Review

Non-HLA genes in ankylosing spondylitis: what meta-analyses have shown?

A. Chatzikyriakidou[1], P.V. Voulgari[2], A.A. Drosos[2]

[1]*Laboratory of General Biology and Genetics, Medical School, Aristotle University of Thessaloniki, Greece, and* [2]*Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Greece.*

Anthoula Chatzikyriakidou
Paraskevi V. Voulgari, MD
Alexandros A. Drosos, MD, FACR

Please address correspondence to:
Alexandros A. Drosos,
Rheumatology Clinic,
Department of Internal Medicine,
Medical School,
University of Ioannina,
45110 Ioannina, Greece.
E-mail:
adrosos@cc.uoi.gr; www.rheumatology.gr

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ABSTRACT

HLA-B27 association with ankylosing spondylitis (AS) is one of the strongest ever reported in the literature. However, only a small proportion of 5–8% of HLA-B27 positive individuals of the general population develops the disease. In recent years, polymorphisms of many non-HLA genes were reported to be associated with AS. In this review, we summarise the current knowledge of non-HLA genetic factors contributing to AS susceptibility based on meta-analyses in order to overcome the limitations of individual genetic studies e.g. the small samples' sizes, the small samples' origin diversities, and the low statistical power of statistical analyses.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory arthropathy that affects the spinal joints and sacroiliac joints, causing symptoms of pain and stiffness, and progressive fusion of involved joints. AS is the second-most common cause of inflammatory arthritis worldwide, with wide variation of prevalence in the different areas of the world (1). HLA-B27 association with AS is one of the strongest ever reported in the literature, it is associated with AS in many ethnic groups of patients, while appropriate transgenic animals develop spondyloarthritides (SpAs) similar to human SpAs.

In most studies, 80–95% of patients with AS are positive for the HLA-B27, which confers a high relative risk (2). The concordance rate is 63% for HLA-B27 positive monozygotic twin siblings and 23% for dizygotic twin siblings (3). As a result, many theories have been proposed in order to explain the possible role of HLA-B27 subtypes in the pathogenesis of SpAs (4). However, even though over 90% of whites with AS are HLA-B27 positive (5), less than 5% of the HLA-B27 positive subjects of the general population develop SpAs (6). Therefore, the identification of other genetic factors in AS manifestation is under investigation.

Today, there is an increasing number of independent studies exploring the genetic basis of AS with conflicted results for some genes and polymorphisms. Even though genome wide association studies explore the association of polymorphisms in increased samples' sizes the majority of them are referred to a specific sample origin *e.g.* European, Chinese, Korean, Japanese. Meta-analyses, however, combine the data of comparable studies and also of genome wide association studies, and therefore increase both the sample size and the sample diversity. As a result, meta-analyses increase the power of statistical analysis and draw more compelling conclusions in comparison to individual studies. The aim of the present review is to summarise the data concerning the non-HLA factors in the genetic basis of AS based on the published meta-analyses.

Review design

Using the key words: ankylosing spondylitis, meta-analysis and polymorphism, we searched the PubMed database for the associated articles. The same search in the Web of Knowledge database did not reveal additional articles. Up to mid-January 2014, 31 articles were published but 22 meta-analyses eventually fulfilled the aforementioned criteria and highlighted the current findings on the genetic factors contributing to AS susceptibility. The remaining 9 articles were not relevant to the aim of the manuscript (4 articles referred to other diseases, 2 articles referred to the HLA-B27 and HLA-B60 locus, in 2 articles no meta-analysis was conducted, 1 article was written in Chinese).

Results

The genetic factors associated with AS according to meta-analyses are summarised in Table I. Data concerning population size and origin is also given in Table I.

TNF-α

Tumour necrosis factor alpha (TNF-α) is a potent pro-inflammatory cytokine with many biological effects including protection from infection, surveillance against tumours and stimulation of inflammatory responses (7). A number of studies have been intensively focused on the promoter polymorphisms -308 G/A (rs1800629) and -238 G/A (rs361525) leading to inconsistent results due to the small sample sizes and the insufficient statistical power. Up today, four meta-analyses were conducted over the role of TNF-α polymorphisms and AS predisposition. Three of them were referred to the promoter polymorphisms -308 G/A and -238 G/A and no association with AS was reported in overall, HLA-B27 positive and ethnic subgroups of the studied populations (8-10).

