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**Full title of manuscript**: Genome-wide Sequencing Identified Rare Genetic Variants for Childhood-onset Monogenic Lupus

**Short running head**: Rare Variants Monogenic Lupus

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**Abstract**

**Objective:** Genetics play an important role in systemic lupus erythematosus (SLE) pathogenesis. We calculated the prevalence of rare variants in known monogenic lupus genes, among children suspected of monogenic lupus.

**Methods:** We completed paired end genome-wide sequencing (whole-genome or whole-exome) in patients suspected of monogenic lupus, and focused on 36 monogenic lupus genes. We prioritized rare (minor allele frequency <1%) nonsynonymous and splice variants with predicted pathogenicity classified as deleterious variants (CADD, Polyphen, SIFT scores). Additional filtering restricted to predicted damaging variants by considering reported zygosity. In those with WGS, n=69, we examined copy number variants (CNVs) >1kb in size. We created additive non-HLA and HLA SLE genetic risk scores (GRSs) using common SLE-risk SNPs. We tested the relationship between SLE-GRSs and the number of rare variants with multivariate logistic models, adjusted for sex, ancestry and age of diagnosis.

**Results:** The cohort included 71 patients, 80% female, with a mean age at diagnosis of 8.9 years (SD 3.2 years). We identified predicted damaging variants in 9 patients (13%) who were significantly younger at diagnosis compared to those without a predicted damaging variant (6.8 years [SD 2.1] vs. 9.2 years [SD 3.2], $P$=0.013). We did not identify damaging CNVs. There was no significant association between non-HLA or HLA SLE-GRSs and the odds of carrying one or more rare variant in multivariate analyses.

**Conclusion**: In a cohort of patients with suspected monogenic lupus who underwent genome-wide sequencing, 13% carried rare variants for monogenic lupus. Additional studies are needed to validate our findings.

**Abstract word count:** 250/250



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## Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease with a broad spectrum of clinical manifestations. There is evidence that SLE arises as a consequence of both genetic and environmental factors, yet the precise disease pathogenesis is not completely understood. Epidemiologic studies estimate SLE heritability, the proportion of SLE risk attributable to genetics, at 66%. Genome-wide association studies (GWAS) have identified over 100 common genetic variants (minor allele frequency (MAF) ≥5%) for SLE that individually contribute small effect to SLE risk(1,2). These GWAS-identified susceptibility variants collectively account for only 30% of SLE heritability(2).

A portion of this missing heritability may be due to rare variants (MAF <1%), some in genes previously identified for monogenic forms of SLE and lupus-like disease(3). Whole genome sequencing (WGS) and whole exome sequencing (WES) studies have identified 36 genes for monogenic forms of SLE and lupus-like disease(4). These monogenic forms of lupus provide insights into the pathogenesis of SLE and implicate potential therapeutic targets. Our study aimed to calculate the proportion of patients with rare variants in known monogenic lupus genes, among patients suspected of monogenic lupus.

## Methods

### Study Population

From the Hospital for Sick Children (SickKids) Lupus Clinic (1987-2018), we identified patients with lupus or lupus-like disease that were suspected of monogenic lupus due to one or more features of: (i) young-onset of disease (<11y); (ii) history of consanguinity in parents. We extracted prospectively collected demographic, clinical and laboratory data from the SickKids



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Lupus Clinic database, supplemented by medical records. This included a review of medications used to control disease. This study was approved by the Institutional Research Ethics Board (REB no. 1000058324).

**Genome-wide Sequencing (whole genome sequencing or whole exome sequencing)**

A total of n=71 lupus patients that consented for genome-wide sequencing were included in the study. We collected peripheral blood from patients and completed paired end WGS using an Illumina HiSeq X platform (n=69) (read depth 37–40X) or paired end WES with an Illumina HiSeq 2500 platform (n=2) (read depth 70-118X) following enrichment with the Agilent SureSelect clinical research exome V1 kit. Variant and base calling were performed with GATK v3.7 and HiSeq Analysis Software (HAS) v2-2.5.55.1311, and functional annotation with ANNOVAR. We focused on 36 genes identified from familial and candidate gene studies to cause lupus or lupus-like disease (Supplementary Table S1)(4).

We prioritized rare (MAF<1%) exonic, nonsynonymous (missense, stop-gain and frameshift) and splice variants, hereinafter referred to as rare variants. We predicted deleterious variants according to CADD (>10), Polyphen2 (>0.5) and/or SIFT (<0.05) scores. We further restricted to predicted damaging variants in monogenic lupus genes by considering reported zygosity. We identified copy number variants (CNVs) from WGS and restricted to CNVs >1kb in 36 monogenic lupus genes.

