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Ankylosing spondylitis risk factors: a systematic literature review

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Abstract

Radiographic axial spondyloarthritis (also known as ankylosing spondylitis [AS]) is a chronic immune-mediated arthritis characterized by inflammation of the axial skeleton, peripheral joints, and entheses. It is estimated that 1 in every 200 people are affected by AS, making it an important healthcare and socioeconomic issue. In this review, we aim to explore the current understanding of AS risk factors and provide a comprehensive update. Multiple search strings were used to identify articles of interest published in PubMed between January 1, 2013, and February 1, 2021. On the basis of the literature review and analysis, we present up-to-date information on the risk factors of developing AS and our viewpoints on disease onset and progression. Multiple genetic and nongenetic risk factors have been suggested in the onset of AS. HLA-B27 is known to have a strong association with the disease, but other genes have been implicated in disease development. Aside from genetics, other factors are thought to be involved; up to 70% of patients with AS have subclinical intestinal inflammation, suggesting that the origin of the disease may be in the gut. The exact mechanism by which AS onset begins is most likely complex and multifactorial.

Keywords

Ankylosing spondylitis; Genetics; HLA-B27; Pathogenesis; Radiographic axial spondyloarthritis; Risk factors

Introduction

Radiographic axial spondyloarthritis (axSpA, also known as ankylosing spondylitis [AS]) is a chronic, progressive, immune-mediated arthritis characterized by the absence of

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rheumatoid factor and presence of inflammation of the axial skeleton, peripheral joints, entheses, and extra-articular sites such as the eye and bowel. AS is perhaps one of the best recognized forms of spondyloarthritis (SpA), which comprises axSpA, peripheral SpA (including psoriatic arthritis, reactive arthritis, and arthropathy of inflammatory bowel disease), and undifferentiated SpA. Radiographic sacroiliitis is the key distinguishing feature of AS although patients usually report symptoms such as back pain for several years before radiographic changes are observed [1]. The presentation of axSpA without radiographic sacroiliitis denotes nonradiographic axSpA (nr-axSpA) [2]. In 2009–2010, the National Health and Nutrition Examination Survey estimated that the prevalence of axSpA among adults in the USA varies from 0.9 to 1.4% [3]. Approximately, 1 in 200 people are affected by AS and over one in 100 by axSpA (although there are marked variations in estimates, which are thought to be partially due to differences in study methodology and criteria used) and the number of AS cases in Europe and Asia is estimated to be 1.30–1.56 million and 4.63–4.98 million, respectively [4]. The onset of AS usually occurs before the age of 45 years [5], when adults are in their peak productive years, and patients experience limited physical function, significant loss of work productivity, and a decreased quality of life during this period after disease onset [6]. Thus AS is an important healthcare and socioeconomic issue.

Great recent progress has been made in elucidating the pathogenesis of AS, which has led to a better understanding of risk factors and disease causation, and to the development of targeted treatments. Genetic studies have made a significant contribution to our understanding of AS [7]. Gut involvement in patients with AS is also common, and as such, the role of the intestinal microbiome in AS onset is an active area of research [8]. The role of other environmental triggers (i.e., infection, mechanical stress) has also provided important clues [9], and changes in the immune system composition and function have also been noted in patients with AS vs healthy controls [10].

Overall, it remains unclear how interactions between genes, microbes, mechanical stress, gender, and other environmental and lifestyle factors predispose patients to the development of AS. The exact mechanisms are complex and multifactorial and the research agenda continues forward. Recognizing the risk factors, as well as understanding gene-gene and gene-environment interactions, may offer valuable insights into the etiology of AS and have important implications for diagnosis and treatment strategies. Numerous reviews have recently been published on the genetics of AS, and several systematic literature reviews have been published on AS susceptibility [11–15], but these reviews only considered one or two individual risk factors. Thus, the aim of this review is to provide a more in-depth update on current research and comprehensively outline risk factors associated with AS.

Methods

Search strategy

The design of the present analysis was based on a systematic literature review using theoretical recommendations suggested by The PRISMA Group [16]. Multiple search strings using Medical Subject Headings (MeSH) and MeSH major topics (majr) were used to identify articles of interest published in PubMed between January 1,

2013, and February 1, 2021. The primary search included the terms ("Spondylitis, Ankylosing"[majr] AND "Spondylitis, Ankylosing/etiology"[MeSH]) OR ("Spondylitis, Ankylosing"[majr] AND "Spondylitis, Ankylosing/ethnology"[MeSH]) OR ("Spondylitis, Ankylosing"[majr] AND "risk factors"[MeSH]) OR ("Spondylitis, Ankylosing"[majr] AND "sex distribution"[MeSH]), OR ("Spondylitis, Ankylosing"[majr] AND "*Klebsiella*" MeSH]). Two individuals independently reviewed the titles and available abstracts to retrieve potentially relevant studies, and an adjudicator made the final decision on any difference in reviewer opinion. The full texts and bibliographies of relevant English-language articles were evaluated for specific data relating to risk factors in patients with AS. Case studies and comments were not included. Additional articles were identified from the bibliographies of the articles from the primary search or through secondary searches using related terms and included based on clinical expert opinion. Only those manuscripts reporting studies deemed relevant to the objectives of this study, along with those recommended by clinical experts, were included.

Study inclusion and characteristics

According to the defined search strategy, the literature search identified 1066 articles, which are summarized in Fig. 1. Through examination of the title and abstract, 500 studies were identified for full-text analysis. Of these, 436 were excluded due to lack of relevance with the study objectives, leaving 64 articles from the initial searches for inclusion. These were supplemented with an additional 45 articles of interest from the authors, including several preceding the time period of the review felt important to this review and five added that were published after the search was conducted while the article was being prepared for publication as well as secondary analyses of the literature. Overall, a total of 128 articles were included in this review.

Results

Risk factors for the development of AS

We identified multiple genetic, nongenetic, and stochastic risk factors in the development of AS; these are summarized in Table 1 and detailed herein.

Genetics

AS is widely regarded as an inherited disease, with over 90% of the risk of development attributed to HLA-B27 [113]. HLA-B27 positivity is present in 85 to 95% of White and Han Chinese patients and over 86% of Hispanic patients with AS [17, 18], although only ≤ 8% of the general population overall [19]. In fact, only approximately 5% of HLA-B27–positive individuals in the general population have SpA [20]. In the Middle East and North Africa, and in American Black patients, the prevalence of HLA-B27 among patients with AS ranges from approximately 50 to 84% [18, 21]. AS cases that do not involve HLA-B27 comprise > 10%, and twin concordance rates are not 100% [113]. Concordance rates of 63% and 27%, respectively, were reported for HLA-B27-positive monozygotic (17 of 27 patients) and dizygotic (4 of 15 patients) twins [113]. However, HLA-B27 is still considered an important factor that is highly associated with the development of AS, particularly for the magnitude and severity of bone marrow edema lesions in the sacroiliac joints in early

