Genome-Wide Sequencing Identified Rare Genetic Variants for Childhood-Onset 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 sequencing [WGS] or whole exome sequencing) in patients suspected of monogenic lupus, and focused on 36 monogenic lupus genes. We prioritized rare (minor allele frequency < 1%) exonic, nonsynonymous, and splice variants with predicted pathogenicity classified as deleterious variants (Combined Annotation Dependent Depletion [CADD], PolyPhen2, and Sorting Intolerant From Tolerant [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) > 1 kb in size. We created additive non-HLA and HLA SLE genetic risk scores (GRSs) using common SLE-risk single-nucleotide polymorphisms. 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 (SD 3.2) years. We identified predicted damaging variants in 9 (13%) patients who were significantly younger at diagnosis compared to those without a predicted damaging variant (6.8 [SD 2.1] years vs 9.2 [SD 3.2] years, $P = 0.01$). We did not identify damaging CNVs. There was no significant association between non-HLA or HLA SLE GRSs and the odds of carrying ≥ 1 rare variant in multivariate analyses.

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

Key Indexing Terms: genetic studies, pediatric rheumatic diseases, systemic lupus erythematosus

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 effects 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 of which are in genes previously identified for monogenic lupus and lupus-like disease.[3] Whole genome sequencing (WGS) and whole exome sequencing (WES) studies have identified 36 genes for monogenic lupus and lupus-like

disease.[4] These monogenic forms of lupus provide insight 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 SLE or lupus-like disease who were suspected of monogenic lupus due to one or more features of (1) young-onset of disease (< 11 yrs), and (2) a history of consanguinity in parents. We extracted prospectively collected demographic, clinical, and laboratory data from the SickKids Lupus Clinic database, supplemented by medical records. This included a review of medications used to treat disease. This study was approved by the SickKids Research Ethics Board (REB no. 1000058324).

Genome-wide sequencing (WGS or WES). A total of 71 patients with suspected monogenic lupus who 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 Genome Analysis Toolkit version 3.7 and HiSeq Analysis Software version 2-2.5.55.1311, and functional annotation with ANNOVAR. We focused on 36 genes identified from familial and candidate gene studies that cause SLE or lupus-like disease (Supplementary Table S1, available with the online version of this article).[4]

We prioritized rare (MAF < 1%) exonic, nonsynonymous (missense, stop-gain, and frameshift), and splice variants, hereafter referred to as rare variants. We predicted deleterious variants according to Combined Annotation Dependent Depletion (CADD > 10), PolyPhen2 (> 0.5), and/or Sorting Intolerant From Tolerant (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 > 1 kb in 36 monogenic lupus genes.

Ancestry inference. Patients were also genotyped on the Illumina Multiethnic Array or Global Screening Array, and ancestry was genetically inferred with ADMIXTURE 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 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 GWAS to date.[1] We calculated an additive non-HLA GRS using 39 non-HLA SLE-risk single-nucleotide polymorphisms and an HLA SLE GRS using 7 HLA SLE-risk alleles identified in Europeans (Supplementary Tables S2 and S3, available with the online version of this article). Additive allelic weighted GRSs were generated with weights taken from the log-odds ratio for SLE from GWAS.[1]

Analysis. Mean and 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 exact test 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 the Genome Aggregation Database (gnomAD) version 2.1.1[5] and Trans-Omics for Precision Medicine (TOPMed) version hg19[6] using chi-square tests with Yates correction (Bonferroni adjusted $P < 0.001$ 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 and HLA GRSs and the number of rare monogenic lupus variants in individuals with and without (1) rare variants and (2) 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 multivariate adjusted models for sex, ancestry, and age at SLE diagnosis. The significance thresholds were adjusted for 4 independent tests ($P < 0.01$; additional details can be found in the supplementary material, available with the online version of this article).

