Cw7

- Beyaz ırktaki en tutarlı birliktelikler, DRB1 lokusundaki DR2 ve DR3 allelleri ile…
- DRB1*03 ve DQB1*02 allellerini taşıyan veya DQw1 ve DQw2 heterozigot hastalarda anti-Ro/SSA ve anti-La/SSB ile çok güçlü birliktelik var…

Rishmueller et al. [33]	1998	Australian	244 (80/164)	DR3-DQA1*0501-DQB1*02
Bolstad et al. [34]	2001	Norwegian Caucasian	95 (31/64)	DRB1*03-DQB1*02-DQA1*0501
Nakken et al. [40]	2001	Norwegian Caucasian	210 (29/181)	DRB1*0301
Anaya et al. [39]	2002	Colombian	149 (73/76)	DRB1*0301
Gottenberg et al. [35]	2003	French	371 (149/222)	DRB1*03
Manoussakis et al. [44]	2004	Greek	301 (55/246)	DRB1*0301
Kovács et al. [37]	2006	Hungarian	98 (48/50)	DQB1*0201-DRB1*03-DQB1*0501
Cruz-Tapias et al. [21]	2012	Meta-analysis	7636 (1166/6470)	DQA1*0501-DQB1*0201-DRB1*0301-DQA1*0201-DQA1*0301-DQB1*0501
Li et al. [46]	2013	Chinese	5622 (1845/3777)	HLA class II locus
Lessard et al. [45]	2013	Caucasian	10916 (4712/6204)	HLA class II locus

Table 2: Associations of non-HLA genetic locus with Sjögren's syndrome.

Gene/chromosome	Polymorphism	Population	Sample size (patients/controls)	p value	Relative risk	Study/year
		Interferon pathways				
IRF5/Chr7	rs2004640	Caucasians	364 (210/154)	0.01	1.93	Miceli-Richard et al. 2007 [51]
	rs10488631	Norwegian/Swedish	1079 (368/711)	$2.4 * 10^{-5}$	1.49	Nordmark et al. 2009 [52]
	CGGGG promoter insertion/deletion	Caucasians	824 (385/439)	$6 * 10^{-6}$	2.00	Miceli-Richard et al. 2009 [53]
IRF5/TNPO3/Chr7	CGGGG promoter insertion/deletion	Norwegian/Swedish	1072 (540/532)	$5.5 * 10^{-6}$	1.70	Nordmark et al. 2011 [54]
	rs13246321	Caucasians	10916 (4712/6204)	$2.73 * 10^{-19}$	1.44	Lessard et al. 2013 [45]
STAT4/Chr2	rs3757387	Caucasians	1232 (120/1112)	0.01	1.47	Korman et al. 2008 [55]
	rs7574865	Norwegian/Swedish	1079 (368/711)	0.0014	1.41	Nordmark et al. 2009 [52]
	rs7582694	Colombian/German	800 (277/523)	$7.7 * 10^{-6}$	1.40	Palomino-Morales et al. 2010 [56]
	rs7574865	Norwegian/Swedish	1072 (540/532)	$7 * 10^{-4}$	1.40	Nordmark et al. 2011 [54]
	rs7582694	Chinese	5622 (1845/3777)	$1.77 * 10^{-17}$	1.44	Li et al. 2013 [46]
	rs10168266	Caucasians	10916 (4712/6204)	$6.8 * 10^{-15}$	1.43	Lessard et al. 2013 [45]
	rs10553577			$9.45 * 10^{-9}$	1.32	
	rs13426947			$1.17 * 10^{-10}$	1.30	
IL12A/Chr3	rs485497	Caucasians	10916 (4712/6204)	$9.88 * 10^{-9}$	1.27	Lessard et al. 2013 [45]
	rs583911					
NCR3/NKp30/Chr6	rs11575837	French/Scandinavian	1902 (1010/892)	0.0039	0.48	Rusakiewicz et al. 2013 [57]
	rs2736191			0.0019	0.56	
PTPN22/Chr1	rs2476601	French	3.55 (183/172)	ns	ns	Ittah et al. 2005 [58]
		Colombian	378 (70/308)	0.01	2.42	Gomez et al. 2005 [59]

