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Holistic approach related to ankylosing spondylitis: A review

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Abstract

Ankylosing spondylitis (AS) is an autoimmune, chronic inflammatory illness that mostly affects the spine, sacrum, and limb joints. The precise pathophysiology and causes of AS are still unknown as of this writing. The pathogenesis is thought to be influenced by genetic, environmental, immune, and other factors. The role of genetic variables in the development of AS has been the subject of the most extensive research among them. The role of epigenetic alteration and environmental predisposition in the pathogenesis of AS has, however, received much interest in recent years. This article provides an overview of the inappropriate epigenetic alterations at genomic loci linked with ankylosing spondylitis, including DNA methylation, histone modification, and microRNA. In summary, this review's findings make an effort to explain how epigenetic alteration affects the occurrence and progression of AS. To further our understanding of the pathphysiology of AS, there are a number of unresolved and complex issues that require study.

Key Words: - Ankylosing spondylitis, Epigenetic, Histone Modification, DNA Methylation and MicroRNA.

ANKYLOSING SPONDYLITIS[1]

Ankylosing spondylitis (AS) is a chronic, seditious disease of the axial spine. Chronic reverse pain and progressive spinal stiffness are the most common features of this disease. Involvement of the spine, sacrolitis joints, supplemental joints, integers, and entheses are characteristics. Impaired spinal mobility, postural abnormalities, buttock pain, hipsterism pain, supplemental arthritis, enthesitis, and dactylitis are all generally associated with ankylosing spondylitis.

INTRODUCTION[2]

Spondyloarthritis (SpA) is an inflammatory rheumatic disease affecting the axial skeleton and peripheral joints and entheses. As Compared to other rheumatic diseases inflammation in SpA is associated with a serious illness. Skeletal structures are altered in a pathological and consequently a barrier. there are two primary mechanisms that lead to the signs of SpA. First, bone marrow inflammation Osteitis or enthesitis of the entheses is painful and stiffness in the afflicted joints, including the spine. Second, the altered function of the spine is caused by bony overgrowth (ankylosis), which results in restricted mobility and reduced thoracic excursions during respiration. Spinal ankylosis, which is present throughout the entire vertebral column in later stages of the disease, produces a radiographic picture of a bamboo-like spine. We are currently going through a transition from an anatomically based explanation of SpA to a molecular pathophysiologic understanding of the disease, using the classic example of radiographic definition of "ankylosing spondylitis" (AS).

SpA has a strong genetic component. The link between SpA and HLA-B27 has been known for almost 40 years. There is now a growing emphasis on the various HLA-B27 subtypes and how they present antigens differently. Furthermore, new genetic connections in SpA have been found by genome-wide association studies (GWAS), which may provide more insight into the pathogenesis of this inflammatory disease. Novel insights into the regulation of cytokine cascades including the tumour necrosis factor (TNF)- and interleukin (IL)-17/IL-23 pathways will advance our understanding of SpA and are closely related to recent genetic insights in SpA. In order to describe the mechanisms of syndesmophyte formation and ankylosis in SpA, it is crucial to consider bone remodelling.

HISTORY[3]

Realdo Colombo, an anatomist and surgeon, first described what could have been the disease in 1559, and Bernard Connor was the first to describe pathologic changes to the skeleton that might be related to AS in 1691. Benjamin Brodie was the first doctor to record a patient with possible active AS who also had iritis in 1818.

Galen first identified ankylosing spondylitis from rheumatoid arthritis in the second century AD, giving the condition a long medical history. The skeletal remains of a 5000-year-old Egyptian mummy with evidence of bamboo spine were through to find skeletal evidence of the disease (ossification of joints and enthuses particularly of the axial skeleton, called as "bamboo spine"). However, a subsequent report found that was not case.

In 1858, David Tucker published a brief booklet describing Leonard Trask's case, who had developed significant spinal deformity as a result of AS. Trask's health worsened after he fell off a horse in 1833, leaving him with a serious deformity.

GLOBAL PREVALENCE OF ANKYLOSING SPONDYLITIS[4]

The mean AS prevalence per 10000 (from 36 eligible studies) was 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America and 7.4 in Africa .Additional estimates for Europe, Asia, and Latin America were derived as 18.6, 18.0, and 12.2 accordingly, weighted by study size. The number of cases in Europe and Asia was estimated to be 1.301.56 million and 4.634.98 million, respectively, based on appropriate investigations.

