Genetic and Epigenetic Modifications in Systemic Lupus Erythematosus: Challenges to Homeostatic Immune Responses

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ABSTRACT: Systemic lupus erythematous (SLE) is characterized by the body's lack of distinction between self- and nonself-antigens amounting to hyperactive immune reactions. In most cases, this type of autoimmune disorder has no exact known causal factor and can be caused by both genetic and epigenetic influences. One of the major points of interest in SLE research is understanding the disease biology from a wide landscape involving both the genome and epigenome of SLE patients. Availability of high-throughput gene sequencing, genome-wide association studies, and gene enrichment analysis has facilitated our understanding of the pathogenesis of SLE. However, the correlation of these genetic and epigenetic changes is still poorly understood, and therefore, this review makes a first overarching attempt to bridge the existing gap in the scientific domain.

KEYWORDS: systemic lupus erythematosus, SNPs, gene copy number, transcription factor enrichment, strong enhancers, DNA methylation, histone marks, noncoding RNAs

CITATION: Satapathy and Bhuyan. Genetic and Epigenetic Modifications in Systemic Lupus Erythematosus: Challenges to Homeostatic Immune Responses. *Clinical Medicine Reviews in Therapeutics* 2016:8 1–6 doi: 10.4137/CMRT.S38125.

TYPE: Review

RECEIVED: December 03, 2015. **RESUBMITTED:** February 01, 2016. **ACCEPTED FOR PUBLICATION:** February 02, 2016.

ACADEMIC EDITOR: Garry M Walsh, Editor in Chief

PEER REVIEW: Two peer reviewers contributed to the peer review report. Reviewers' reports totaled 383 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

Systemic lupus erythematous (SLE) is an autoimmune disorder caused due to the body's loss of distinction between self- and nonself-antigens, ultimately leading to hyperactivation of autoreactive immune complexes. The disease diversity includes a range of disease phenotypes associated with varied severity, differential selection of target organs, and the responsiveness to the available therapeutics and associated side effects. Characterized by the breach of B-cell and T-cell tolerance for self-antigens, this disease involves the production of autoreactive antibodies. Most of the autoreactive antibodies produced are either antinuclear antibodies or anti-extractable nuclear antibodies.[1]

Pathophysiology of SLE involves hyperactivation of T-cells and hyperstimulation of B-cells, induction of apoptosis and necrosis of T-cells, Fas ligand and Fas receptor overexpression, and oxidative stress and mitochondrial dysfunction of immune cells (B-cells, T-cells, and macrophages).[1,2] Accumulation of cellular debris is another factor leading to SLE-like phenotype where overactivation of B-cells occurs by the presentation of self-antigens (processed from accumulated cellular debris) by plasmacytoid dendritic cells (pDCs) followed by excessive antigen–antibody immune complex formation.[2] However, such an erroneous immunogenic reactivity leads to systemic tissue damage of target organs, such as the heart, kidney, lungs, joints, brain, and skin, where fatality can be of a higher grade.

Several functional pathway-based gene-specific enrichment analyses have identified immune signaling pathways, such as Toll-like receptor (TLR) signaling (eg, TLR7 and TLR9), type-1 interferon signaling (α- and β-interferon), and Nuclear Factor-κβ (NF-κβ) signaling, involved in the pathogenesis of SLE. Literature-based evidences have accounted for an uncontrolled and unprotective level of proinflammatory cytokines [interleukin (IL)-6, α-interferon, Tumor Necrosis Factor-α (*TNF-α*), *IL-17*, *IL-23*, *IL-21*, etc].[3–5] However, although several ongoing and past studies have tried to dissect the mechanism of SLE, the clinical manifestation of symptoms still lacks a definitive pattern, challenging our approaches for effective prognosis, early detection, and targeted therapeutic interventions. One of the primary reasons felt is that there have been multiple lines of research broadly based on two approaches. Genomic and epigenomic alterations to the host genome in case of patients suffering from SLE have been the basis of majority of basic and translational studies on SLE. However, increasing number of evidences hint that there is no particular approach of these alterations, which can be accounted as the major contributor of SLE, and thus, there is a need of the moment to develop

Table 1. List of common genetic changes associated with SLE.