		B-cell function				
	rs12549796	Norwegian/Swedish	1072 (540/532)	$4.7 * 10^{-4}$	1.37	Nordmark et al. 2011 [54]
	rs7812879	Chinese	1152 (555/597)	0.045	—	Sun et al. 2013 [60]
BLK-FAM167A/Chr8	rs2736345	Caucasians	10916 (4712/6204)	$4.97 * 10^{-10}$	1.30	Lessard et al. 2013 [45]
	rs2729935			$6.85 * 10^{-10}$	1.30	
	rs6998387			$7.96 * 10^{-8}$	1.26	
CXCR5/Chr11	rs7119038	Caucasians	10916 (4712/6204)	$1.0 * 10^{-8}$	0.74	Lessard et al. 2013 [45]
	4936443			$6.82 * 10^{-8}$	0.75	
BAFF/Chr13	−2841 T → C. −2704 T → C. −2701 T → A. −871 C → T	Caucasians	259 (123/136)	<0.001	—	Nossent et al. 2008 [61]
	rs1224141	Greek	330 (193/137)	<0.05	—	Nezos et al 2014 [62]
	rs12583006					
	rs9514828					
	rs1041569					
	rs9514827					
GTF2I/chr7	rs117026326	Chinese	5622 (1845/3777)	$1.31 * 10^{-53}$	2.20	Li et al. 2013 [46]
EBF1/Chr5	rs3843489	Norwegian/Swedish	1072 (540/532)	$9.9 * 10^{-5}$	1.68	Nordmark et al. 2011 [54]
	rs1234315	Norwegian/Swedish		$7.4 * 10^{-4}$	1.34	Nordmark et al. 2011 [54]
Ox40L-TNFSF4/Chr1	rs2205960	Chinese	643 (250/393)	<0.05	—	Kong et al. 2013 [63]
	rs1234313					

Table 2: Continued.

Gene/chromosome	Polymorphism	Population	Sample size (patients/controls)	p value	Relative risk	Study/year
		NF-κB pathway				
TNFAIP3/chr6	rs2230926	Caucasians	(18/397)	0.038	3.38	Musone et al. 2011 [64]
	rs5029939	Chinese	5622 (1845/3777)	$7.75 * 10^{-5}$	1.67	Li et al. 2013 [46]
	rs6933404	Caucasians	10916 (4712/6204)	$6.53 * 10^{-8}$	1.26	Lessard et al. 2013 [45]
	rs35926684			$7.21 * 10^{-8}$	1.26	
	rs2230926	Caucasians	1025 (574/451)	0.01	3.36	Nocturne et al. 2013 [65]
TNIP1/Chr5	rs6579837	Caucasians	10916 (4712/6204)	$3.30 * 10^{-8}$	1.43	Lessard et al. 2013 [45]
	rs7732451			$5.32 * 10^{-7}$	1.34	
	rs3792783	Scandinavian/British	5565 (1105/4460)	$3.4 * 10^{-5}$	1.33	Nordmark et al. 2013 [66]
	rs7708392			$1.3 * 10^{-3}$	1.21	
LTA/LTB/TNF gene clusters	rs1800629	Norwegian/Swedish	1060 (527/532)	$1.6 * 10^{-11}$	—	Bolstand et al. 2012 [67]
	rs909253			$4.42 * 10^{-8}$	—	
BAFF-R/Chr22	His159Tyr	Greek	427 (247/180)	0.01	2.75	Papageorgiou et al. 2015 [68]

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Review

Genetics and epigenetics in primary Sjögren's syndrome

Juliana Imgenberg-Kreuz [1,*], Astrid Rasmussen [2,*], Kathy Sivils [2] and Gunnel Nordmark [1]