disease [22]. The HLA-B27 family has a high degree of genetic polymorphism and consists of 328 alleles and 231 protein subtypes ranging from *HLA-B*27:01 to HLA-B*27:232* (the subtype *HLA-B*27:22* was found to be in error and was withdrawn); these subtypes differ from each other in only a few amino acids, which may alter the peptide-binding specificity of the molecule [23, 114]. The most common HLA-B27 subtype, the ancestral subtype *HLA-B*27:05*, is distributed ubiquitously worldwide, is found in all races and ethnicities, and is strongly associated with AS [18, 24, 25]. Specific populations have other HLA-B*27 subtypes that are positively associated with AS (Table 2) such as the "major" or most common subtypes *HLA-B*27:02* (in people of European, Chinese, and Mediterranean or Northern African ancestry), *HLA-B*27:04* (in Eastern Asia and China), HLA-B*27:07 (in Western Asia), and HLA-B*27:15 (derived from *HLA-B*27:04* and found in China). Other less rare HLA-B27 subtypes that are not associated with AS include *HLA-B*27:03* (in West Africa), *HLA-B*27:06* (found in Southeast Asia and derived from *HLA-B*27:04*) [26], and *HLA-B*27:09* (found primarily in Sardinia) [24], the latter two rarely, if ever, occurring in patients with AS.

Other HLA-B27 subtypes are rare, representing amino acid substitutions derived from *HLA-B*27:05* and its major subtypes (Fig. 2). Studies show that those positive for specific HLA-B27 subtypes have an increased risk of developing AS and specific AS manifestations, including peripheral joint involvement [25, 27] and uveitis [28] in some populations.

The role that HLA-B27 plays in the pathogenesis of AS is a subject of much investigation. Six mechanisms have been proposed:

a. Presentation of an "arthritogenic" peptide [29]. HLA-B27, a major histocompatibility complex (MHC) class I molecule, presents endogenous peptides, such as those from viruses, bacteria, neoplastic, or "self" peptides that have been degraded intracellularly in lysosomes to the αβ T cell receptor on CD8+ T lymphocytes or to the killer immunoglobulin (KIR) receptor on natural killer (NK) cells. Despite a great deal of work that has gone into identifying a peptide specific for SpA, this has proven to be an elusive target. That said, CD8+ T lymphocytes have a role in AS pathogenesis, and recent data do suggest AS patients have a reduced cytotoxic CD8+ T cell profile in their peripheral blood, and an enrichment in the inflamed joint [30].

b. HLA-B27 heavy chains have the rather unique tendency to misfold in the endo/ ; plasmic reticulum (ER) compared to other HLA-B alleles [31–33]. HLA-B27 misfolding (i.e., incorrect folding and loading of peptides) has been postulated as one reason for genetic susceptibility [31]. One study demonstrated that the AS-associated HLA-B27 subtypes *B*27:02, B*27:05*, and *B*27:07* differed from the non–AS-associated *B*27:06* and *B*07:02* alleles by a greater tendency to accumulate in intracellular ER-derived vesicles, at high expression levels examining cells from SpA patients or HLA–B27/human β_2-microglobulin (hβ_2m)–transgenic rats [32, 33]. This misfolding and the accumulation of misfolded HLA-B27 heavy chains in the ER results in ER-associated degradation of the heavy chains and leads to a proinflammatory unfolded protein response, which activates the innate immune response and upregulates proinflammatory

cytokines such as interferon gamma and interleukin (IL)-23, as well as other cytokines, especially those in the T helper 17 (Th17) pathway [31–33].

c. HLA-B27 heavy chains have a striking tendency to self-adhere and form homodimers by virtue of having a cysteine residue at position 67 in the « 1 domain (and elsewhere). These homodimers have been detected at the cell surface and are recognized by KIR and leukocyte immunoglobulin-like receptors. How and if homodimerization affects predisposition to AS is unclear, especially in that HLA-B27 subtypes that are associated with AS (*HLA-B*27:02, B*27:04, B*27:05, B*27:07*) and those not disease-associated (*B*27:06, B*27:09*) share this property, with the exception of *B*27:03*, which does not efficiently-self adhere [34].

d. d. HLA-B27–positive individuals exhibit alteration of intracellular invasion and killing of arthritogenic bacteria. This is especially seen for reactive arthritis, where impaired intracellular killing of causative microorganisms has been described, leading to intracellular bacterial persistence and upregulated cytokine production [35].

e. HLA-B27 itself, either through the trimolecular complex of B27 heavy chain, α2 microglobulin, and peptide, or of free B27 heavy chains or homodimers (or peptides derived therefrom) are recognized as antigenic by the T cell receptor (or peptides bound therein) on CD4+ T lymphocytes, generating an autoimmune response [36].

f. HLA-B27–positive individuals have an altered microbiome, which influences disease susceptibility (discussed below).

MHC genes other than HLA-B27

Other HLA-B alleles have also been implicated with AS susceptibility, albeit to a much lesser extent than HLA-B27. The development of AS has been positively associated with *HLA-B*40* and negatively associated with *HLA-B*07, B*35*, and *B*57*, as demonstrated in studies of Whites, Han Chinese, and Blacks [18, 25, 37, 38]. *HLA-B*15* favors the development of peripheral vs axial spondyloarthritis [39]. In HLA-B27-negative West Africans, *HLA-B*14:03* may render susceptibility to AS [38]; this subtype was not observed in African Americans [18]. *HLA-A*02:01* was independently linked to AS susceptibility in a large multinational imputation analysis [40]. DNA sequencing implicated the MHC related gene *MICA* in a large cohort of White American patients with AS and confirmed in a Han Chinese cohort [41]; however this was not confirmed in a much larger imputation study [42]. Similarly, HLA-C alleles were associated with AS in a study of Taiwanese patients [43], although this was not seen in a larger study of American White patients after correcting for linkage with HLA-B27 [18]. More compelling were associations of AS with MHC class II alleles, including HLA-DRB1 and especially with alleles at HLA-DPA1 and DPB1 [18, 28, 44, 45]. Correlations with other MHC loci, such as TAP and TNF [12, 46], are likely explained by linkage to HLA-B27 haplotypes.

Non-MHC genes

Genome-wide association studies have identified and characterized the role of > 100 susceptibility genes or loci outside the MHC locus genes for AS, Crohn's disease, ulcerative colitis, and psoriasis, which are summarized in Fig. 3. Especially important are the genes endoplasmic reticulum aminopeptidase 1 (*ERAP1*) and interleukin 23 receptor (*IL23R*); *ERAP1* is more frequently identified in patients with AS who are HLA-B27 positive than in those who are HLA-B27 negative. AS susceptibility genes that have been identified by genomewide association and gene chip studies, including *ERAP1*, are summarized in Supplemental Table 1 [7, 11, 12, 40, 44, 47–69]. Of particular note is a recent study comparing 2752 patients with AS with acute anterior uveitis (AAU) and 3836 patients with AS without AAU; novel AAU-associated associations were discovered [45] (Supplemental Table 1). A major achievement of these studies relates to the identification of important biological pathways that are likely responsible for AS pathogenesis. This identification has led to the discovery of novel therapeutic targets. Understanding genetic differences in AS pathogenesis may allow better patient and treatment matching.