RESULTS

Our study included 71 patients with suspected monogenic lupus, 69 with WGS and 2 with WES. The majority met inclusion for young-onset disease (< 11 yrs; n = 59), with 18% (n = 13) included for a history of consanguinity. There was only 1 sibling-pair in the cohort. A total of 61 (86%) patients met the American College of Rheumatology (ACR) criteria, 63 (89%) met the Systemic Lupus International Collaborating Clinics (SLICC) criteria, and 67 (94%) met the European Alliance of Associations for Rheumatology (EULAR)/ACR criteria. The majority of patients were female (80%), the mean age at diagnosis was 8.9 (SD 3.2) years, and patients were followed for a mean of 7.6 (SD 4.7) years after diagnosis. Of the 71 patients, 23 (32%) were ancestrally admixed and 20 (28%) were of European ancestry. Review of SLE features demonstrated that 69 (97%) were antinuclear antibody (ANA) positive and 52 (73%) had a malar rash. A total of 22 (31%) patients had biopsy-confirmed nephritis and 14 (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 to be deleterious (Supplementary Table S4, available with the online version of this article). When accounting for allele frequency, zygosity, and inheritance, we identified 9 rare, predicted damaging variants in monogenic lupus genes in 10 patients. After removing a related individual (n = 1), 9 (13%) patients 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 canonical splice donor variant located one 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 structural variation breakpoints that overlap with AluSz SINE elements and with an enhancer from GeneHancer derived from ENCODE that is predicted to interact with 28 genes,

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

	Total, n = 71[a,b]	Children With Predicted Damaging Variants, n = 10[a,c]	Children Without Predicted Damaging Variants, n = 61[a]	P[*]
Age at diagnosis, yrs, mean (SD)	8.9 (3.2)	6.8 (2.1)	9.2 (3.2)	**0.01**
Duration of follow-up, yrs, mean (SD)	7.6 (4.7)	9.2 (4.7)	7.3 (4.6)	0.14
Female	57 (80)	7 (70)	50 (82)	0.40
Ancestry				> 0.99
EUR	20 (28)	2 (20)	18 (30)	
EAS	9 (13)	1 (10)	8 (13)	
SAS	6 (8)	1 (10)	5 (8)	
MEAS	4 (6)	3 (30)	1 (2)	
AFR	4 (6)	0 (0)	4 (7)	
AMR	3 (4)	1 (10)	2 (3)	
ADM	23 (32)	2 (20)	21 (34)	
History of consanguinity	13 (18)	2 (20)[d]	10 (16)	0.67
SLE clinical features				
Malar rash	52 (73)	8 (80)	44 (72)	0.72
Arthritis	47 (66)	8 (80)	39 (64)	0.48
Alopecia	31 (44)	4 (40)	27 (44)	> 0.99
Fever	26 (37)	5 (50)	21 (34)	0.48
Nephritis	22 (31)	3 (30)	19 (31)	> 0.99
Class III/IV[e]	17 (77)	2 (20)	15 (25)	
Class V[e]	7 (33)	2 (20)	5 (8)	
Oral ulcers	22 (31)	2 (20)	20 (33)	0.71
Neuropsychiatric	14 (20)	1 (10)	13 (21)	0.67
Pericarditis	6 (8)	1 (10)	5 (8)	> 0.99
Pleuritis	4 (6)	1 (10)	3 (5)	0.46
SLE laboratory features				
Leukopenia	37 (52)	4 (40)	33 (54)	0.50
Thrombocytopenia	28 (39)	2 (20)	26 (43)	0.30
Hemolytic anemia	24 (34)	2 (20)	22 (36)	0.48
Autoantibodies				
ANA[f]	69 (97)	10 (100)	59 (97)	> 0.99
Anti-DNA	46 (65)	6 (60)	40 (66)	0.73
Anti-Sm	28 (39)	5 (50)	23 (38)	0.50
Anti-cardiolipin	27 (38)	1 (10)	26 (43)	0.08
LAC	12 (17)	0 (0)	12 (20)	0.19

[a] Values in n (%) unless otherwise specified. [b] Data include 2 individuals without self-identified or genetically inferred ethnicities. [c] Three of these individuals carry confirmed variants, including a pair of siblings. [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. [f] Positive ANA threshold at a titre of ≥ 1:80. [*] Significant values in bold. ADM: admixed; AFR: African; AMR: Amerindian; ANA: antinuclear antibody; anti-Sm: anti-Smith; EAS: East Asian; EUR: European; LAC: lupus anticoagulant; MEAS: Middle Eastern; SAS: South Asian; SLE: systemic lupus erythematosus.

