Med & Health Aug 2024; 19(2): 362-379 https://doi.org/10.17576/MH.2024.1902.02

REVIEW ARTICLE

Clinical Significance of Ikaros in Systemic Lupus Erythematosus (SLE): A Systematic Literature Review

RAMLI N[1], JOHDI NA[2], KAMARUZAMAN L[3], MOHD R[3], RAJALINGHAM S[4], AZIZAN EA[1], MOHAMED SAID MS[4], SHAHARIR SS[4]*

[1]Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, 56000 Cheras, Kuala Lumpur
[2]UKM Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, 56000 Cheras, Kuala Lumpur
[3]Nephrology Unit, [4]Rheumatology Unit, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, 56000 Cheras, Kuala Lumpur

Received: 03 Jan 2024 / Accepted: 13 Feb 2024

ABSTRAK

Sistemik lupus eritematosus (SLE) adalah penyakit autoimun kronik yang melibatkan pelbagai sistem. Ikaros ialah faktor transkripsi utama yang dikodkan oleh gen Ikaros family zinc finger 1 (IKZF1). Ikaros memainkan peranan penting di dalam sistem darah (hematopoiesis) dan pengawalan sistem imun kerana ia membantu dalam pembezaan sel limfoid. Fungsi Ikaros telah ditunjukkan dengan jelas dalam model tikus dan kini terdapat data tentang peranannya dalam patogenesis dan target perawatan SLE. Ulasan sistematik ini menghuraikan perkaitan klinikal yang signifikan antara Ikaros and IKZF1 dalam pesakit SLE, melalui carian yang menyeluruh menggunakan pangkalan data OVID, PubMed dan Cochrane. Istilah "SLE", "lupus", "ikaros transcription factor", "ikaros zinc finger" and "IKZF" telah digunakan bagi tujuan pencarian dan semua artikel yang relevan telah dianalisa. Hanya kajian yang melibatkan manusia dimasukkan dan berdasarkan kriteria inklusi, sebanyak 22 artikel yang berkaitan dengan Ikaros di dalam SLE telah terpilih. Polimorfisme IKZF1 telah terbukti berkaitan secara signifikan dengan SLE yang berlatar belakang pelbagai etnik. Hubungan ini telah mencetuskan beberapa kajian klinikal dalam SLE, menggunakan iberdromide yang bertindak terhadap Ikaros. Walau bagaimanapun, kajian tentang ekspresi gen Ikaros dan paras protein didapati tidak konsisten, dan ini kemungkinan disebabkan oleh kepelbagaian ciri klinikal penyakit SLE ini. Kesimpulannya, walaupun Ikaros berpotensi menjadi protein

Address for correspondence and reprint requests: Syahrul Sazliyana Shaharir. Rheumatology Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-8921 5555 Email: sazliyana@ukm.edu.my

target rawatan di dalam SLE, kajian selanjutnya diperlukan bagi mengenalpasti kesan sebenar Ikaros, serta subset pesakit SLE yang mungkin mempunyai respon yang baik terhadap rawatan tersebut.

Kata kunci: Autoimun; gen; Ikaros; lupus; protein

ABSTRACT

Systemic lupus erythematosus (SLE) is a multi-systemic chronic autoimmune disease. Ikaros is a family member of transcription factors, encoded by the Ikaros family zinc finger 1 (IKZF1) gene. It is important in hematopoiesis and immune system regulation as it helps in lymphoid cell differentiation. Ikaros functions in the pathogenesis and therapeutic target in SLE are well demonstrated in mice. This systematic review highlighted the clinical significance of Ikaros and IKZF1 in SLE patients via a comprehensive search using OVID, PubMed, and Cochrane databases. The following terms "SLE", "lupus", "Ikaros transcription factor", "Ikaros zinc finger" and "IKZF" were searched and all of the relevant publications were scrutinised. Only human studies were included. A total of 22 relevant publications of Ikaros in SLE patients were included. IKZF1 polymorphisms were demonstrated to be significantly associated with SLE across different ethnicities of SLE. This association had led to clinical trials in SLE, using iberdomide that targets Ikaros. However, studies on the Ikaros gene expression and protein levels were found to be conflicting in SLE, which suggested clinical heterogeneity of the disease. In conclusion, further studies are needed to determine the exact effects of Ikaros and which subtypes of SLE patients will benefit from treatment.

Keywords: Autoimmune; gene; Ikaros; lupus ; protein

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease characterised by autoantibody production that attacks various organs and systems in the body (Kaul et al. 2016). This disease commonly affects young women and Asian patients, tends to have the severe form of the disease with higher mortality and morbidity (Jakes et al. 2012). The reported prevalence of SLE in Malaysia was around 40-60/100,000 populations (Wang et al. 1997). Malaysian patients tend to have more severe form of SLE with a high rate of major organ, especially renal in up to 60% (Selvananda et al. 2020; Teh et al. 2015), which carries high morbidity due to organ damage (Shaharir et al. 2014; Shaharir et al. 2016; Shaharir et al. 2019).

SLE has a complex aetiopathogenesis that involves interactions between genetics, epigenetics and

environmental factors (Abd Talib et al. 2021). Various susceptibility gene loci have been validated in our Malaysian SLE population (Molineros et al. 2014; Selvaraja et al. 2021; Abd Talib et al. 2022), but the exact function of these gene variants in the immunopathogenesis of SLE is still poorly understood (Pan et al. 2020). This has hampered the efforts to establish reliable biomarkers and effective targeted treatments for SLE (Felten et al. 2019). Ikaros family zinc finger 1 (IKZF1) gene is located in 7p12 of the chromosome, and its polymorphisms have been demonstrated to be associated with SLE (Nam et al. 2021), including in our Malaysian SLE cohort (Molineros et al. 2014; Abd Talib et al. 2022). IKZF1 gene encodes Ikaros, a potent transcriptor factor that is implicated in immune cell development, homeostasis, and function (Molnár et al. 1996).

Ikaros or IKZF1 is a transcription protein and is one of the members of the IKZF family which consists of four other members: Helios (encoded by the gene IKZF2), Aiolos (IKZF3), Eos (IKZF4) and Pegasus (IKZF5). The common character of these factors is they contain two domains ie N-terminal zinc finger (ZF) domains, which mediate direct interactions with DNA, and C-terminal ZFs, which facilitate homo- and heterodimerisation between IKZF family members and isoforms (Molnár & Georgopoulos 1994). A total of six zinc finger domains are found in the Ikaros protein, with the first four at the N terminus (ZF1-ZF4), and the last two at the C terminus (ZF5 & ZF6) (Figure 1).

Ikaros proteins are expressed mainly in hematopoietic cells, and they play a pivotal for immune cell differentiation. They regulate the target genes' expression and can act as transcriptional activators and repressors via chromatin remodeling through DNA binding (Boast et al. 2021). Apart from translating into full-length Ikaros (IK1), the IKZF1 gene produces multiple isoforms through alternate splicing, and at least eleven isoforms (IK2-IK12) have been identified (Li et al. 2011). These isoforms differ in the composition of their N-terminal DNA binding domain, and hence they have diverse functions and effects in the hematopoietic and immune cells (Li et al. 2011).

