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Genetic and phenotypic landscape of monogenic lupus: insights from an international cohort

Sulaiman M Al-Mayouf ,[1,2] Vahid Ziaee,[3,4] Nasim Movahedi,[5,6] Mikhail Kostik ,[7] Raghad Alhuthil,[1] Abdullah Alsonbul,[1] Abdulrahman Asiri,[8] Stefano Volpi,[9,10] Marco Gattorno,[9] Mahmoud Majeed,[11] Safiya Al Abrawi,[12] Mada Yateem ,[13] Ashwag Alharthi,[14] Sima Al-Saoud,[15] Anas M Alazami,[16] Alhanouf AlSaleem[1]

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SMA-M and AAlSa contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Sulaiman M Al-Mayouf; almayoufsulaiman@yahoo.com

ABSTRACT

Objective To characterise the clinical, immunologic and molecular genetic features of monogenic lupus in a large, ethnically diverse paediatric cohort and to evaluate genotype-phenotype correlations.

Methods We conducted a retrospective multicentre study of 100 children with genetically confirmed monogenic lupus diagnosed before the age of 14 years. Patients were enrolled between 2000 and 2025 from centres in Saudi Arabia, Iran, Russia, Italy, Palestine and Oman. Demographic data, clinical manifestations, immunological findings, genetic results, treatments and outcomes were systematically analysed. Multivariable logistic regression was used to evaluate associations between specific genotypes and clinical phenotypes.

Results The median age at onset was 24 months, with 69% of patients carrying homozygous pathogenic mutations. The most frequently implicated genes were *C1Q* (26%) and *DNASE1L3* (25%), representing complement and type I interferon pathways, respectively. Mucocutaneous (84%), musculoskeletal (74%) and neurological (42%) were the most common clinical features. Disease burden was substantial, reflected by a median Paediatric Systemic Disease Index score of 3 and a mortality rate of 16%. Distinct ethnic clustering of specific gene mutations was observed. Genotype-phenotype analysis revealed that *C1Q* pathway defects were significantly associated with neurologic involvement, recurrent infections and anti-Sjögren's syndrome antibody A (SSA)/SSB positivity, defining a characteristic clinical profile. In contrast, *DNASE1L3*-related disease showed inverse associations with several clinical features, including recurrent infections, suggesting a different pathogenic and clinical trajectory.

Conclusion This large international cohort highlights the clinical and genetic heterogeneity of monogenic lupus. *C1Q* and *DNASE1L3* mutations account for most cases and display distinct phenotypic profiles. These findings underscore the need for genotype-guided diagnostic and therapeutic approaches in monogenic lupus.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Monogenic lupus is a rare, early-onset form of childhood lupus caused by single-gene defects, with more than 30 implicated variants.

⇒ Its non-specific, multisystem presentation often overlaps with sporadic lupus and other immune-dysregulation disorders, contributing to diagnostic delays.

WHAT THIS STUDY ADDS

⇒ This study represents the largest international cohort of children with genetically confirmed monogenic lupus.

⇒ Genetic pathways distribution differed across ethnic groups, suggesting potential ethnic influences on disease-associated variants.

⇒ *DNASE1L3* and *C1QA* were the most frequent mutations, each demonstrating distinct clinical phenotypes.

⇒ C1Q deficiencies were associated with increased infections, neurologic involvement and anti-Sjögren's syndrome anSyndrome Antibody A (SSA)/SSB positivity.

⇒ Interferon-pathway mutations were linked to milder disease and fewer infections.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Underscores the value of early genetic testing for accurate diagnostic stratification and individualised management.

⇒ Supports the implementation of genotype-guided diagnostic and therapeutic strategies in monogenic lupus.

INTRODUCTION

SLE is a complex autoimmune disease characterised by defects in the adaptive immune system, B-cell dysregulation and the production of autoantibodies. While its pathogenesis remains incompletely understood, it involves a combination of environmental, hormonal, immunoregulatory and genetic factors. Up to 100 susceptibility loci have been associated with polygenic SLE, and single-gene mutations have been identified in monogenic

lupus and lupus-like, particularly in Arab, European and Asian populations, emphasising the crucial role of genetic factors, especially in paediatric cases.[1–3]

Childhood-onset SLE (cSLE) accounts for 10–20% of all SLE cases and tends to have a more severe and diverse clinical presentation than adult-onset SLE.[4–6] Monogenic or Mendelian lupus refers to high-penetrance genetic variants, either dominantly or recessively inherited, that cause early-onset, severe disease. These variants affect both innate and adaptive immune regulation and lead to overlapping autoimmune and autoinflammatory features.[7]

Advancements in genetic testing, including whole exome sequencing (WES) and next-generation sequencing (NGS), have identified over 30 pathogenic and novel variants associated with monogenic lupus or lupus-like disorders.[1 2] The most commonly affected pathways include the complement system, especially C1q, C4 and C2 deficiencies, and the type I interferon (IFN) signalling pathway.[8–10]

Patients with monogenic lupus often present with severe disease early in life, frequently within consanguineous families, and show a strong familial predisposition.[11–13] Despite advancements in our understanding of disease mechanisms, effective and targeted therapeutic interventions remain limited.