SI NO. 10	GENES OVEREXPRESSED	GENES DOWNREGULATED	SINGLE GENE DEFECTS OF COMPLEMENT SYSTEM
1	Interleukin-10	UBE2L3	C1q
2	ATG 5	ETS-1	C2
3	Granzyme A	TNFA1P3	C4
4	TLR9/7	DNMT1	–
5	NF-κβ	–	–
6	α- interferon, IRF5<, IRF7	–	–
7	BAFF	–	–
8	TREX1	–	–
9	Protein phosphatase 2Ac	–	–
10	HMGB1 and GADD45α	–	–
11	Mannose binding lectins (MBLs)	–	–

Notes: Different genes are either upregulated (IL-10, ATG-5, granzyme A, TLR7/9, NF-κβ, IRF7, TREX1, BAFF, PP2 Ac, MBLs, HMGB1, and GADD45) or downregulated (UBE2 L3, ETS-1, TNFA1P3, and DNMT1). In addition, several single gene defects have been reported in complement system (C1q, C2, and C4).

an integrative landscape of both genomic and epigenomic changes in SLE.

Therefore, this review tries to bridge the existing gap of integrating both genomic and epigenomic modifications associated with SLE and also look for the broader effect of these changes on the immune system. In addition, we have tried to summarize the effect on both innate and adaptive immune systems along with that of the antigen presentation process machinery. This is another first of its kind scientific text where such a wide range of immune response associated with SLE will be discussed.

Genetic Regulation of SLE: Adding, Depleting, and Altering Genes

Several genetic and epigenetic causal factors of SLE have been elucidated in the past years. Single-nucleotide polymorphisms (SNPs), variation in specific locus of target genes, and increase in gene copy number are the identified few of these modes of genetic variation contributing to systemic lupus erythematosus.

Lupus-like phenotype associated with chronic granulomatous disease and autoimmune lymphoproliferative syndrome involves an upregulation of lymphatic cell apoptosis via FasL/Fas overexpression and subsequent inability to clean the resulting cellular debris.[4]

Overexpression of single gene candidates with susceptibility to SLE includes interleukin-10 (*IL-10*); autophagy-related gene 5, granzyme A, TLR genes for sensation of nucleic acids (*TLR9/7*), NF-κβ signaling genes, type-1 interferon pathway genes (α-interferon, *IRF5*, and *IRF7*), B-cell activating factor, *TREX1* (three primer repair exonuclease 1 involved in damaged DNA degradation), and protein phosphatase 2 *Ac* (PP2 Ac) Table 1.[4–6] PP2 Ac leads to decreased mitogen-activated Ras signaling due to loss of phosphorylation of Mitogen activated Kinases /Extracellular signal Regulated Kinases (*MEK/ERK*) (mitogen receptor kinases).[5] Overexpression and heterodimer formation of high mobility group protein 1 and growth and DNA damage 45α form a negative repression by methylation of immune sensitive *CD11a* and *CD70* promoter regions (Table 1).[6,7]

Genes that are downregulated in SLE cohorts include *UBE2 L3* (involved in degradation of excessive TLRs),[4] V-ets erythroblastosis virus *E26* oncogene homolog 1 (*ETS-1* mostly confirmed in animal lupus models and involved in Th17 and B-cell development),[6] *TNFA1P3* (encodes A20 protein, an ubiquitin ligase enzyme, which downregulates NF-κβ signaling),[7] and DNA methyl transferase 1 (*DNMT1*; involved in impaired phosphorylation of protein kinase C-δ and erroneous ERK signaling) (Fig. 1).[6]