Gut microbiota and associated factors

On the basis of the current understanding of AS pathogenesis, it is most likely that the microbiome plays a role, especially in those who are already genetically susceptible. This is supported by current human research as well as studies carried out in animal models. The introduction of commensal bacteria such as *Bacteroides vulgatus* into the transgenic animals led to the development of arthritis [71]. Additionally, the transfer of the HLA-B27–transgenic rats from their sterile environment to a conventional rat colony led to the development of SpA symptoms [71]. In a cross-sectional study assessing the relationship between disease activity and infections among Mexican patients with different forms of SpA, more infections were found to occur among those with HLA-B27 positivity, particularly enteric infections [72], thus supporting a role for genetics and microbial infection in AS development. HLA-B27 may render susceptibility to AS by altering the gut microbiome and displaying a separate and divergent array of peptides in the gut, thereby introducing a microenvironment that leads to microbial imbalance, inflammation, and subsequent overproduction of IL-23 and other proinflammatory mediators [73], an effect that is even seen in HLA-B27 positive "healthy controls"[74]. Additionally, gut permeability is increased among patients with AS and their first-degree relatives as well as in experimental animal models, which perhaps allows for a greater systemic exposure to potentially pathogenic gut microbes [115]. In this regard, Paneth cells, a subset of specialized secretory host-defense epithelial cells located in the small intestines, have been shown to secrete IL-23 and activate key IL-23 responsive cells such as group 3 innate lymphoid cells (ILC3), γδ T cells, and mucosal-associated invariant T (MAIT) cells, which recirculate from the gut to sites of inflammation important in SpA pathogenesis, such as the entheses [116].

The gut microbiome—Several families of gut bacteria have been associated with AS development in humans, including *Lachnospiraceae, Prevotellaceae, Rikenellaceae, Porphyromonadaceae, Ruminococcaceae*, and *Bacteroidaceae* [8], and these AS-associated microbial families have been linked to fecal calprotectin levels, a marker of intestinal

inflammation, but not to other clinical parameters [75]. A metagenomics study analyzed gut microbial DNA from 211 Chinese individuals and found that patients with AS had an increased load of *Prevotella melaninogenica, Prevotella copri*, and *Prevotella* sp. *C561*, and decreases in *Bacteroides* sp. [76]. It is noteworthy that the *Bifidobacterium* genus, which is commonly used in probiotics, accumulates in patients with AS [76]. Another study, again in Chinese AS patients, confirmed previous reports of gut dysbiosis in AS, and TNFi therapy was correlated with a restoration the perturbed microbiome that was observed in untreated AS cases compated to that of healthy controls [77].

Asymptomatic intestinal inflammation, usually involving the terminal ileum, is also known to occur in a large proportion of patients with AS (57 to 70%) and is especially apparent in those with peripheral arthritis, again suggesting a link between the gut and AS [117]. However, no evidence of an exact connection of AS with subclinical gut inflammation has been found to date [118]. The overproduction of IL-23 by Paneth cells lining the epithelium of the small intestine has been implicated in regulating gut mucosal immunity. Among patients with AS and Crohn's disease, a marked upregulation of *IL-23p19* transcripts was observed in the terminal ileum, suggesting an association between polymorphisms in the IL-23 receptor and gut inflammation [119].

Gut-induced protection through breastfeeding—Only one study to date has examined breastfeeding history in patients with AS [80]. This retrospective case-control study suggested that breastfeeding has a protective effect on the development of AS [80]. Patients with AS were breastfed less often than healthy controls. Patients with AS and HLA-B27 positivity were breastfed less often than their siblings who did not have AS as well as unrelated, healthy controls, which suggested that breastfeeding may decrease the familial prevalence of AS, perhaps through factors induced in the gut for those who were breastfed.

Infections

Klebsiella pneumoniae—*Klebsiella* was implicated in AS pathogenesis when an increased fecal carriage was found in patients with "active" disease [81]. Subsequently, another study reported that patients with HLA-B27 positivity had lower in vitro lymphocyte responsiveness to *Klebsiella* antigens [82]. However, these early findings were not confirmed by others [120, 121].

Nevertheless, molecular mimicry between *Klebsiella* (and other enterobacteria) capsular antigens and HLA-B27 was proposed with the discovery of cross-reactivity between antigens in several Gram-negative microorganisms and lymphocytes of patients who were HLA-B27 positive [83]. Patients with SpA were also reported to have an increased frequency of antibodies to a homologous region shared by HLA-B27 and *Klebsiella* nitrogenase compared with HLA-B27–positive controls [84]. This suggested that AS represents an autoimmune response directed against HLA-B27 that was initially induced against nitrogenase proteins of *K. pneumoniae*. However, this finding could not be independently confirmed [122]. Other reports postulated that active AS was characterized instead by elevated IgA antibodies to various enterobacteria in both AS and AAU regardless

of HLA-B27 status [123, 124], raising doubts about the molecular mimicry theory. Alternatively, modification by a *Klebsiella* K43 plasmid-derived soluble cell wall factor of specific MHC-associated gene products was implicated in the pathogenesis of the HLA-B27–linked arthropathies [85], which likewise could not be confirmed by others [125, 126]. Studies of patients with AS or their affected or unaffected family members with familial AS have not demonstrated a specific *K. pneumoniae* antibody response for AS [127, 128].

By the middle of the 2000s, the lack of any consistent compelling story implicating *Klebsiella* in AS susceptibility or severity caused the interest in further researching this topic to wane; however, there has been a recent systematic review [14], a report demonstrating *Klebsiella* protein antibody responsiveness persisting in patients with AS [86], and another addressing the popularity of "low starch" diets, as well as "anti-*Klebsiella*" dietary supplements [87], albeit with little evidence of their effect on disease activity. Of note, previous results implicating *Klebsiella* in the gut have not been confirmed in recent studies of the gut microbiome [8, 78, 127].

Infections during childhood hospitalization—In a Swedish national case-control study, childhood hospitalization (with infections) was associated with later development of AS [88]. The study included 2453 patients with AS and 10,257 control subjects, of whom 17.4% and 16.3%, respectively, had been hospitalized with an infection before 17 years of age [88]. Appendicitis was associated with a decreased risk of AS, whereas rates of respiratory tract infections and tonsillitis, respectively, were increased in patients with AS vs controls. There were no associations between AS and any other type of infection.

Mechanical stress

McGonagle and colleagues first proposed an enthesitis-based model for the pathogenesis of SpA, whereby interactions between biomechanical factors and the innate immune response may lead to disease [89]. In a mouse model in which a 69-base pair deletion comprising the tumor necrosis factor (TNF) AU-rich elements (ARE) yielded $TNF^{\Delta ARE}$-mutant mice with chronic inflammatory arthritis and Crohn's disease, mechanical stress was found to be involved in the development of enthesitis in the Achilles' tendon [90], where hind limb unloading could efficiently prohibit the development of enthesitis in those sites. In more recent work [91] examining human spinal entheseal tissue, Vδ1 and Vδ2 subsets of T lymphocytes were shown to be tissue resident cells with inducible IL-17A production and that the Vδ1 subset does so independently of IL-23R expression.

