Genetic Susceptibility to Ankylosing Spondylitis: Current Insights and Future Perspectives

Soumyajit Sarkar, Rojina Khatun, Malavika Bhattacharya*

Department of Biotechnology, Techno India University, West Bengal

EM4, Salt-Lake, Sector V, Kolkata 700091, West Bengal, India

ABSTRACT

Ankylosing Spondylitis (AS) is a prototype axial spondylarthritis characterised by persistent inflammatory disease of the sacroiliac joints and spine, enthesitis, and progressive ankylosis in certain cases. There is a considerable heritable influence on AS, with both MHC and non-MHC genes contributing significantly to the risk of developing AS. In the last ten years, genome-wide association studies, functional genetics, and mechanisms research have greatly widened the list of AS-related genetic loci from HLA-B27 to others, such as aminopeptidases (ERAP1, ERAP2), cytokine pathways (IL23R, IL6R, TYK2, STAT3), transcription factors (RUNX3, TBX21), immune receptors (IL7R, GPR65), and additional loci involved in antigen processing, innate immunity, and bone formation. Epistatic interactions between HLA-B27 and ERAP1/ERAP2 variants have also been demonstrated. Genetic risk factors associated with type-17 (IL-23/IL-17) immune responses and JAK/STAT pathways suggest possible targets for therapy. Nevertheless, genetic risk factors vary by population ancestry and disease subtype, and many GWAS hits have not yet been functionally characterised. This review provides an overview of the PubMed literature published over the past decade (2015–2025) concerning genetic variations in AS, presents a summary of functional studies that link genetic variations to cellular pathways, explores interactions between genes and between genes and environment, and elaborates on the translational aspects of the findings for the diagnosis, prognosis, and therapeutic management of AS.

Keywords: Ankylosing spondylitis; Genetic susceptibility; HLA-B27; Single nucleotide polymorphism (SNP); Genome-wide association studies (GWAS); Cytokines; Inflammation; Immune dysregulation; ERAP1; IL-23/IL-17 axis; Epigenetics; Autoimmune disease

1. Introduction

Ankylosing Spondylitis (AS) is a systemic disease that features chronic inflammation in its nature and involves the immune system's participation, predominantly influencing the axial skeleton, such as the sacroiliac joint and the spine. The disease belongs to a class of axial spondyloarthritis and is characterized by several clinical criteria, namely, inflammatory back pain, prolonged morning stiffness, limited spinal mobility, and progressive dysfunction. The aetiology of the pathology lies in chronic inflammation at entheses, or sites, where ligaments

and tendons attach to bones. Consequently, structural lesions emerge, leading to secondary lesions in the form of new bone formation – syndesmophytes, vertebral fusion, and ankylosis [1].

Being a systemic inflammatory disease, AS possesses various complications outside the postural region, including acute anterior uveitis, inflammatory bowel disease, and psoriasis. They are the consequences of analogous immunopathologic mechanisms and have identical genetic predispositions. Additional conditions linked to AS include cardiovascular, osteoporotic, and fatiguing diseases [2].

The occurrence of the disease tends to happen at quite an early stage in life, specifically in the second and third decades of life, and it is characterized by a chronic progression. Taking into account the early age of the disease onset and its impact on the body throughout a lifetime, AS can become a burden in socioeconomic aspects with respect to work efficiency and health care costs [3].

As already mentioned before, the pathology of AS includes different components, which may be connected with genetics, immunity, or environmental factors, which interrelate with each other and affect the development of the disease. The first component includes the genetic predisposition, as the disease is known to be inherited in almost 80-90% cases. The environmental factors include the intestinal microflora, infections, and mechanical factors of the enthesis in the case of a predisposed patient [4].

The key breakthrough that has contributed to gaining a better understanding of AS is the discovery that AS has a high association with human leukocyte antigen HLA-B27. This breakthrough defined AS as a genetic disorder and opened a path for further studies of the molecular mechanism of the disease. Yet, HLA-B27 could not provide an explanation for the appearance of AS since not all those positive for HLA-B27 experience AS. Also, it could not explain the variation of AS symptoms in different patients regarding their severity, progression, and development of extra-articular manifestations [5].

Many scientific achievements related to AS have been achieved recently thanks to genome-wide association studies (GWAS), next generation sequencing, and genomics. A lot of non-HLA genetic loci involved in different biological processes have been identified, including antigen processing and presentation, cytokine signaling, immune cell differentiation and activation, and bone modeling and formation. All this information contributes to understanding the biology of AS and highlights the essential role of inflammation and immunity in the pathogenesis of the disease [6].

It is worth mentioning that these genetic discoveries have not only led to a better understanding of disease mechanisms but also to the creation of effective treatments. The implementation of genetic information allowed the creation of effective targeted therapies like tumour necrosis factor (TNF) inhibitors, interleukin-17 (IL-17) inhibitors, and Janus kinase (JAK) inhibitors, which completely changed the practice of managing the disease. Moreover, studying gene-gene interactions, epigenetics, and interactions between genes and

environment can help improve the understanding of disease heterogeneity and potentially lead to new precision medicine techniques [7].