GWAS'da pSjS için Belirlenmiş Risk Lokusları

Gene	SNP	OR[a] (95% CI)	*P*-value	Population	References
Risk loci associated at genome-wide significance level (*P* < 5.0E-08)					
HLA-DQB1	rs115575857	3.53 (3.03, 4.11)	7.65E-114	European	Lessard *et al*. [11]
HLA-DQA1	rs116232857	2.53 (2.24, 2.86)	1.33E-96	European	Lessard *et al*. [11]
HLA-DRB1, HLA-DQA1	rs9271573	2.02 (1.82, 2.23)	3.00E-42	Multi-ethnic[b]	Taylor *et al*. [12]
	rs9271573	2.29 (2.01, 2.62)	3.00E-34	European	Taylor *et al*. [12]
	rs9271588	0.57 (0.53, 0.63)	8.52E-37	Han Chinese	Li *et al*. [13]
HLA-DQA1, HLA-DQB1	rs3021302	2.24 (1.97, 2.54)	2.00E-35	Multi-ethnic[b]	Taylor *et al*. [12]
HLA-DQB1, HLA-DQA2	rs9275572	2.28 (1.99, 2.61)	7.00E-33	European	Taylor *et al*. [12]
HLA-DPB1, COL11A2	rs4282438	1.58 (1.45, 1.72)	8.77E-25	Han Chinese	Li *et al*. [13]
MICA	MICA*008	1.90 (1.56, 2.31)	9.37E-09	European	Carapito *et al*. [14]
IRF5-TNPO3	rs3757387	1.44 (1.29, 1.62)	2.73E-19	European	Lessard *et al*. [11]
	rs17339836	1.58 (1.36, 1.84)	2.43E-16	European	Lessard *et al*. [11]
	rs3823536	1.49 (1.34, 1.65)	3.00E-14	Multi-ethnic[b]	Taylor *et al*. [12]
	rs3823536	1.54 (1.36, 1.76)	7.00E-11	European	Taylor *et al*. [12]
	rs59110799	1.72 (1.49, 1.99)	3.00E-13	Multi-ethnic[b]	Taylor *et al*. [12]
	rs3807306	1.50 (1.32, 1.71)	6.00E-10	European	Taylor *et al*. [12]
STAT4	rs10553577	1.43 (1.26, 1.62)	6.80E-15	European	Lessard *et al*. [11]
	rs10168266	1.44 (1.32, 1.57)	1.77E-17	Han Chinese	Li *et al*. [13]
	rs11889341	1.40 (1.26, 1.56)	9.00E-10	Multi-ethnic[b]	Taylor *et al*. [12]
	rs7574865	1.51 (1.31, 1.75)	2.00E-08	European	Taylor *et al*. [12]
IL12A	rs485497	1.30 (1.16, 1.46)	1.17E-10	European	Lessard *et al*. [11]
BLK	rs2736345	1.30 (1.16, 1.47)	4.97E-10	European	Lessard *et al*. [11]
CXCR5	rs7119038	0.74 (0.64, 0.86)	1.10E-08	European	Lessard *et al*. [11]
TNIP1	rs6579837	1.43 (1.20, 1.71)	3.30E-08	European	Lessard *et al*. [11]
OAS1	rs10774671	0.75 (0.66, 0.86)	2.59E-09	European	Li *et al*. [15]
TNFAIP3	rs5029939	1.67 (1.40, 1.99)	7.75E-09	Han Chinese	Li *et al*. [13]
GTF2IRD1-GTF2I-NCF1	rs117026326	2.20 (1.99, 2.43)	1.31E-53	Han Chinese	Li *et al*. [13]
	rs117026326	1.98 (1.67, 2.35)	1.10E-15	Han Chinese females	Song *et al*. [16]
	rs117026326	2.03 (1.06, 2.57)	4.60E-09	Chinese	Zhao *et al*. [17]
IKZF1	rs4917129	0.70 (0.61, 0.79)	4.24E-08	Han Chinese	Qu *et al*. [18]