It is well established that patients with AS who are engaged in physically demanding jobs are more likely to experience permanent or temporary work disability [92], especially in occupations requiring dynamic flexibility (i.e., the ability to repeatedly bend, stretch, twist, or reach), because patients with AS tend to have more functional limitations than those whose past jobs required little or no dynamic flexibility [92]. This finding was underscored by a recent study showing that radio-graphic progression of AS was higher in blue-collar vs white-collar workers [93]. This would suggest that a young patient with AS, in evaluating his/her future employment, consider avoiding those with physically demanding tasks.

Gender at birth

Despite the equivalent prevalence of HLA-B27 between men and women [19], AS reportedly affects more men than women (approximately 2:1 ratio, although this varies greatly between studies) [94, 95], and this gender disparity is not seen in nraxSpA, where there is relatively equal proportion of men and women, or even a female preponderance [3]. Male gender has been implicated as a risk factor for progression from nr-axSpA to radiographic axSpA, but this has not been examined in longitudinal studies [7, 96, 97].

There also exists a gender-at-birth difference in the severity of AS, the type of clinical manifestations, and response to treatment [93, 97]. A Swedish study reported the higher prevalence of anterior uveitis among men with AS vs women and of peripheral arthritis and psoriasis among women with AS vs men [94]. Furthermore, men with a family history of AS are at a higher risk of developing AS than both women with a family history and men without a family history of AS [27]. The differences observed in men are, in part, due to genetic factors predisposing them to AS development, and to immunological and lifestyle differences (e.g., smoking, diet).

The onset of AS is reportedly earlier among men than among women, which leads to a more rapid diagnosis [98]; however, women experience more delay in receiving an AS diagnosis [99]. Furthermore, compared with women, men have lower disease activity as measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score, and a better quality of life (Ankylosing Spondylitis Quality of Life Questionnaire) but have worse spinal mobility (Bath Ankylosing Spondylitis Metrology Index) and a more severe radiographic involvement (Bath Ankylosing Spondylitis Radiology Index) [100]. With regard to clinical AS manifestations, women usually have more peripheral arthritis and an increased prevalence of arthritis, dactylitis, and enthesitis compared to men [100]. Women also report lower response rates to anti–TNF treatment than men [100]. However, data appear conflicting. In a small prospective cohort study ($N = 216$) using data from the Outcome in AS International Study, no gender-at-birth–attributable differences in physical function or disease activity over time were found; however, radiographic damage was more severe in men [101]. This supports previous reports documenting that men with longstanding AS had more severe radiographic changes compared with women [100]. Despite this, men report a better quality of life than women over time [101]. Additionally, distinct sexual dimorphism in the activation status of the immune system in patients with AS, particularly in the Th17 axis, has been observed, possibly explaining clinical gender-related differences among men and women with AS [102]. This dimorphism may suggest gender-specific AS treatment.

Other genetic differences (*IL-22* copy number variants, rs11428092 and rs10208769 in USP34, and IRGM) have also been observed between the genders (Supplemental Table 1).

Social and lifestyle factors

Older siblings—Using the Swedish National Patient Register to identify patients with AS, Lindström and colleagues examined the impact of perinatal characteristics and/or presence of older siblings on the risk of developing AS [103]. Having older siblings was strongly

associated with greater risk of developing AS and birth weight below 3000 g, but not low birth weight (i.e., < 2500 g), was weakly associated with the risk of AS development. As this was a single study, the findings are not conclusive and would need to be repeated and confirmed in other cohorts.

Vitamin D levels—Although there has been little focus on the potential immunomodulatory role of vitamin D in AS, current data suggest that it may have significant effects on both innate and acquired immunity and that its deficiency may be associated with both susceptibility and disease severity in AS and other autoimmune diseases [15]. Higher levels of serum vitamin D have been associated with a decreased risk of AS and decreased disease activity [15, 104].

Smoking cigarettes and e-cigarettes—Current smoking (but not a history of smoking) appears to be a risk factor for AS and is linked to disease activity level in those with AS. This is not surprising, given the known proinflammatory and prooxidative effects of smoking, especially in contributing to disease onset in a genetically predisposed individual and to the evolution of nr-axSpA into AS [105]. In the population-based Nord-Trøndelag health study, incident AS was associated with current smoking and hypertension [105]. Present smoking was significantly associated with incident self-reported AS in logistic regression adjusted for potential confounders. Furthermore, a meta-analysis evaluating the associations between smoking and disease outcome among Chinese patients with AS showed that current, former, or ever smokers had significantly higher BASDAI and worse functional capacity than non-smokers [106], and among French AxSpA patients smoking was independently associated with more MRI-detected SI joint inflammation at each visit over a 5-year period of follow-up [107]. Although no data are available for patients with AS who smoke e-cigarettes, data from a murine model of arthritis found that nicotine exacerbated inflammatory arthritis [108], thus suggesting that nicotine-containing products, including e-cigarettes, may have deleterious effects on patients with AS.

Other risk factors

Immunological aspects have been an area of research for their clear involvement in disease pathogenesis. A wide variety of immune cell types have been suggested to be involved in AS development [109, 110]. In a flow cytometry analysis of peripheral blood from patients with AS, HLA-B27+ individuals without AS and healthy controls, the percentage of regulatory T cells in patients with AS was lower than that in healthy individuals [111]. Furthermore, patients with AS had lower expression of negative checkpoint regulators such as PD-1 and Tim-3 on T lymphocytes, and lower IL-10 production by CD4+ T cells, with higher IL-6 production by CD8+ T cells compared with healthy individuals; these data suggest negative regulation of the immune response is impaired in patients with AS [111]. In another study, compared with healthy volunteers and patients with rheumatoid arthritis and osteoarthritis, patients with AS had significantly higher levels of baseline serum macrophage migration inhibitory factor (MIF), which independently predicted AS progression [112]. High MIF levels were detected predominantly in the synovial fluid of patients with AS, and the primary producers of MIF (i.e., macrophages and Paneth cells) were enriched in the

intestines [112]. MIF production led to the generation of TNF-α in monocytes and activated β-catenin in osteoblasts and induced osteoblastic mineralization [112].

Limitations

The specific keyword searches on which this systematic review was based would omit papers that were not directly relevant. However, with further searches and inclusion of manuscripts deemed of interest, we believe that this review provides comprehensive insight into the current understanding of risk factors in AS. The search methodology covered a limited period (January 1, 2013, and February 1, 2021). However, this was supplemented with papers of key interest from the last several decades based on clinical expert opinion. PubMed was the only database used and only articles in the English language were included.