From 36 studies that were considered, the mean AS prevalence per 10,000 people was 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America, and 7.4 in Africa. Additional estimates for Europe, Asia, and Latin America were derived as 18.6, 18.0, and 12.2 accordingly, weighted by study size. The number of cases in Europe and Asia was estimated to be 1.301.56 million and 4.634.98 million, respectively, based on appropriate investigations.

SYMPTOMS[5]

- Pain and redness in the eyes (uveitis or iritis).
- Dactylitis, which is pain and swelling along the tendons in the fingers or toes, and enthesitis, which typically affects the rear or bottom of the heel.
- Psoriasis, an inflammatory skin condition.
- Chrohn's disease, ulcerative colitis, or inflammatory bowel illness.
- Pain, bloating, and other stomach symptoms.
- Lower back pain and stiffness.
- Hip pain.
- Joint pain.
- Neck pain.
- Difficulty breathing.
- Fatigue.
- Loss of appetite and unexplained weight loss.
- Abdominal Pain and diarrhea.
- Skin rash.
- Vision problems.

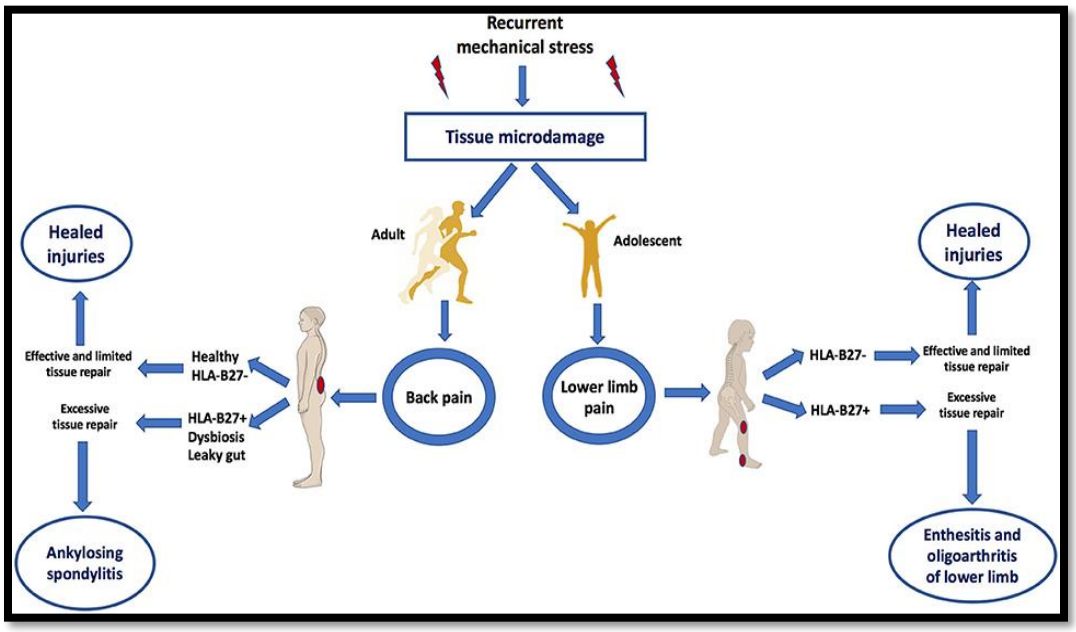

Fig.1 Phases of Ankylosing spondylitis

MECHANISM OF ANKYLOSING SPONDYLITIS[35]

The onset of ankylosing spondylitis has not been attributed to a single agent. The immune system, elevated blood IgA (immunoglobulin A) levels, acute phase reactants of inflammation, and the HLA-B27 gene appear to interact extensively. Enthesitis is a typical histopathological finding. Enthesis is the medical term for the insertion of a tendon, ligament, capsule, or fascia into bone. Ankylosing spondylitis often causes this enthesis to become inflamed at the vertebrae.