However, in the last meta-analysis, which included data of additional studies, it was revealed that AS had a significantly lower frequency of -308GA, -857CT (rs1799724), -863AA (rs1800630), -863CA, -1031TC and a significantly higher frequency of -238AA and -850TT genotypes. In the subgroup analysis by race, it was found that -238AA genotype had a significantly higher frequency in Caucasians and -857CT had a significantly lower frequency in Asian patients. Finally, the authors suggested no association of -376G/A and -646G/A polymorphisms with AS (11). It is worth mentioning, however, that the conclusions over polymorphisms -863 C/A, -1031 T/C, -850 C/T, -646 G/A and -376 G/A are questionable since the meta-analysis of these variants was based only in one study. Taking into account that authors' conclusions are referred to specific genotypes' associations with AS and no to differences in alleles' distribution between AS patients and controls more studies are needed to be performed before getting the final conclusion over the TNF-α role in AS predisposition.

TLR4

The toll-like receptors (TLRs) act as the sentinel factors of innate immunity and therefore are essential for host defense. TLRs detect the presence of conserved molecular patterns of potentially pathogenic microorganisms and contribute in both cellular and humoral immune responses (12). Two missense variations were studied in independent studies for their role in AS susceptibility, the Asp299Gly (rs4986790, in exon 3) and the Thr399Ile (rs4986791, in exon 3). In a current meta-analysis, no association of these polymorphisms and AS was reported (13).

TNFRSF1, LTBR

TNFRSF1A (Tumour necrosis factor receptor super family member 1A) encodes type 1 (p55) tumour necrosis factor receptor (TNFR1) which has a pivotal role in TNF related pathways leading to NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells)-mediated activation of pro-inflammatory genes and FADD (Fas-associated protein with death domain)-mediated apoptosis (14). Polymorphisms rs4149577 (T/C in intron) and rs4149578 (G/A in intron) of TNFRSF1A were positively associated with AS in a meta-analysis of European populations' data (15). Moreover, the intergenic polymorphism rs11616188 (A/G) between the genes TNFRSF1 and LTBR [lymphotoxin beta receptor (TNFR superfamily, member 3)] was also implicated in AS predisposition in a meta-analysis of European populations (16). LTBR plays a role in signalling during the development of lymphoid and other organs, in immune responses, and in programmed cell death. Therefore, the suggested functions of LTBR and TNFRSF1A genes could ascribe them a role in AS susceptibility.

IL-23R

IL-23 (interleukin-23) is an important determinant of the production of IL-17 (interleukin-17), a cytokine with consequence in inflammation and bone destruction. IL-23 activity is mediated by its binding to IL-23 receptor (IL-23R). Polymorphisms of IL-23R were also studied for their role in AS predisposition and six meta-analyses were performed to evaluate the suggested genetic association (16-21). In general, positive association was recorded for IL-23R polymorphisms in European and no in Asian populations. Specifically, polymorphisms rs11209032 (G/A), rs1004819 (C/T in intron), rs10489629 (A/G in intron), rs1343151 (C/T in intron), rs1495965 (A/G), rs2201841 (T/C in intron), rs11209026 (Arg-381Gln, in exon 9), and rs11465804 (T/G in intron) were associated in all pooled populations but in populations' subgrouping according to their ethnicity it was observed that these associations stem from Europeans populations (16-20). The same negative result was reported in a meta-analysis restricted in East-Asian populations (21). In addition, the rs7517847 (T/G in intron) polymorphism was found to be significantly associated with AS susceptibility in both Europeans and Asians, while no association was reported for polymorphism rs10889677 (C/A in the 3'-UTR) neither in Europeans nor in Asians (20). Finally, polymorphisms rs1343151, rs10489629, rs7517847, rs11465804 and rs11209026 were suggested to have a protective effect, while rs1004819, rs1495965 and rs11209032 seemed to be the susceptible variants (17, 19, 22).

