Poster # P157

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

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Background

Systemic lupus erythematosus (SLE) is a chronic multisystem and phenotypically heterogeneous autoimmune disease. Diagnosis is made based on clinical and laboratory findings, according to established classification criteria (ACR 1997, SLICC 2012, and ACR/EULAR 2019). Many patients do not meet classification criteria and are described by terminology including “incomplete lupus” and “lupus-like” disease.

Loss of immune tolerance leads to the generation of autoreactive immune cells leading to inflammation and damage of multiple organs, including the skin, kidney, and CNS. Strong evidence suggests a genetic component in SLE pathogenesis, with over 50 genes having been claimed as potential causes of monogenic lupus or lupus-like disease. 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.

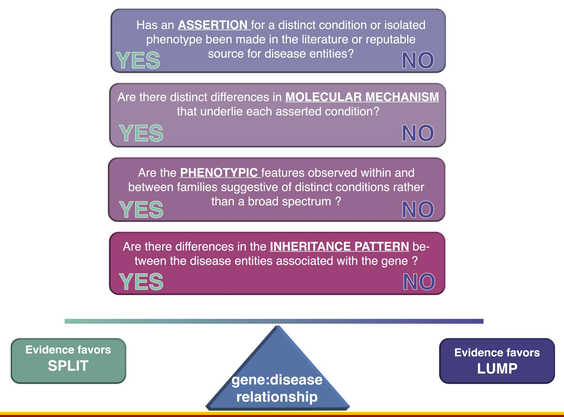
Methods

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.. Biocurators present their curations to the experts for review and discussion on monthly virtual meetings.

To determine which disease(s) to curate for each gene, the Lupus GCEP is utilizing ClinGen Lumping and Splitting guidelines (detailed in the diagram to the right).

ClinGen Lumping and Splitting Process



Results

Lupus GCEP Classifications

Gene	Disease Entity	Genetic Evidence	Experimental Evidence	Total Points	Replication Over Time	Classifications
DNASE1	MONDO:0007915	0.95	1.50	2.45	No	Limited
DNASE1L3	MONDO:0013743	12	6	18	Yes	Definitive
SAT1	MONDO:0019725	2.25	2.25	4.5	No	Limited
PRKCD	MONDO:0007915	12	4.5	16.5	Yes	Definitive
TLR7	MONDO:0859083	4	6	10	No	Moderate
TLR5	MONDO:0011138	0	1	1	No	Limited

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” evidence, while **TLR5** only reached a “limited” level of classification due to a lack of genetic evidence.

ClinGen Gene-Disease Curation

Initial Genes Prioritized

- **DNASE1** and **DNASE1L3** (DNase family of endonucleases, play essential roles in degradation of extracellular DNA and maintenance of immune homeostasis)
- **SAT1** (encodes spermidine / spermine N1-acetyltransferase)
- **PRKCD** (encodes member of protein kinase C family)
- **TLR7** and **TLR5** (toll-like receptors)

ClinGen Gene-Disease Classification Definitions

	Definitive	Role has been repeatedly demonstrated in research & clinical diagnostic settings • Upheld over time (in general, at least 3 years) • No convincing contradictory evidence
	Strong	≥2 independent studies with: • Multiple pathogenic variants in unrelated probands • AND • Several different types of supporting experimental data • OR • Excess of pathogenic variants in cases vs. controls • No convincing contradictory evidence
	Moderate	≥1 independent study with: • Several unrelated probands with pathogenic variants • Some supporting experimental data • No convincing contradictory evidence
	Limited	≥1 independent study with: • <3 unrelated probands with pathogenic variants • OR • Multiple variants reported in unrelated probands but *without* sufficient evidence for pathogenicity • No convincing contradictory evidence
	No Known Disease Relationship	No evidence reported for a causal role in disease (candidate genes, etc.), therefore no pathogenic variants have been identified in humans to date.
Conflicting Evidence Reported	Disputed	Convincing evidence disputing a role for this gene in this disease has arisen • Disputing evidence need not outweigh existing evidence supporting the gene:disease association
	Refuted	Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role • Applied at the discretion of clinical domain experts after thorough review of available evidence

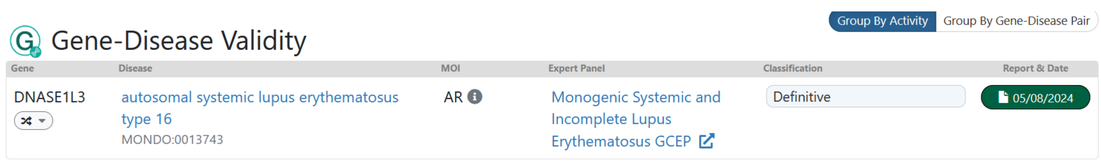
Classification levels for gene-disease are detailed above. Certain categories (e.g. Refuted) are applied by domain experts following evidence review rather than through scoring alone.

ClinGen Gene-Disease Scoring Matrix

The scoring matrix to the right details categories of points (e.g. genetic evidence, experimental evidence) that can be assigned through evaluation of supporting evidence. Criteria like replication over time are necessary to demonstrate sufficient association to consider assigning a Definitive classification. Contradictory evidence is also considered.

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points				
CALCULATED CLASSIFICATION		LIMITED	1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 AND replication over time	
Valid contradictory evidence? (Y/N)	List PMIDs and describe evidence:			
CURATOR CLASSIFICATION				
FINAL CLASSIFICATION				

Publication to the ClinGen Website



Once a gene-disease validity classification has been approved by the GCEP, it is published to the ClinGen website. The Evidence Summary gives an overview of the evaluated evidence, which can be accessed through the gene report, alongside a breakdown of how each category of evidence has been scored.

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.

Future Directions

The Lupus GCEP continues curation on the initial list of 55 genes within scope. Currently, pre-curation has been completed for **C1R, C1QA, UNC93B1**, and **C1S**, and is in process for **C4A**, **C4B**, **C2**, **C8A**, **C8B**, and **C8G**.

Acknowledgments

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