Studies show that the immune system and inflammation destroy the entheseal fibro cartilage in ankylosing spondylitis. It was long believed that enthesitis was a sign of ankylosing spondylitis. In addition, it has been reported that mild and harmful synovitis (inflammation of the synovium, which forms a cushion in the joints) occurs. The myxoid subchondral bone marrow is also affected.

As the condition deteriorated, the adjacent articular or joint tissues are destroyed. The old and new cartilages are changed over to bone through fusion. This causes the joint bones to fuse together, resulting in stiffness and immobility. In ankylosing spondyliytis, this is the most common symptoms in the spine.

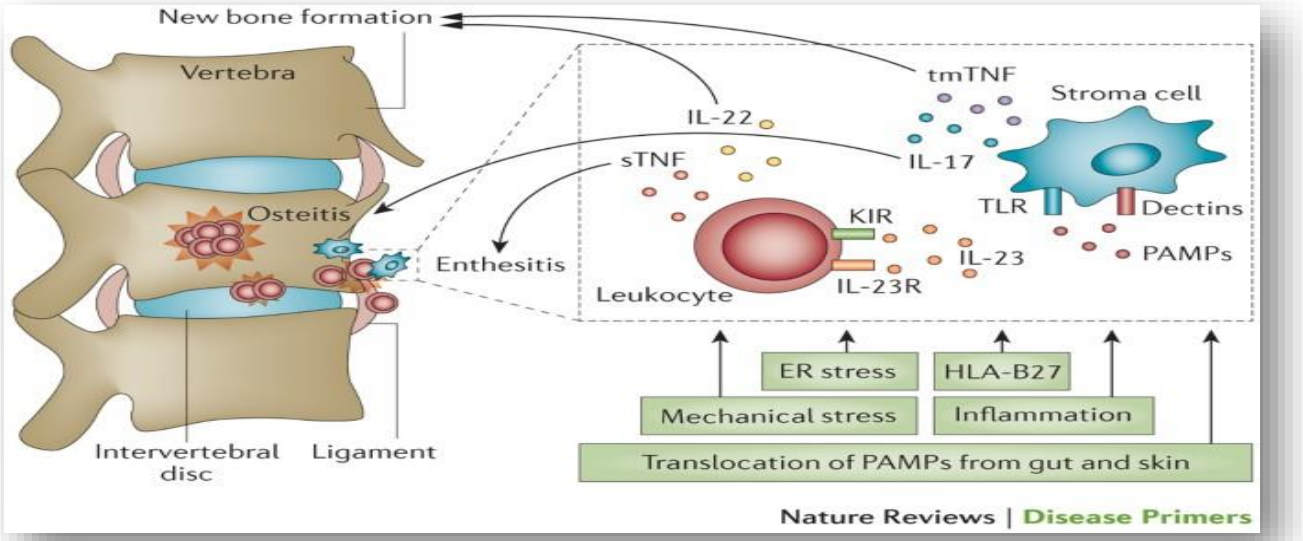

Fig.2 Mechanism of Ankylosing Spondylitis

PATHOPHYSIOLOGY [7]

A systemic rheumatoid condition, ankylosing spondylitis affects the entire body. The disease affects 1-2% of those with the HLA-B27 genotype. There is a strong genetic link because the HLA-B27 genotype is expressed in about 85% of individuals with AS. TNF-alpha (tumour necrosis factor alpha) and IL-1 are other factors linked to ankylosing spondylitis. No autoantibodies that are specific for AS have been found. Anti-neutrophil cytoplasmic antibodies (ANCAs) are associated to AS, but do not correlate with disease severity.

Ankylosing spondylitis cases have increased in a group drawn from the United Kingdom, Australia, and Canada because of the single nucleotide polymorphism (SNP) A/G variant rs10440635 near the PTGER4 gene on human chromosome 5. This disease is predisposed to by the PTGER4, perhaps through affecting the production or expression pattern of EP4. The relationship between AS and HLA-B27 suggests that CD8 T cells, which interact with HLA-B, are involved in the disease. Although it has not been established that this interaction involves a self-antigen, the antigens possibly implicated are generated from intracellular microorganisms, at least in the similar reactive arthritis that occurs after infections. However, since HLA-B27 appears to have a number of peculiar properties, including possibly the ability to interact with T cells receptors in association with CD4 (typically CD8+ cytotoxic T cells with HLA-B antigen as it is an MHC class 1 antigen), it is possible that CD4+ T lymphocytes are involved in an aberrant manner.

