RMD Open
Rheumatic & Musculoskeletal Diseases

EDITORIAL

Polygenic risk score: the potential role in the management of systemic lupus erythematosus

Chi Chiu Mok

To cite: Mok CC. Polygenic risk score: the potential role in the management of systemic lupus erythematosus. *RMD Open* 2024;**10**:e004156. doi:10.1136/rmdopen-2024-004156

Received 27 January 2024
Accepted 21 February 2024

Linked

► http://dx.doi.org/10.1136/rmdopen-2023-003293

Check for updates

Department of Medicine and Geriatrics, Tuen Mun Hospital, New Territories, Hong Kong

Correspondence to
Dr Chi Chiu Mok;
ccmok2005@yahoo.com

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterised by substantial clinical and serological heterogeneity, leading to a high variability in the disease course, treatment response and prognosis in different patients. Although the exact pathoaetiology of SLE remains elusive, complex interaction among genetic, epigenetic and environmental factors such as ultraviolet light, hormones, drugs and viral infections is probably involved.[1]

Genetic risk alleles may assist SLE management in various ways. These potentially include: (1) identification of individuals who are more susceptible to the disease development and thus help in differentiation of SLE from other autoimmune diseases during the diagnostic process; (2) stratification of patients according to disease severity/prognosis for clinical trials and treatment decisions; (3) prediction of response and adverse effects to drug therapies; and (4) identification of molecular targets for pharmacological development. Over the past two decades, genome-wide association studies (GWAS) have identified more than 200 risk loci in SLE, which underscores it is a complex polygenic disease. Guga *et al*[2] summarised 2 human leucocyte antigen (HLA), 127 non-HLA and 2 X chromosome novel SLE risk loci from GWAS published in the past 5 years, with 75 of the non-HLA loci being Asian specific and five being European specific. However, as more than 90% of these risk alleles are located within the non-coding regions, the functional significance of the genetic variants is poorly understood.[3] Detection of the true causal variants within a given risk locus is challenging due to the linkage disequilibrium among the associated variants.[4] Although the Bayesian method, statistical fine mapping approaches, expression quantification loci studies, as well as transcriptomic analyses have helped to uncover the putative causal variants and their relevance to the underlying biological processes in SLE, the explained heritability by the risk alleles remains low, with figures quoted from 17% to 28% in various studies.[2 5 6]

In view of the relatively small contribution of each risk allele to disease susceptibility, the genetic risk score (GRS) or polygenic risk score (PRS) is developed for better risk prediction and stratification based on an aggregation of single nucleotide polymorphisms derived from GWAS data. In patients with SLE, higher PRS (genetic load) has been associated with childhood-onset disease, earlier age of disease onset in adults, occurrence of more serious manifestations such as lupus nephritis (LN), a higher prevalence of autoantibodies and organ damage, including reduced estimated glomerular filtration rate (eGFR), as well as an increased risk of mortality[5 7–17] (table 1). As shown, there are relatively few studies of PRS in Asian patients with SLE. One study reported higher GRS in East Asians than Europeans, which might be relevant for the observed higher prevalence of SLE in Asia.[5]

In this issue of *RMD Open*, Chen *et al*[18] from Taiwan genotyped 2782 adult patients with SLE using a Han Chinese-specific GWAS tool. The PRS was calculated by using the standard clumping and thresholding method. Patients with SLE were divided into four quartiles according to the PRS. It was reported that the highest quartile of the PRS was significantly associated with earlier age of SLE onset (by 5 years), higher prevalence of anti-dsDNA, hypocomplementaemia and the development of LN at 1 year after SLE onset, as well as a trend of more severe renal disease (higher proportion of proliferative types of LN and lower eGFR). The association between PRS

Table 1 Genetic risk score studies of systemic lupus erythematosus (SLE)