Summary

Genetic predisposition fails to fully explain the cause of AS, and this has led to a strong effort to identify additional predisposing factors. The inappropriate expression of HLA-B27 and ERAP1 peptides to adaptive immune cells may compromise recognition of self-antigens, rendering susceptibility to AS development [55]. In the B27 rat model of AS, rats housed under germ-free conditions did not develop AS-like symptoms, thus demonstrating that microbes, at least in this model, are important for disease occurrence [71]. The gut microbiota may therefore become a potential target for AS treatment in the future. Mechanical stress may also play an important role in triggering enthesitis and driving radiographic progression in AS [90, 91].

The numerous investigations and studies carried out within the last decade have markedly improved our understanding of the pathogenesis and risk factors of AS and have facilitated the development of new treatment strategies. HLA-B27 remains the most important genetic risk factor in AS, followed by *IL23R* and *ERAP1* [7, 70]. In addition to (or in combination with) genetic aspects, various triggering factors have been implicated in the development of AS. Despite concerns regarding some aspects of microbial involvement in AS, overall, available data strongly suggest involvement of the gut microbiome in the pathogenesis of AS [75–77, 79]. The characterization of the species composition of the microbiota associated with AS and the exact mechanism for the functional role of intestinal microbiome in disease onset and progression should be the focus of more research in the future; the role of mechanical stress in triggering/worsening AS is also an active area of investigation.

Despite the progress being made in understanding the functions and potential pathogenic roles of some of these risk factors, much work remains to better comprehend their complex interactions. Further studies with longitudinal designs are required to better understand whether optimizing vitamin D levels in AS is a potential disease-modifying intervention [15]. Smoking (including smoking of e-cigarettes) should be discouraged in those at a higher risk of developing AS (i.e., those with a family history of AS or who are HLA-B27 positive). The role of mechanical entheseal stress on disease or flare triggering should be considered, especially in planning future employment. The exact trigger of AS onset and achieving even more efficient control through eliminating known risk factors (wherever possible), along

with improved disease-modifying treatments, will help reduce the burden and severity of AS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- It remains unclear how interactions between genes, microbes, mechanical stress, gender, and other environmental and lifestyle factors predispose patients to the development of ankylosing spondylitis (AS).
- The exact mechanisms of AS are complex and multifactorial which will require much future research
- Recognizing the risk factors, as well as understanding gene-environment interactions, may offer valuable insights into the etiology of AS and have important implications for diagnosis and treatment strategies