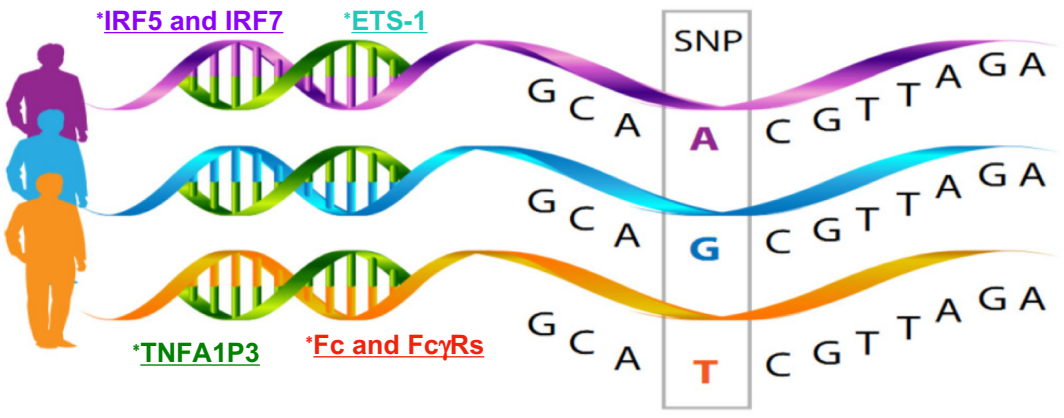

Figure 1. Role of single-nucleotide polymorphisms in genetic susceptibility to SLE. ETS-1, IRF5/7, and TNFA1P3 and Fc portion of immunoglobulins along with their Fc receptors are known to accumulate SNPs.

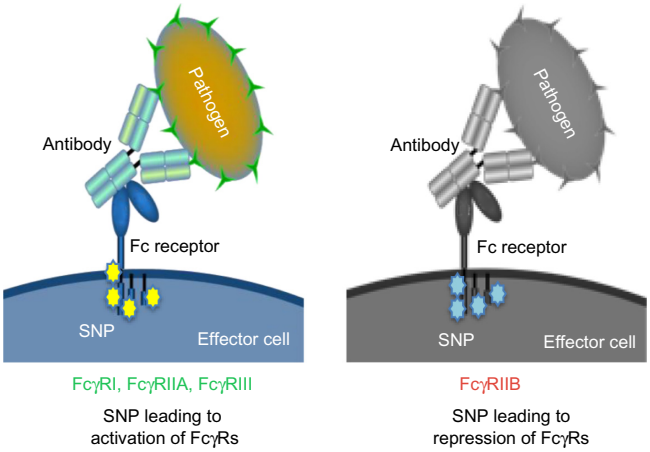

Figure 2. SNPs in the regulation of immunoglobulins and their cognate receptors. Accumulation of multiple SNPs lead to either activation or repression of the Fc-mediated immunoglobulin signaling. FcγRI, FcγRIIA, and FcγRIII are the SNPs, which activate the Ig-mediated signaling, whereas FcγRIIB leads to the repression of similar signaling process.

In a report of 2013, Frangou et al suggested that the study of bone marrow mononuclear cells helps to better understand the heterogenous expression of genes involved in cell death, differential growth, and proliferation. This serves to be more effective than similar studies on that of the peripheral blood mononuclear cells of SLE cohorts.[7]

In the complement system, the soluble arms of immune sentinels have been reported for their duality with respect to SLE. Single gene defects of C1q, C2, and C4 are associated with failure of the complement system in the phagocytic clearance of cellular debris.[8] On the other hand, upregulation of complement system genes, mannose-binding lectins, and other glycoproteins have been implicated in case of lupus glomerulonephritis.[9]

Variations in SLE manifestation between different cohorts depend on genetic manipulation of the commonly reported target organs. Synovium and Kidney show a marked upregulation of IFN-inducible genes and downregulation of extracellular matrix homeostatic genes.[8]

SNPS in Regulation of SLE

However, very recently, SNP has gained momentum in SLE research, which varies with the ethnic and racial background of study populations.[9]

Interferon regulatory factors, ie, *IRF5* and *IRF7* (Q412R), with distinct SNPs are the keynote genes for SLE susceptibility. These SNPs of IRF genes share a positive correlation with SLE progression and severity.[10,11]

ETS-1 (involved in cell cycle senescence, stem cell development, and tumorigenesis) is known to exist in multiple variants where each variant differs by their accumulated SNPs. *TNFA1P3*, a NF-κβ signal regulator, shows a distinct polymorphic dinucleotide haplotype (TT > A), which is associated with reduction of A20 inhibitory action on NF-κβ signaling (Fig. 1).[11]

The Fc portion of immunoglobulins and their receptors regulate a wide range of immune functions, such as phagocytosis, antibody-dependent cellular cytotoxicity, B-cell activation, production of cytokines, immune complex clearance, and dysregulation of antigen presentation.[10] However, this specific functionality of different Fcγ receptors originates from SNPs and loci variants leading to groups of activating receptor subunits (FcγRI, FcγRIIA, and FcγRIII) and a group of repressing receptor subunits (FcγRIIB) (Fig. 2).[12] These Fcγ receptors are not only associated with disease onset but also distinctly associated with disease progression, eg, a variant of FcγR3A is seen in late-stage lupus nephritis.[12]