**Ancestry Inference**

Patients were also genotyped on the Illumina Multiethnic Array (MEGA) or Global Screening Array (GSA), and ancestry was genetically inferred with ADMIXURE using the 1000 Genomes Project phase 3 as a referent. A small proportion of patients without genetically inferred ancestries were classified according to Canada census categories of self-reported



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ethnicity. Individuals were classified into 7 ancestral groups: African, Amerindian, East Asian, European, Middle Eastern, South Asian, and Admixed.

**Genetic Risk Scores**

We calculated genetic risk scores (GRSs) with genome wide significant risk alleles reported in one of the largest SLE GWASs to date(1). We calculated an additive non-HLA GRS using 39 non-HLA SLE risk SNPs and an HLA SLE GRS using 7 HLA SLE risk alleles identified in Europeans (Supplementary Table S2 and S3). Additive allelic weighted GRSs were generated with weights taken from the log-odds ratio for SLE from GWAS(1).

**Analysis**

Means and standard deviations (SD) were calculated for continuous normally distributed variables, and counts and proportions were calculated for categorical variables. We compared the characteristics of individuals with and without predicted damaging variants using Fisher's exact tests for categorical values and Mann-Whitney U test for continuous variables.

We identified variants that were significantly more common in our population compared to ancestrally matched general populations in gnomAD v2.1.1(5), and TOPMed hg19 populations(6), using Chi-squared tests with Yates correction (Bonferroni adjusted $P<1.0\text{x}10^{-3}$ for 49 independent tests). Ancestral groups not represented in gnomAD (Admixed, Amerindian and Middle Eastern populations) were compared to the total gnomAD population frequency.

We examined the association between both SLE non-HLA GRS and HLA GRSs and the number of rare monogenic lupus variants in individuals with and without (i) rare variants and (ii) a subset of predicted damaging variants, using Kruskal-Wallis tests. We also tested the association between GRSs and the odds of carrying rare variants, in unadjusted logistic (0 vs. ≥1 variants) and multivariate (0 vs. 1 or >1 variants) regression models, and in marginal and



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multivariate adjusted models for sex, ancestry and age at lupus diagnosis. The significance thresholds were adjusted for 4 independent tests (*P*<0.01) (additional details in Supplement).

**Results**

Our study included 71 patients with suspected monogenic lupus, n=69 with WGS and n=2 with WES. The majority met inclusion for young-onset disease (<11y) (n=59), with 18% (n=13) included for a history of consanguinity. There was only one sibling-pair in the cohort. A total of 61 patients (86%) met ACR criteria, 63 (89%) met SLICC criteria and 67 (94%) met EULAR/ACR criteria. The majority of patients were female (80%), the mean age at diagnosis was 8.9 years (SD 3.2), and patients were followed for a mean of 7.6 years (SD 4.7) after diagnosis. Of the 71 patients, 23 were ancestrally Admixed (32%) and 20 were of European Ancestry (28%). Review of lupus features demonstrated that 97% were ANA positive and 73% had a malar rash. A total of 22 patients had biopsy confirmed nephritis (31%) and 20% had neuropsychiatric lupus (Table 1).

Genome-wide sequencing identified a total of 624 variants in monogenic lupus genes among 71 patients. Of those, 61 were rare variants and a subset of 49 variants were predicted deleterious (Supplementary Table S4). When accounting for allele frequency, zygosity and inheritance, we identified 9 rare predicted damaging variants in monogenic lupus genes in 10 lupus patients. After removing a related individual (n=1), 9 lupus patients (13%) carried predicted damaging variants (Supplementary Figure S1). These patients were homozygous for autosomal recessive variants in *C1QA, MAN2B1, C4A* and *DNASE1L3* or heterozygous for autosomal dominant variants in *C1R, C1S, PTEN* and *IFIH1* (Table 2). The *C4A* variant was a



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canonical splice donor variant located 1 base downstream of the exon intron boundary, resulting in a high impact variant that is likely loss of function.

Analysis of 192 CNVs in monogenic lupus genes failed to identify damaging CNVs. We identified a 6000 base pair heterozygous tandem duplication (6:31878001-31884000) in *C2* that was challenging to interpret. This CNV is not inverted with respect to the reference and has no sequence rearrangement at the junction. This variant consists of SV breakpoints that overlap with AluSz SINE elements, and overlaps with an enhancer from GeneHancer derived from ENCODE that is predicted to interact with 28 genes, including *C2* (GH06J031910 at chr6:31877939-31879970). Although this CNV is rare, it occurs deep in the first intron of C2 and is therefore unlikely to result in a functional consequence to the protein.