Summing up all mentioned above, it should be noted that ankylosing spondylitis is a multifactorial polygenic systemic inflammatory disease, where genetic susceptibility is considered the main driver of disease development along with other environmental and immune system components [8].

2. Heritability and Familial Aggregation

Ankylosing Spondylitis is one of the most inheritable common inflammation illnesses. Genetic inheritability of AS has been evaluated in numerous twin studies and familial research; the results suggest that there is a very high possibility of AS heritability, being somewhere between 80% and 90%. That would mean that almost all variations in terms of susceptibility to the disease come from genetic inheritability [9]. Monozygotic twins showed greater similarity than dizygotic twins.

One feature of this illness is its aggregation in families. First-degree relatives of AS patients are significantly more predisposed to the development of the disease compared to other individuals. While the chances of acquiring AS are quite low in people from general population, the chances of acquiring AS in their first-degree relatives could be increased by several times. However, should an individual test positive on HLA-B27, his or her chances will be higher than those of others [10].

However, it should be noted that the occurrence of family clustering is not caused solely by the presence of HLA-B27. Indeed, there are a lot of situations when several people within the same family get different types of AS. The emergence of such situations clearly indicates that in addition to HLA susceptibility genes, there are other factors responsible for the penetrance of AS. Thus, AS is regarded as a polygenic disease but not a monogenic disease that involves HLA.

Also, the term "incomplete penetrance" is important for a more thorough explanation of the genetics of AS, since not all people having the genotype HLA-B27 develop this condition. Thus, in addition to HLA susceptibility genes, there should be some other genetic elements responsible for the development of the disease. For example, they can be represented by genes such as ERAP1, IL23R, and RUNX3. Moreover, the impact of epigenetic regulation can be possible [11].

Furthermore, recent scientific studies also stress the significance of polygenic risk scores (PRS). They account for the cumulative genetic risk that can enhance risk prediction among patients who come from families with cases of AS. Despite the lack of implementation in clinical settings, PRS takes into account several alleles that are not associated with any significant risk for an individual.

Another advance that is related to the population genetics field indicates that heritability and genetic risk can differ depending on ethnicity and allele frequency. For example, there are

some differences in the prevalence and impact of the HLA-B27 subtype among various populations, which contribute to the variability of disease development and manifestations around the globe. Moreover, gene-gene interactions such as epistasis between HLA-B27 and ERAP1/ERAP2 refine susceptibility by affecting antigen processing and immune response mechanisms [12].

Last but not least, family longitudinal studies show that, apart from affecting disease onset, genetic predisposition also plays a crucial role in predicting its course and therapy response in patients.

3. HLA-B27 and Classical Major Histocompatibility Complex Associations

The association between AS and HLA-B27 remains the most prominent one. In the overwhelming majority of cases – approximately 85% to 95% – AS patients are positive for HLA-B27; however, HLA-B27 frequency differs significantly from one ethnic population to another. Still, the presence of HLA-B27 does not always result in disease development, meaning that the allele must be considered a prerequisite for AS development rather than a necessity for the process to occur [13].

Peptide mimicry theory

HLA-B27 may present both self-antigen peptides and microbial antigen peptides that closely resemble each other. The structural similarity might provoke an autoimmune reaction [14].

Protein misfolding and unfolded protein response

The molecule tends to misfold within the endoplasmic reticulum. Misfolded proteins induce endoplasmic reticulum stress and cause activation of the unfolded protein response. In turn, inflammation and pro-inflammatory cytokine secretion, primarily IL-23 and IL-17, intensify [15].

Heavy chain homodimers

HLA-B27 may generate heavy chain homodimers at the cellular membrane. The structures act as ligands for innate immunity receptors, which results in inflammation enhancement [16].

Diverse HLA-B27 variants have distinct disease associations. Specifically, HLA-B27:05 and HLA-B27:04 have high associations with AS, while HLA-B27:06 and HLA-B27:09 are poorly associated with AS. This implies that slight differences in peptide binding properties may play a significant role in the disease pathogenesis [17].

In addition to the aforementioned processes, HLA-B27 contributes to the modulation of innate and adaptive immunity by changing antigen presentation and activating immune cells. In particular, it increases the number of IL-17-producing cells, such as Th17 and innate-like T cells, which ensures chronic inflammation at enthesis sites. Besides, HLA-B27 also interacts with genetic factors, mainly ERAP1 and ERAP2, in order to change peptide processing and

presentation. Moreover, new data show that HLA-B27 may alter the composition of gut microbiota, connecting mucosal and systemic inflammation in AS [18].

It has been demonstrated that another feature of HLA-B27 is its impact on cytokine profile by promoting IL-23 synthesis by antigen-presenting cells, which leads to further IL-17 response. Inflammation associated with HLA-B27 can result from this cytokine imbalance and cause inflammation and destruction. Furthermore, HLA-B27 might affect recruitment and positioning of immune cells in entheses via controlling adhesion molecules and chemokine receptors. Not only is inflammation related to immune response activation; moreover, HLA-B27 can have an effect on the pathological bone remodelling process, in which inflammation signals lead to bone degradation due to osteoclast function and abnormal osteoblast activity resulting in bone formation [19].