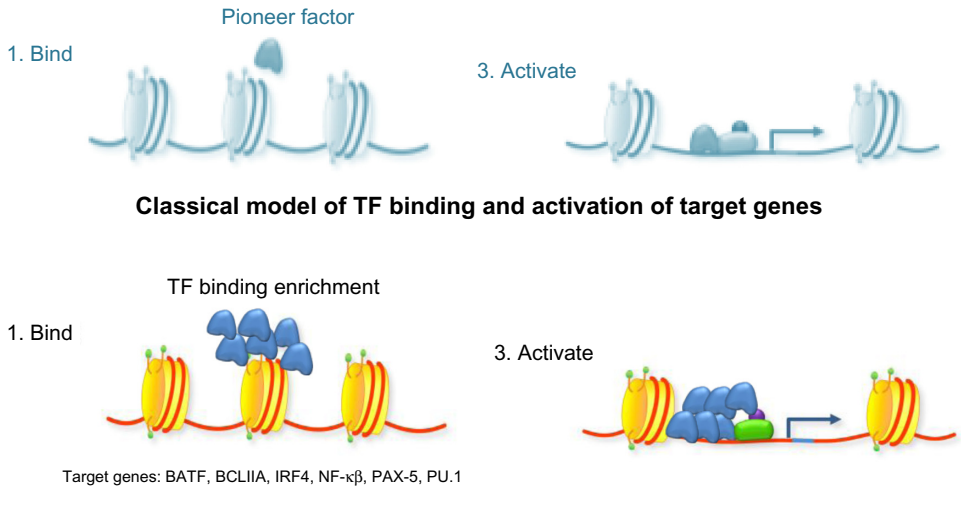

Figure 3. TF-binding site enrichment in target genes of SLE. A comparative schematic model for TF enrichment and downstream activation of signaling pathway. Some of the target genes listed are BATF, BCLIIA, IRF4, NF-κβ, PAX5, and PU.1.

Figure 4. microRNA expression profile in B-cell of SLE patients. miR-155, miR-25, miR-106b, and miR-21 are significantly upregulated in SLE with miR-21 and also involved in hypomethylation of T-helper cells ($CD4^+$). In contrast, miR-150, miR-15a, and miR-16 are downregulated in B-cells of SLE patients.

To sum up our idea on genetic regulation of SLE, the operational forces are broadly defined as SNPs, loci variants, and increase in gene copy numbers associated with and mostly targeted by SLE. These genetic modifications are heritable and can affect both transcriptional and post-transcriptional regulations. This calls for further research on the molecular mechanism that facilitates the pathogenesis and progression of SLE. Identification and characterization of such putative genetic targets associated with SLE can be promising candidates for personalized pharmacogenomics development.

Our understanding of genetic basis of SLE is just halfway in our exploration for molecular basis of this autoimmune disorder. A clear picture, however, relies on the cues of environmental and epigenetic modifications of gene expression and a characteristic role in SLE.

Epigenetic Regulation of SLE: *Exploring SLE Susceptibility Beyond Genetic Constitution*

Epigenetic regulation of SLE susceptible genes is of major interest nowadays. With the multiple identification of epigenomic signatures and the elucidation of associated mechanism, there has been a significant understanding of the processes involved in chromatin remodeling and variations in gene expression leading to SLE.

Three such major events that are often reported include the enrichment of transcriptional factor (TF)-binding sites (TFBSs), DNA methylation[13] with histone marks by post-translational modifications,[14] and the alterations in chromatin compaction, otherwise known as *chromatin segmentation*.[15]

Regulation of gene expression by noncoding RNAs (eg, microRNAs) is an emerging field of research.[15] Genome-wide association studies available from Encyclopedia of DNA Elements in collaboration with experimental data have aided our understanding of epigenetic regulation of SLE.[13–15]

TFBS Enrichment

TFBSs' enrichment is reported for SLE susceptible genes. The major TFs associated with SLE are basic leucine zipper associated transcription factor (*BATF*),[16] BCLIIA (suppressor of hemoglobin F production), *IRF4*, NF-κβ,[17,18] paired box 5 (*PAX5*),[18] and *PU.1* (stem cell factor).[19] The enrichment of these TFs, however, interferes with the binding of RNA polymerase II in the promoter region leading to its depletion (Fig. 3).