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 [SD 2.1] yrs vs 9.2 [SD 3.2] yrs, $P = 0.01$). There was no significant difference between individuals with and without damaging variants with regard to consanguinity ($P = 0.67$), ancestry ($P > 0.99$), 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

significant difference (1.90 [SD 1.14] vs 1.85 [SD 1.52], respectively, $P = 0.69$; data not shown).

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, 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 Figure S2, available with the online version of this article).

Table 2. Predicted damaging variants in monogenic lupus genes.

Pathway	Gene	Variant Position (Chr-bp)	Allele Change	HGVS Consequence[a]	CADD Score	Het/Hom	ClinVar Interpretation	Predicted Effect
Complement	*C1QA*	1-22965784	C-T	p.Gln208Ter	35.0	Hom	Pathogenic	LOF
	C1R	12-7187985	C-T	p.Val605Ile	22.7	Het	Unknown	LOF
	C1S	12-7169782	C-G	p.Cys3Trp	15.4	Het	Unknown	LOF
	C1S	12-7174347	G-A	p.Arg331His	13.3	Het	Unknown	LOF
	C4A	6-31964378	G-A	c.3676+1G>A	25.0	Hom	Unknown	LOF
DNA clearance	*DNASE1L3*[b]	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] Human Genome Variation Society protein or coding sequence. [b] Variant shared by full siblings born to consanguineous parents. bp: base pair; CADD: Combined Annotation-Dependent Depletion; Chr: chromosome; Het: heterozygous; HGVS: Human Genome Variation Society; Hom: homozygous; LOF: loss-of-function.

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 patients with childhood-onset SLE.

Our study population was comparable to other cohorts of patients suspected of monogenic lupus reported in the literature regarding the 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 patients with monogenic lupus that found 90% met 2019 EULAR/ACR criteria and 94% met SLICC criteria.[7] That study also found that the majority of patients (96%) were ANA positive. Another study of 7 patients with young-onset SLE with WES found that 86% were ANA positive.[8] These proportions of patients with ANA-positive young-onset SLE are consistent with our study, where 97% of patients were ANA positive, and with other studies that have reported a lower prevalence among young patients with SLE.[9] The study of 7 patients with young-onset SLE also reported that all patients had a malar rash, which was the most common clinical feature in our study cohort.[8] By examining SLE features manifested over the course of observation, and not only those present at diagnosis, we described the range of serologic and clinical SLE manifestations. This is also reflected by the prevalence of other manifestations such as neuropsychiatric lupus (found in 20% of patients), which is comparable to prior studies of patients with SLE with 5 to 10 years of follow-up reporting a prevalence of 12%.[10] The mean age of diagnosis in our study was 8.9 (SD 3.2) years, which is similar to that reported in the study of 49 patients with monogenic lupus (median age at onset of 6 years) and a next-generation sequencing study of 117 patients with juvenile-onset SLE (median age at onset of 12 years).[7,11]

Genome-wide sequencing identified predicted damaging variants in 13% of our selected population. This is between the 7% reported in a WGS study of 117 children diagnosed with SLE before 16 years of age[11] and 27% reported in a WES study of 15 children with SLE restricted to those with severe or atypical presentation, additional comorbidities, or consanguineous parents.[3] We identified 2 patients carrying biallelic variants predicted to be disease-causing 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 SLE may implicate targeted therapies, as demonstrated in a study of C1q-deficient patients with SLE treated with fresh frozen plasma to reduce flares of disease.[13] Our results demonstrate the clinical utility of sequencing for known SLE genes in a selected population.

We identified additional predicted damaging variants, not previously reported in the 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 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 3 patients. We hypothesize that these variants are not solely causal but may contribute to SLE susceptibility, as only biallelic variants in these genes cause monogenic lupus.

