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Curating Genetic Associations with Rheumatologic Autoimmune Diseases to Improve Patient Outcomes

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Notes from the Field

Curating Genetic Associations with Rheumatologic Autoimmune Diseases to Improve Patient Outcomes

Short title: Curating Genetic Associations with Rheumatologic Diseases

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Rheumatologists have a remarkable array of therapeutics to treat rheumatic diseases, but still largely rely on trial-and-error approaches to optimize management of individual patients. One important way to advance the goals of precision medicine is to better understand the genetic underpinnings of clinically recognized phenotypes and their contributions to responses to medications and to patient outcomes. There are multiple rheumatologic conditions with autoimmune features (pathologic immune responses to self-antigens causing tissue or organ damage). The knowledge base of genetic influences on susceptibility, severity, and treatment responses to these rheumatologic autoimmune diseases continues to expand rapidly. There is a concomitantly growing need to better quantify and validate the associations of genetic variants throughout the genome with these inflammatory conditions to allow better diagnosis and inform therapeutic decisions in individual patients.

The Clinical Genome Resource (ClinGen; https://clinicalgenome.org/) is an NIH-funded consortium dedicated to defining the clinical relevance of genes and genetic variants for use in patient diagnosis, research, and precision medicine (1). With over 2,300 contributors from 69 countries, ClinGen harmonizes efforts to curate genomic data. In this context, curation is defined as the process of collecting disparate clinical genetic and experimental data sources, extracting key data types, interpreting, and evaluating them based on a specified set of criteria, and assigning context and relevance after careful systematic evaluation (Figure 1). ClinGen is broadly focused on gene and variant curation within four thematic areas: gene-disease validity, variant pathogenicity, dosage sensitivity, and clinical actionability. The NIH National Library of Medicine NCBI

data repository ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), which aggregates information about genomic variation and its relationship to human health, is the data repository that supports ClinGen.

ClinGen's role is to provide a critically important point of reference for the validity of genetic tests for human diseases, which guides clinical practice, supports actionable diagnoses and treatments, and reduces the risk of harm to patients (2). Of note, there is a growing trend of patients using Direct-To-Consumer (DTC) genetic testing and presenting the results to their health care providers. For example, 23andMe offers a panel of over 1,900 genetic markers to estimate the likelihood of developing lupus (https://www.23andme.com/topics/health-predispositions/lupus/). Dante Labs offers a whole genome sequence-based Autoimmunity Report that includes genetic variants that "increase the risk of developing autoimmune/autoinflammatory conditions such as systemic lupus erythematosus or ankylosing spondylitis" (https://us.dantelabs.com/collections/genomic-reports/products/autoimmunity-panel). In a recent survey of primary care and specialist physicians at Kaiser Permanente, 35% of respondents reported receiving at least one DTC health risk genetic result from a patient in the past year, and 12% reported receiving at least one DTC pharmacogenomic test result (3). In addition, a study of 2490 patients recruited from an outpatient rheumatology clinic suggested that 28.0% and 26.9% of patients would potentially benefit from genetic testing for therapeutic or diagnostic purposes, respectively (4). Thus, it is imperative that commercial testing panels include valid, clinically important genetic variants to provide the best information to patients and

physicians. The RAD CDWG curations will help facilitate creators of commercial testing panels to include genetic variants that will allow optimal sensitivity and specificity of tests for diagnosis, choice of optimal therapy (e.g. pharmacogenomics), or other intended uses.

Initially targeting a broad array of monogenic diseases, ClinGen has recently constituted the Rheumatologic Autoimmune Diseases Clinical Domain Working Group (RAD CDWG) to focus on complex, multigenic, non-Mendelian disorders, including those impacted by Human Leukocyte Antigen (HLA) gene variants (see Figure 1). Expert panels in key RADs are led by senior and junior chairs alongside physicians, scientists, clinical geneticists, genetic counselors, and population and statistical geneticists. A roster of members involved in the work of the RAD CDWG is available online (https://clinicalgenome.org/working-groups/clinical-domain/rheumatologic-autoimmune-disease-cdwg/). Potential contributors to our efforts in gene and variant curation are welcomed and are encouraged to contact the RAD coordinator listed on the ClinGen website shown above. Diseases for initial analysis were selected based on differing gene and variant curation needs, heritability, disease prevalence among different world-wide populations, clinical heterogeneity, impact of HLA, and other factors. The conditions first chosen for curation include rheumatoid arthritis (5); ankylosing spondylitis (6); systemic lupus erythematosus (SLE) (7); gout (8), and scleroderma (9), which collectively are associated with more than 400 gene loci (including those in the HLA region). This set of diseases represents a starting point for the development of curation algorithms extending beyond monogenic disease.