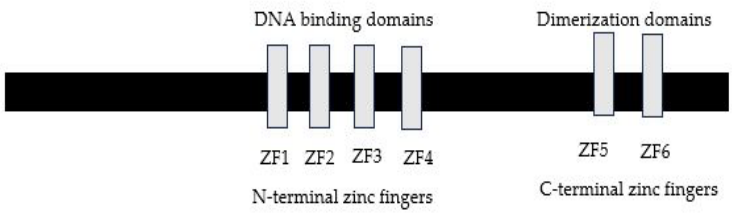

FIGURE 1: Structure of a full-length Ikaros protein. The first four zinc finger domains are at the N terminus (ZF1-ZF4), which are responsible for DNA binding, and the last two at the C terminus (ZF5% ZF6), which are responsible for protein dimerisation

The crucial role of Ikaros in hematopoiesis has been well established. Mice that have an absence of N-terminal domains for DNA bindings (dominant negative isoforms) could not produce early lymphoid lineage cells such as T and B lymphocyte progenitors, as well as Natural Killer cells (Georgopoulos et al. 1994; Georgopoulos et al. 1992). The absence of dimerisation domains also leads to a severe lymphoid cell development arrest (Wang et al. 1996). Subsequent studies in humans have further confirmed its role by demonstrating the associations between the IKZF1 mutations and Ikaros dysfunctions with different types of diseases such as immunodeficiencies (Kuehn et al. 2021), as well as hematological malignancies such as acute leukemia (Chen et al. 2019; Conserva et al. 2023; Srinivasan et al. 2023). Mutations of the C-terminal (ZF5-6) dimerisation mutations are also found to be associated with hematologic diseases but with less infection (Kuehn et al. 2021). For management implication, the presence of IKZF1 mutation indicates poor prognosis to treatment response and outcomes in acute lymphoblastic leukemia (ALL) (Mullighan et al. 2009). As these hematopoietic cells are also crucial in the immune system regulations, there is accumulating evidence of the role of IKZF1 or Ikaros in the pathogenesis of autoimmune diseases. Development of lymphadenopathy and splenomegaly with auto-antibody productions were observed in dominant negative Ikaros transgenic mice (Wojcik et al. 2007). Subsequently, several case series have demonstrated that the mutations in IKZF1 were not only associated with hypogammaglobulinemia/ immunodeficiencies but might also be associated with juvenile-onset SLE and other autoimmune diseases (Belot et al. 2020; Hoshino et al. 2017; Van Nieuwenhove et al. 2018). The expression of Ikaros was found to be altered in various autoimmune diseases including Sjögren's syndrome, systemic sclerosis, and rheumatoid arthritis, compared to the control group (Duque-Suárez et al. 2018). A recent study suggested that Ikaros may prevent autoimmunity, as mice model with Ikaros deletion in mature B cells experienced activations of self-reactive B and T cells, leading to systemic autoimmunity (Schwickert et al. 2019). In SLE, despite significant associations between the IKZF1 polymorphisms in various populations, the exact function of Ikaros and their clinical significance in this disease is still perplexing. Hence, this narrative review focused on the clinical significance of Ikaros or IKZF1 in SLE, and highlighted its potential role as a disease biomarker and a therapeutic target.

MATERIALS AND METHODS

Search Strategy

Articles related to Ikaros and IKZF1 in the context of SLE were primarily sought through a structured systematic search using MeSH terms on MEDLINE, Cochrane Library, Ovid from database inception until April 2023. The following terms: "Ikaros",

"lupus", and "IKZF1" were used in the search strategy. To achieve extensive coverage without missing any relevant articles, pertinent articles obtained from searching references in the articles found in the primary search were also reviewed. The search strategy was performed by N.S.R and S.S.S. This systematic review was conducted by the standards set by the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) Statement (Moher et al. 2009).

Selection Criteria

The main objective of this review was to summarise the clinical significance of the IKZF1 or Ikaros in patients with SLE. Therefore, all human studies written in English that studied the role and clinical significance of IKZF1 or Ikaros in adult-onset SLE (>16 years old) were included-any study design including cohort, case-control, cross-sectional, observational studies, meta-analysis, and randomised controlled trials. We excluded studies published before 2000, articles in other languages, animal studies, abstracts or proceedings, case reports or case series, editorials, and review articles. The evidence collection framework was summarised in Figure 2.

Data Extraction

After compiling the relevant studies, the authors extracted the relevant data from each paper, including year

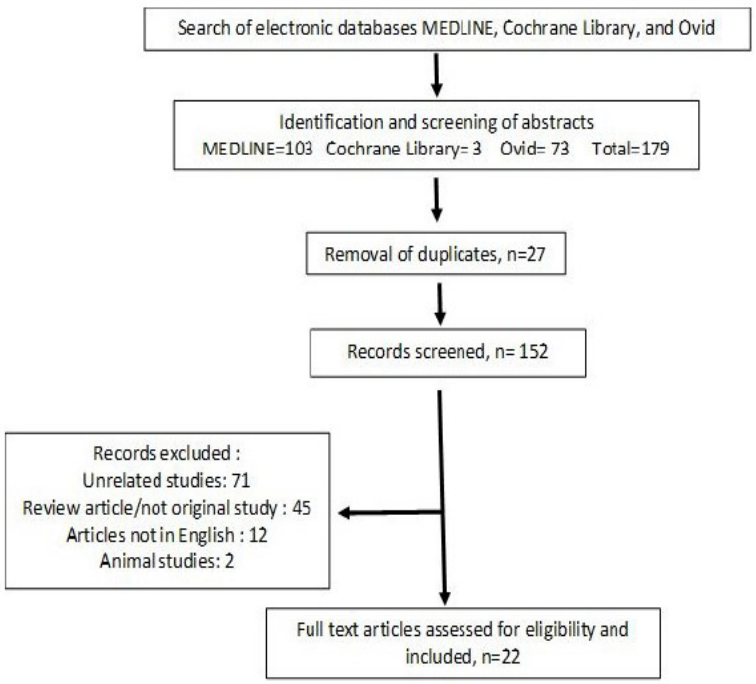

FIGURE 2: Search strategy and evidence collection framework

of publication, number of subjects, study population/country, study methodology and their relevant key findings. Four reviewers (N.A.J, L.K, R.M, M.S.M, S.R and S.S.S) independently screened the articles and solved disagreements by discussion.

Data Analysis

Upon information extraction, meta-analysis was decided as an unlikely option to answer the research question. This was due to the heterogeneity of the various study selection and outcome measurements among the included articles. Therefore, a narrative synthesis of the evidence was chosen to analyse these studies. Each included studies or article were tabulated to highlight the clinical associations or significance of SLE with Ikaros or IKZF1.

RESULTS

IKZF1 Gene Polymorphisms in SLE

The first genome-wide association studies (GWAS) by Han et al. (2009) first confirmed the significant association between rs4917014 in IKZF1 among the Chinese Han SLE population, OR 0.7, $p=2.75 \times 10^{-23}$. This finding was further replicated in other Chinese populations (Chen et al. 2020; Dang et al. 2014; Leng et al. 2012), with OR of approximately 0.6-0.7 and in Malay, with OR of 0.39 (Molineros et al. 2014). The rs4917014 in IKZF1 was also found to be significantly associated with SLE in Caucasian-Swedish (Wang et al. 2013) and European (Bentham et al. 2015), with OR 1.22 and 1.18 respectively. Other IKZF1 SNPs that were documented to be associated with SLE include rs921916 in Sweden and the US (Gateva et al. 2009), rs2366293 in the UK (Cunninghame Graham et al. 2011), with OR 1.15 and 1.2, respectively. However, the rs2366293 in IKZF1 was not replicated in the Chinese SLE population (You et al. 2015).