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Non- MHC Genler

IFN İlişkili Genler

↓

Özellikle anti-Ro/SSA ve anti-La/SSB pozitif hastalarda

GWAS'da pSjS için Belirlenmiş Risk Lokusları

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Non- MHC Genler

B Hücresi ile İlişkili Genler

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Non- MHC Genler

NFkB ile İlişkili Genler

GWAS'da pSjS Düşündürücü Risk Lokusları

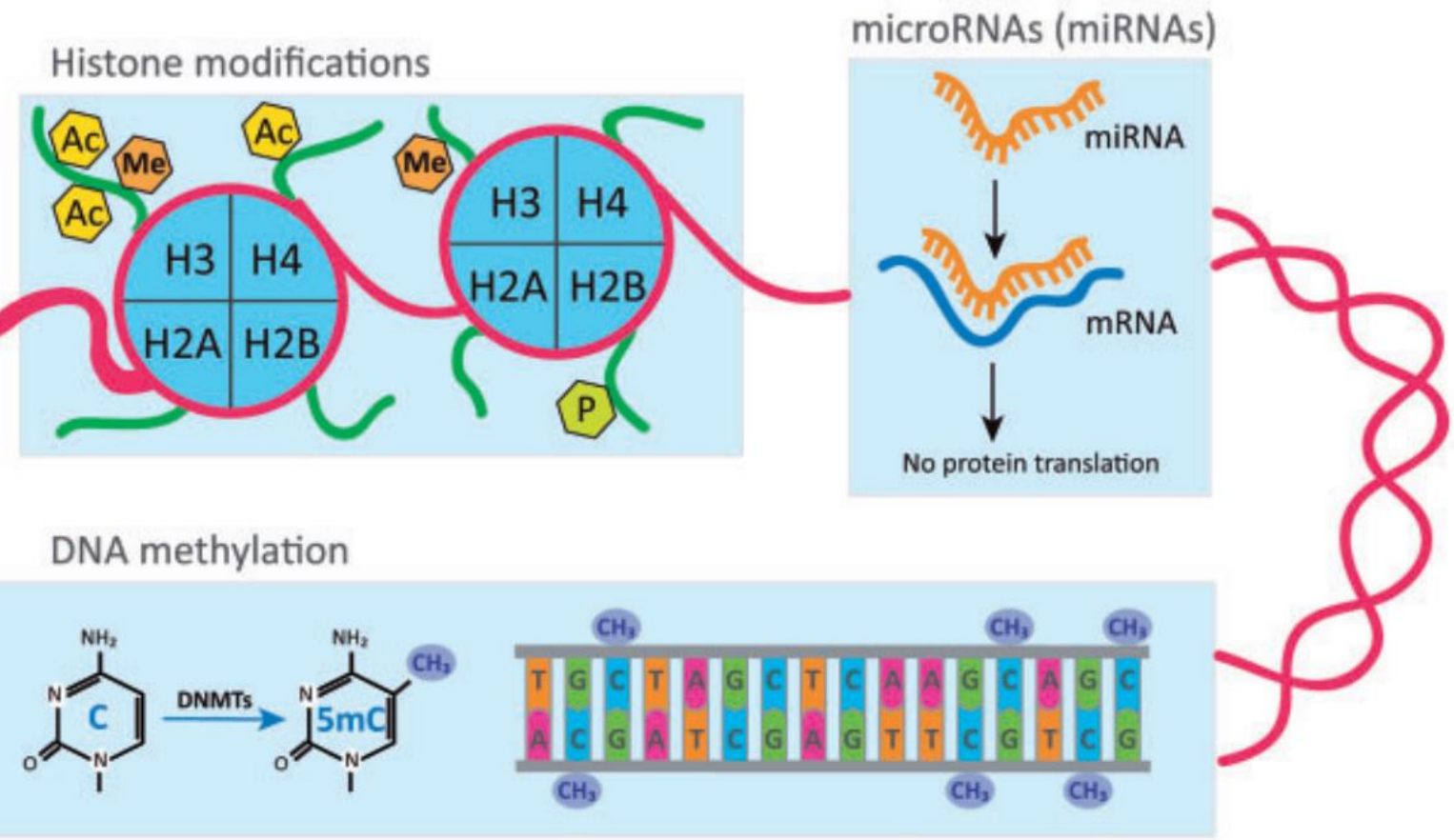
Suggestive risk loci associated at significance level $P > 5.0E-08$