IL-1

The interleukin-1 (IL-1) family gene cluster contains nine genes, IL-1A, IL-1B, IL-1F7, IL-1F9, IL-1F6, IL-1F8, IL-1F5, IL-1F10, and IL-1 receptor antagonist (IL-1RN) (23). In a number of studies the following 12 polymorphisms were studied for their role in AS pathogenesis: IL-1A rs2856836 (T/C in the 3'-UTR), IL-1A rs17561 (Ala-114Ser in exon 5), IL-1A rs1894399 (G/A in intron), IL-1A rs1800587 (C/T in the 5'-UTR), IL-1B rs16944 (G/A, in promoter), IL-1B rs1143634 (Phe105Phe, in exon 5), IL-1F7 rs2723187 (Pro108Leu, in exon 4), IL-1F10 rs3811058 (Asp24Asp, in exon 2), IL-1RN rs419598 (Ala23Ala, in exon 3), IL-1RN VNTR, IL-1RN rs315952 (Ser/Ser, in exon 5), IL-1RN rs315951 (G/C in the 3'-UTR). Three meta-analyses were conducted to re-evaluate the above IL-1 family gene cluster polymorphisms in AS predisposition con-

Table I. Association data of specific gene polymorphisms with ankylosing spondylitis' predisposition according to meta-analyses. The association by ethnicity is given wherever data are available. The *p*-value, odds ratio and confidence intervals derive from the largest conducted meta-analysis and in accordance to the mentioned patients' origin association for each gene. (Complete gene name is given in the text).