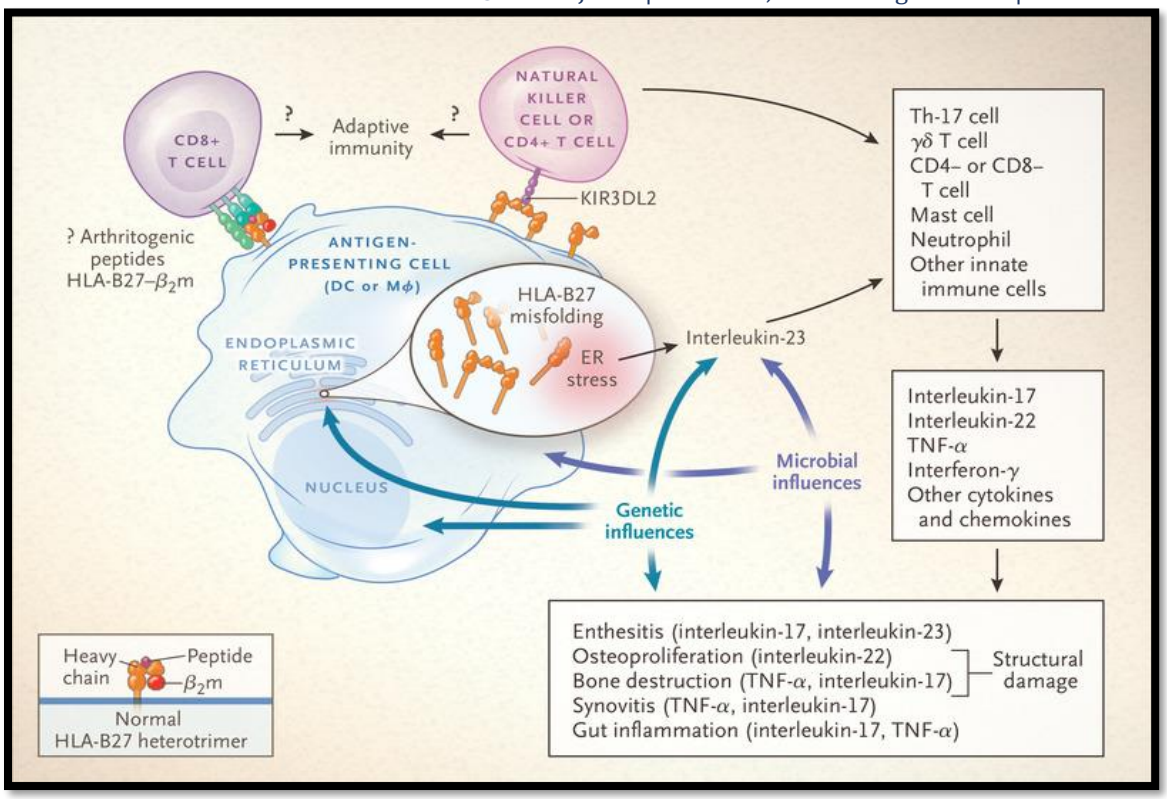

Fig. 3 Pathophysiology related to ankylosing spondylitis

DIAGNOSIS [8]

Imaging tests

X-rays allow doctors to check for changes in joints and bones, through the visible signs of ankylosing spondylitis might not be evident early in the disease.

An MRI uses radio waves and a strong magnetic field to provide more-detailed images of bones and soft tissues. MRI scans can reveal evidence of ankylosing spondylitis earlier in the disease process.

Lab Tests

There are no specific lab tests to identify ankylosing spondylitis. Certain blood tests can check for markers of inflammation, but inflammation can be caused by many different health problems.

Blood can be tested for the HLA-B27 gene. But many people who have that don't have ankylosing spondylitis and people can have the disease without having the gene.

TREATMENT

The goal of treatment is to relieve pain and stiffness and prevent or delay complications and spinal deformity. Ankylosing spondylitis treatment is most successful before the disease causes irreversible damage.