4. Non-HLA Genetic Susceptibility Loci

While HLA-B27 is responsible for a considerable amount of genetic susceptibility, it still does not account for all disease heritability. GWAS have detected over a hundred non-HLA genes that predispose to AS. The presence of these loci reflects the complex genetic basis of AS and significantly contributes to the missing heritability other than HLA-B27 [20].

These susceptibility loci are mainly grouped into biological pathways involved in:

Antigen processing and presentation,

Cytokine signaling,

Immune cell activation and differentiation,

Innate immunity,

Bone remodeling.

Important genes include ERAP1, ERAP2, IL23R, TYK2, STAT3, RUNX3, TBX21, IL7R, GPR65, CSF2, CCR6, and PTGER4.Collectively, these loci have led to the postulation that AS results from alterations in immune recognition, deregulation of cytokine and inflammation levels, but not due to the presence of a mutated gene. It should be emphasized that the majority of these genes have common biological functions, for instance, in the IL-23/IL-17 pathway, indicating a potential involvement of the pathway and not necessarily the individual gene in disease pathogenesis [21].

Moreover, some of these genes display pleiotropic behavior, as they share features with other autoimmune diseases, such as psoriasis and inflammatory bowel disease. Most of the time, the majority of GWAS-associated variants are localized in the non-coding parts of the genome. This suggests that regulation is a critical determinant in the disease pathogenesis process. Thanks to the rise of functional genomics experiments, there is now a trend towards mapping these variants to cell types and biological pathways.

4.1 ERAP1 and ERAP2

ERAP1 and ERAP2 are responsible for coding endoplasmic reticulum aminopeptidases, which hydrolyse peptides before loading them onto MHC class I proteins. It is essential for producing peptides of an optimal size capable of being presented on HLA class I proteins, such as HLA-B27 [23].

Genetic variations in ERAPs lead to a change in the effectiveness of peptide trimming. Excessive trimming and insufficient trimming may cause:

Peptide composition alteration,

Peptide-HLA binding instability,

Increased risk of HLA-B27 misfolding,

Disruption of immune system recognition.

The most important genetic finding in AS is the epistatic interaction of HLA-B27 with ERAP alleles. ERAP1 and ERAP2 genes are mostly associated with disease vulnerability in HLA-B27-positive subjects, suggesting gene-gene interactions. It provides a solid basis for considering that alterations in peptide presentation contribute significantly to the development of AS.

Apart from their function in peptide trimming, ERAPs can regulate cytokine receptor shedding and signalling pathways. There are variations in ERAP2 expression among individuals, which affects their vulnerability to disease and immune system reactions [24].

4.2 The IL-23/IL-17 Signaling Axis

Among the inflammatory pathways involved in the pathogenesis of AS, one could name the IL-23/IL-17 pathway. The link between IL-23 and IL-17 in AS is well-documented due to a number of genetic studies revealing that AS-related genes include IL23R, IL12B, TYK2, STAT3, and TRAF3IP2 loci.

IL-23 induces IL-17-producing cell growth and cell survival, including:

Th17 cells,

γδ T cells,

ILC3,

MAIT cells.

IL-17 activity results in pro-inflammatory factor production by stromal and immune cells, neutrophil migration, and extracellular matrix destruction.

Enthesitis (synovium inflammation) and altered bone remodelling [25] are among the outcomes of these activities.

Nevertheless, IL-17 production may occur independently of IL-23 in some immune cells in the enthesis. This could be a reason behind the higher clinical efficiency of IL-17 blockade therapy than IL-23 inhibition [26]. Besides, there is some cross-talk between the IL-23/IL-17 pathway and other pathways, e.g., the TNF pathway.

4.3 JAK/STAT Signalling Pathway

The JAK/STAT signaling pathway couples cytokine receptor stimulation on the cellular surface to nuclear transcriptional response. This is integral to AS as it integrates signals from many different cytokines involved in AS.

TYK2, STAT3, and related components have been shown genetically to be involved in AS susceptibility. The cytokines that are involved in AS – IL-23, IL-6, IL-7, IL-12, and type I interferons – all use JAK/STAT pathways to signal. These pathways induce:

the survival and proliferation of inflammatory lymphocytes,

Th17 development and stability,

Continuous cytokine secretion,

Chronic inflammation amplification.

As the JAK/STAT signaling pathway integrates the actions of multiple cytokine pathways at once, it acts as a critical link between genetic susceptibility and persistent immune system activity.

From a clinical standpoint, inhibition of JAK signaling serves as an effective anti-inflammatory mechanism, and JAK inhibitors have been found to effectively treat AS patients, especially those non-responsive to current biologic therapy [27].

4.4 Transcription Factors

Transcription factors have been identified to regulate genetic variations responsible for the immune cell phenotype and immune cell functions.

RUNX3

The RUNX3 factor regulates the development and activities of $CD8^+$ T-cells and innate-like lymphocytes. AS-associated genetic variations can influence the functions of $CD8^+$ T-cells, including their cytotoxicity, antigenicity, and regulation of immune responses within the entheses, resulting in inflammation.