Furthermore, for all the identified transcription factors, their corresponding binding sites exhibit a typical colocalization.[18] However, this colocalization pattern further bifurcates into two subtypes where NF-κβ, *BATF*, *PAX5*, *BCLIIA*, and *IRF4* form a group of transcription factors with overlapping TFBSs,[16,18] whereas *PU.1* has its distinct binding site.[18]

Most of the SLE susceptible genes considered here are encoded by human leukocyte antigen (*HLA*) loci on chromosome 6 in SLE patients in comparison to healthy controls.[18,19]

Chromatin Segmentation

Most of the enriched transcription factors at the binding site are involved in chromatin loosening, which arises from posttranslational modifications (hypermethylation and hypoacetylation of histones).[20] Interestingly DNA also undergoes methylation (hypo and hyper, depending upon the target gene), leading to predisposition for SLE.[21] A stretch of DNA in the upstream regulatory region called *strong enhancers* has been reported to be enriched in the euchromatin region of the nucleosome of SLE patients,[22] with reports of no change of these strong enhancers in the heterochromatin regions.[21,22]

DNA Methylation and Histone Marks

SLE not only varies among racial and ethnic cohorts but also has a gender bias for women due to global hypermethylation of X chromosome. At the molecular level, regulation of chromatin

compaction in nucleosomes takes place via methylation of DNA at the CpG islands, mostly located outside 200–500 bp of the transcription start site.[21] Even methylation of histones with mono- or divalent domains takes place where methyl group addition occurs at the lysine residues of N-terminal amino acids of histones (H3K4me1, H3K4me2, H3K4me3, H3K27me3, and H3K79me2).[22]

Such stable and irreversible methylation of histones involves removal of acetyl group from histones (histone deacetylases), inhibition of acetyl transferases, recruitment of DNA methyl transferases (*DNMT3a/3b* in in utero and *DNMT1* in ex utero, *G9* methyl transferases),[23] and depletion of dinucleotide terminal transferases.[22] These methylations have been observed with higher frequencies in human SLE (mono/di/tri) than those in the murine lupus models. The level of DNA and histone methylation together confer expressional pattern to genes susceptible to SLE.

DNA methylation of target genes is known to reduce the expression by interfering with mRNA formation following the steady recruitment of splicing factor family of serine arginine proteins (SR-rich proteins). Apart from methylation, transient phosphorylation of SR-rich proteins leads to hindered access of RNA polymerase II.[24] The importance of DNA methylation arises from the characteristic downregulation of certain genes in SLE patients.

DNA/histone methylations in innate immunity. The histone mark and posttranslational modification of histones also occur in the neutrophil extracellular traps (NETs).[8] NETs are a group of SLE effector cells, which participate in extracellular bacterial and fungal clearance via a mechanism called NETosis, which involves degradation of nuclear material of NETs and surface expression of these histones and chromatins on the extracellular traps.[8] Such a presentation of antigens activates pDCs, thus hyperactivating B- and T-cell responses.

Apoptotic clearance of cellular debris and immune complexes involves phagocytic engulfment, which is mostly hindered in SLE patients. Even the phagocytic activity of neutrophils, macrophages, and tingible body macrophages is limited due to the reduction in *CD44* surface expression because of hypermethylation of *CD44* genes.[24] This epigenetic modulation of innate immune response is seen in most SLE cohorts. In SLEs, the accumulation of cellular debris causes the presentation of self-antigens via NETs, thus producing the autoreactive antinuclear antibodies.

Acetylation of histones (H2B) and methylation of histones (H3K4me3) increase the susceptibility of presentation of self-antigens via NETs during NETosis.[8] However, the levels of acetylation of histone in SLEs and acetylation of histones of NET origin are negatively related and, thus, lead to a debate on whether the acetylation of NET histones relates to SLE susceptibility. In other cases, there might be an inhibition of acetyl transferases leading to SLE pathogenesis.[8] Growing evidences also suggest that acetylation of H2B in NETs is effective in predisposing for SLE, when the NETs originate from precursor low-density granulocytes than those of canonical neutrophils.[8,25]

DNA/histone methylations in adaptive immunity. The presence of a subpopulation of transformed $CD4^-$ $CD8^-$ (ie, cluster of differentiation factor) double-negative T-cells in SLE patients is primarily due to hypermethylation of CD8 cluster by *DNMT1/3a/3b* and *G9* methyl transferases.[26] Similar levels of $CD4^+$ T-cells are also reported. However, in such cases where there is an increase in $CD4^+$ cells, there is no reportedly significant reduction in the population of $CD8^+$ T-cells.