Monogenic Autoimmune/Autoinflammatory Conditions

Monogenic systemic autoinflammatory diseases (SAIDs) are rare rheumatologic disorders caused by dysregulation in the innate immune system. Features typically include recurrent fever, skin, joint, and bone lesions, gastrointestinal and lung inflammation, and, in severe cases, central nervous system inflammation. Curation of monogenic conditions is included in the RAD CDWG for several reasons. 1. Many of these conditions (TRAPS, etc.) are cared for by pediatric or adult rheumatologists and the RAD CDWG seems a good fit for their genetic curation. 2. While individual monogenic rheumatologic autoimmune diseases are rare, an increasing number of patients with DADA2, VEXAS and haploinsufficiency A20 are being diagnosed throughout the world and novel monogenic diseases with different phenotypes are being increasingly recognized (10). 3. Understanding the genetic underpinnings of monogenic RADs can provide significant insights into multigenic forms of diseases with overlapping clinical manifestations. 4. To provide the highest degree of accuracy, genetic testing panels should be optimized to include the most relevant and reproducible variants. 5. Curating monogenic disease associated variants is more straightforward than curating GWAS-identified variants for complex rheumatological diseases, as very few GWAS risk alleles have been functionally validated.

Because of a wide array of clinical phenotypes that often overlap with diseases such as early-onset lupus and monogenic primary immunodeficiencies, these diseases are challenging to diagnose and classify in clinical practice. Genetic testing has become a crucial diagnostic tool for physicians in choosing targeted therapies and is essential for genetic counseling in families. The RAD CDWG has implemented two Gene Curation

Expert Panels (GCEPs) for monogenic diseases: monogenic SAIDs (e.g. Familial Mediterranean Fever) and monogenic SLE. These GCEPs will assess the strength of evidence supporting a gene-disease association using a semi-quantitative framework (11).

SAIDs, while monogenic, are complex and include classical dominantly and recessively inherited diseases, as well as digenic and oligogenic conditions (12). Pathogenic variants in the same gene can have variable effects on protein function and can result in distinct clinical phenotypes, even with a potentially unifying biochemical mechanism. Low-frequency variants of lesser effects have been linked to more common rheumatologic diseases via targeted case-control association and genome-wide association studies (GWAS). The SAIDs GCEP is assessing 59 genes, including those on the International Union of Immunological Societies Autoinflammatory List (13) and commercially available next-generation sequencing panels. The Lupus GCEP is assessing the clinical significance of 55 genes reportedly associated with monogenic lupus or lupus-like disease.

The RAD CDWG has also established a SAIDs Variant Curation Expert Panel (VCEP). This VCEP will curate variants in genes that the SAIDs GCEP determines are definitively associated with a particular disease (14). The VCEP will prioritize curation of SAID-associated variants in public databases including Infevers (https://infevers.umai-montpellier.fr/web/index.php) as well as those identified through comprehensive literature review. The VCEP will curate variants according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines for sequence variant interpretation to classify genomic variants (15). Curations will be

published to the ClinGen website once completed and will be publicly available. As soon as the curation is completed, the information will become publicly available on ClinGen website.

It is critical to evaluate the validity of potential genetic contributors to these diseases, as genetic testing is already in use for some RADs and has the capacity to become an even more critical diagnostic tool. Additionally, the clinical relevance of variants of unknown significance must be interpreted with care before their significance to disease is dismissed or confirmed. Updated gene and variant classification will facilitate reporting of molecular diagnostic testing results, and will inform physicians and patients about disease prognosis, outcome, and targeted therapies.

Development of a Framework for Curation of HLA-Disease Associations

Autoimmune and immune-mediated conditions represent significant global public health burdens, yet systematic review and application of HLA-association evidence in clinical genetic settings is currently lacking. Over 38,000 HLA alleles (defined by nucleotide sequence) have been described in the Immuno Polymorphism Database's IMmunoGeneTics/HLA (IPD-IMGT/HLA) Database (https://www.ebi.ac.uk/ipd/imgt/hla/), and more than 2,000 studies of HLA-disease associations have been added to PubMed in the last decade. Understanding the role of HLA variants in disease is of paramount importance in the evolving landscape of precision medicine. Thus, the HLA Working Group (HLA WG) was formed within the RAD CDWG. The goal of the HLA WG is to create an HLA-specific framework to curate HLA-disease associations and HLA-drug interactions in conjunction with an interface that can process complex HLA

nomenclature. The ultimate objective is to curate the literature for relevant HLA associations for their application to precision medicine. The combined framework and interface will serve as a centralized resource for curation of complex immune-mediated conditions. The final product will be a systematically scored allele-disease relationship informed by multiple independent investigations. This benefits both patient and clinical communities by providing a consistent evaluation across multiple immune-mediated diseases.

Development of a Methodology for Curation of Complex, Multigenic Diseases

The RAD CDWG represents the first ClinGen clinical domain focusing on multigenic diseases which have complexities extending beyond the realm of HLA-associated disease. Thus, the Multigenic Disease Taskforce was established within the RAD CDWG to address the complex multigenic inheritance of many RADs. The Multigenic Disease Taskforce is developing: 1) a method for curation of putative causal gene(s) at a particular genetic locus, 2) a method for determining which loci are important to curate and how to view their combined/interactive effects, and 3) guidelines for determining the potential clinical significance of associated risk variants to multigenic diseases. Of note, the RAD CDWG is not involved in curating or applying polygenic risk scores, as that area falls under the purview of other ClinGen Working Groups (16). Gout was selected as an exemplar complex disease that is not significantly attributable to monogenic or HLA associations. The Multigenic Disease Taskforce consists of experts in the genetics of multigenic diseases, including translation of signals obtained through GWAS into biological knowledge, in functional studies of genetic variants, in clinical aspects of these diseases, and in computational genomics. The group is planning to develop a

computational model to curate hundreds of candidate causal risk genes and variants (including those non in coding regions) associated with individual RADs. In subsequent phases, the group will refine these methods based on initial results and test other diseases within the RAD clinical domain. This work will benefit patients by identifying genes, proteins and pathogenic pathways that can be targeted to prevent and treat RADs and improve patient outcomes. In addition, this work will help ClinGen curators to analyze multigenic diseases in other clinical domains.