TBX21 (T-bet)

TBX21 factor encodes for the protein T-bet, which plays a critical role in the differentiation of Th1 cells and production of interferon-gamma. Overexpression of TBX21 can result in hyper-responsiveness of Th1 cells and enhance signalling in the interactions of Th17 cells in inflammation.

STAT3

STAT3 plays an important role in the differentiation and survival of Th17 cells. Increased STAT3 activity results in persistent inflammation via IL-17 production and survival of pathogenic immune cells.

Such transcription factors provide insights into the mechanism of the effect of susceptibility alleles on immune cell phenotypes and chronic inflammation. Imbalance of inflammatory and regulatory immune responses in AS patients may also be attributed to such transcription factors.

5. Genome-Wide Association Studies and Polygenic Architecture

Indeed, genome-wide association studies (GWAS) revolutionized the genetics of AS because they made possible the discovery of disease susceptibility variants all around the genome. In contrast to candidate gene analysis, GWAS facilitate the finding of new susceptibility loci without any a priori assumption regarding disease mechanisms. More than one hundred susceptibility loci have already been discovered, and consequently, the AS genetic profile has been largely expanded beyond the major histocompatibility complex. This was a great step forward in our understanding of the underlying biological processes in AS [29].

GWAS data convincingly indicate that AS is a disease with a polygenic aetiology, wherein many common genetic variations with modest effects sum up and contribute to disease development. In contrast to one mutation responsible for increased risk of AS, many loci scattered throughout the genome have relatively small effects and combine their effects in increasing the disease risk. It provides a reasonable explanation of disease expression variability and the lack of complete penetrance, including HLA-B27 carriers [30].

The most interesting finding in the sphere of GWAS can be considered pleiotropy, or the ability of a certain gene to influence multiple diseases, each with its own phenotype. For example, some AS loci have been associated with other immune disorders such as psoriasis, inflammatory bowel disease, and uveitis. This reveals a considerable amount of shared genetics among them, implying that there must be some similar immune mechanisms in play, particularly related to mucosal immunity and cytokine signaling [31].

In particular, mutations associated with AS have been found by several GWAS studies. Among them were the genes involved in IL-23/IL-17 signaling – IL23R, IL12B, TYK2, and STAT3. These genes are known to control the development of Th17 cells and their cytokines. Based on these results, the significant role of the IL-23/IL-17 pathway in AS can be concluded [32].

One of the most significant observations made during GWAS is that the vast majority of genetic variants associated with a disease occur in the non-coding regions of the genome, such as enhancers, promoters, and other types of regulatory sequences. These variants affect the function of the corresponding genes indirectly by either influencing the interaction of transcription factors with their target genomic sequences or modulating chromatin

remodeling. Therefore, the analysis of GWAS results should be combined with epigenomic and transcriptomic data for the identification of specific target cell types [33].

The progress achieved in recent years in the fields of fine-mapping, single-cell RNA sequencing, and the study of chromatin interactions has allowed us to significantly narrow down the region harbouring causative variants and target genes. The application of these techniques enabled researchers to reveal that numerous genetic risk loci associated with AS are active in cell types relevant to AS, such as Th17 cells, dendritic cells, and innate lymphoid cells. Additionally, population-specific variations in the genetic risk landscape of AS are being addressed in multi-ethnic GWAS studies [34].

Moreover, the use of polygenic risk scores (PRS) constructed from GWAS data is considered a powerful technique for assessing the sum of genetic risks. PRS considers the effect of several susceptibility variants together and thus can help to recognize people with an increased risk of developing a certain disease. Even though PRS is still being applied clinically only at the beginning stage, it promises to facilitate the diagnosis process, stratification of patients' risks, and the formulation of individual therapies for AS [35].

Generally speaking, GWAS have led to the transition from the view of AS as a condition that depends primarily on HLA genes to a much more complex phenomenon that is characterized by the interaction of multiple genes and pathways. Further progress in research requires combining genomic, epigenomic, and functional information for further clinical applications.

6. Functional Genomics and Mechanistic Insights

The greatest difficulty in studying the genetics of AS involves linking genetic associations with functional relevance. The GWAS approach has provided numerous loci associated with the condition; however, it cannot shed light on the mechanism by which genetic polymorphisms cause the disease. This is where functional genomics becomes relevant in understanding the biology underlying AS.

Some of the methods include eQTL mapping, chromatin accessibility using ATAC-seq, single-cell transcriptomics, and gene editing with CRISPR. This helps identify causal loci, the genes under regulation, and the cell types responsible for this regulation. For example, eQTL analysis has revealed that most of the variants are involved in regulating gene expression and not modifying its amino acid sequence [36].

In the case of functional genomics studies, there is clear evidence of overlap onto several critical pathogenic processes, including antigen presentation defects, dysregulation of cytokine signaling, particularly IL-23 and IL-17 axes, altered immune cell differentiation, and tissue-specific inflammation in the enthesis. With single-cell analysis, several immune cell subsets, including Th17 cells and innate lymphoid cells, were implicated in the pathogenesis of AS.