HLA-DPB1	rs9277554	1.65 (1.37, 2.00)	3.00E-07	Asian	Taylor *et al*. [12]
HLA-DPB1/COL11A2	rs3117221	1.47 (1.26, 1.71)	9.52E-07	Han Chinese	Li *et al*. [13]
HLA-DQA1	rs9405117	0.54 (0.42, 0.69)	9.83E-07	Han Chinese	Li *et al*. [13]
HLA-DQB1	rs6928482	1.43 (1.23, 1.66)	2.52E-06	Han Chinese	Li *et al*. [13]
HLA-DMB/PSMB9	rs11756897	1.57 (1.32, 1.87)	2.76E-07	Han Chinese	Li *et al*. [13]
LOC105370283-PTMAP5	rs17074492	1.53 (1.31, 1.79)	6.00E-08	European	Taylor *et al*. [12]
TNFAIP3	rs6933404	1.29 (1.13, 1.47)	6.53E-08	European	Lessard *et al*. [11]
PTTG1	rs2431098	0.81 (0.73, 0.91)	2.28E-07	European	Lessard *et al*. [11]
RELN	rs7341475	1.39 (1.23, 1.57)	3.00E-07	Multi-ethnic[b]	Taylor *et al*. [12]
PDRM1/ATG5	rs548234	1.52 (1.29, 1.78)	3.61E-07	Han Chinese	Li *et al*. [13]
STAT4	rs3821236	1.47 (1.27, 1.71)	2.92E-07	Han Chinese	Li *et al*. [13]
KLRG1	rs1805673	0.62 (0.51, 0.74)	6.00E-07	Asian	Taylor *et al*. [12]
MIS18BP1/LINC00871	rs1957173	0.61 (0.50, 0.74)	7.00E-07	Multi-ethnic[b]	Taylor *et al*. [12]
IRAK1BP1	rs1507153	1.26 (1.11, 1.43)	7.09E-07	European	Lessard *et al*. [11]
HTR2A/LINC00562	rs7999279	1.42 (1.23, 1.63)	1.00E-06	Multi-ethnic[b]	Taylor *et al*. [12]
SHISA9	rs9938751	0.59 (0.48, 0.73)	1.00E-06	European	Taylor *et al*. [12]
ZNF208	rs10416159	1.49 (1.26, 1.75)	1.54E-06	Han Chinese	Li *et al*. [13]
PRCC/SH2D2A	rs16837677	1.54 (1.29, 1.84)	2.00E-06	Multi-ethnic[b]	Taylor *et al*. [12]
NFAT5	rs7192380	1.28 (1.16, 1.42)	2.00E-06	Multi-ethnic[b]	Taylor *et al*. [12]
ITSN2	rs1545257	0.81 (0.71, 0.91)	2.47E-06	European	Lessard *et al*. [11]
LINC00648/RPS29	rs67617551	0.62 (0.50, 0.76)	2.73E-06	Han Chinese	Li *et al*. [13]
EGLN3/SPTSSA	rs712299	1.48 (1.25, 1.74)	2.84E-06	Han Chinese	Li *et al*. [13]
PRDM1	rs526531	1.22 (1.09, 1.38)	2.93E-06	European	Lessard *et al*. [11]
PDE8B	rs181851	0.67 (0.56, 0.79)	3.00E-06	European	Taylor *et al*. [12]
NACC2	rs4842091	1.39 (1.21, 1.61)	5.00E-06	European	Taylor *et al*. [12]
GRIP2/CCDC174	rs79407237	0.61 (0.49, 0.75)	5.00E-06	European	Taylor *et al*. [12]
ZNF43/ZNF208	rs2522092	1.45 (1.24, 1.70)	5.86E-06	Han Chinese	Li *et al*. [13]
PHIP	rs10943608	1.23 (1.08, 1.40)	6.22E-06	European	Lessard *et al*. [11]
C7orf72, IKZF1	rs4917014	0.68 (0.57, 0.81)	9.86E-06	Han Chinese	Li *et al*. [13]
RBMS3	rs13079920	1.35 (1.17, 1.55)	2.90E-05	Han Chinese	Song *et al*. [16]
GTF2IRD1-GTF2I-NCF1	rs117026326	3.12 (1.36, 7.17)	7.30E-03	European American	Zhao *et al*. [17]

Gen Ekspresyonunun Düzenlenmesinde Yer Alan Ana Epigenetik Mekanizmalar

Histon proteinlerinin N-terminal ucunda yer alan kovalan post-translasyonal modifikasyonlar: H3 ve H4 histonlarda lizin rezidülerinin Ac, Me ve P

Kromatin yapısını ve DNA'nın transkripsiyonel ulaşılabilirliğini düzenleyerek gen ekspresyonunu değiştirebilir….



DNA metilasyonu, tipik olarak CpG dinükleotidlerinde görülen, C rezidülerinin 5mC'ye kovalan modifikasyonudur….