Gene	Chromosome	Reference of meta-analysis	Polymorphism	Ethnicity	AS/Controls	*p*-value	OR (95% CI)[Ref]	Model of analysis*
TNF-α	6p21.3	8-11	rs1800629	Overall	3,925/4,031	0.360	0.810 (0.510–1.280)[10]	R
TNF-α	6p21.3	8-11	rs361525	Overall	3,572/4,266	0.180	0.740 (0.480–1.150)[10]	R
TLR4	9q33.1	13	rs4986790	Overall	711/701	0.890	0.96(0.57–1.63)[13]	F
TLR4	9q33.1	13	rs4986791	Overall	595/530	0.760	0.91(0.50–1.65)[13]	F
TNFRSF1A	12p13.2	15	rs4149577	European	4,555/7,677	0.002	1.1 (1.04-1.18)[15]	F
TNFRSF1A	12p13.2	15	rs4149578	European	4,555/7,677	0.006	0.9 (0.77-0.96)[15]	F
TNFRSF1A-LTBR	12p13	16	rs11616188	European	5,034/13,262	4.1×10^{-12}	NA[16]	F
IL-23R	1p31.3	17-21	rs11209032	European	3,647/4,279	0.000	1.234 (1.159–1.313)[20]	F
IL-23R	1p31.3	17-21	rs1004819	European	3,647/4,279	0.000	1.242 (1.166–1.324)[20]	F
IL-23R	1p31.3	17-21	rs10489629	European	3,647/4,279	0.000	0.892 (0.840–0.947)[20]	F
IL-23R	1p31.3	17-21	rs1343151	European	3,441/4,044	0.000	0.838 (0.785–0.895)[20]	F
IL-23R	1p31.3	17-21	rs1495965	European	3,441/4,044	0.000	1.155 (1.087–1.228)[20]	F
IL-23R	1p31.3	17-21	rs2201841	European	1,453/1,369	0.046	1.146 (1.002–1.310)[20]	F
IL-23R	1p31.3	16-21	rs11209026	European	6,598/10,937	0.000	0.611 (0.551–0.677)[20]	F
IL-23R	1p31.3	17-21	rs11465804	European	3,076/3,544	0.001	0.677 (0.538–0.852)[20]	R
IL-23R	1p31.3	17-21	rs7517847	Overall	2,176/2,154	0.001	0.858 (0.781–0.942)[20]	F
IL-23R	1p31.3	17-21	rs10889677	Overall	3,740/4,386	0.150	1.105 (0.964–1.266)[20]	R
IL-1A	2q14	24	rs2856836	Overall	2,589/2,554	0.0034	1.14 (1.05-1.25)[24]	R
IL-1A	2q14	24	rs17561	Overall	2,675/2,592	0.000019	0.82 (0.75-0.9)[24]	R
IL-1A	2q14	24	rs1894399	Overall	2,270/2,117	0.0003	1.2 (1.09-1.32)[24]	R
IL-1A	2q14	25	rs1800587	European	1,094/564	0.007	1.357 (1.085-1.697)[25]	F
IL-1B	2q14	24,25	rs16944	Overall	5,363/4,383	0.173	0.918 (0.812-1.038)[25]	R
IL-1B	2q14	25	rs1143634	Overall	2,046/1,482	0.205	1.130 (0.369-1.364)[25]	F
IL-1F7	2q12-q14.1	25	rs2723187	European	1,430/778	0.201	1.273 (0.879-1.845)[25]	F
IL-1F10	2q13-q14.1	24,25	rs3811058	European	3,959/3,172	0.043	0.775 (0.605-0.992)[25]	R
IL-1RN	2q14-q21	24,26	rs419598	Overall	2,611/2,561	0.830	1.03 (0.77-1.38)[26]	R
IL-1RN	2q14-q21	24-26	VNTR	Overall	4,782/4,394	0.450	1.071 (0.897-1.278)[25]	R
IL-1RN	2q14-q21	24,26	rs315952	Overall	2,212/2,070	0.07	1.08 (0.99-1.18)[26]	F
IL-1RN	2q14-q21	24,26	rs315951	Overall	1,681/1,735	0.38	0.93 (0.79-1.10)[26]	R
ERAP1	5q15	28,29	rs27044	Overall	4,078/3,369	0.001	1.57 (1.342-1.836)[29]	R
ERAP1	5q15	16,28,29	rs30187	Overall	5,070/4,806	0.001	1.348 (1.264-1.439)[29]	F
ERAP1	5q15	28,29	rs17482078	European	2,730/2,131	$<1 \times 10^{-9}$	0.726 (0.655-0.805)[28]	F
ERAP1	5q15	28,29	rs10050860	European	3,722/3,568	$<1 \times 10^{-9}$	0.724 (0.665-0.787)[28]	F
ERAP1	5q15	28,29	rs2287987	European	2,730/2,131	$<1 \times 10^{-9}$	0.708 (0.639-0.784)[28]	F
ERAP1	5q15	29	rs27037	Overall	3,478/7,603	0.001	1.257 (1.182-,1.336)[29]	F
ERAP1	5q15	29	rs27434	Overall	3,478/7,603	0.230	1.128 (0.927-1.372)[29]	R
JARID1A	12p13	31	rs11062385	European	1,730/4,379	0.0001	1.21 (1.10-1.33)[31]	F
NFKB1	6q25.1	33	-94delATTG	Overall	546/630	0.550	1.07 (0.85–1.36)[33]	F
TGF-b1	19q13	34	rs1800470	Overall	206/290	0.819	0.980 (0.830-1.160)[34]	F
CARD9	9q34.3	35	rs4077515	European	1,637/4,343	0.000005	1.2 (1.1-1.3)[35]	F
CARD9	9q34	16	rs10781500	European	5,034/13,262	1.1×10^{-6}	NA[16]	F
KIF21B	1q32	16	rs2297909	European	5,034/13,262	5.2×10^{-12}	NA[16]	F
RUNX3	1p36	16	rs11249215	European	5,034/13,262	9.2×10^{-11}	NA[16]	F
ANTXR2	4q21	16	rs4389526	European	5,034/13,262	9.4×10^{-8}	NA[16]	F
PTGER4	5p13	16	rs10440635	European	5,034/13,262	2.6×10^{-7}	NA[16]	F
TBKBP1	17q21	16	rs8070463	European	5,034/13,262	5.3×10^{-8}	NA[16]	F
IL-12B	5q33	16	rs6556416	European	5,034/13,262	1.9×10^{-8}	NA[16]	F
NA	2p15	16	rs10865331	European	5,034/13,262	6.5×10^{-34}	NA[16]	F
NA	21q22	16	rs378108	European	5,034/13,262	2.1×10^{-11}	NA[16]	F
NA	16q22.1	36	rs9939768	European	1,645/4,324	0.0008	1.31 (1.12 to 1.54)[36]	F
NA	16q22.1	36	rs6979	European	1,647/4,344	0.0009	1.15 (1.06 to 1.23)[36]	F