Authors, year	Patients (n)	Ethnicity	Main relevant findings
Webb *et al*, 2011[7]	1317	Multiethnic (USA)	More serious manifestations, higher prevalence of autoantibodies and higher number of SLE risk alleles in childhood-onset than adult-onset SLE (especially in African Americans).
Morris *et al*, 2016[5]	5686	Europeans and Chinese	GRS (genetic load) higher in East Asians than Europeans; relevant for the higher prevalence of SLE in Asia.
Gianfrancesco *et al*, 2016[8]	942	Multiethnic (USA)	Overall GRS not associated with higher self-reported SLE activity; but certain SNPs associated with higher self-reported activity.
Joo *et al*, 2018[9]	781	Koreans	PRS significantly higher in childhood-onset than adult-onset SLE; PRS inversely correlated with the age of SLE onset.
Chen *et al*, 2020[11]	1659	Chinese	Higher PRS associated with younger SLE onset and the presence of LN.
Reid *et al*, 2020[10]	5524	Caucasians	Highest quartile of PRS associated with earlier SLE onset (by 6 years), higher prevalence of autoantibodies and LN, renal dysfunction, organ damage and all-cause mortality.
Taylor *et al*, 2011[13]	1919	Caucasians	Higher PRS associated with younger age of SLE onset and higher prevalence of autoantibodies and fulfilment of the immunological domain of the ACR SLE criteria.
Wang *et al*, 2021[12]	2618	Chinese	Higher PRS associated with increased risk of SLE.
Dominguez *et al*, 2021[14]	1540	Caucasians	HLA GRS associated positively with age of SLE onset. Non-HLA GRS associated negatively with age of SLE onset.
Tang *et al*, 2023[15]	1158	Caucasians	Higher eGFR loci PRS associated with lower mean eGFR in longitudinal cohorts of adult and childhood SLE.
Hedenstedt *et al*, 2023[16]	1248	Caucasians	Higher PRS of B cell genes and B cell activation genes associated with higher prevalence of anti-dsDNA and LN development.
Kwon *et al*, 2023[17]	1655	Koreans	GRS higher in childhood than adult-onset SLE; higher GRS associated with higher prevalence of LN and anti-Sm antibody.

ACR, American College of Rheumatology; eGFR, estimated glomerular filtration rate; GRS, genetic risk score; HLA, human leucocyte antigen; LN, lupus nephritis; PRS, polygenic risk score; SNP, single nucleotide polymorphism.;

and renal disease was more marked in patients with an onset of SLE before the age of 50 years. Although this study involves a large number of Asian patients with SLE and suggests a link between PRS and SLE prognosis, there are some limitations that warrant discussion.

Previous studies have demonstrated a higher PRS in childhood compared with patients with adult-onset SLE,[7 9 17] and within the adult SLE population, a higher PRS was associated with an earlier age of disease onset.[11 13] The unavailability of a group of patients with childhood-onset SLE in the study by Chen *et al*[18] precludes a thorough analysis on the relationship between PRS and disease severity of SLE adjusted for age of onset. Second, as this is not a planned prospective study, the prevalence of medical comorbidities (organ damage) at 1 year was retrieved by classification codes from an insurance database, and thus accuracy could not be verified. Moreover, whether the outcome of LN was worse in those with higher PRS was not certain as there were no long-term follow-up data beyond 1 year such as renal and extrarenal flares, as well as the rate of decline of eGFR over time, development of chronic kidney disease and end-stage renal failure. Furthermore, the initial immunosuppressive therapies were

not fully adjusted in the multivariate models. Finally, the unavailability of data on family history of SLE in this study has missed an opportunity to evaluate the role of genetic load on disease severity and treatment response in those with familial tendency of SLE. The most important observation in Chen *et al*'s study[18] is that in Chinese patients with SLE, higher PRS was associated with an increased risk of proliferative types of LN during the first year of SLE diagnosis, which was translated to a 'worse' prognosis. The same observation has previously been reported by other investigators from mainland China.[11]

Despite these caveats, the study by Chen *et al*[18] reiterates the potential prognostic value of the PRS in patients with SLE. GRS, coupled with immune phenotyping by flow cytometry, mass spectrometry and single cell RNA sequencing, which could be analysed by artificial intelligence and machine learning of large data sets, as well as biomarker panels identified by multiomic analyses,[19] may eventually enable stratification of patients with SLE according to their susceptibility to develop more serious disease phenotypes, resistance to therapies and poorer prognosis. This approach will also aid in recruitment of patient subsets to therapeutic trials of novel agents, as well as clinical treatment decisions, such as upfront combination of standard of care with biological/targeted agents for patients at risk of disease progression[20] and withdrawal of maintenance immunosuppression in lower risk patients. However, before this happens in real-life clinical practice, better characterisation of the clinical outcomes of longitudinal cohorts of patients with SLE in different ethnic groups is mandatory to allow vigorous validation of the diagnostic and prognostic significance of the PRS, alone or in combination with other biomarkers. Multinational collaboration is deemed necessary to collectively evaluate the applicability, cost and predictive value of genetic and non-genetic biomarkers in patients with SLE and LN.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iD