TABLE 3 Epigenetic studies in primary Sjögren's syndrome

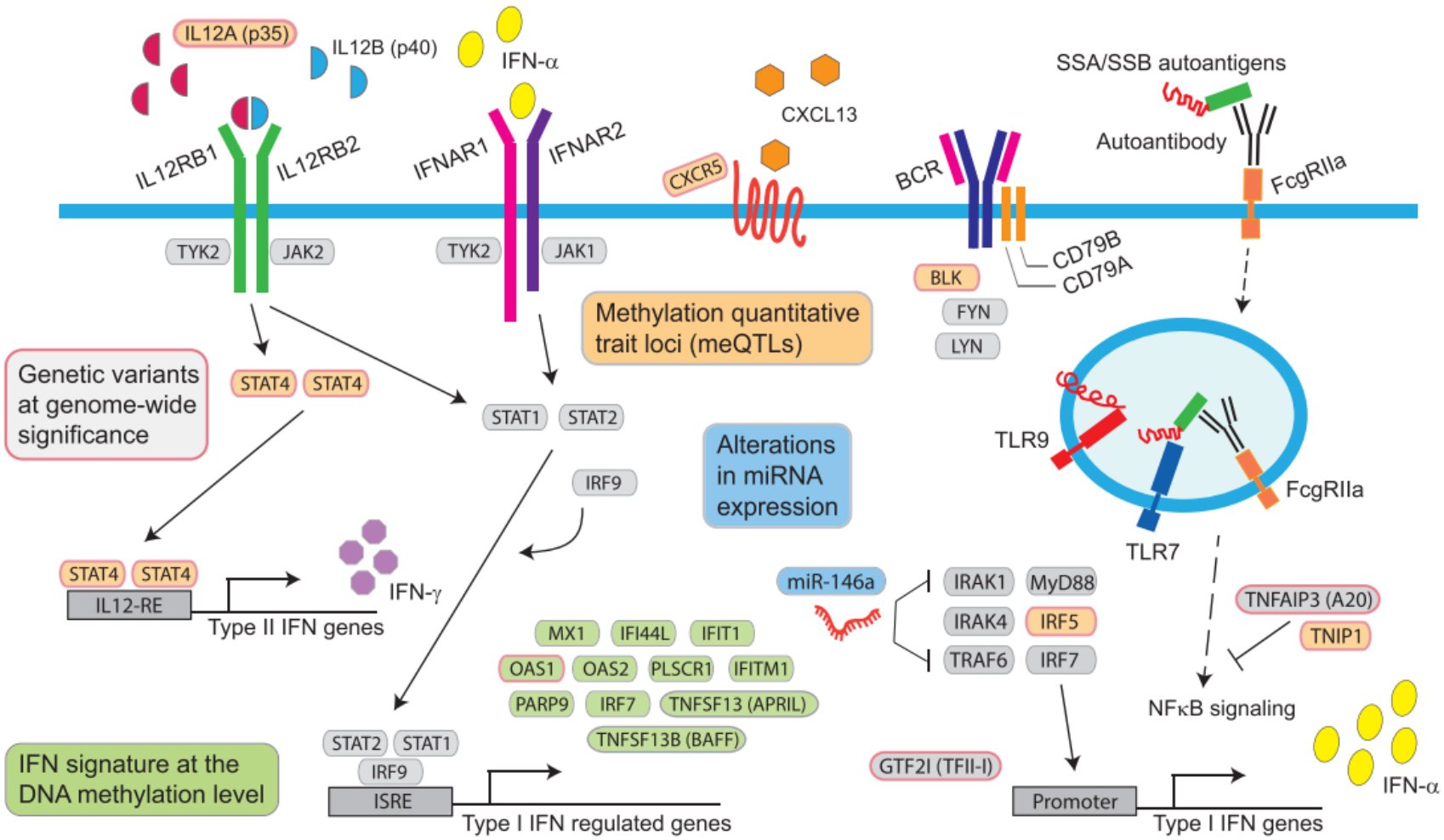
Genome-wide studies of DNA methylation using HM450k array technology			
Cells/tissues	**Number of cases/controls**	**Main outcome**	**References**
Naïve $CD4^+$ T cells	11/11	Hypomethylation at *LTA* and IFN-induced genes	Altorok *et al*. [75]
$CD4^+$ T cells, $CD19^+$ B cells	26/22	Larger methylation differences in B cells than in T cells	Miceli-Richard *et al*. [76]
Whole blood, $CD19^+$ B cells, minor salivary glands	100/400, 24/47, 15/13	Hypomethylation at IFN-induced genes; meQTL effects at pSS GWAS risk loci	Imgenberg-Kreuz *et al*. [77]
Whole blood	24/24 (case–case)	Hypomethylation at a ncRNA in high fatigue	Braekke-Norheim *et al*. [78]
Minor salivary glands	13/13	Enrichment for differential methylation in promoters	Cole *et al*. [79]
SGECs	8/4	Hypomethylation at IFN-induced genes	Charras *et al*. [80]

AB: autoantibody; meQTL: methylation quantitative trait loci; RT-qPCR: reverse transcriptase quantitative PCR; SGECs: salivary gland epithelial cells.