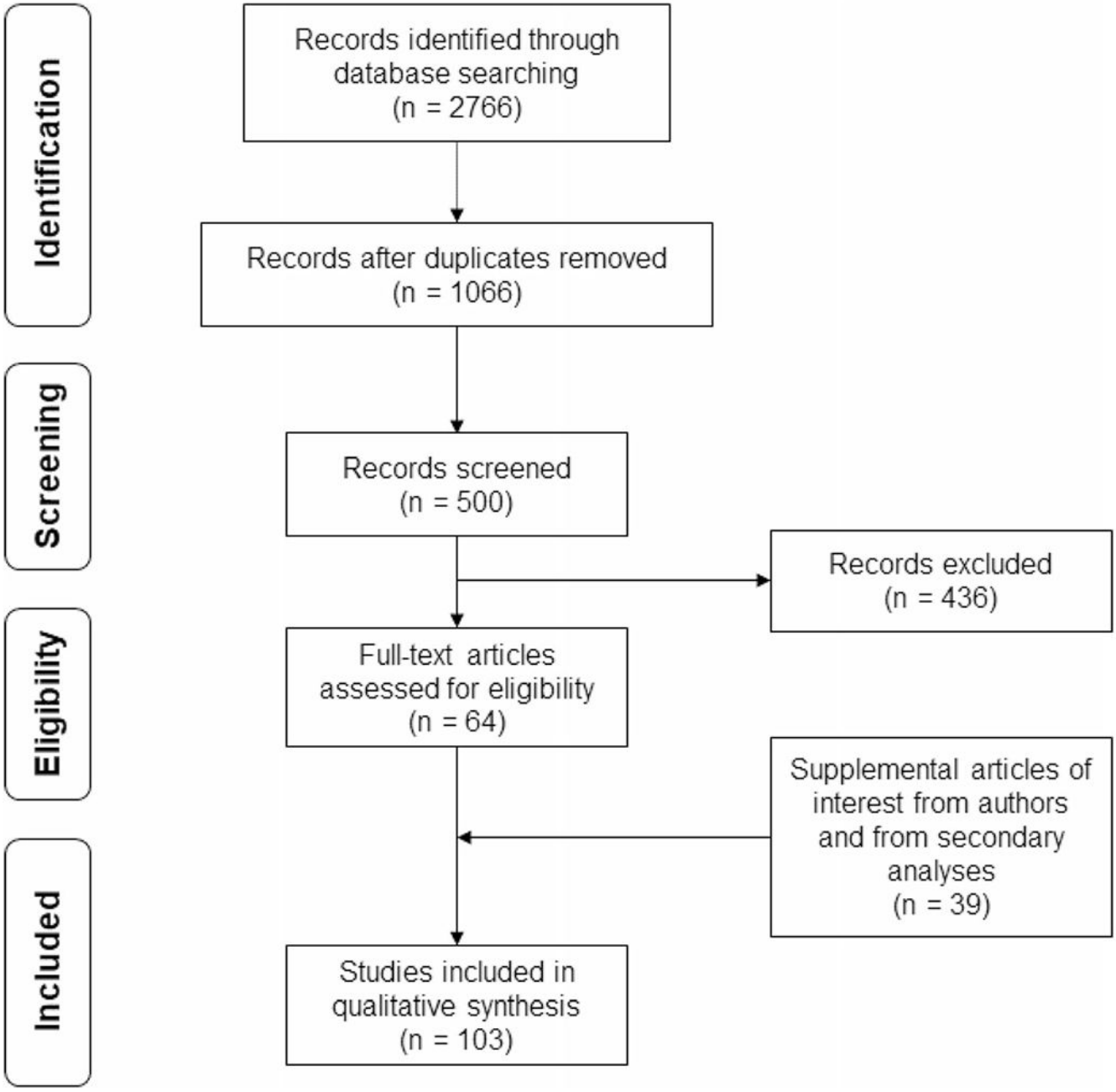

Fig. 1.
PRISMA flow diagram

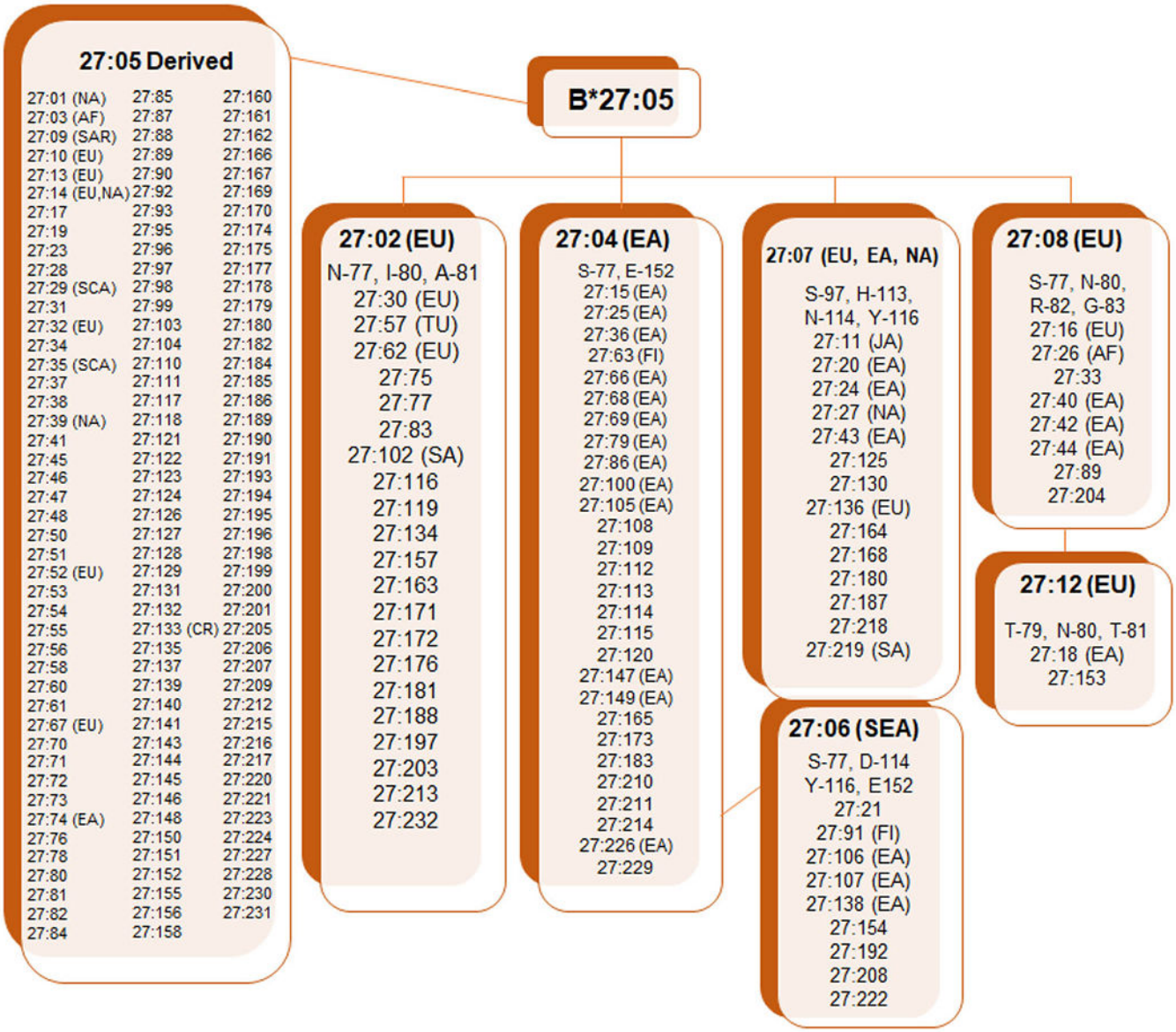

Fig. 2.

Derivation of main and rare HLA-B27 subtypes from founder *HLA-B*27* allele *B*27:05*. AF, African; EA, Eastern Asian; EU, European; FI, Filipino; JA, Japanese; NA, North American; SA, South American; SCA, Scandinavian; SEA, Southeast Asian; TUR, Turkic. Subtypes where ethnicity origin was not designated derived from individuals where ethnicity was not recorded. Source: https://www.ebi.ac.uk/ipd/imgt/hla/allele.html; accessed September 27, 2020

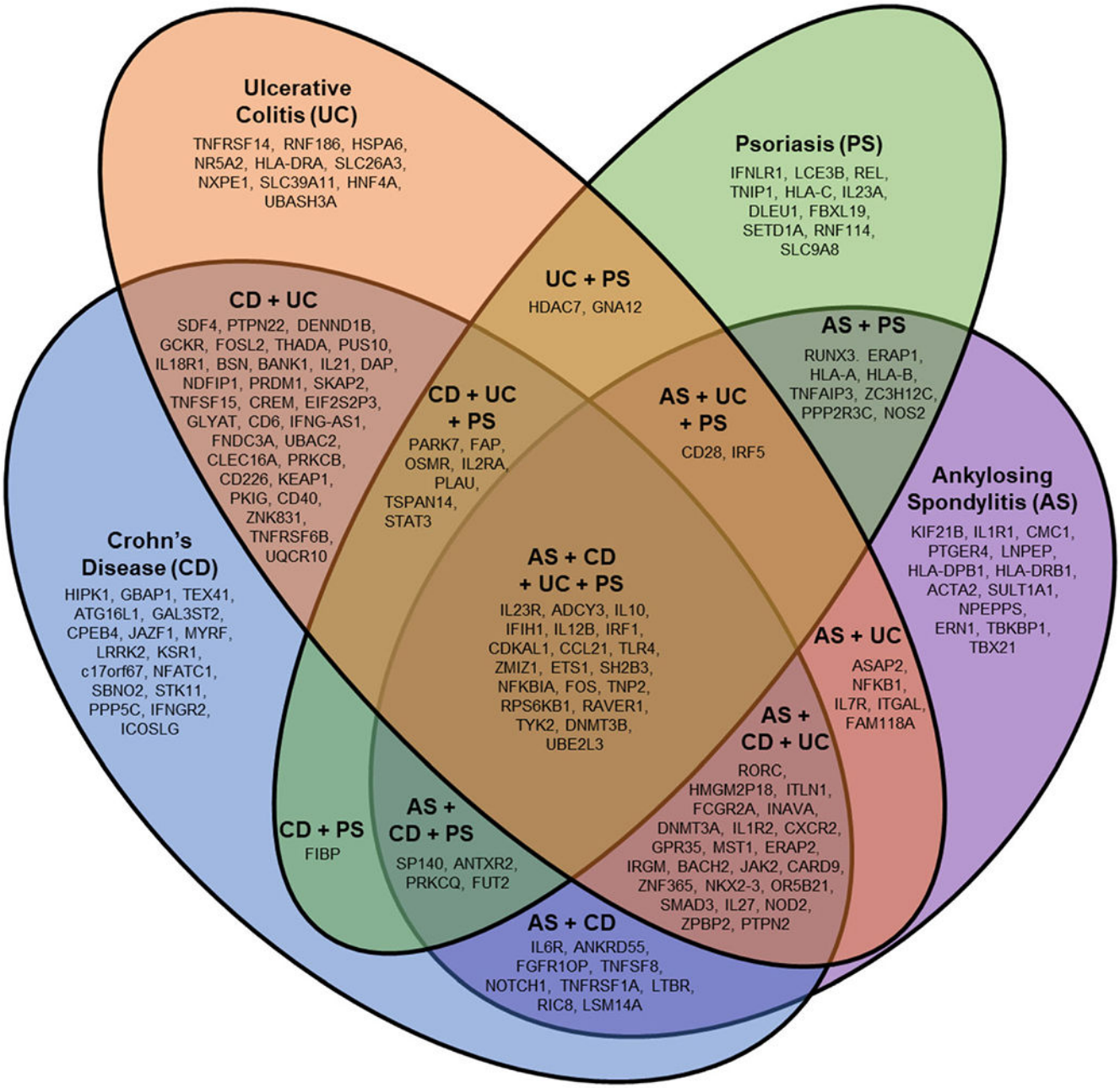

Fig. 3.