A large trans-ancestral SLE ImmunoChip study involving African (AA), European (EA), and Hispanic-Amerindian (HA) populations revealed significant associations between five IKZF gene variants (rs4917014, rs11185603, rs4385425, rs876036 and rs876037) with AA and EA, with OR 0.7-0.9. However, among the HA population, only three of these variants were significant (rs4917014, rs11185603, and rs876037) with OR 0.8-0.9, p= 0.02 (Langefeld et al. 2017). A comparison of GWAS between East Asian and European populations showed that the rs4917014 variant had a significantly stronger effect in East Asians (OR = 1.33, $p = 5.18^{-29}$) than in Europeans (OR = 1.16, $P = 1.34^{-06}$) (Wang et al. 2021). Table 1 summarised the studies on IKZF1 gene polymorphisms in SLE patients.

Associations of IKZF1 Polymorphisms with Gene Expression and Clinical Phenotype in SLE

Among Chinese patients, the mRNA expression of IKZF was found to be significantly lower in PBMCs (Hu et al. 2011; Zhang et al. 2017) and

TABLE 1: Summary of studies on IKZF1 gene polymorphisms in SLE

Authors (year of publication)	**Country/ Ethnic**	**Study design/ Method**	**Sample size**	**Variant** (RS number) Allele	OR/ P value
Han et al. (2009)	Han Chinese	Case-control GWAS study	4199 SLE, 8255 controls	rs4917014 C/A	OR 0.72 (0.68-0.77), $p = 2.75 \times 10^{-23}$
Gateva et al. (2009)	Sweden and US	Case control replication study	1963 SLE, 4329 control	rs921916 Risk allele C	OR 1.15 (1.07-1.23), $p = 2.0 \times 10^{-6}$ (Combined)
Cunninghame Graham et al. (2011)	UK	Case control replication study	870 SLE and 5551 controls	rs2366293 Risk allele G	OR 1.20, $p = 8.77 \times 10^{-3}$
Leng et al. (2012)	Chinese	Case control replication study	858 SLE and 967 controls	rs4917014 G/T	0.74 (0.64-0.85), $p = 2.56 \times 10^{-5}$
Wang et al. (2013)	Caucasians (Sweden, Finland)	Case control replication study	1129 SLE and 2060 controls	rs4917014 A/C	Swedish: OR 1.22 (1.09-1.38), $p = 8.8 \times 10^{-4}$ Finland: OR 0.93 (0.72-1.21), p = 0.61
Molineros et al. (2014)	Malaysia (Chinese & Malay)	Case control replication study	347 SLE cases and 356 controls	rs4917014	Malay: OR 0.39 (0.21-0.74), $p = 3.25 \times 10^{-3}$ Chinese: OR 0.79 (0.61-1.03), p = 0.07
				rs11185603 G/C	Malay : OR 0.39 (0.21-0.74), $p = 3.25 \times 10^{-3}$ Chinese: OR 0.79 (0.61-1.03), p = 0.0761
Dang et al. (2014)	Northern Han Chinese	Case control replication study	946 SLE and 576 healthy	rs4917014 G/T Risk allele G	0.709 (0.578-0.870), P = 0.001
Bentham et al. (2015)	European ancestry	Case control replication study and meta-analysis with previous GWAS datasets	7,219 SLE and 15,991 controls	rs4917014 G<T Risk Allele T	OR (1.18 1.13 - 1.24), $p = 6.39^{-14}$
				rs11185603 Risk Allele C	OR 1.15, $p = 4.36^{-7}$
You et al. (2015)	China	Case control replication study	395 SLE patients and 378 healthy controls	rs2366293	No significant associations

Langefeld et al. (2017)	African (AA) European (EA) Hispanic Amerindian (HA)	Case control replication study	27,574 SLE cases and controls from three ancestral groups (AA: 2,970 cases, 2,452 controls; EA: 6,748 cases, 11,516 controls; HA: 1,872 cases and 2,016 controls)	**Variant/Ethnic**	**AA (OR, p value)**	**EA (OR, p value)**	**HA (OR, p value)**
				rs4917014	0.728, 1.48×10^{-5}	0.866, 3.67×10^{-9}	0.897, 0.02
				rs11185603	0.742, 4.29×10^{-5}	0.870, 8.99×10^{-9}	0.897, 0.02
				rs4385425	0.831, 1.83×10^{-5}	0.872, 1.51×10^{-9}	0.934, 0.14
				rs876036	0.890, 9.52×10^{-3}	0.869, 7.49×10^{-9}	0.913, 0.053
				rs876037	0.731, 1.87×10^{-5}	0.873, 2.23×10^{-8}	0.897, 0.02
Chen et al. (2020)	Han Chinese	Case control replication study	400 SLE patients and 676 healthy controls	rs4917014/G rs4132601/G rs11980379/C	0.75 (0.62 - 0.92), p<0.005 0.65 (0.50 - 0.84), p<0.001 0.65 (0.50 - 0.84), p<0.001		
Wang et al. (2021)	8252 Han Chinese descent from Hong Kong (HK), Guangzhou (GZ) and Central China (CC) and European	Case control replication study in Chinese and meta-analysis with previous datasets	11,283 SLE cases and 24,086 controls	rs4917014 Risk allele T	East Asian: 1.33, p = 5.18E-29 European 1.16, p = 1.34E-06		

tubulointerstitial renal tissues of lupus nephritis patients (Zhang et al. 2017). In contrast, a higher IKZF1 mRNA expression was found in the PBMCs of a small cohort of SLE patients in the US (Schafer et al. 2018). There were only two studies that had explored the association between the Ikaros gene expression with IKZF1 genotypes, in both failed to demonstrate any significant finding (Dang et al. 2014; Hu et al. 2011).

Studies on the associations between the IKZF1 or Ikaros with SLE clinical phenotypes in SLE were limited to the Han Chinese SLE population (Chen et al. 2020; He et al. 2010). The SNP rs4917014 of IKZF1 was demonstrated to be associated with increased susceptibility to renal involvement or lupus nephritis (OR = 1.13, p = 0.02). In contrast, this variant was found to be protective in cutaneous lupus (OR = 0.83, p = 0.00038) (He et al. 2010). In addition, another protective allele A of rs1456896 IKZF1 was associated with LN among another Chinese cohort (OR 0.8) (Zhang et al. 2017). However, a different direction was found with cutaneous lupus (OR = 0.83, p = 0.00038) (He et al. 2010). Han Chinese SLE patients with the GG genotype of rs4917014 were also found to have a lower frequency of hematological disorder than the patients with TG and TT genotypes (Chen et al. 2020). Only one study explored the correlation between IKZF1 with disease activity and this study found no correlation between IKZF1 mRNA expression levels and SLE disease activity index (SLEDAI) scores among Chinese patients (Hu et al. 2011).

A study by Duque-Suárez et al. (2018) measured the gene expression of several exons of IKZF1, which was conducted among the Latin-Americans with various autoimmune diseases including SLE. This study suggested that different Ikaros isoforms presented in rheumatoid arthritis and SLE, as SLE patients had lower expression levels for IE3–4, while RA had the highest expression levels of this region. Table 2 summarised the associations of IKZF1 gene polymorphisms, RNA expression and clinical manifestations in SLE patients.