The higher presence of activated T-helper cells facilitates survival signal-mediated maturation of naive B-cells after it has been selected by the follicular dendritic cells.[26] Apart from methylation, acetylation- and phosphorylation-mediated posttranslational modification of the histones are reversible and unstable and thereby mostly excluded from the causative epigenetic changes in SLE, which are inherited.

SLE patients have reported a hypomethylation status of their genomic DNA, although $CD8^+$ T-cells are known to be hypermethylated cells.[24] This leads to an understanding of differential methylation of different target genes leading to SLE pathogenesis.

In few other studies, there have been reports on significant epigenetic changes in B-cell lineages only (Epstein–Barr virus [EBV]-transformed B-lymphoblastoid cell lines), thus confirming a keynote role of B-cells as effector cells in SLE.[26]

Noncoding RNAs' Regulation of SLE

Noncoding RNAs or particularly short noncoding RNAs (microRNAs) regulate heterogeneous gene expression in SLEs by transcriptional inhibition (competitive binding at promoter region) or targeted protein degradation (cleavage of complementary mRNA strand).[27] Frangou et al have classified a wide range of microRNAs either upregulated or downregulated in SLE patients.[7]

For example, in SLE patients, four signature microRNAs (miR-142–3p, miR-106a, miR-17, and miR-20a) bring about the manipulation of differentiation fates of B- and T-cells by altering the TGF-β signaling pathway.[28]

Specifically, the B-cells, the major source of attention in SLE patients, are reported to have a reduced expression of miR-150, miR-15a, and miR-16 and an upregulated expression of miR-155, miR-25, miR-106b, and miR–21.[28,29] Significantly, miR-21 regulation of B-cell shows an expressional pattern in accordance to disease severity and stage of disease progression.[29] Even this microRNA has been implicated with the hypomethylation of $CD4^+$ T-cells by direct or indirect reduction of *DNMT1*.[30]

Although the epigenetic modification of nonhistone proteins can be further suggestive, the scant availability of experimental data and the insignificant identification of nonhistone protein-based epigenetic modifications in SLE have further limited our understanding in this area.

Conclusion

Systemic lupus erythematosus has been in focus for understanding the disease biology. The regulation by genetic and epigenetic factors leading to either idiopathic or drug-induced SLE with a pleotropic range of etiologies is still not fully understood. Genetic regulation in the form of SNP, loci variant, and increase in gene copy number are broad ranges of genetic mechanisms driving SLE or lupus-like pathologies.

In addition, regulation of gene expression by transactivation or repression at gene deserts along with those within the transcription start and end sites, DNA methylation, histone marks, and microRNA or noncoding RNAs add to our understanding of epigenetic modifications. Distinctively, we highlight how both of these mechanisms influence the innate and adaptive immune response and highlight the keynote genes and proteins along with regulatory noncoding RNAs, which confer SLE susceptibility.

However, the existing discordant pattern of molecular modifications of gene expression has given rise to insignificant characterization of target genes in large SLE sample studies. The concern of identification of shared and distinct genetic and epigenetic modifications will arm our interest in developing pharmacogenomics or pharmacoepigenomics against SLE. This article summarizes the recent findings of genetic and epigenetic regulation of a systemic immune regulation and operative forces driving aberrant autoreactive immunogenic reactions. Several potential questions related to the molecular regulation of gene expression indeed need deeper investigations.

Author Contributions

Conceived the concepts: SS. Analyzed the data: SS, KB. Wrote the first draft of the manuscript: SS. Contributed to the writing of the manuscript: KB. Agree with manuscript results and conclusions: SS, KB. Jointly developed the structure and arguments for the paper: SS, KB. Made critical revisions and approved final version: SS. Both authors reviewed and approved of the final manuscript.

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