**Initial findings of the ClinGen Monogenic Systemic and Incomplete Lupus Gene Curation Expert Panel**

*Rachel Shapira, ScM, CGC, Stanford University, Department of Biomedical Data Science, Rachel Shapira, ScM, CGC, Monica Bowen, PhD, Yevgeniya Gartshteyn, MD, MSc, Yuke He, PhD, Megan Johnson, BS, Ingrid Keseler, PhD, MS, Nasim Monfared, MSc, CGC, Andrra Nimoni, BSc, Ivona Aksentijevich, MD, FACMG, Louis Bridges, Jr, MD, PhD, Teri E. Klein, PhD, Steven J. Mack, PhD, Ruth Fernandez Ruiz, MD, MS, George Tsokos, MD*

## Introduction:

Systemic lupus erythematosus (SLE) is a chronic multisystem and phenotypically heterogeneous autoimmune disease. Loss of immune tolerance leads to the generation of autoreactive antibodies and immune cells, leading to inflammation and damage of multiple organs, including the skin, kidney, and central nervous system. The diagnosis of SLE is made based on clinical and laboratory findings, according to established classification criteria (ACR 1997, SLICC 2012, and ACR/EULAR 2019). Despite improvements over time, these criteria fail to identify all cases, and many patients, particularly at the time of initial presentation, do not meet classification criteria and are described as having “incomplete lupus” or “lupus-like” disease. Strong evidence suggests a genetic component in the pathogenesis of SLE, with over 50 genes having been claimed as potential causes of monogenic lupus or lupus-like disease. In addition, several gene variants have also been associated with SLE. However, the level of certainty and strength of gene-disease associations have not been sufficiently characterized.

The Clinical Genome Resource (ClinGen) Monogenic Systemic and Incomplete Lupus Erythematosus Gene Curation Expert Panel (Lupus GCEP) was formed in 2023 under the auspices of the Rheumatologic Autoimmune Disease Clinical Domain Working Group (RAD CDWG) to curate the validity of gene-disease associations in the context of clinical phenotypes consistent with lupus

## Methods:

Experts developed an initial list of 55 genes claimed to cause monogenic SLE based on literature review and refined in discussion with members of the Lupus GCEP and the RAD CDWG.

Using the semiquantitative ClinGen gene-disease clinical validity framework, the Lupus GCEP is assessing the strength of evidence of each gene-disease relationship. To determine which disease(s) to curate for each gene, the Lupus GCEP is utilizing ClinGen Lumping and Splitting guidelines. Biocurators present their curations to the experts for review and discussion on monthly virtual meetings.

The first six genes prioritized for curation include *DNASE1* and *DNASE1L3*, members of the DNase family of endonucleases, which play essential roles in the degradation of extracellular DNA and the maintenance of immune homeostasis; *SAT1*, which encodes spermidine/spermine N1-acetyltransferase; *PRKCD*, which encodes a member of the protein kinase C family; and the toll-like receptors, *TLR7* and *TLR5*. All six of these genes have been implicated in the pathogenesis of SLE.

**Results:**

Although all six of the genes have been reported to cause monogenic SLE or lupus-like disease, the amount and strength of evidence varies substantially. An illustrative example are the genes encoding DNase1 and DNase1L3; while *DNASE1L3* has sufficiently replicated evidence to attain a “definitive” level of gene-disease validity as SLE causing gene, the evidence for *DNASE1* only reached “limited” level due to insufficient genetic evidence to date. Similarly, while there is strong experimental evidence supporting the role of *SAT1* in causing SLE, to date only one primary study has provided supporting genetic evidence. As a result, the *SAT1*-SLE gene validity classification is currently at the “limited” level. Due to preponderant genetic and experimental evidence, *PRKCD* reached a “definitive” level of classification validity as a cause of autosomal recessive SLE. *TLR7* was found to have a “moderate”, while *TLR5* only reached a “limited” level of classification.

**Conclusions:**

The initial findings of the ClinGen Lupus GCEP reveal a mixed range of evidence in support of reported claims of genes causing monogenic lupus. This underscores the need for further systematic curation of gene-disease relationships in SLE. More data will be needed on most genes reported to cause monogenic lupus before evidence-based clinical genetic testing can be recommended.

This work is funded by the Baylor College of Medicine/Stanford University NIH Grant #U24HG009649.