Ikaros as a Therapeutic Target in SLE

Given the substantial role of Ikaros in SLE, there has been an interest in targeting the protein as a therapeutic target in SLE. Iberdomide is a cereblon modulator that has a high affinity binding to cullin-RING E3 ubiquitin ligase 4 complex which subsequently promotes ubiquitination and degradation of Ikaros and Aiolos (Merrill et al. 2022; Nakayama et al. 2017). To date, there were one phase 1 (Schafer et al. 2018) and two phase 2 clinical trials on Iberdromide in SLE (Furie et al. 2022; Merrill et al. 2022), which showed safety and efficacy of the treatment in SLE. In addition, Iberdromide-induced depletion of Ikaros is shown to have multiple immunomodulatory effects including increased levels of regulatory T cells, interleukin-2, and interleukin-10, and decreased levels of pro-inflammatory type I interferon pathways and B-cell differentiation (Lipsky et al. 2022;

TABLE 2: Summary of studies on the associations between IKZF1 gene polymorphisms with gene expression and clinical characteristics of SLE

Authors (Year of publication)	Subjects (number and ethnic/ population)	SNP	mRNA expression	Clinical characteristics
He et al. (2010)	Case-control of SLE cases (4199 SLE cases) Han Chinese	rs4917014	N/A	Significant association between rs4917014 of IKZF1 with: - lupus nephritis (OR = 1.13, p = 0.02) - malar rash (OR = 0.83, p = 0.00038)
Hu et al. (2011)	Case-control (60 SLE cases and 60 healthy controls) Han Chinese	rs4917014	-↓ in PBMCs of SLE compared to controls (0.156 ± 0.14 vs 0.54 ± 0.40, p < 0.001) -no correlation with genotype	-No correlation between IKZF1 mRNA expression levels with disease activity (SLEDAI score)
Dang et al. (2014)	Cross-sectional 36 SLE Han Chinese	rs4917014	-no significant correlation between RNA expression and genotypes	N/A
Zhang et al. (2017)	Case-control (i) Genotyped 500 LN patients and 500 healthy controls, and replication study in 798 LN and 704 healthy controls (ii) mRNA in PBMCs (61 LN vs controls) and renal tissue (32 LN vs 15 pre-transplate living donor controls) Han Chinese	rs1456896	-↓ in PMBCs LN (67843.41 ± 1334.21 vs.9040.20 ± 773.33 p = 2.85 x 10^{-4}) -↓ in tubulointerstitial samples for LN (4.17 ± 0.10 vs. 4.28 ± 0.14, p = 5.00 x 10^{-3})	- Minor allele A associated with LN (OR 0.80,p= 1.36 10 3) -Genotype AA have later onset, lesser male, lower proteinuria levels, higher eGFR levels, lower serum creatinine levels, lower SLEDAI scores, a lower ratio of histological classes III and IV, and a higher treatment remission rate (In 279 LN patients who had at least 1 year follow-up)
Schafer et al. (2018)	PBMCs (11 SLE vs 10 healthy controls)	N/A	Higher IKZF1 mRNA expression in SLE (2.1-fold)	N/A
Chen et al. (2020)	1)Genotyped 400 SLE patients and 676 healthy controls Han Chinese	rs4917014 rs11980379 rs4132601	N/A	Significant associations between: -rs4132601 and malar rash (P=0.01) -rs4917014 and hematological disorder (P=0.005)

AIDs: autoimmune diseases; PBMCs: peripheral blood mononuclear cells; RA: rheumatoid arthritis; SLE: systemic lupus erythaematosus; SNP: Single nucleotide polymorphism; SSc: systemic sclerosis; SS: Sjögren's syndrome; SLEDAI: SLE disease activity index; LN: lupus nephritis; IKZF1: Ikaros family zinc finger protein 1; OR: Odd ratio; p: probability value; eGFR: Estimated glomerular filtration rate; PBMC: peripheral blood mononuclear cells; TLR7: Toll-like receptor 7; ATEP: Active treatment extension phase; pDC: plasmacytoid dendritic cells DNA: deoxyribonucleic acid; IFN: interferon
↑ : increased expression; ↓ : decreased expression

Nakayama et al. 2017; Schafer et al. 2018). Table 3 summarised the in vitro and clinical phases 1 and 2 of iberdomide treatment in SLE.

DISCUSSION

SLE is a complex disease that involves multiple immune cascades and cell types, which contributes to the clinical heterogeneity of this disease. Despite strong evidence to support the role of IKZF1 genes in SLE, their functional effects in the SLE immune pathogenesis and clinical phenotypes remain elusive. The function of Ikaros in immune cells is mainly derived and extrapolated from the mice models. It has been demonstrated that Ikaros is essential for the generation and differentiation of B cells to antibody-secreting plasma cells and plasmacytoid dendritic cells (pDCs) (Allman et al. 2006; Kirstetter et al. 2002; Sellars et al. 2011). These cells are crucial in the development of autoantibodies and type I IFN producers in SLE. Ikaros is also a transcriptional repressor of the IL-2 gene in CD4+ T cells (Thomas et al. 2007). In SLE, the inability to generate normal amounts of IL-2 upon activation is considered a hallmark of T cells from patients with SLE (Mak 2022). It is suggested that regulation of T-cells by Ikaros also occurs via repressing the serine/threonine protein phosphatase 2A (PP2A) expression in a study involving healthy subjects (Nagpal et al. 2014). This supports the possible role of Ikaros in this pathway, as an earlier study has demonstrated an elevated level of protein and catalytic activity of PP2A in T cells isolated from SLE patients, and this in turn partly responsible for the decreased production of anti-inflammatory cytokine, IL-2 (Katsiari et al. 2005). Other evidence suggested that Ikaros is essential in regulating the transcription of STAT4, which was reported to be associated with SLE (Good et al. 2009; Yap et al. 2005). Ikaros also regulates numerous signal activators and transducers, including IFN-α producers (Hu et al. 2013).

Apart from SLE, IKZF1 has been reported to be associated with another autoimmune disease (AID), but with different gene variants such as rs1456896 in Crohn's disease, rs1456896 in ulcerative Colitis, and rs201847125 in multiple sclerosis. However, it is important to note that the associated IKZF1 gene variant in SLE, rs4917014 has limited linkage disequilibrium (LD) ($r2 = 0.25$) and has higher minor allele frequency (MAF) compared to the aforementioned variants in other AID among Europeans (Vyse & Cunninghame Graham 2020). Results from various ethnic and populations suggest that some of the IKZF1 gene variants for SLE may be population or ethnic-specific. It is important to note there are differences in the IKZF1 gene variants between Chinese and Caucasian populations. This suggests the presence of other environmental risk factors and differences in the clinical phenotypes between the two populations. Indeed, several distinct phenotypes were found to be associated with different IKZF1 gene variants, such as rs4917014 with lupus nephritis (OR = 1.13) and malar rash (OR = 0.83) among Han Chinese population (He et al. 2010).