PHARMACOLOGICAL TREATMENT TO ANKYLOSING SPONDYLITIS [9]

Table no. 1 Pharmacological treatment to ankylosing spondylitis

Non Steroidal Anti-inflammatory drugs	Disease Modifying Antirheumatic drugs	TNF Inhibitors	Interleukin Inhibitors	Personalized medicine
Celecoxib Diclofenac Ibuprofen Indomethacin Meloxicam Naproxen	Methotrexate Sulfasalazine	Adalizumab Certolizumab Etanercept Golimumab Infliximab	Itekizumab Secukinumab	Brodaluma

NON PHARMACOLOGICAL TREATMENT TO ANKYLOSING SPONDYLITIS [9]

- The patient is diagnosed, a regular exercise regimen must be initiated as part of their treatment.
- Doing personal exercises at home is more effective than doing none at all.
- Group physiotherapy is less effective than SpA treatment when combined with group exercise.
- Physical therapy patients must receive training on proper posture, walking and sleeping mechanics, and adequate exercise. Specific exercises, such as joint range-of-motion exercises, deep breathing exercises, and spine extension, must be used at least twice daily.
- Patients need to be taught the proper walking, sitting, and lying down positions.
- Kyphosis and hip flexion contracture may be avoided by lying face down for 15 to 30 minutes several times per day.
- Sleeping on a firm bed, whether with a thin pillow or without one, may lessen the chance of spine deformity.
- To accomplish all of these physiotherapy goals, swimming and hydrotherapy are the most efficient exercises.
- Sports that promote axial mobility should be selected above those that increase the risk of bone fracture (swimming, badminton, volleyball, running, skiing, etc). (Cycling, horse riding, boxing, and football).

Therapy

Physical therapy is an important part of treatment and can provide a number of benefits, from pain relief to improved strength and flexibility. A physical therapist can design specific exercises for your needs.

- Range of motion and stretching exercise.
- Strengthening exercises for abdominal and back muscles.
- Proper sleeping and walking positions.[8]

Lifestyle and home remedies

Lifestyle choices can also help manage ankylosing spondylitis

- Stay active. Exercise can help ease pain, maintain flexibility and improve your posture.
- Don't smoke. If you smoke, quit. Smoking is generally bad for your health, but it creates additional problem for people with ankylosing spondylitis, including hampering breathing.
- Good posture. Practicing standing straight in front of a mirror can help you avoid some of the problems associated with ankylosing spondylitis.[8]

GENETIC PREDISPOSITION TO SPONDYLOARTHRITIS [10]

Table no. 2 Genes whose variability is involved in spondyloarthritis

Genes	Function	References
HLA-B27	Antigen presentation	Ito et al., 2001; Revelle 2011; Tyagi et al., 2012; Vecellio et.al., 2019; Chimenti et al., 2020
IL-$1R_2$	Interferon signaling	O Rlelly and Rahman, 2013
TNF-A	NFkB signaling	Tsui et al., 2010
$TBKBP_1$	NFkB activation and signaling	Vecellio et al., 2019
TBX21	Th1 cell expression	Reveille et al., 2010
MICA	NK and T cells activation	Wand and Zhou, 2015
PTGER4	Th17 signaling	Vecellio et al., 2019
$IRAK_1$	NFkB signaling	Chimenti et al., 2019
$ANTXR_2$	Bone remodeling	Vecellio et al., 2019
$STAT_3$	Th17 signaling	Berlinberg and Khun, 2020
$CYP2D_6$	unknown	Berlinberg and Khun, 2020
TLR_4	NFkB signaling	O Rlelly and Rahman, 2013
$TNIP_1$	NFkB activation and signaling	Vecellio et al., 2019
$KIR3DL_1$	NK and T cells activation	Chimenti et al., 2019
ANO_6	Bone remodeling	Vecellio et al., 2019

Epigenetics [10]

Epigenetic is a branch of genetics that investigates stably heritable phenotypes deriving from changes in the chromosome with no alterations in DNA sequence. It focuses on the heritable variation in a chromosome that affects gene expression without alter the genome.