Studies of differential miRNA expression			
Method	**Cells/tissues**	**Main outcome**	**References**
RT-qPCR	PBMCs	Dysregulation of miR-146a/b, miR-155, miR-223, miR-483-5p	Pauley *et al*. [81], Kapsogeorgou *et al*. [82], Zilahi *et al*. [83], Shi *et al*. [84], Gourzi *et al*. [85], Chen *et al*. [86]
	SGECs	Upregulation of miR-200b-5p, in AB-positive pSS down-regulation of let-7b	Kapsogeorgou *et al*. [82], Gourzi *et al*. [85]
		Downregulation of miR200-5p predictive of pSS lymphoma	Kapsogeorgou *et al*. [87]
	Minor salivary glands	Dysregulation of miR-16 and miR-181a	Gourzi *et al*. [85], Wang *et al*. [88]
RT-qPCR OpenArray	Serum	Correlation of miRNA expression with clinical parameters	Lopes *et al*. [89]
Microarray	PBMCs	Upregulation of miR-181a	Peng *et al*. [90]
	$CD14^+$ monocytes	Dysregulation of miRNAs in TGF-β pathway	Williams *et al*. [91]
	$CD4^+$ T cells, $CD19^+$ B cells	Inverse correlation of miR-30b-5p and *BAFF* expression in B cells	Wang-Renault *et al*. [92]
	Minor salivary glands	Inverse correlation of miR-768-3p and miR-574 with focus score	Alevizos *et al*. [93]
Next-generation sequencing	PBMCs	Downregulation of miR-105-5p	Chen *et al*. [94]
	Minor salivary glands	Upregulation of miR-5100	Tandon *et al*. [95]

AB: autoantibody; meQTL: methylation quantitative trait loci; RT-qPCR: reverse transcriptase quantitative PCR; SGECs: salivary gland epithelial cells.

FIG. 3 Schematic summary of genetic and epigenetic mechanisms associated with pSS susceptibility



Boxes with pink borders represent genes with SNPs associated with pSS susceptibility at genome-wide significance outside of the HLA region and include *BLK*, *CXCR5*, *GTF2I*, *IL12A*, *IRF5*, *OAS1*, *STAT4*, *TNFAIP3* and *TNIP1*. Green boxes: IFN-induced genes such as *MX1*, *IFI44L*, *OAS1*, *OAS2*, *TNFSF13B* and *IRF7,* with hypomethylated CpG sites in pSS. Orange boxes: meQTLs, referring to association between a genetic variant (SNP) and the methylation level at a nearby CpG site demonstrated at *BLK*, *CXCR5*, *IL12A*, *IRF5-TNPO3*, *STAT4* and *TNIP1*. Blue boxes: Alterations in miRNA expression, including miRNA-146a, have been identified in pSS. meQTL: methylation quantitative trait loci.

Özet

- Yeni bir meta-analiz ile pSjS insidansı 6.9/100 000 kişi-yılı ve prevalansı 60.82/100 000 olarak tahmin edilmiştir. K/E insidans oranı 9.29, prevalans oranı ise 10.72 olarak bulunmuştur

- Son yıllarda tamamlanan GWAS çalışmaları ile pSjS'de HLA genleri ile güçlü birliktelik net olarak gösterilmiştir; non-HLA genleri IRF5 ve STAT4 ile ilişki daha zayıftır

- Genetik risk varyantlarının çoğu intergenik bölgelerde bulunur ve çoğunun fonksiyonel etkisi net olarak anlaşılmamıştır

- DNA metilasyonu, histon modifikasyonu gibi epigenetik mekanizmalar ve miRNA'lar gen ekspresyonu üzerindeki düzenleyici etkileri ile pSjS patogenezinde yer alır