TABLE 3: Summary of studies on the potential therapeutic target of Ikaros in SLE using iberdromide

Author (Year of publication)	Type of Study	Study design/ population	Objective	Method	Key Findings
Nakayama et al. (2017)	In-vitro	SLE (n=7) and HCs / US	To study the effects of iberdomide on treated PBMCs from HCs and SLE patients	-Measurement of Ikaros and Ailos protein levels in B cell subsets after in vitro treatment with iberdromide	-Iberdromide reduced Ikaros and Ailos protein levels in the B cell subsets measured from both HCs and SLE patients within 24 h in a dose-dependent manner. -No difference in Ikaros protein levels between SLE and HCs
Schafer et al. (2018)	In vitro and clinical phase 1 iberdromide study	-Phase 1 clinical iberdromide study: 56 healthy volunteers / US	-To study the effects of iberdomide on healthy controls and SLE autoantibody production in vitro -To study the pharmacology effects of iberdomide in SLE patient cells and in a phase 1 healthy volunteer	- Measurements of Ikaros protein levels -Measurements of Anti-dsDNA and anti-phospholipid autoantibodies in SLE PBMC cultures treated for 7 days with iberdomide -Phase 1 : Healthy volunteers were randomised to a single dose of iberdomide (0.03–6 mg, n=6 across seven cohorts)	- Treatment of HCs' whole blood with increasing concentrations of iberdomide 1–100 nM significantly reduced Ikaros protein levels in B cells, T cells and monocytes, but not granulocytes - In cultures of PBMCs from patients with SLE (n=10), iberdomide inhibited anti-dsDNA and anti-phospholipid IgM autoantibody production -Phase 1: iberdomide administration resulted in increased IL-2 production and decreased IL-1β production in whole blood ex vivo -no serious AEs
Rivellese et al. (2021)	In-vitro	41 SLE patients/ UK	-To evaluate the effects of iberdomide on the activation and differentiation of B-cells from patients with SLE. -TO study the impact of Iberdomide on gene expression in naïve B cells and plasmablasts	- CD19+ B-cells isolated from the peripheral blood of patients with SLE (n=41) -In vitro stimulation with TLR7 agonist resiquimod in combination with IFN for 5 days, without or with iberdromide	-Iberdomide inhibits TLR7-mediated activation and differentiation of SLE B cells and inhibit production of ANA - Treatment of SLE B cells with iberdomide significantly affects gene expression downstream of Ikaros

Furie et al. (2022)	Clinical Phase 2 (multicentre, double-blind, placebo-controlled study)	42 SLE patients/ 64% Caucasian	To evaluate safety, pharmacokinetics, pharmacodynamics and efficacy of iberdomide in patients with SLE.	A 12-week dose-escalation study in active SLE followed by a 2-year, open-label ATEP	-Improvement of PGA and CLASI activity scores improved relative to baseline and placebo in all iberdomide groups, with a trend toward continued score improvements in the ATEP. - In the dose-escalation phase, iberdomide treatment resulted in dose-dependent reductions in total B cells and pDCs in blood.
Merrill et al. (2022)	Clinical Phase 2 (Randomised, placebo-controlled, double-blind study)	SLE patients (n=288)/ Multi-centre (US, Canada, Europe, South America, Mexico, and Russia)	To evaluate iberdomide (0.45 mg) efficacy (SRI-4) and safety in SLE. To conduct exploratory analysis of SRI-4 response in groups defined according to IKZF1 gene-expression at baseline (high vs. low)	SLE patients were randomly assigned in a 2:2:1:2 ratio to receive oral iberdomide (at a dose of 0.45, 0.30, or 0.15 mg) or placebo once daily for 24 weeks, in addition to standard medications.	-↑ SRI-4 response in iberdromide vs placebo. -↓ B-cell counts, pDCs, and Anti-ds DNA and higher levels of IL-2 and regulatory T cells in iberdromide group -No difference in the SRI-4 responses in patients with high Ikaros expression at baseline -Iberdomide-associated AEs : UTI, URTI and neutropenia.
Lipsky et al. (2022)	Clinical Phase 2 (Randomised, placebo-controlled, double-blind study)	288 SLE patients from the the phase 2, multinational, randomised, placebo-controlled, double-blind study	To evaluate the pharmacodynamics and pharmacokinetics of oral iberdomide in patients with active SLE	SLE patients were randomly assigned in a 2:2:1:2 ratio to receive oral iberdomide (at a dose of 0.45, 0.30, or 0.15 mg) or placebo once daily for 24 weeks, in addition to standard medications.	Iberdromide group vs placebo: -↓ CD19+ and CD20+ B cells, expression of gene modules representing the type I IFN, Ikaros eQTL type I IFN gene signature and B cell pathways -↑ CD8+ cytotoxic T cells, IL-2 level -↑ expression of Ikaros genes from baseline

AEs: Adveres events; ANA: anti-nuclear antibody; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index; HCs: healthy controls; IL-2: Interleukin 2; pDCs: plasmacytoid dendritic cells; PGA: Physician's Global Assessment; SLE: Sytemic lupus erythematosus; SRI-4: SLE Responder Index; URTI: upper respiratory tract infection; UTI: urinary tract infection; PBMC: peripheral; blood mononuclear cells; TLR7: Toll-like receptor 7; ATEP: active treatment extension phase; pDC: plasmacytoid dendritic cells; DNA: deoxyribonucleic acid; IFN: interferon
↑ : increased expression; ↓ : decreased expression

Our preliminary genotype study in the Malaysian multi-ethnic cohort also found a significant association between the variant with lupus nephritis in Malay patients (OR 3.29 p=0.023) (Abd Talib et al. 2022).

The mRNA expressions in the PBMCs of SLE patients also varied between different ethnicities or populations. The mRNA expressions of IKZF were found to be significantly lower in PBMCs (Hu et al. 2011; Zhang et al. 2017) and tubulointerstitial renal tissues of lupus nephritis in Chinese (Zhang et al. 2017). In contrast, a higher IKZF1 mRNA expression was found in the PBMCs of a small cohort of SLE patients in the US (Schafer et al. 2018). The expressions were also not correlated with the IKZF gene variants and disease activity (Hu et al. 2011). With regards to the Ikaros protein levels, Nakayama et al. (2017) found no difference in the levels between SLE and healthy controls, but the study was limited to a small sample size. However, it is important to note that SLE patients have different Ikaros isoform expressions compared to healthy controls and other rheumatic diseases, suggesting that the presence of different isoforms in SLE can serve as a biomarker (Duque-Suárez et al. 2018). A recent study has demonstrated that the risk alleles in IKZF1 did not cause amino acid changes in the Ikaros protein and the findings suggest that the risk alleles acted via epigenetic mechanisms, such as DNA methylation and DNA hypersensitivity (Vyse & Cunninghame Graham 2020).

In SLE patients, B cell differentiation into plasmablasts was blocked upon in vitro inhibition of IKZF1/IKZF3 inhibition by iberdomide, a cereblon ligand that promotes degradation of Ikaros and Aiolos (Manou-Stathopoulou et al. 2019). Anti-dsDNA and anti-phospholipid autoantibodies were also found to be reduced with in vitro treatment PBMC cultures of SLE patients with iberdomide (Schafer et al. 2018). Based on these preliminary findings, Iberdomide is currently in the pipeline as a therapeutic target for SLE in phase I (Schafer et al. 2018) and II clinical trials (Furie et al. 2022). However, although Ikaros has a potential therapeutic target in SLE (Boulougoura & Tsokos 2022), it is still not known which sub-set of SLE patients will have a good response to this treatment.