Factors influencing epigenetic modifications:-

Epigenetic marks can be affected by variety of factors described below. These factors are important to keep in mind when considering an experimental design to identify specific alteration of the epigenome in a given disease to avoid spurious findings.

a) **Cell type**
On the contrary to the primary sequence of the human genome which is largely preserved in all human cell types and tissue, the epigenome varies considerably among cell types, as extensively studied by the NIH Roadmap Epigenomics program and Encyclopedia of DNA Elements (ENCODE) project.[11.12] This cell specificity must be considered in analytic perspectives, especially to critically evaluate epigenomic studies, taking into account that a high proportion has been performed in peripheral blood with a mixture of different cell types. Thus, differences observed between conditions might be related to a difference in the proportion of different cell types rather than to the studied condition.

b) **Individual characteristics:-**
Age is one demographic component that appears to have a significant impact on epigenetic markers. Epigenome is also influenced by ethnicity.[13,14]

c) **Lifestyle and environmental factors:-**
Exposure to environmental factors like air pollution and lifestyle factors like smoking, taking medications, drinking alcohol, and eating a certain way can change all epigenetic marks.[15,16]

d) **Interindividual variations of the DNA sequence:-**
Epigenetic markings are largely determined by interindividual changes in DNA sequence (such as single nucleotide polymorphism). DNA polymorphism can affect the methylation status of DNA [17], miRNA expression [18] and the level of histone post-translational modifications [19]. Finding the functional effects of disease-associated variations may be especially beneficial [20].

EPIGENETIC MECHANISMS IN SPONDYLOARTHRITIS [22]

Epigenetic is a key mechanism regulating the gene expression of genes. There are three main and interrelated mechanisms: DNA methylation, Post-translational modifications of histone proteins and non-coding RNA.

DNA methylation [22]

DNA methylation generally prevents genes from being expressed, especially when it occurs in the promoter and enhancer regions of genes. Recent studies have reported that changes in chromatin structure, DNA conformation, and DNA stability carried on by DNA methylation can control how genes are expressed. DNA methylation is the chemical modification process in which s-adenosyl methionine (SAM) serves as the methyl donor and DNA methyltransferase (DNMT) catalyses the attachment of a methyl group to specified bases in the DNA sequence. These DNA methylation sites can be located at the cytosine 5 (c-5), adenine 6 (n-6), and guanine 7 (n-7) positions.
In general studies, DNA methylation mostly refers to the methylation process of the fifth carbon atom on cytosine in CpG dinucleotides, which is typically concentrated in a particular region of the genome, called CpG Island, found on the promoter of about 60% of the genes. One type of DNA methylation, known as de novo methylation, involves DNA that is not methylated in either strand. The second type of methylation, known as maintenance methylation, occurs when one strand of double-stranded DNA is already methylated but the other strand is not. DNA methylation is a stable alteration state that may be passed on to new progeny DNA during DNA replication, which is a key epigenetic mechanism. DNA methyltransferase is responsible for this transfer of DNA methylation.

Histone Modification:-

Histone is an essential protein found in prokaryotic cells and eukaryotic somatic chromatin, which combined with DNA form the nucleosome structure. They are the primary proteins that make up chromatin, which serve as spools for DNA entanglement and are important for controlling gene expression. These proteins are split into two main classes: connective proteins (H1 and H5) and core proteins (H2A, H2B, H3 and H4). Another significant type of histone modification is histone methylation, which is essential for the creation and maintenance of DNA methylation Histone methyltransferase catalyses the process of histone methylation, which mostly affects the lysine and arginine residues of H3 and H4 histones. Lysine-specific histone methyltransferase and arginine-specific histone methyltransferase are the two main forms of histone methyltransferase. The acetylation and methylation of lysine or arginine residues at the end of the N terminal of histones, which can depolymerize or fold chromosomal structures and hence influence gene transcriptional activity, are now the most extensively studied types of histone modification.

miRNA[23]

Small, single-stranded, non-coding RNA molecules known as miRNA. The microprocessor complex made up of Drosha and DGCR8 transcribes the first DNA sequence into primary miRNA, which is then secondary cleaved into precursor miRNAs. This results in a complex dynamic modulation of gene expression, which has been shown to play an important role in a number of cellular processes including development, proliferation, invasion, and apoptosis. miRNA may have hundreds of different mRNA targets, and a given target may be regulated by multiple miRNA. The ability of miRNAs to be released into extracellular fluids and their potential to function as autocrine, paracrine, or endocrine regulators to influence cellular functions have also been shown in various studies. Typically, miRNAs reduce the expression of their target genes rather than totally inhibiting them.