Overlap between AS, Crohn's disease, ulcerative colitis, and psoriasis susceptibility genes. *ACTA2*, alpha actin 2, smooth muscle aortic; *ADCY3*, adenylate cyclase 3; *ANKRD55*, ankyrin repeat domain-containing protein 55; *ANTXR2*, anthrax toxin receptor 2; *ASAP2*, ArfGAP with SH3 domain, ankyrin repeat and PH domain 2; *ATG16L1*, autophagy16-like 1; *BACH2*, BTB and CNC homology 2; *BANK1*, B cell scaffold protein with ankyrin repeats-1; *BSN*, bassoon mouse, homolog of (zinc finger 231); *C17orf67*, chromosome 17 open reading frame 67; *CARD9*, caspase recruitment domain family member 9; *CCL21*, C-C motif chemokine ligand 21; *CD6*, CD6 molecule; *CD28*, CD28 molecule; *CD40*,

CD40 molecule; *CD226*, CD226 molecule; *CDKAL1*, CDK5 regulatory subunit associated protein 1 like 1; *CLEC16A*, C-type lectin domain containing 16A; *CMC1*, C-X9-C motif containing 1; *CPEB4*, cytoplasmic polyadenylation element binding protein 4; *CREM*, cAMP responsive element modulator; *CXCR2*, C-X-C motif chemokine receptor 2; *DAP*, death-associated protein; *DENND1B*, DENN domain containing 1B; *DLEU1*, deleted in lymphocyte leukemia 1; *DNMT3A*, DNA methyltransferase 3 alpha; *DNMT3B*, DNA methyltransferase 3 beta; *EIF2S2P3*, eukaryotic translation initiation factor 2 subunit 2 beta pseudogene 3; *ERAP1*, endoplasmic reticulum aminopeptidase 1; *ERAP2*, endoplasmic reticulum aminopeptidase 2; *ERN1*, endoplasmic reticulum to nucleus signaling 1; *ETS1*, ETS proto-oncogene 1, transcription factor; *FAM118A*, family with sequence similarity 118 member A; *FAP*, fibroblast activation protein alpha; *FBXL19*, F-box and leucine rich repeat protein 19; *FCGR2A*, Fc fragment of IgG receptor IIa; *FGFR1OP*, FGFR1 oncogene partner; *FIBP*, FGF1 intracellular binding protein; *FNDC3A*, fibronectin type III domain containing 3A; *FOS-V*, Finkel-Biskis-Jinkins murine osteosarcoma viral oncogene homolog; *FOSL2*, FOS-related antigen 2; *FUT2*, fucosyltransferase 2; *GAL3ST2*, galactose-3-O-sulfotransferase 2; *GBAP1*, glucosylceramidase beta pseudogene 1; *GCKR*, glucokinase regulator; *GLYAT*, glycine-N-acyltransferase; *GNA12*, G protein subunit alpha 12; *GPR35*, G protein-coupled receptor 35; *HDAC7*, histone deacetylase 7; *HIPK1*, homeodomain interacting protein kinase 1; *HLA-A*, human eukocyte antigen A; *HLA-B*, human leukocyte antigen B; *HLA-C*, human leukocyte antigen C; *HLA-DP*, human leukocyte antigen DP; *HLA-DRA*, human leukocyte antigen DR alpha; *HLA-DRB1*, human leukocyte antigen DR beta 1; *HMGN2P18*, high mobility group nucleosomal binding domain 2 pseudogene 18; *HNF4A*, hepatocyte nuclear factor 4-alpha; *HSPA6*, heat shock 70kd protein 6; *ICOSLG*, inducible T cell costimulator ligand; *IFIH1*, interferon-induced helicase C domain-containing protein 1; *IFNG-AS1*, interferon gamma; *IFNGR2*, interferon gamma receptor 2; *IFNLR1*, interferon lambda receptor 1; *IL1R1*, interleukin 1 receptor type 1; *IL1R2*, interleukin 1 receptor type 2; *IL2RA*, interleukin 2 receptor alpha; *IL6R*, interleukin 6 receptor; *IL7R*, Interleukin 7 receptor; *IL10*, interleukin 10; *IL12B*, interleukin 12B (IL12 p40 subunit); *IL18R1*, interleukin 18 receptor 1 (alpha chain); *IL21*, interleukin 21; *IL23A*, interleukin 23 alpha (IL12 p19 subunit); *IL23R*, interleukin 23 receptor; *IL27*, interleukin 27; *INAVA*, innate immunity activator; *IRF1*, interferon regulatory factor 1; *IRF5*, interferon regulatory factor 5; *IRGM*, immunity-related GTPase family, M; *ITGAL*, integrin alpha-L; *ITLN1*, intelectin 1; *JAK2*, Janus kinase 2; *JAZF1*, JAZF zinc finger 1; *KEAP1*, kelch like ECH associated protein 1; *KIF21B*, kinesin family member 21B; *KSR1*, kinase suppressor of ras 1; *LCE3B*, late cornified envelope 3B; *LNPEP*, leucyl-cystinyl aminopeptidase; *LRRK2*, leucine rich repeat kinase 2; *LSM14A*, LSM14A mRNA processing body assembly factor; *LTBR*, lymphotoxin B receptor; *MST1*, macrophage stimulating 1; *MYRF*, myelin regulatory factor; *NDFIP1*, neural precursor cell expressed, developmentally downregulated 4 family-interacting protein 1; *NFATC1*, nuclear factor of activated t cells, cytoplasmic, calcineurin-dependent 1; *NFIP1;* Nedd4 Family Interacting Protein 1;*NFKB1*, nuclear factor kappa-b, subunit 1; *NFKBIA*, nuclear factor of kappa light chain gene enhancer in b cells inhibitor, alpha; *NKX2-3*, NK2 homeobox 3; *NOD2*, nucleotide-binding oligomerization domain protein 2; *NOS2*, nitric oxide synthase 2A; *NOTCH1*, NOTCH, Drosophila, homolog of, 1; *NPEPPS*, aminopeptidase, puromycin-sensitive; *NR5A2*, nuclear receptor subfamily 5 group A member 2; *NXPE1*, neurexophilin