The limitation of this review is that although previous studies have discovered the association of gene variants of IKZF1 and its possible gene effects in SLE manifestations, it needs to be highlighted that the disease manifestations could be influenced by other possible environmental factors like as well. Genetic susceptibility only poses 20% of SLE risk. However, other environmental factors like ultraviolet (UV) light exposure, hormonal changes, smoking, vaccinations, medications and occupational status were not investigated together in previous studies. Most of the reviewed studies have not emphasised the gene-environment interactions by assessing the trends of physical activities, UV light exposures and diet intake by SLE patients. Therefore, future analyses are needed in assessing the gene-environment interaction to discover

the missing heritability of genetic risks and pathogenesis of IKZF1 in SLE manifestation.

Discovering that the gene variants of IKZF1 may pose functional effects in the upregulation of the Type 1 IFN gene in SLE, the genotype calls of the gene variant may pose a possible functional validation in SLE diagnosis biomarker. Identifying the roles of SNPs in IKZF1 and its relations with other genes could offer a targeted regimen plan for suppressing the uncontrolled expression of Type 1 IFN in SLE patients. This could enhance the development of medication aside from Iberdomide and personalised therapeutic intervention for SLE patients with minimal side effects.

CONCLUSION

In conclusion, Ikaros transcription factors are an important transcription factor in regulating the immune cells' function. IKZF1 genes that encode the protein are well established to be significantly associated with SLE across different ethnicities. However, the exact role and function of the gene variants and their protein in determining the clinical disease activity, phenotypes, biomarkers, and treatment still warrant further research.

FUNDING

This research was funded by Fundamental Grant Faculty of Medicine, Universiti Kebangsaan Malaysia (FF-2022-101)

REFERENCES

Abd Talib, A.K.A., Tan, S.C., Azizan, E.A., Shaharir, S.S., Abdul Murad, N.A. 2021. Associated genetic polymorphisms and clinical manifestations in systemic lupus erythematosus in Asian populations - A systematic literature review. *Med J Malaysia* **76**(4): 541-50.

Abd Talib, A.K.A., Shaharir, S.S., Abdul Murad, N.A., Abdullah, N., Azizan, E.A., Abdul Gafor, A.H., Mustafar, R., Mohamed Said, M.S., Rajalingham, S., Jamal, A.R.A., Abdul Latiff, Z. 2022. POS0394 Validation of the SLE susceptible gene loci in the multi-ethnic malaysian systemic lupus erythematosus (SLE) cohort and their associations with clinical manifestation. *Ann Rheum Dis* **81**(Suppl 1): 453.

Allman, D., Dalod, M., Asselin-Paturel, C., Delale, T., Robbins, S.H., Trinchieri, G., Biron, C.A., Kastner, P., Chan, S.. 2006. Ikaros is required for plasmacytoid dendritic cell differentiation. *Blood* **108**(13): 4025-34.

Belot, A., Rice, G.I., Omarjee, S.O., Rouchon, Q., Smith, E.M.D., Moreews, M., Tusseau, M., Frachette, C., Bournhonesque, R., Thielens, N., et al. 2020. Contribution of rare and predicted pathogenic gene variants to childhood-onset lupus: A large, genetic panel analysis of British and French cohorts. *Lancet Rheumatol* **2**(2): e99-e109.

Bentham, J., Morris, D.L., Graham, D.S.C., Pinder, C.L., Tombleson, P., Behrens, T.W., Martín, J., Fairfax, B.P., Knight, J.C., Chen, L., et al. 2015. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet* **47**(12): 1457-64.

Boast, B., Nunes-Santos, C.J., Kuehn, H.S., Rosenzweig, S.D. 2021. Ikaros-associated diseases: From mice to humans and back again. *Front Pediatr* **9**: 705497.

Boulougoura, A., Tsokos, G.C. 2022. Ikaros, Aiolos and other moving targets to treat SLE. *Nat Rev Rheumatol* **18**(9): 499-500.

Chen, L., Niu, Q., Huang, Z., Yang, B., Wu, Y., Zhang, J. 2020. IKZF1 polymorphisms are associated with susceptibility, cytokine levels, and clinical features in systemic lupus erythematosus. *Medicine (Baltimore)* **99**(41): e22607.

Chen, Q., Shi, Y., Chen, Y., Ji, T., Li, Y., Yu, L. 2019. Multiple functions of Ikaros in hematological malignancies, solid tumor and autoimmune diseases. *Gene* **684**: 47-52.

Conserva, M.R., Redavid, I., Anelli, L., Zagaria, A., Tarantini, F., Cumbo, C., Tota, G., Parciante, E., Coccaro, N., Minervini, C.F., Minervini, A., Specchia, G., Musto, P., Albano, F. 2023. IKAROS in acute leukemia: A positive influencer or a mean hater? *Int J Mol Sci* **24**(4): 3282.

Cunninghame Graham, D.S., Morris, D.L., Bhangale, T.R., Criswell, L.A., Syvänen, A.C., Rönnblom, L., Behrens, T.W., Graham, R.R., Vyse, T.J. 2011. Association of NCF2, IKZF1, IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. *PLoS Genet* **7**(10): e1002341.

Dang, J., Shan, S., Li, J., Zhao, H., Xin, Q., Liu, Y., Bian, X., Liu, Q. 2014. Gene-gene interactions of IRF5, STAT4, IKZF1 and ETS1 in systemic lupus erythematosus. *Tissue Antigens* **83**(6): 401-8.

Duque-Suárez, L.K., Quintana, L.G., Coral-Alvarado, P.X., Méndez, P.A., Groot deRestrepo, H., López-Segura, V. 2018. IKAROS expression profiles characterize different autoimmune diseases. *Transl Med Commun* **3**(1): 11.

Felten, R., Sagez, F., Gavand, P.E., Martin, T., Korganow, A.S., Sordet, C., Javier, R.M., Soulas-Sprauel, P., Rivière, M., Scher, F., Poindron, V., Guffroy, A., Arnaud, L. 2019. 10 most important contemporary challenges in the management of SLE. *Lupus Sci Med* **6**(1): e000303.

Furie, R.A., Hough, D.R., Gaudy, A., Ye, Y., Korish, S., Delev, N., Weiswasser, M., Zhan, X., Schafer, P.H., Werth, V.P. 2022. Iberdomide in patients with systemic lupus erythematosus: A randomised, double-blind, placebo-controlled, ascending-dose, phase 2a study. *Lupus Sci Med* **9**(1): e000581.

Gateva, V., Sandling, J.K., Hom, G., Taylor, K.E., Chung, S.A., Sun, X., Ortmann, W., Kosoy, R., Ferreira, R.C., Nordmark, G., et al. 2009. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. *Nat Genet* **41**(11): 1228-33.

Georgopoulos, K., Bigby, M., Wang, J.H., Molnar, A., Wu, P., Winandy, S., Sharpe, A. 1994. The Ikaros gene is required for the development of all lymphoid lineages. *Cell* **79**(1): 143-56.

Georgopoulos, K., Moore, D.D., Derfler, B. 1992. Ikaros, an early lymphoid-specific transcription factor and a putative mediator for T cell commitment. *Science* **258**(5083): 808-12.

Good, S.R., Thieu, V.T., Mathur, A.N., Yu, Q., Stritesky, G.L., Yeh, N., O'Malley, J.T., Perumal, N.B., Kaplan, M.H. 2009. Temporal induction pattern of STAT4 target genes defines potential for Th1 lineage-specific programming. *J Immunol* **183**(6): 3839-47.