Epigenetic Factors involved in Ankylosing spondylitis:-

1. Genetic
2. Thought process
3. Environment and Dietary
4. Lifestyle and Natures law
5. Science and spirituality
6. Universal truth and Behavior

Genetics-Lifestyle-Environment Interplay [24]

The effects on cellular or physiological phenotypic traits can originate from lifestyle and environmental factors. Genetics, lifestyle and the environment may interact with each other due to the role of epigenetic modification**.**

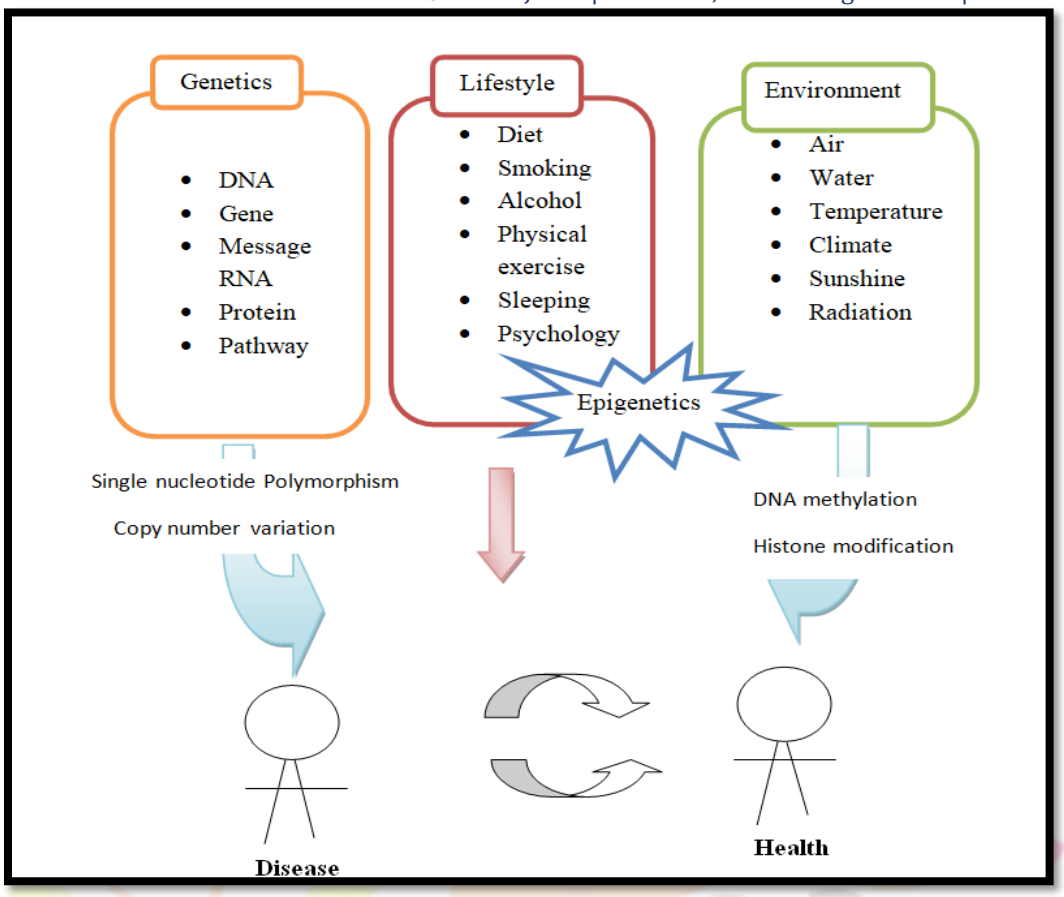

Fig. 4 genetics-lifestyle-environment interaction. Besides genetic factors, the lifestyle and environment can affect people health through epigenetic modification.