*F: Fixed-effect model, R: Random-effect model. NA: not assigned.

cerning each analysis different variants (24-26). IL-1A gene polymorphisms rs2856836, rs17561, rs1894399 were associated with AS in all-pooled populations in the meta-analysis by Sims *et al*. (24). In addition, in a meta-analysis of 2 European populations, Lea *et al*. suggested that IL-1A rs1800587 variant was associated straight fully and IL-1F10 rs3811058 marginally with AS (25). For the remaining polymorphisms the association was negative (24-26).

ERAP1

Endoplasmic reticulum aminopeptidase 1 (ERAP1) gene trims peptides to the optimal length for MHC class I presentation and cleaves several cell-surface cytokine receptors (27). In the meta-analysis by Lee *et al*. polymorphisms rs27044 (Gln730Glu, in exon 15) and rs30187 (Lys528Arg, in exon 11) were associated with AS in all pooled populations, in distinct European and Asian samples, while polymorphisms rs17482078 (Arg725Gln, in exon 15), rs10050860 (Asp575Asn, in exon 12)

and rs2287987 (Met349Val, in exon 6) were associated with AS only in European populations. It is worth mentioning that only one population was of Asian origin in the aforementioned meta-analysis (28). Moreover, the aforementioned association of rs30187 polymorphism with AS in European patients was also the finding of another meta-analysis conducted in the data of two genome wide association studies (16).
Finally, in another meta-analysis the study was conducted to the same as above polymorphisms and to two more, the rs27037 [this G/T variant recently was mapped in intron of CAST (calpastatin) gene] and the rs27434 (Ala356Ala, in exon 6) (29). This meta-analysis included more Caucasian cases and controls with more diverse origins but the data for each studied polymorphism of Asian cases and controls were from one population. All the polymorphisms with the exception of rs27434 were associated with AS in all pooled populations, while no analysis was performed according to population origins (29).
Taking into account that the data of the Asian populations were restricted in the aforementioned meta-analyses, we conclude that further studies should be conducted to determine whether the ERAP1 polymorphisms confer susceptibility to AS in non-Caucasian populations.

JARID1A
JARID1A (jumonji, AT-rich interactive domain 1A) demethylates the trimethylated and the di-methylated histone 3 lysine 4 (H3K4) marking genes as transcriptionally active. As a result, JARID1A has an epigenetic role in many genes' transcription (30). In a meta-analysis performed on the JARID1A gene polymorphism rs11062385 (Met865Thr), the statistical analysis revealed positive association with AS predisposition in Caucasian cases (31).

NFKB1
Nuclear factor-kB (NFkB) is a transcription factor showing rapid post-translational activation in response to pathogenic signals, participation in cytoplasmic/nuclear signalling, and potency to activate the transcription of a many genes encoding immune related proteins (32). In the promoter region of NFkB1, there is a 4-bp deletion polymorphism which results in its reduced binding potency to nuclear proteins and reduced promoter activity of NFKB1 gene. In a meta-analysis, which included data only from one European and one Asian population, no association was revealed between this polymorphism and AS susceptibility (33).

TGF-β1
Transforming growth factor beta (TGF-β) is a polypeptide member of the TGF beta superfamily of cytokines and regulates cell growth, cell proliferation, cell differentiation, cell migration and apoptosis. Up today, two studies examined the role of TGF-b1 promoter polymorphism -869C/T (rs1800470) with AS predisposition. In the meta-analysis of the two performed studies, one in European population and one in Asian population, no association was revealed between AS and the studied TGF-β1 gene polymorphism (34), but more studies are needed before getting a final conclusion.