Children with a predicted damaging variant were diagnosed at a significantly younger age compared to those without a predicted damaging variant (6.8 years [SD 2.1] vs. 9.2 years [SD 3.2], $P$=0.01). There was no significant difference between individuals with and without damaging variants with regards to consanguinity (P=0.67), ancestry ($P$=1.00), sex ($P$=0.40), or prevalence of individual SLE EULAR/ACR clinical features ($P$>0.05) (Table 1). A comparison of the number of immune-suppressant medications used to treat patients with predicted damaging variants to those without demonstrated no difference (1.90 (SD 1.14) vs. 1.85 (SD 1.52), respectively, $P$=0.69).

We calculated an SLE non-HLA GRS in 69 patients and an SLE HLA GRS in 19 patients of European ancestry. There was no significant association between non-HLA or HLA GRSs and age at diagnosis ($P$=0.94 and $P$=0.15, respectively). We did not observe a significant difference in non-HLA or HLA GRSs in patients with and without rare variants or in patients with and without predicted damaging variants. In logistic or multivariate models adjusted for sex, ancestry



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and age at diagnosis, SLE non-HLA or HLA GRSs were not significantly associated with the odds of carrying one or more rare variants, compared to no rare variants (Supplementary Table S5 and Supplementary Figure S2).

**Discussion**

The aim of this study was to estimate the prevalence of rare variants in known monogenic lupus genes, in 71 children with suspected monogenic lupus. We identified predicted damaging variants in monogenic lupus genes in 13% of patients. Patients with predicted damaging variants were significantly younger at disease-onset compared to those without a damaging variant. This study demonstrates the potential diagnostic yield of genome-wide sequencing in selected childhood-onset lupus patients.

Our study population was comparable to other cohorts of patients suspected of monogenic lupus reported in the literature, with regards to prevalence of lupus manifestations and age at diagnosis. The majority of our patients satisfied classification criteria for SLE. This is similar to a study of 49 monogenic lupus patients that found 90% met EULAR/ACR- 2019 criteria and 94% met SLICC criteria(7). That study also found that the majority of patients were ANA positive (96%). Another study of 7 young-onset SLE patients with WES found that 86% were ANA positive(8). These proportions of ANA positive young-onset SLE patients are consistent with our study (97%) and other studies that have reported a lower prevalence among young SLE patients(9). The study of 7 young-onset SLE patients reported all patients had a malar rash, which was the most common clinical feature in our study cohort(8). By examining all SLE features manifested over the course of observation, and not limited to those at diagnosis, we improve the likelihood of capturing the range of serologic and clinical SLE manifestations. This



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is also reflected by the prevalence of other manifestations such as neuropsychiatric lupus (20%) which is comparable to prior studies of SLE patients with 5-10 years of follow-up reporting a prevalence of 12%(10). The mean age of diagnosis in our study was 8.9 years (SD 3.2), which is similar to that reported in the study of 49 monogenic lupus patients (median age at onset of 6 years), and a next-generation sequencing study of 117 juvenile-onset SLE patients (median age at onset of 12 years)(7,11).

Genome-wide sequencing identified predicted damaging variants in 13% of our selected population, which is intermediate to 7% in a WGS study of n=117 children diagnosed with SLE before 16 years of age(11), and 27% reported in a WES study of n=15 children with lupus restricted to those with severe or atypical presentation, additional comorbidities, or consanguineous parents(3). We identified two patients carrying biallelic predicted disease-causing variants in *DNASE1L3* (3:58191226 [p.Thr97IlefsTer2]) or *C1QA* (1:22965784 [p.Gln208Ter]) that have been previously described in patients with SLE and lupus-like disease(8). The same *DNASE1L3* variant we identified in siblings born to consanguineous parents has been previously reported in the literature, where defective DNase activity was suggested to cause persistent antigenic stimulus(12). The understanding of the pathogenesis of these monogenic forms of lupus may implicate targeted therapies, as demonstrated in a study of C1q deficient SLE patients treated with fresh frozen plasma to reduce flares of disease(13). Our results demonstrate the clinical utility of sequencing for known lupus genes in a selected population.

