Background: Most (~90%) of the ankylosing spondylitis (AS) susceptibility locus are undefined and located in non-coding regions. Epigenetic changes may alter the expression of genes involved in AS and explain part of the missing heritability. 

Objectives: To identify novel DNA methylation sites significant for AS and comprehensively understand the underlying pathological mechanism.

Methods: Genome-wide DNA methylation of blood samples from 30 AS patients and 15 healthy controls was measured on the Infinium® MethylationEPIC BeadChip microarray. Methylome data were analyzed with ChAMP package in R.

Results: The epigenome-wide association analysis identified 4,794 differentially methylated positions (DMPs) (FDR < 0.05 and delta β > 0.50), including 3,294 (68.7%) hypermethylated and 1,500 (31.3%) hypomethylated positions in AS patients (Figure 1A). The identified DMPs allowed clear distinction of most AS cases from controls in the PCA (Figure 1B) and unsupervised hierarchical clustering (Figure 1C). KEGG pathway analysis of AS-associated DMPs enriched in T cell signaling pathways, pathways of Th1 and Th2 cell differentiation. Besides, a total of 1,048 differentially variable positions (DVPs) were identified, the majority of which (974, 92.9%) were hypervariable in AS, while only 74 DVPs were hypovariable. The increased DNA methylation variability in disease were in line with the previous observation in other diseases, indicating the intrinsic heterogeneity in AS patients, which might be influenced by diverse factors, such as disease activity and treatment.

Conclusion: Peripheral blood mononuclear cells from AS patients display aberrant DNA methylation and increased DNA methylation variability. The results enhanced our understanding of the important role of DNA methylation in pathology of AS and offered the possibility of identifying new targets for intervention.

REFERENCES:
[3] Chen YG, Satpathy AT, Chang HY. Gene regulation in the immune system by long noncoding RNAs (lncRNAs) and miRNAs (DEMs). DAVID and WebGestalt were used to perform enrichment analysis. Cytoscape was used to construct protein-protein network, co-expression network and competitive endogenous RNA network to reveal the regulatory mechanism of IncRNAs in transcriptome level. The expression of these selected IncRNAs in SLE patients and healthy controls were verified by qPCR.

Results: A total of 1737 DELs and 4078 DEMs were identified between 5 SLE patients and 5 healthy controls. Most of upregulated genes were enriched in defense and immune response, while downregulated genes were mainly enriched in SLE related pathways. Topology network analysis reveal the regulatory mechanism of IncRNAs in transcriptome level including directly acting on mRNA or indirectly affecting gene expression after acting on miRNA. Ten IncRNAs and eight genes were verified by qPCR in bigger samples including 77 SLE patients and 25 healthy controls. LncRNA NONHSAT101022.2 was significantly downregulated in SLE patients (p=0.001) and the expression of NONHSAT101022.2 showed a significant negative correlation with SLE disease activity index (SLEDAI, r=-0.3952, p=0.0013). Conclusion: In this work, we identified a large number of mRNAs and novel IncRNAs by transcriptome sequence. The function and regulatory mechanism of these IncRNAs were analyzed by bioinformatics methods. LncRNA NONHSAT101022.2 is significantly downregulated in SLE patients and significantly correlated to the activity and severity of disease. Additionally, we put forward that NONHSAT101022.2 may enhance the signal transduction of β2-AR by cis-regulating its target gene, LMRBD2, which induces NK cells to produce high levels of IFN-γ, thereby exacerbating SLE.

REFERENCES:

Acknowledgements: We appreciate all the staff members of the department of rheumatology of the Third Affiliated Hospital of Sun Yat-sen University for assistance and support in the patient's recruitment and sample collection.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.129