Curation of Disease-Associated Somatic Variants

Postzygotic genetic variations (primarily in myeloid cells) are well-known features of cancer and aging. The aging-related somatic phenomenon clonal hematopoiesis of indeterminate potential (CHIP) has been implicated in gout (17), SLE (18), and scleroderma (19). Importantly, a disease caused by somatic mutations in myeloid cells in aging men has recently been described: VEXAS syndrome (vacuoles, E1-ubiquitin-activating enzyme, X-linked, autoinflammatory, somatic mutations) (20). Many patients with VEXAS syndrome have features of relapsing polychondritis, a rare condition typically managed by rheumatologists. Reports of somatic mutations in SAIDs have changed how researchers consider the genetics of rheumatological diseases. The development of new next-generation DNA sequencing and single-cell RNA sequencing technologies will likely result in identification of other somatic mutations contributing to RADs. The community of clinicians and researchers will need a new way to curate these genetic mutations and their associations with RADs to optimize diagnosis and treatment strategies.

In conclusion, ClinGen's RAD CDWG is focused on enabling novel insights into the genetic basis of RAD phenotypes in global populations. This effort is an important step in laying the foundation for the future of genomic medicine in rheumatology. Ultimately, these efforts should lead to more effective strategies to prevent, diagnose, or perhaps even cure these rheumatologic diseases with autoimmune features.

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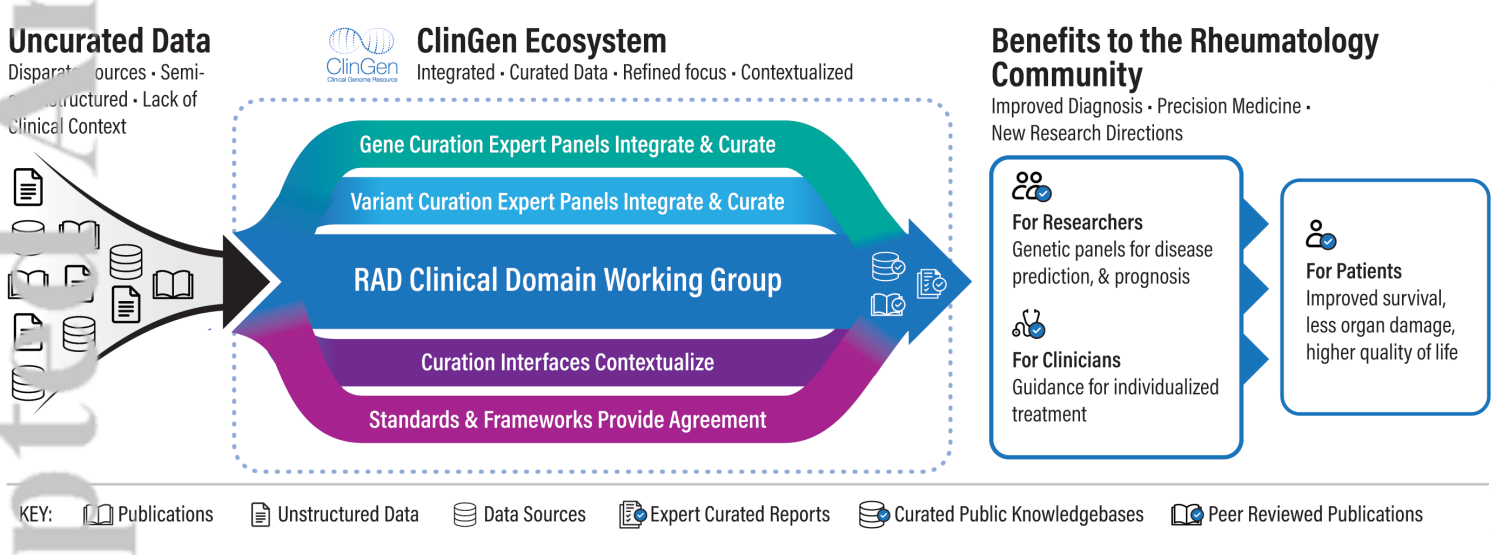
Figure Legend

Figure 1. Activities of the RAD CDWG. Disparate data sources (*e.g.*, publications, databases) are curated by experts, integrated into validated assertions about gene, variant, and disease relationships, and used to develop content that enables researchers and clinicians to improve diagnosis and treatment of patients with rheumatological disease.



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