We identified additional predicted damaging variants not previously reported in literature, in genes associated with monogenic lupus: *IFIH1, PTEN, C1S, C4A, C1R* and *MAN2B1*(4,14). We considered autosomal dominant modes of inheritance for *C1R* and *C1S* as



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prior studies have linked these inheritance patterns with SLE and lupus nephritis(15). We found single heterozygous predicted damaging variants in *C1R* and *C1S* in three patients.
We hypothesize that these variants are not solely causal but may contribute to SLE susceptibility, as only bi-allelic variants in these genes cause monogenic SLE.

Patients with predicted damaging variants were significantly younger at disease-onset compared to those without a damaging variant. These results validate our selection strategy for WES/WGS to identify monogenic lupus damaging variants. WES studies have also prioritized younger patients for sequencing (≤5 years), but our results suggest that selection for monogenic lupus patients can be broadened to children under 11 years of age(8).

Prior studies have demonstrated an inverse association between the number of SLE-risk alleles and SLE age of onset(1,16). These studies included patients spanning childhood-onset and adult-onset SLE. In our selected cohort of patients suspected of monogenic lupus, we did not observe an association between GRSs comprised of common SLE risk alleles and age of diagnosis. We also did not find an association between SLE GRSs and the odds of carrying rare nonsynonymous lupus variants. This is likely due to selecting young-onset patients, which thereby limited the range of age of diagnosis and GRS score, and in turn the power to detect an association with a relatively modest sample size.

We did not identify any predicted damaging CNVs. Although previous studies have identified CNVs that lead to SLE(17), no study to date has reported a monogenic lupus causing CNV. Our study may not have identified damaging CNVs due to our stringent filtering criteria to reduce false positives, potentially omitting causal CNV changes. Future trio studies among family members would allow us to apply additional filtering information to improve the quality of calling and improve detection of de novo variants to further investigate CNVs.



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We acknowledge potential limitations of our study. By focusing on rare variants in known monogenic lupus genes, we may have missed causal variants in novel lupus genes. We also identified predicted damaging variants based on bioinformatic tools that predict functional consequences, but were unable to perform functional validation. Conversely, restricting to the American College of Medical Genetics (ACMG) guidance on sequence variant interpretation, designed for clinical reporting, are exceedingly stringent for reporting the prevalence of rare variants in known monogenic genes. Our singleton analysis also precluded us from identifying *de novo* variants in known lupus genes. Trio analyses would enable identification of *de novo* variant discovery. Among these known genes, we filtered based on predicted inheritance in all but two patients, in which we were able to verify *DNASE1L3* inheritance through Sanger sequencing of unaffected family members. Considering our conservative methods, we found a sizable proportion of our selected population harboured variants leading to disease.

Our study had a number of strengths. We completed genome-wide sequencing of a large cohort of patients suspected of monogenic lupus. Our study also included diverse ancestry representation, which allowed us to examine variant frequency in specific ancestral subpopulations.

We identified predicted damaging lupus variants in 13% of sequenced patients with suspected monogenic lupus. We did not detect a significant correlation between SLE GRSs and the number of rare variants, with younger age at diagnosis being the sole factor distinguishing patients with rare causal variants. Studies of independent cohorts are needed to validate our findings. Identification and understanding how genetic variants lead to disease provide insights into pathogenesis and can potentially identify therapeutic targets for monogenic lupus and lupus more broadly.



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Table 1. Demographic, clinical and laboratory features of children with and without predicted damaging genetic variants.