Interestingly, the majority of GWAS signals in AS lie within the non-coding regions of genes, affecting enhancer and promoter functions, as well as transcription factors' binding. CRISPR

experiments have started to corroborate these findings. Overall, functional genomics is providing crucial insight into the mechanisms of immune dysregulation and chronic inflammation in AS [37].

7. Population-Specific Genetic Variation and Ancestral Diversity

However, the distribution and effect sizes of AS alleles vary among distinct populations around the world according to genetic makeup and evolutionary history. For example, one locus that exhibits marked variation is HLA-B27, which has been found to exhibit geographical variability. This allele is prevalent in people from northern Europe, moderate in East Asians, and very rare in most African ethnicities, similar to AS epidemiology [38].

In addition to HLA-B27, there are other non-HLA-associated risk variants that show ancestral differences in allele distribution and effect sizes. These variations may influence not only the susceptibility to AS but also the characteristics of AS and its management. As a case in point, some ERAP1 polymorphisms were more important in HLA-B27-positive patients of European origin compared with others that are critical in Asians [39].

The implications of this study for future research and healthcare practice include the following. First, the polygenic risk scores, which are mostly tailored for people with European ancestry, may not have efficacy among other populations because of their limited applicability. Second, genetics is one of the contributing factors in understanding the varied presentations of the condition among those who exhibit both joint and extra-joint symptoms.

Importantly, future genetic studies must be undertaken with genetic samples that reflect diversity to avoid any biases in the development of precision medicine. This is because the GWAS studies will help improve risk stratification and treatments for AS patients around the globe.

9. Translational and Therapeutic Implications

Advancements in genetics and molecular knowledge about AS have made great translational progress in treating AS patients. As a result of discovering important inflammatory pathways like the IL-23/IL-17 pathway and TNF signaling, targeted biological drugs such as TNF inhibitors and IL-17 inhibitors were produced, contributing significantly to the success of therapy. In addition, with more research done on intracellular signaling pathways, JAK inhibitors can now also be used in treating AS, especially for those who did not respond well to biological drugs [40].

Genetic findings have also shown that personalized treatments based on patient-specific genetics are possible. Additionally, with the discovery of genes that are responsible for the risk of developing AS, a strategy of polygenic risk scoring for early diagnoses can now be pursued.

10. Limitations and Future Perspectives

Though there have been remarkable advancements, several drawbacks still have to be resolved before achieving a comprehensive understanding of the genetics of AS. Firstly, the heritability part remains unclear, while most GWAS results lack a functional effect on AS development. Secondly, the vast majority of the detected loci are situated in non-coding areas of the genome; hence, elucidation of their contribution to AS is difficult. Finally, almost all of the research investigating the genetic aspect of AS is conducted using European populations. The interaction between genetic and environmental risk factors is worth additional investigation.

Multimodal omics-based research can be of great use in studying the development and the functional effects of genetic variants on AS. Moreover, in order to advance genetic prediction of AS, various ethnicities should be considered. CRISPR technology, together with single-cell analysis, can help in validating the functional impact of genetic variants.

11. Conclusion

Ankylosing spondylitis is a complicated autoimmune disease characterized by polygenetics; multiple alleles together act to determine disease susceptibility, clinical manifestation, and progression. Of all genetic markers identified in AS, the most strongly associated is HLA-B27. Other than HLA-B27, there are various non-HLA markers for ankylosing spondylitis, which impact the disease by altering various biological functions, for example, antigen processing (ERAP1, ERAP2), cytokine signaling (IL23R, TYK2, IL7R, CSF2), transcription (RUNX3), and immune cell differentiation (GPR65). Functional genomics shows that these genetic factors come together at specific inflammatory pathways, which include the IL-23/IL-17 pathway responsible for chronic inflammation and tissue destruction.

There is evidence showing genetic heterogeneity amongst different populations, where there is variation in terms of allele frequencies and penetrance. Pleiotropy of some genes causes extraskeletal manifestations, for example, uveitis, and variation in the radiographic progression of ankylosing spondylitis.

The discovery of emerging data from GWAS, epigenetics, and transcriptomics has contributed to the elucidation of the mechanisms of AS pathology even further. Gene-gene and gene-environment interactions have been discovered by these methods, in which an environment, such as gut microbiota and mechanical stress, interacts with a person's genetic disposition to trigger disease. Moreover, epigenetics is associated with changes in the DNA molecule, such as DNA methylation and histone modification, which affect the activity of genes but do not involve any DNA sequence changes. Finally, the use of technologies that allow single-cell sequencing has allowed identifying immune cell subsets like Th17 cells and innate lymphoid cells that reside within the affected tissue and induce inflammation.

To sum up, the combination of HLA and non-HLA genetics has greatly enhanced our knowledge about AS pathogenesis and made possible the development of therapy that inhibits cytokines and Janus kinases.

Acknowledgment

We would like to express our heartfelt gratitude to the Chancellor of Techno India University.