and PC-esterase domain family member 1; *OR5B21*, olfactory receptor family 5 subfamily B member 21; *OSMR*, oncostatin M receptor; *PARK7*, Parkinsonism associated deglycase; *PKIG*, cAMP-dependent protein kinase inhibitor gamma; *PLAU*, plasminogen activator, urokinase; *PPP2R3C*, protein phosphatase 2 regulatory subunit B double prime gamma; *PPP5C*, protein phosphatase 5 catalytic subunit; *PRDM1*, PR domain-containing protein 1; *PRKCB*, protein kinase C beta; *PRKCQ*, protein kinase C theta; *PTGER4*, prostaglandin E receptor 4, EP4 subtype; *PTPN2*, protein tyrosine phosphatase, non-receptor type 2; *PTPN22*, protein tyrosine phosphatase, non-receptor type 22; *PUS10*, pseudouridylate synthase 10; *RAVER1*, RAVER1, mouse, homolog of; *RIC8B*, RIC8, *C. elegans*, homolog of, B; *RNF114*, ring finger protein 114; *RNF186*, ring finger protein 186; *RORC*, RAR-related orphan receptor C; *RPS6KB1*, ribosomal protein S6 kinase, 70-Kd, 1; *RUNX3*, runt-related transcription factor 3; *SBNO2*, strawberry notch, *Drosophila*, homolog of, 2; *SDF4*, stromal cell derived factor 4; *SETD1A*, SET domain-containing protein 1A; *SH2B3*, SH2B adaptor protein 3; *SKAP2*, SRC kinase-associated phosphoprotein 2; *SLC9A8*, solute carrier family 9 (zinc transporter), member 8; *SLC26A3*, solute carrier family 26 (zinc transporter), member 26; *SLC39A11*, solute carrier family 39 (zinc transporter), member 11; *SMAD3*, mothers against decapentaplegic, *Drosophila*, homolog of, 3; *SP140*, nuclear body protein SP140; *STAT3*, signal transducer and activator of transcription 3; *STK11*, serine/threonine protein kinase 11; *SULT1A2*, sulfotransferase family 1A, cytosolic-phenol preferring member 2; *TBKBP1*, tank binding kinase binding protein 1; *TBX21*, T-box 21; *TEX41*, testis expressed 41; *THADA*, thyroid adenoma associated gene; *TLR4*, Toll receptor 4; *TNFAIP3*, tumor necrosis factor alpha-induced protein 3; *TNFRSF1A*, tumor necrosis factor receptor superfamily, member 1A; *TNFRSF6B*, tumor necrosis factor receptor superfamily, member 6B; *TNFRSF14*, tumor necrosis factor receptor superfamily, member 14; *TNFSF8*, tumor necrosis factor ligand superfamily, member 8; *TNFSF15*, tumor necrosis factor ligand superfamily, member 15; *TNIP1*, TNFAIP3-interacting protein 1; *TNP2*, transition protein 2; *TSPAN14*, tetraspanin 14; *TYK2*, tyrosine kinase 2; *UBAC2*, UBA domain-containing protein 2; *UBASH3*, ubiquitin-associated and SH3 domain-containing protein A; *UBE2L3*, ubiquitin conjugating enzyme 2EL 3; *UQCR10*, ubiquinol-cytochrome c reductase complex, 7.2 kd subunit; *ZPBP2*, zona pellucida-binding protein 2; *ZC3H12C*, zinc finger CCCH domain-containing protein 12C; *ZMIZ1*, Zinc finger MIZ-domain containing 1; *ZNF365*, zinc finger protein 365; *ZNF831*, melanoma, cutaneous malignant-susceptibility to 1. Not shown are genetic markers from noncoding regions: *AC008697.1*, Homo sapiens chromosome 5 clone *CIT978SKB_70D3; AC020743.4*, Homo sapiens chromosome 7 clone RP11-813 K3; *AL031590.1*, Homo sapiens chromosome 22, clone 232D4; *AP001057.1*, uncharacterized LOC107983952; CTD-2260A1, DNA marker; *NPM1P17*, nucleophosmin 1 pseudogene 17; *RP1-66C13.4; RP11-24F11.2; RP11-129 J12.1; RP11-300 J18.1; RP11-1C1.5; RP11-84D1.2*; and *RP11-672A2.7*

Table 1

Summary of AS risk factors

Genetic
HLA-B27 [17–38]
MHC genes other than HLA-B27 [12, 18, 25, 28, 38–46]
ERAP1/2 [7, 25, 47–56]
SNPs within or adjacent to other genes (detailed in Table 3) [7, 11, 12, 40, 45, 47–70]
Gut microbiota and associated factors [71–74]
Altered gut microbiota, most notably a presence of [8, 75–79]: • *Lachnospiraceae* • *Prevotellaceae* • *Ruminococcaceae* • *Rikenellaceae* • *Porphyromonadaceae* • *Bacteroidaceae*
Lack of gut-induced protection by absence of breast feeding [80]
Infections
Klebsiella pneumoniae [81–87] (not established)
Respiratory tract infections and tonsillitis during childhood hospitalization [88]
Mechanical stress [89–93]
Gender at birth
Male [27, 94–102]
Social and lifestyle factors
Having older siblings [103]
Vitamin D deficiency [15, 104]
Smoking (including e-cigarettes) [105–108]
Other
Altered immune system and functionality [109–112]: • Lower number of Tregs [111] • Lower IL-10 production by CD4+ T cells but higher IL-6 production by CD8+ T cells [111] • Increased MIF levels in serum and synovial fluid [112]

IL, interleukin; *MIF*, macrophage migration inhibitory factor; *SNP*, single-nucleotide polymorphism; *Treg*, regulatory T cell

Table 2

MHC genes associated with the development of AS and associated risks

MHC class	Populations	Associated/increased risks
*HLA-B*27*	Overall [17, 18, 21, 22, 24, 25, 27–36, 113]	AS
*HLA-B*27:02*	White [18, 25]	AS
	Chinese [18]	
	Mediterranean [21]	
*HLA-B*27:03*	West African [24, 39]	AS
*HLA-B*27:04*	Chinese [18, 24]	AS, AS with peripheral joint involvement in Chinese patients with AS [27]
	Eastern Asian [24]	
*HLA-B*27:05*	White [18, 25	AS
	Chinese [18, 24]	
	Eastern Asian [18]	
*HLA-B*27:06*	Southeast Asian [24, 26]	Negatively associated with AS [26]
*HLA-B*27:07*	Western Asian [24]	
*HLA-B*27:08*	Southern Asian [24]	AS
*HLA-B*27:09*	Sardinia [24]	Negatively associated with AS [24]
*HLA-B*27:15*	Chinese [18]	AS
*HLA-B27/HLA-B*40* (B60 when defined by alloantisera)	Dutch [36], US white, black, Han Chinese [18], European white [25]	AS
*HLA-B*07, B*15, B*35*	White, black, Han Chinese [18], Colombians [38]	Negatively associated with AS but positively with peripheral SpA [36]
*HLA-A*02:01*	European and American white [25, 40]	AS
*HLA-C*12:02:02*	Taiwanese [43]	AS
*HLA-DRB1*15:01/DQB1*06:02*	White [18, 25, 28, 45]	Negatively associated with AS, positively with uveitis
*HLA-DPA1/DPB1 (DPB1*03:01)*	US and European whites [18, 25, 40, 44, 45]	AS

AS, ankylosing spondylitis; *MHC*, major histocompatibility complex