| | Total n= 71 [a] | Children without predicted damaging variants (n=61) | Children with predicted damaging variants (n=10) [b] | *P* |
|---|---|---|---|---|
| Mean age diagnosis, yrs (±SD) | 8.9 (3.2) | 9.2 (3.2) | 6.8 (2.1) | 0.01* |
| Mean duration of follow-up, yrs (±SD) | 7.6 (4.7) | 7.3 (4.6) | 9.2 (4.69) | 0.14 |
| Female (%F) | 57 (80) | 50 (82) | 7 (70) | 0.40 |
| Ancestry (%) [c] | | | | 1.00 |
| EUR | 20 (28) | 18 (30) | 2 (20) | |
| EAS | 9 (13) | 8 (13) | 1 (10) | |
| SAS | 6 (8) | 5 (8) | 1 (10) | |
| MEAS | 4 (6) | 1 (2) | 3 (30) | |
| AFR | 4 (6) | 4 (7) | 0 (0) | |
| AMR | 3 (4) | 2 (3) | 1 (10) | |
| Admixed | 23 (32) | 21 (34) | 2 (20) | |
| History of Consanguinity | 13 (18) | 10 (16) | 2 (20) [d] | 0.67 |
| *Lupus Clinical Features* | | | | |
| Malar Rash | 52 (73) | 44 (72) | 8 (80) | 0.72 |
| Arthritis | 47 (66) | 39 (64) | 8 (80) | 0.48 |
| Alopecia | 31 (44) | 27 (44) | 4 (40) | 1.00 |
| Fever | 26 (37) | 21 (34) | 5 (50) | 0.48 |
| Nephritis | 22 (31) | 19 (31) | 3 (30) | 1.00 |
| Class III/ IV [e] | 17 (77) | 15 (25) | 2 (20) | |
| Class V [e] | 7 (33) | 5 (8) | 2 (20) | |
| Oral Ulcers | 22 (31) | 20 (33) | 2 (20) | 0.71 |
| Neuropsychiatric | 14 (20) | 13 (21) | 1 (10) | 0.67 |
| Pericarditis | 6 (8) | 5 (8) | 1 (10) | 1.00 |
| Pleuritis | 4 (6) | 3 (5) | 1 (10) | 0.46 |
| *Lupus Laboratory Features* | | | | |
| Leukopenia | 37 (52) | 33 (54) | 4 (40) | 0.50 |
| Thrombocytopenia | 28 (39) | 26 (43) | 2 (20) | 0.30 |
| Hemolytic Anemia | 24 (34) | 22 (36) | 2 (20) | 0.48 |
| *Autoantibodies* | | | | |
| ANA [f] | 69 (97) | 59 (97) | 10 (100) | 1.00 |
| Anti-DNA | 46 (65) | 40 (66) | 6 (60) | 0.73 |
| Anti-Sm | 28 (39) | 23 (38) | 5 (50) | 0.50 |
| Anti-Cardiolipin | 27 (38) | 26 (43) | 1 (10) | 0.08 |
| Lupus Anticoagulant (LAC) | 12 (17) | 12 (20) | 0 (0) | 0.19 |

[a] Data includes 2 individuals without self-identified or genetically inferred ethnicities.
[b] Three of these individuals carry confirmed variants, including a pair of siblings.
[c] EUR= European, EAS= East Asian, SAS= South Asian, MEAS= Middle Eastern, AFR= African, AMR= Amerindian.
[d] A total of 2 patients with damaging variants were from consanguineous unions, after removing related individuals (n=1).
[e] Total proliferative and membranous cases (%) are a percentage of total nephritis cases. Some patients may have more than one type of nephritis.

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[f]Positive ANA threshold at a titre of ≥1:80.

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Table 2. Predicted damaging variants in monogenic lupus genes.

| Pathway | Gene | Variant position (Chr-bp) [a] | Allele Change | HGVS Consequence [b] | CADD Score | Het/Hom [c] | ClinVar Interpretation | Predicted Impact [d] |
|---|---|---|---|---|---|---|---|---|
| Complement | *C1QA* | 1-22965784 | C-T | p.Gln208Ter | 35 | Hom | Pathogenic | LOF |
| | *C1R* | 12-7187985 | C-T | p.Val605Ile | 22.7 | Het | Unknown | LOF |
| | *C1S* | 12-7169782 | C-G | p.Cys3Trp | 15.38 | Het | Unknown | LOF |
| | *C1S* | 12-7174347 | G-A | p.Arg331His | 13.27 | Het | Unknown | LOF |
| | *C4A* | 6-31964378 | G-A | c.3676+1G>A | 25 | Hom | Unknown | LOF |
| DNA Clearance | *DNASE1L3* [e] | 3-58191226 | ATG-A | p.Thr97IlefsTer2 | 22.9 | Hom | Pathogenic | LOF |
| Interferon | *IFIH1* | 2-163124759 | A-G | p.Met882Thr | 24.1 | Het | Unknown | Uncertain |
| Carbohydrate Metabolism | *MAN2B1* | 19-12763007 | G-A | p.Pro669Leu | 23.4 | Hom | Likely benign | Uncertain |
| Apoptosis | *PTEN* | 10-89624071 | C-G | p.His122Asp | 21.2 | Het | Unknown | LOF |

[a] Chr= chromosome, bp= base pair.
[b] Human Genome Variation Society protein or coding sequence.
[c] Het= heterozygous, Hom= homozygous.
[d] LOF=loss of function
[e] Variant shared by full siblings born to consanguineous parents.

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