Genetics of emotion [25]

The genetic origins of individual differences in emotion processing by focusing on functional variants at five genes: catechol-O-methyltransferase (COMT), serotonin transporter (SLC6A4), neuropeptide Y (NPY), a glucocorticoid receptor-regulating co-chaperone of stress proteins (FKBP5) and pituitary adenylate cyclase activating polypeptide receptor(ADCYAP1R1).

Emotionality is moderately heritable (40-60%) but is also strongly influenced by exposure to stress in a pattern consistent with gene environment interaction. Our understanding of human behavior and the risk of developing disease will be strengthened by the discovery of the mechanisms that result in inter-individual variations in emotional stability and susceptibility to stress and anxiety. [26]

Table no.3 Genes responsible for emotion

Gene	Role	Author
COMT	Metabolizes dopamine, catecholamine and non-adrenaline.	Yavich L, et al., 2007
5- HTTLPR	Depression and anxiety	Lech K.P, et al., 1996
NPY	Anxiolytic neuropeptide	Morgan, C.A et al., 2000
FKBP5	Antidepressants	Kovacs et al., 2000
ADCYAP1R1	PTSD in females	Ressler K.J, et al., 2011

Genes and their role in Nutrition

The personalized approach to the person, as based on the 4P principles (personalized, predictive, preventative, participative), both in the fields of medicine and nutrition, plays an important role, because the prevention and treatment of the body depend on the right rational nutrition. Proper nutrition is part of a healthy lifestyle, and its disturbances cause various diseases.[32]

Genes Responsible for the Digestion and Absorption of Carbohydrates and Fats

There are nine genes responsible for the absorption of carbohydrates and fats: ADRB2 (rs1042714 and rs1042713polymorphisms), TCF7L2 (rs12255372, rs7903146), FABP2 (rs1799883), PPARG (rs1801282), CETP (rs5882), ADRB3 (rs4994), A5 (s662799, rs3135506), LEPR (rs1137101), ApoE (rs429358, rs7412).[33]

Table no.4 Genes responsible for nutrition

Gene	Role	Author
ADBR2	Control of the cardiovascular, pulmonary, vascular.	Cropano C, et al., 2017
TCF7L2	Development of pancreatic beta cells	Turkovic L.F, et.al., 2012
FABP2	transport of fatty acids	Kovtum O, et al., 2018
PPARG	Metabolism of lipids and carbohydrates	Bhshueva O.Y, et.al., 2015
CETP	Converts "good" HDL cholesterol into "bad" LDL	Daghestani M, et al., 2018
ADRB3	lipolysis regulation	Li Y.Y, et al., 2018
APOA5	Regulating the level of triglycerides in blood.	Yuan L, et al., 2015
LEPR	Regulation of body weight and energy metabolism	Coronel J, et al., 2019.

Genes Responsible for Eating Preferences

The list of genes influencing eating preferences includes: FTO (rs9939609), MC4R (rs17782313), DRD2 (rs1800497).

FTO

The FTO gene encodes the protein that participates in energy metabolism, oxidative reactions and the metabolism of fatty acids.[46]

MCAR

The MC4R gene produces the membrane-bound receptor protein, which is a key player in the control of eating preferences and energy homeostasis. The protein, in association with melanotropin, becomes responsible for the feeling of saturation. [47]

DRD2 Encodes for the D2 dopamine receptor, which reduces adenyl cyclase activity. The central nervous system's many functions, including eating, drinking, drug, and smoking addiction, are all regulated by dopamine.[48]

Table no.5 Genes responsible for eating preferences

Gene	Role	Author
FTO	Metabolism of fatty acids	Khoshi A, et al., 2019
MCAR	Energy homeostasis	Wang S, et al., 2017
DRD2	Reduces adenyl cyclase activity	Sun X, et al., 2017

Genes related to spirituality

Genes to complex human traits, such as personality type or disease susceptibility, abound in the news media and popular culture. The God Gene: How faith is hardwired into our Genes, Dean Hamer argues that a variation in the VMAT2 gene plays a role in one's openness to spiritual experiences.[49]

VMAT2

VMAT2 encodes a transporter protein that imports several monoamine neurotransmitters into vesicles in the brain. Therefore, a change in the transporter may have an impact on the concentrations of various neurotransmitter types, altering brain function.[50]

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