CARD9
In a meta-analysis, polymorphism rs4077515 (Ser12Asn) in CARD9 (caspase recruitment domain-containing protein 9) gene and rs3812571 (His-799Gln) in SNAPC4 (snRNA-activating protein complex subunit 4) gene were associated with AS in Caucasian patients (35). Subsequently, the extension of the genotypic analysis to other samples and variants of this region of chromosome 9 and the interrogation of an mRNA expression database revealed that polymorphisms associated with AS were those linked with CARD9 expression. As a result, CARD9 could be the plausible candidate for AS due to its important role in the regulation of cell apoptosis. Moreover, the same is suggested by another meta-analysis which implicates polymorphism rs10781500 (C/T) of CARD9 gene in AS susceptibility of European patients (16).

TRADD, CTCF
The association of polymorphisms rs9939768 (G/C) and rs6979 (A/G) on chromosome 16q22.1 with AS in Caucasian patients was revealed in a meta-analysis (36). Additional genotypic analyses of the region pointed out more associated polymorphisms, all of which span a chromosome region that contains plausible AS candidate genes such as the TRADD (tumour necrosis factor receptor type 1-associated death domain) which plays a crucial role in the regulation of NFκB signalling and the regulation of proinflammatory cytokines, and the CTCF (CCCTC binding factor) which seems to have a role in the expression of MHC class II genes (37, 38).

More and more gene loci in AS susceptibility
Apart from the aforementioned genes and polymorphisms, in a meta-analysis, which was conducted in two genome wide associations studies of European groups, more genes and chromosome loci were associated with AS (16). Specifically, the chromosome loci 2p15 (rs10865331, A/G), and 21q22 (rs378108, A/G) and the following genes KIF21B [kinesin family member 21B, rs2297909 (in intron C/T)], RUNX3 [runt-related transcription factor 3, rs11249215 (A/G)], ANTXR2 [anthrax toxin receptor 2, rs4389526 (in intron A/T)], PTGER4 [prostaglandin E receptor 4, rs10440635 (A/G)], TBKBP1 [TBK1 binding protein 1, rs8070463 (C/T)], and IL-12B [interleukin 12B, rs6556416 (A/C)] were revealed as possible AS related loci. It is worth mentioning that the association of AS with the aforementioned loci was also studied in independent genetic association studies of patients with origin other than the European. Therefore, a new study which will combine the data of the European and the other ethnic groups seem to be the open window in a future meta-analysis.

Meta-analyses and their limitations
Even though meta-analyses increase the statistical power of analysis compared to individual genetic association studies, they do have their limitations which can be summarised in the following main points:
1. AS is a complex disease and therefore, heterogeneity and confounding factors may often distort meta-analyses.

Analysis of data stratified by gender, disease activity, severity, or HLA-B27 status would have provided more information, but this information was not available for the majority of studies included in meta-analyses.

2. Publication bias can affect the obtained results, because studies that produce negative results may not be published or may be missed. Furthermore, since meta-analysis is a retrospective research, it is subjected to methodological deficiencies in study selection and data extraction.

3. In some cases, the number of studied groups was small and the amount of ethnic stratification in subgroups' analysis was smaller or no data existed for specific ethnicities. Therefore, in such cases more studies are required to increase the statistical power of the analysis for definite conclusions of the genetic factors associated with AS predisposition worldwide or in specific ethnicities.

Conclusions

Twenty-one non-HLA genes were reviewed in twenty two meta-analyses for their association with AS susceptibility. Among them, polymorphisms nearby or into the sequence of 14 genes were associated with AS and for some genetic variants this association was restricted only to European populations. Due to the small sample size of some ethnic groups or the absence of data of some others, more individual genetic association studies are needed so as to increase the statistical power of the future similar meta-analyses and to reach to accurate conclusions for the genetic factors contributing to AS susceptibility.

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