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 patients with monogenic lupus 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 comprising 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 SLE 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 CNVs predicted to be damaging. Although previous studies have identified CNVs that lead to SLE,[17] to our knowledge, no study to date has reported a CNV causing monogenic lupus. 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.

We acknowledge potential limitations of our study. By focusing on rare variants in known monogenic lupus genes, we may have excluded causal variants in novel SLE genes. We also identified predicted damaging variants based on bioinformatic tools that predict functional consequences, but we were unable to perform functional validation. Conversely, we did not restrict to the American College of Medical Genetics guidance on sequence variant interpretation since it is designed for clinical classification and is 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 SLE genes. Trio analyses would enable identification of de novo variant discovery. Among these known genes, we filtered based on predicted inheritance in all but 2 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 harbored variants predicted to contribute 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 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 predicted damaging variants. Studies of independent cohorts are needed to validate our findings. The identification and understanding of how genetics lead to disease provides insights into pathogenesis and can potentially identify therapeutic targets for monogenic lupus and SLE more broadly.

REFERENCES

1. Langefeld CD, Ainsworth HC, Cunninghame Graham DS, et al. Transancestral mapping and genetic load in systemic lupus erythematosus. Nat Commun 2017;8:16021.
2. Yin X, Kim K, Suetsugu H, et al. Meta-analysis of 208370 East Asians identifies 113 susceptibility loci for systemic lupus erythematosus. Ann Rheum Dis 2020;80:632-40.
3. Tirosh I, Spielman S, Barel O, et al. Whole exome sequencing in childhood-onset lupus frequently detects single gene etiologies. Pediatr Rheumatol 2019;17:52.
4. Crow YJ, Chase DS, Lowenstein Schmidt J, et al. Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A 2015;167A:296-312.
5. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature 2020;581:434-43.
6. Taliun D, Harris DN, Kessler MD, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature 2021;590:290-9.
7. Al-Mayouf SM, Akbar L, Abdwani R, et al. Performance of the EULAR/ACR 2019 classification criteria for systemic lupus erythematous in monogenic lupus. Clin Rheumatol 2022; 41:2721-7.
8. Batu ED, Koşukcu C, Taşkıran E, et al. Whole exome sequencing in early-onset systemic lupus erythematosus. J Rheumatol 2018;45:1671-9.
9. Charras A, Smith E, Hedrich CM. Systemic lupus erythematosus in children and young people. Curr Rheumatol Rep 2021;23:20.
10. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: A comparison of early and late manifestations in a cohort of 1,000 patients. Medicine 2003;82:299-308.
11. Belot A, Rice GI, Omarjee SO, et al. Contribution of rare and predicted pathogenic gene variants to childhood-onset lupus: a large, genetic panel analysis of British and French cohorts. Lancet Rheumatol 2020;2:e99-109.
12. Özçakar ZB, Foster J 2nd, Diaz-Horta O, et al. DNASE1L3 mutations in hypocomplementemic urticarial vasculitis syndrome. Arthritis Rheum 2013;65:2183-9.
13. Ekinci Z, Ozturk K. Systemic lupus erythematosus with C1q deficiency: treatment with fresh frozen plasma. Lupus 2018; 27:134-8.
14. Almlöf JC, Nystedt S, Leonard D, et al. Whole-genome sequencing identifies complex contributions to genetic risk by variants in genes causing monogenic systemic lupus erythematosus. Hum Genet 2019;138:141-50.
15. Lee WF, Fan WL, Tseng MH, Yang HY, Huang JL, Wu CY. Characteristics and genetic analysis of patients suspected with early-onset systemic lupus erythematosus. Pediatr Rheumatol 2022;20:68.
16. Webb R, Kelly JA, Somers EC, et al. Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. Ann Rheum Dis 2011;70:151-6.
17. Barbosa FB, Simioni M, Wiezel CEV, et al. Copy number variation in the susceptibility to systemic lupus erythematosus. PLoS ONE 2018;13:206683.