Han, J.W., Zheng, H.F., Cui, Y., Sun, L.D., Ye, D.Q., Hu, Z., Xu, J.H., Cai, Z.M., Huang, W., Zhao, G.P., et al. 2009. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat Genet* **41**(11): 1234-7.

He, C.F., Liu, Y.S., Cheng, Y.L., Gao, J.P., Pan, T.M., Han, J.W., Quan, C., Sun, L.D., Zheng, H.F., Zuo, X.B., Xu, S.X., Sheng, Y.J., Yao, S., Hu, W.L., Li, Y., Yu, Z.Y., Yin, X.Y., Zhang, X.J., Cui, Y., Yang, S. 2010. TNIP1, SLC15A4, ETS1, RasGRP3 and IKZF1 are associated with clinical features of systemic lupus erythematosus in a Chinese Han population. *Lupus* **19**(10): 1181-6.

Hoshino, A., Okada, S., Yoshida, K., Nishida, N., Okuno, Y., Ueno, H., Yamashita, M., Okano, T., Tsumura, M., Nishimura, S., et al. 2017. Abnormal hematopoiesis and autoimmunity in human subjects with germline IKZF1 mutations. *J Allergy Clin Immunol* **140**(1): 223-31.

Hu, S.J., Wen, L.L., Hu, X., Yin, X.Y., Cui, Y., Yang, S., Zhang, X.J. 2013. IKZF1: A critical role in the pathogenesis of systemic lupus erythematosus? *Mod Rheumatol* **23**(2): 205-9.

Hu, W., Sun, L., Gao, J., Li, Y., Wang, P., Cheng, Y., Pan, T., Han, J., Liu, Y., Lu, W., Zuo, X., Sheng, Y., Yao, S., He, C., Yu, Z., Yin, X., Cui, Y., Yang, S., Zhang, X. 2011. Down-regulated expression of IKZF1 mRNA in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. *Rheumatol Int* **31**(6): 819-22.

Jakes, R.W., Bae, S.C., Louthrenoo, W., Mok, C.C., Navarra, S.V., Kwon, N. 2012. Systematic review of the epidemiology of systemic lupus erythematosus in the Asia-Pacific region: Prevalence, incidence, clinical features, and mortality. *Arthritis Care Res* **64**(2): 159-68.

Katsiari, C.G., Kyttaris, V.C., Juang, Y.T., Tsokos, G.C. 2005. Protein phosphatase 2A is a negative regulator of IL-2 production in patients with systemic lupus erythematosus. *J Clin Invest* **115**(11): 3193-204.

Kaul, A., Gordon, C., Crow, M.K., Touma, Z., Urowitz, M.B., van Vollenhoven, R., Ruiz-Irastorza, G., Hughes, G. 2016. Systemic lupus erythematosus. *Nat Rev Dis Primers* **2**: 16039.

Kirstetter, P., Thomas, M., Dierich, A., Kastner, P., Chan, S. 2002. Ikaros is critical for B cell differentiation and function. *Eur J Immunol* **32**(3): 720-30.

Kuehn, H.S., Niemela, J.E., Stoddard, J., Mannurita, S.C., Shahin, T., Goel, S., Hintermeyer, M., Heredia, R.J., Garofalo, M., Lucas, L., et al. 2021. Germline IKAROS dimerization haploinsufficiency causes hematologic cytopenias and malignancies. *Blood* **137**(3): 349-63.

Kuehn, H.S., Nunes-Santos, C.J., Rosenzweig, S.D. 2021. IKAROS-associated diseases in 2020: Genotypes, phenotypes, and outcomes in primary immune deficiency/inborn errors of immunity. *J Clin Immunol* **41**(1): 1-10.

Langefeld, C.D., Ainsworth, H.C., Cunninghame, G.D.S., Kelly, J.A., Comeau, M.E., Marion, M.C., Howard, T.D., Ramos, P.S., Croker, J.A., Morris, D.L., et al. 2017. Transancestral mapping and genetic load in systemic lupus erythematosus.

Nat Commun **8**: 16021.

Leng, R.X., Wang, W., Cen, H., Zhou, M., Feng, C.C., Zhu, Y., Yang, X.K., Yang, M., Zhai, Y., Li, B.Z., Wang, X.S., Li, R., Chen, G.M., Chen, H., Pan, H.F., Ye, D.Q. 2012. GenegGene and gene-sex epistatic interactions of MiR146a, IRF5, IKZF1, ETS1 and IL21 in systemic lupus erythematosus. *PLOS ONE* **7**(12): e51090.

Li, Z., Perez-Casellas, L.A., Savic, A., Song, C., Dovat, S. 2011. Ikaros isoforms: The saga continues. *World J Biol Chem* **2**(6): 140-5.

Lipsky, P.E., Vollenhoven, R.V., Dörner, T., Werth, V.P., Merrill, J.T., Furie, R., Petronijevic, M., Velasco-Zamora, B., Majdan, M., Irazoque-Palazuelos, F., et al. 2022. Biological impact of iberdomide in patients with active systemic lupus erythematosus. *Ann Rheum Dis* **81**(8): 1136-42.

Mak, A. 2022. T Cells, interleukin-2 and systemic lupus erythematosus-from pathophysiology to therapy. *Cells* **11**(6): 980.

Manou-Stathopoulou, S., Rivellese, F., Mauro, D., Goldmann, K., Pyne, D., Schafer, P., Bombardieri, M., Pitzalis, C., Lewis, M. 2019. 235 IKZF1 and IKZF3 inhibition impairs B cell differentiation and modulates gene expression in systemic lupus erythematosus. *Lupus Sci Med* **6**(Suppl 1): A174-A5.

Merrill, J.T., Werth, V.P., Furie, R., van Vollenhoven, R., Dörner, T., Petronijevic, M., Velasco, J., Majdan, M., Irazoque-Palazuelos, F., Weiswasser, M., et al. 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol* **62**(10): 1006-12.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* **339**(b2535): 1-8.

Molineros, J.E., Chua, K.H., Sun, C., Lian, L.H., Motghare, P., Kim-Howard, X., Nath, S.K. 2014. Evaluation of SLE susceptibility genes in Malaysians. *Autoimmune Dis* **2014:** 305436.

Molnár, A., Georgopoulos, K. 1994. The Ikaros gene encodes a family of functionally diverse zinc finger DNA-binding proteins. *Mol Cell Biol* **14**(12): 8292-303.

Molnár, A., Wu, P., Largespada, D.A., Vortkamp, A., Scherer, S., Copeland, N.G., Jenkins, N.A., Bruns, G., Georgopoulos, K. 1996. The Ikaros gene encodes a family of lymphocyte-restricted zinc finger DNA binding proteins, highly conserved in human and mouse. *J Immunol* **156**(2): 585-92.

Mullighan, C.G., Su, X., Zhang, J., Radtke, I., Phillips, L.A., Miller, C.B., Ma, J., Liu, W., Cheng, C., Schulman, B.A., et al. 2009. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med* **360**(5): 470-80.

Nagpal, K., Watanabe, K.S., Tsao, B.P., Tsokos, G.C. 2014. Transcription factor Ikaros represses protein phosphatase 2A (PP2A) expression through an intronic binding site. *J Biol Chem* **289**(20): 13751-7.