Chi Chiu Mok http://orcid.org/0000-0003-3696-1228

REFERENCES

1 Mok CC. Biological and targeted therapies of systemic lupus erythematosus: evidence and the state of the art. *Expert Rev Clin Immunol* 2017;13:677–92.
2 Guga S, Wang Y, Graham DC, *et al*. A review of genetic risk in systemic lupus erythematosus. *Expert Rev Clin Immunol* 2023;19:1247–58.
3 Ha E, Bae SC, Kim K. Recent advances in understanding the genetic basis of systemic lupus erythematosus. *Semin Immunopathol* 2022;44:29–46.
4 Rao S, Yao Y, Bauer DE. Editing GWAS: experimental approaches to dissect and exploit disease-associated genetic variation. *Genome Med* 2021;13:41.
5 Morris DL, Sheng Y, Zhang Y, *et al*. Genome-wide association meta-analysis in Chinese and European individuals identifies ten new Loci associated with systemic lupus erythematosus. *Nat Genet* 2016;48:940–6.
6 López-Cortegano E, Caballero A. Inferring the nature of missing heritability in human traits using data from the GWAS catalog. *Genetics* 2019;212:891–904.
7 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.
8 Gianfrancesco MA, Balzer L, Taylor KE, *et al*. Genetic risk and longitudinal disease activity in systemic lupus erythematosus using targeted maximum likelihood estimation. *Genes Immun* 2016;17:358–62.
9 Joo YB, Lim J, Tsao BP, *et al*. Genetic variants in systemic lupus erythematosus susceptibility Loci, Xkr6 and Glt1D1 are associated with childhood-onset SLE in a Korean cohort. *Sci Rep* 2018;8:9962.
10 Reid S, Alexsson A, Frodlund M, *et al*. High genetic risk score is associated with early disease onset, damage accrual and decreased survival in systemic lupus erythematosus. *Ann Rheum Dis* 2020;79:363–9.
11 Chen L, Wang Y-F, Liu L, *et al*. Genome-wide assessment of genetic risk for systemic lupus erythematosus and disease severity. *Hum Mol Genet* 2020;29:1745–56.
12 Wang Y-F, Zhang Y, Lin Z, *et al*. Identification of 38 novel Loci for systemic lupus erythematosus and genetic heterogeneity between ancestral groups. *Nat Commun* 2021;12:772.
13 Taylor KE, Chung SA, Graham RR, *et al*. Risk alleles for systemic lupus erythematosus in a large case-control collection and associations with clinical subphenotypes. *PLoS Genet* 2011;7:e1001311.
14 Dominguez D, Kamphuis S, Beyene J, *et al*. Relationship between genetic risk and age of diagnosis in systemic lupus erythematosus. *J Rheumatol* 2021;48:852–8.
15 Tang T-S, Liao F, Webber D, *et al*. Genetics of longitudinal kidney function in children and adults with systemic lupus erythematosus. *Rheumatology* 2023;62:3749–56.
16 Hedenstedt A, Reid S, Sayadi A, *et al*. B cell Polygenic risk scores associate with anti-dsDNA antibodies and nephritis in systemic lupus erythematosus. *Lupus Sci Med* 2023;10:e000926.
17 Kwon Y-C, Ha E, Kwon H-H, *et al*. Higher genetic risk loads confer more diverse manifestations and higher risk of lupus nephritis in systemic lupus erythematosus. *Arthritis Rheumatol* 2023;75:1566–72.
18 Chen YJ, Hsaio TH, Lin YC, *et al*. n.d. A Polygenetic risk score predicts earlier onset of systemic lupus erythematosus and first year renal disease in adult Taiwanese patients. *RMD Open (in Press)*
19 Mok CC, Mohan C. Urinary biomarkers in lupus nephritis: are we there yet? *Arthritis Rheumatol* 2021;73:194–6.
20 Mok CC. Combination strategies for lupus nephritis: facts and controversies. *Expert Rev Clin Immunol* 2023;19:527–36.