Author Contributions

Soumyajit Sarkar: Data Collection, Formal Analysis, Writing – Original Draft

Rojina Khatun: Resources, Writing-Editing

Malavika Bhattacharya: Conceptualisation, Supervision

References

1. Bilski, R., Kamiński, P., Kupczyk, D., Jeka, S., Baszyński, J., Tkaczenko, H., &Kurhaluk, N. (2024). Environmental and Genetic Determinants of Ankylosing Spondylitis. International journal of molecular sciences, 25(14), 7814. https://doi.org/10.3390/ijms25147814
2. Zormpa, T., Thireou, T., Beloukas, A., Chaniotis, D., Golfinopoulou, R., Vlachakis, D., Eliopoulos, E., & Papageorgiou, L. (2025). The Genetic Background of Ankylosing Spondylitis Reveals a Distinct Overlap with Autoimmune Diseases: A Systematic Review. Journal of clinical medicine, 14(11), 3677. https://doi.org/10.3390/jcm14113677
3. Navid, F., Chen, L., Bowness, P., & Colbert, R. A. (2025). HLA-B27 and spondyloarthritis: at the crossroads of innate and adaptive immunity. Nature reviews. Rheumatology, 21(2), 77–87. https://doi.org/10.1038/s41584-024-01189-3
4. Rodolfi, S., Davidson, C., & Vecellio, M. (2024). Regulatory T cells in spondyloarthropathies: genetic evidence, functional role, and therapeutic possibilities. Frontiers in immunology, 14, 1303640. https://doi.org/10.3389/fimmu.2023.1303640
5. Wang, H., Yang, C., Li, G., Wang, B., Qi, L., & Wang, Y. (2024). A review of long non-coding RNAs in ankylosing spondylitis: pathogenesis, clinical assessment, and therapeutic targets. Frontiers in cell and developmental biology, 12, 1362476. https://doi.org/10.3389/fcell.2024.1362476
6. Xiao, C., Zhou, J., & Zhang, B. (2023). Differentially expressed protein-coding genes in ankylosing spondylitis: Emerging insights into pathogenesis and therapeutic approaches. International journal of rheumatic diseases, 26(8), 1440–1452. https://doi.org/10.1111/1756-185X.14814
7. Ziade N. (2023). Human leucocyte antigen-B27 testing in clinical practice: a global perspective. Current opinion in rheumatology, 35(4), 235–242. https://doi.org/10.1097/BOR.0000000000000946
8. Nagit, R. E., Rezus, E., &Cianga, P. (2024). Exploring the Pathogenesis of Spondylarthritis beyond HLA-B27: A Descriptive Review. International journal of molecular sciences, 25(11), 6081. https://doi.org/10.3390/ijms25116081

9. Brown, M. A., et al. (2012). The Genetics of Ankylosing Spondylitis and Axial Spondyloarthritis. Rheumatic Disease Clinics of North America, 38(3), 539–553. https://doi.org/10.1016/j.rdc.2012.08.018 ResearchGate
10. Wang, R., Snieder, H., & Hartman, C. A. (2022). Familial co-aggregation and shared heritability between depression, anxiety, obesity and substance use. Translational psychiatry, 12(1), 108. https://doi.org/10.1038/s41398-022-01868-3
11. Wu, V. C., Chueh, J. S., Hsieh, M. Y., Hu, Y. H., Huang, K. H., Lin, Y. H., Yang, S. Y., Chu, T. S., & Kuo, C. F. (2020). Familial Aggregation and Heritability of Aldosteronism with Cardiovascular Events. The Journal of clinical endocrinology and metabolism, 105(6), dgz257. https://doi.org/10.1210/clinem/dgz257
12. Che, W. I., Westerlind, H., Lundberg, I. E., Hellgren, K., Kuja-Halkola, R., & Holmqvist, M. (2021). Familial aggregation and heritability: a nationwide family-based study of idiopathic inflammatory myopathies. Annals of the rheumatic diseases, 80(11), 1461–1466. https://doi.org/10.1136/annrheumdis-2021-219914
13. Cortes, A., Pulit, S. L., Leo, P. J., Pointon, J. J., Robinson, P. C., Weisman, M. H., Ward, M., Gensler, L. S., Zhou, X., Garchon, H. J., Chiocchia, G., Nossent, J., Lie, B. A., Førre, Ø., Tuomilehto, J., Laiho, K., Bradbury, L. A., Elewaut, D., Burgos-Vargas, R., Stebbings, S., … Brown, M. A. (2015). Major histocompatibility complex associations of ankylosing spondylitis are complex and involve further epistasis with ERAP1. Nature communications, 6, 7146. https://doi.org/10.1038/ncomms8146
14. Leung, A., Abacar, K., Marquez-Grap, G., Kranyak, A., Liao, W., & McGonagle, D. (2025). MHC-I-opathy: A Unified Concept for the Etiology of Several Major Histocompatibility Complex-Associated Conditions Including Psoriasis and Psoriatic Arthritis. The Journal of rheumatology, 52(Suppl 3), 55–58. https://doi.org/10.3899/jrheum.2025-0235
15. Chen, B., Li, J., He, C., Li, D., Tong, W., Zou, Y., & Xu, W. (2017). Role of HLA-B27 in the pathogenesis of ankylosing spondylitis (Review). Molecular medicine reports, 15(4), 1943–1951. https://doi.org/10.3892/mmr.2017.6248
16. Carli, L., Calabresi, E., Governato, G., & Braun, J. (2019). One year in review 2018: axial spondyloarthritis. Clinical and experimental rheumatology, 37(6), 889–898.
17. Crux, N. B., & Elahi, S. (2017). Human Leukocyte Antigen (HLA) and Immune Regulation: How Do Classical and Non-Classical HLA Alleles Modulate Immune Response to Human Immunodeficiency Virus and Hepatitis C Virus Infections?. Frontiers in immunology, 8, 832. https://doi.org/10.3389/fimmu.2017.00832
18. Santos, M. R., Couto, A. R., Foroni, I., Bettencourt, B. F., Li, Z., Meneses, R., Wheeler, L., Pereira, J., Pimentel-Santos, F., Fonseca, J. E., Alves, H., Martinho, A., Lima, M., Brown, M. A., & Bruges-Armas, J. (2018). Non-classical human leucocyte antigens in ankylosing spondylitis: possible association with HLA-E and HLA-F. RMD open, 4(1), e000677. https://doi.org/10.1136/rmdopen-2018-000677
19. Bowes, J., Ashcroft, J., Dand, N., Jalali-Najafabadi, F., Bellou, E., Ho, P., Marzo-Ortega, H., Helliwell, P. S., Feletar, M., Ryan, A. W., Kane, D. J., Korendowych, E., Simpson, M. A., Packham, J., McManus, R., Brown, M. A., Smith, C. H., Barker, J. N., McHugh, N., FitzGerald, O., … Barton, A. (2017). Cross-phenotype association