Nakayama, Y., Kosek, J., Capone, L., Hur, E.M., Schafer, P.H., Ringheim, G.E. 2017. Aiolos overexpression in systemic lupus erythematosus B cell subtypes and BAFF-induced memory B cell differentiation are reduced by CC-220 modulation of cereblon activity. *J Immunol* **199**(7): 2388-407.

Nam, S.W., Lee, K.S., Yang, J.W., Ko, Y., Eisenhut, M., Lee, K.H., Shin, J.I., Kronbichler, A. 2021. Understanding the genetics of systemic lupus erythematosus using Bayesian statistics and gene network analysis. *Clin Exp Pediatr* **64**(5): 208-22.

Pan, L., Lu, M.P., Wang, J.H., Xu, M., Yang, S.R. 2020. Immunological pathogenesis and treatment of systemic lupus erythematosus. *World J Pediatr* **16**(1): 19-30.

Rivellese, F., Manou-Stathopoulou, S., Mauro, D., Goldmann, K., Pyne, D., Rajakariar, R., Gordon, P., Schafer, P., Bombardieri, M., Pitzalis, C., Lewis, M.J. 2021. Effects of targeting the transcription factors Ikaros and Aiolos on B cell activation and differentiation in Systemic Lupus Erythematosus. *Lupus Sci Med* **8**(1): e000445.

Schafer, P.H., Ye, Y., Wu, L., Kosek, J., Ringheim, G., Yang, Z., Liu, L., Thomas, M., Palmisano, M., Chopra, R. 2018. Cereblon modulator iberdomide induces degradation of the transcription factors Ikaros and Aiolos: Immunomodulation in healthy volunteers and relevance to systemic lupus erythematosus. *Ann Rheum Dis*;**77**(10):1516-23.

Schwickert, T.A., Tagoh, H., Schindler, K., Fischer, M., Jaritz, M., Busslinger, M. 2019. Ikaros prevents autoimmunity by controlling anergy and Toll-like receptor signaling in B cells. *Nat Immunol* **20**(11): 1517-29.

Sellars, M., Kastner, P., Chan, S. 2011. Ikaros in B cell development and function. *World J Biol Chem* **2**(6): 132-9.

Selvananda, S., Chong, Y.Y., Thundyil, R.J. 2020. Disease activity and damage in hospitalized lupus patients: A Sabah perspective. *Lupus* **29**(3): 344-50.

Selvaraja, M., Chin, V.K., Abdullah, M., Arip, M., Amin-Nordin, S. 2021. HLA-DRB1*04 as a risk allele to systemic lupus erythematosus and lupus nephritis in the Malay population of Malaysia. *Front Med* **7**: 598665.

Shaharir, S., Ghafor, A.A., Said, M.M., Kong, N. 2014. A descriptive study of the factors associated with damage in Malaysian patients with lupus nephritis. *Lupus* **23**(4): 436-42.

Shaharir, S., Ting, W., Abdul Wahab, A., Rajalingham,

S., Abdul Gafor, A.H., Mohamed Said, M.S., Mustafar, R. 2019. AB0560 A 10-year review of damage accrual and progression in a milti-ethnic cohort of systemic lupus erythematosus (SLE) in Malaysia. *Ann Rheum Dis* **78**(suppl 2): 1742.1-2

Shaharir, S.S., Hussein, H., Rajalingham, S., Mohamed Said, M.S., Abdul Gafor, A.H., Mohd, R., Mustafar, R. 2016. Damage in the multiethnic malaysian systemic lupus erythematosus (SLE) cohort: Comparison with other cohorts worldwide. *PLoS One* **11**(11): e0166270.

Srinivasan, S., Ramanathan, S., Kumar, S., Peyam, S., Radhakrishnan, V. 2023. Prevalence and prognostic significance of IKZF1 deletion in paediatric acute lymphoblastic leukemia: A systematic review and meta-analysis. *Ann Hematol* **102**(8): 2165-79.

Teh, C.L., Ling, G.R., Aishah, W.S. 2015. The Sarawak lupus cohort: Clinical features and disease patterns of 633 SLE patients in a single tertiary centre from East Malaysia. *Rheumatol Int* **35**(1): 153-7.

Thomas, R.M., Chunder, N., Chen, C., Umetsu, S.E., Winandy, S., Wells, A.D. 2007. Ikaros enforces the costimulatory requirement for IL2 gene expression and is required for anergy induction in CD4+ T lymphocytes. *J Immunol* **179**(11): 7305-15.

Van Nieuwenhove, E., Garcia-Perez, J.E., Helsen, C., Rodriguez, P.D., van Schouwenburg, P.A., Dooley, J., Schlenner, S., van der Burg, M., Verhoeyen, E., Gijsbers, R., et al. 2018. A kindred with mutant IKAROS and autoimmunity. *J Allergy Clin Immunol* **142**(2): 699-702.e12.

Vyse, T.J., Cunninghame Graham, D.S. 2020. Trans-ancestral fine-mapping and epigenetic annotation as tools to delineate functionally relevant risk alleles at IKZF1 and IKZF3 in systemic lupus erythematosus. *Int J Mol Sci* **21**(21).

Wang, C., Ahlford, A., Järvinen, T.M., Nordmark, G., Eloranta, M.L., Gunnarsson, I., Svenungsson, E., Padyukov, L., Sturfelt, G., Jönsen, A., et al. 2013. Genes identified in Asian SLE GWASs are also associated with SLE in Caucasian populations. *Eur J Hum Genet* **21**(9): 994-9.

Wang, F., Wang, C.L., Tan, C.T., Manivasagar, M. 1997. Systemic lupus erythematosus in Malaysia: A study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. *Lupus* **6**(3): 248-53.

Wang, J.H., Nichogiannopoulou, A., Wu, L., Sun, L., Sharpe, A.H., Bigby, M., Georgopoulos, K. 1996. Selective defects in the development of the fetal and adult lymphoid system in mice with an Ikaros null mutation. *Immunity* **5**(6): 537-49.

Wang, Y.F., Zhang, Y., Lin, Z., Zhang, H., Wang, T.Y., Cao, Y., Morris, D.L., Sheng, Y., Yin, X., Zhong, S.L., et al. 2021. Identification of 38 novel loci for systemic lupus erythematosus and genetic heterogeneity between ancestral groups. *Nat Commun* **12**(1): 772.

Wojcik, H., Griffiths, E., Staggs, S., Hagman, J., Winandy, S. 2007. Expression of a non-DNA-binding Ikaros isoform exclusively in B cells leads to autoimmunity but not leukemogenesis. *Eur J Immunol* **37**(4): 1022-32.

Yap, W.H., Yeoh, E., Tay, A., Brenner, S., Venkatesh, B. 2005. STAT4 is a target of the hematopoietic zinc-finger transcription factor Ikaros in T cells. *FEBS Lett* **579**(20): 4470-8.

You, Y., Zhai, Z.F., Chen, F.R., Chen, W., Hao, F. 2015. Autoimmune risk loci of IL12RB2, IKZF1, XKR6, TMEM39A and CSK in Chinese patients with systemic lupus erythematosus. *Tissue Antigens* **85**(3): 200-3.

Zhang, Y.M., Zhou, X.J., Cheng, F.J., Qi, Y.Y., Hou, P., Zhao, M.H., Zhang, H. 2017. Association of the IKZF1 5′ UTR variant rs1456896 with lupus nephritis in a northern Han Chinese population. *Scand J Rheumatol* **46**(3): 210-4.