mapping of the MHC identifies genetic variants that differentiate psoriatic arthritis from psoriasis. Annals of the rheumatic diseases, 76(10), 1774–1779. https://doi.org/10.1136/annrheumdis-2017-211414

20. Zhang, M., Lyu, L., Ge, L., Wang, Y., & Gu, D. (2025). Genetic architecture of primary biliary cholangitis: strong evidence for HLA and non-HLA risk loci. Frontiers in immunology, 16, 1600364. https://doi.org/10.3389/fimmu.2025.1600364
21. Zhang, Z., Yuan, J., Tian, Z., Xu, J., & Lu, Z. (2017). Investigation of 36 non-HLA (human leucocyte antigen) psoriasis susceptibility loci in a psoriatic arthritis cohort. Archives of dermatological research, 309(2), 71–77. https://doi.org/10.1007/s00403-016-1706-z
22. Bui, A., Kumar, S., Liu, J., Orcales, F., Gulliver, S., Tsoi, L. C., Gulliver, W., & Liao, W. (2023). A partitioned 88-loci psoriasis genetic risk score reveals HLA and non-HLA contributions to clinical phenotypes in a Newfoundland psoriasis cohort. Frontiers in genetics, 14, 1141010. https://doi.org/10.3389/fgene.2023.1141010
23. D'Amico, S., Tempora, P., Lucarini, V., Melaiu, O., Gaspari, S., Algeri, M., & Fruci, D. (2021). ERAP1 and ERAP2 Enzymes: A Protective Shield for RAS against COVID-19?. International journal of molecular sciences, 22(4), 1705. https://doi.org/10.3390/ijms22041705
24. Compagnone, M., Cifaldi, L., & Fruci, D. (2019). Regulation of ERAP1 and ERAP2 genes and their disfunction in human cancer. Human immunology, 80(5), 318–324. https://doi.org/10.1016/j.humimm.2019.02.014
25. Chi, H. H., Hua, K. F., Lin, Y. C., Chu, C. L., Hsieh, C. Y., Hsu, Y. J., Ka, S. M., Tsai, Y. L., Liu, F. C., & Chen, A. (2017). IL-36 Signaling Facilitates Activation of the NLRP3 Inflammasome and IL-23/IL-17 Axis in Renal Inflammation and Fibrosis. Journal of the American Society of Nephrology : JASN, 28(7), 2022–2037. https://doi.org/10.1681/ASN.2016080840
26. Bunte, K., &Beikler, T. (2019). Th17 Cells and the IL-23/IL-17 Axis in the Pathogenesis of Periodontitis and Immune-Mediated Inflammatory Diseases. International journal of molecular sciences, 20(14), 3394. https://doi.org/10.3390/ijms20143394
27. Hu, X., Li, J., Fu, M., Zhao, X., & Wang, W. (2021). The JAK/STAT signaling pathway: from bench to clinic. Signal transduction and targeted therapy, 6(1), 402. https://doi.org/10.1038/s41392-021-00791-1
28. Ogawa, E., Edamitsu, T., Ohmori, H., Kohu, K., Kurokawa, M., Kiyonari, H., Satake, M., & Okuyama, R. (2022). Transcription Factors Runx1 and Runx3 Suppress Keratin Expression in Undifferentiated Keratinocytes. International journal of molecular sciences, 23(17), 10039. https://doi.org/10.3390/ijms231710039
29. Walsh, R., Jurgens, S. J., Erdmann, J., & Bezzina, C. R. (2023). Genome-wide association studies of cardiovascular disease. Physiological reviews, 103(3), 2039–2055. https://doi.org/10.1152/physrev.00024.2022
30. Harris, L., McDonagh, E. M., Zhang, X., Fawcett, K., Foreman, A., Daneck, P., Sergouniotis, P. I., Parkinson, H., Mazzarotto, F., Inouye, M., Hollox, E. J., Birney, E.,

& Fitzgerald, T. (2025). Genome-wide association testing beyond SNPs. Nature reviews. Genetics, 26(3), 156–170. https://doi.org/10.1038/s41576-024-00778-y

31. Levine, Z., Kalka, I., Kolobkov, D., Rossman, H., Godneva, A., Shilo, S., Keshet, A., Weissglas-Volkov, D., Shor, T., Diament, A., Talmor-Barkan, Y., Aviv, Y., Sharon, T., Weinberger, A., & Segal, E. (2024). Genome-wide association studies and polygenic risk score phenome-wide association studies across complex phenotypes in the human phenotype project. Med (New York, N.Y.), 5(1), 90–101.e4. https://doi.org/10.1016/j.medj.2023.12.001
32. Ding, R., Qiu, Y., Zhuang, Z., Ruan, D., Wu, J., Zhou, S., Ye, J., Cao, L., Hong, L., Xu, Z., Zheng, E., Li, Z., Wu, Z., & Yang, J. (2021). Genome-wide association studies reveals polygenic genetic architecture of litter traits in Duroc pigs. Theriogenology, 173, 269–278. https://doi.org/10.1016/j.theriogenology.2021.08.012
33. Byun, J., Han, Y., Ostrom, Q. T., Edelson, J., Walsh, K. M., Pettit, R. W., Bondy, M. L., Hung, R. J., McKay, J. D., Amos, C. I., & for INTEGRAL-ILCCO (2021). The Shared Genetic Architectures Between Lung Cancer and Multiple Polygenic Phenotypes in Genome-Wide Association Studies. Cancer epidemiology, biomarkers &prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 30(6), 1156–1164. https://doi.org/10.1158/1055-9965.EPI-20-1635
34. Narayana, S. G., de Jong, E., Schenkel, F. S., Fonseca, P. A. S., Chud, T. C. S., Powell, D., Wachoski-Dark, G., Ronksley, P. E., Miglior, F., Orsel, K., & Barkema, H. W. (2023). Underlying genetic architecture of resistance to mastitis in dairy cattle: A systematic review and gene prioritization analysis of genome-wide association studies. Journal of dairy science, 106(1), 323–351. https://doi.org/10.3168/jds.2022-21923
35. Liu, M., Wang, L., Zhang, Y., Dong, H., Wang, C., Chen, Y., Qian, Q., Zhang, N., Wang, S., Zhao, G., Zhang, Z., Lei, M., Wang, S., Zhao, Q., & Liu, F. (2024). Investigating the shared genetic architecture between depression and subcortical volumes. Nature communications, 15(1), 7647. https://doi.org/10.1038/s41467-024-52121-y
36. Storz J. F. (2021). High-Altitude Adaptation: Mechanistic Insights from Integrated Genomics and Physiology. Molecular biology and evolution, 38(7), 2677–2691. https://doi.org/10.1093/molbev/msab064
37. Wang, S., Liu, S., Zhang, H., Sun, L., Tan, H., Shi, Y., Pan, L., Geng, M., Chen, M., Gao, B., Wang, K., Zhang, H., Yue, T., Weng, J., & Zheng, X. (2026). Integrative functional genomics and fine-mapping identify regulatory mechanisms of multivariate obesity GWAS and its cardiometabolic implications. Metabolism: clinical and experimental, 177, 156509. https://doi.org/10.1016/j.metabol.2026.156509
38. Dutil, J., Chen, Z., Monteiro, A. N., Teer, J. K., & Eschrich, S. A. (2019). An Interactive Resource to Probe Genetic Diversity and Estimated Ancestry in Cancer Cell Lines. Cancer research, 79(7), 1263–1273. https://doi.org/10.1158/0008-5472.CAN-18-2747

39. Merchant, H. N., Ivanova, A., Hart, D. W., García, C., Bennett, N. C., Portugal, S. J., & Faulkes, C. G. (2024). Patterns of Genetic Diversity and Gene Flow Associated With an Aridity Gradient in Populations of Common Mole-rats, Cryptomyshottentotushottentotus. Genome biology and evolution, 16(7), evae144. https://doi.org/10.1093/gbe/evae144
40. Kenyon, M., Maguire, S., Rueda Pujol, A., O'Shea, F., & McManus, R. (2022). The genetic backbone of ankylosing spondylitis: how knowledge of genetic susceptibility informs our understanding and management of disease. Rheumatology international, 42(12), 2085–2095. https://doi.org/10.1007/s00296-022-05174-5