Depending on the gene variant, monogenic lupus presents a wide spectrum of non-specific clinical manifestations due to multiorgan involvement, often overlapping with features of sporadic lupus, interferonopathies and other inherited immune dysregulation disorders, thereby contributing to delayed diagnosis and appropriate management.[14]

This study aims to describe the clinical and genetic characteristics of patients with monogenic lupus from an international multicentre cohort and identify novel, rare and pathogenic variants associated with monogenic lupus.

MATERIALS AND METHODS

Participants

This multicentre, retrospective observational study included patients diagnosed with monogenic lupus from King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh, Saudi Arabia, as well as other collaborating centres in Saudi Arabia, Iran, Russia, Italy, Palestine and Oman. All patients were seen between June 2000 and May 2025. The included patients were diagnosed before the age of 14 years, met the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria for SLE, and had a confirmed pathogenic or likely pathogenic variant associated with monogenic lupus.[15] Patients heterozygous for autosomal recessive variants were included only if an index case with a confirmed pathogenic variant was identified. Patients with familial cSLE without genetic confirmation or those with insufficient clinical data were excluded.

Data collection

Demographic data including ethnicity and consanguinity, along with clinical features and laboratory findings, were retrospectively collected. Clinical features included constitutional, haematological, neuropsychiatric, mucocutaneous, serosal, musculoskeletal and renal involvement. Data on recurrent infections were collected. Recurrent infection was defined as more than one episode with the same or different organisms, and severity was assessed by the need for parenteral antimicrobials and/or intensive care admission. Laboratory investigations included inflammatory markers, ANA, anti-double-stranded-DNA, anti-Smith, anti-Sjögren's syndrome anSyndrome Antibody A (SSA), anti-SSB, anti-ribonucleoprotein antibody (RNP), phospholipid antibodies and complement levels. Molecular analysis was performed at multiple centres using different methods; some patients underwent WES, while others had targeted gene panels. Variants were interpreted according to standard guidelines at each centre. The analysis comprehensively reviewed all available clinical, laboratory and treatment data from the time of monogenic lupus diagnosis through the follow-up period. All medications were documented from disease onset to study enrolment. Formal assessment of treatment response using disease activity indices was not performed; instead, disease-related damage, measured using the paediatric adaptation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (Paediatric Systemic Disease Index (pSDI)) and lupus-related mortality were recorded.[16]

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plan of this study.

Statistical analysis

Statistical analyses were performed using STATA V.18. Categorical variables were compared using the χ^2 tests, and continuous variables were analysed using the Kruskal-Wallis test. Dunn's test, with Holm-Sidák adjustment for multiple pairwise comparisons, was used to evaluate differences in age at monogenic lupus diagnosis. For multivariable analysis, logistic regression assessed genotype-phenotype associations. A Bonferroni-adjusted significance threshold of $p<0.017$ was applied to account for multiple testing. A p value <0.05 was considered statistically significant.

RESULTS

Out of 104 initial patients, four patients were excluded due to variants of uncertain significance or heterozygous mutations in autosomal recessive genes without a supportive family history of monogenic lupus. A total of 100 patients with genetically confirmed monogenic lupus

Table 1 Demographics, clinical characteristics and outcomes of 100 patients with monogenic lupus

Parameters	Arab No.=57 (%)	Caucasian No.=24 (%)	Persian No.=19 (%)	Overall No.=100 (%)	P value
Demographics					
Female gender	35 (61.4)	15 (62.5)	13 (68.4)	63 (63.0)	0.859
Age at disease onset (months), median (IQR)	36 (8–60)	10 (4.5–16.5)	24 (9–60)	24 (7–60)	0.031
Age at diagnosis (years), median (IQR)	4 (2–8.75)	12 (7.5–16)	5 (2–6)	6 (3–11)	<0.001*†
Consanguinity	52 (91.2)	0 (0.0)	19 (100.0)	71 (71.0)	<0.001*
Family history	35 (61.4)	7 (29.2)	5 (26.3)	47 (47.0)	0.004*
Constitutional symptoms	48 (84.2)	20 (83.3)	12 (63.2)	80 (80.0)	0.125
Organ involvement					
Mucocutaneous involvement	45 (79.0)	21 (87.5)	18 (94.7)	84 (84.0)	0.231
Musculoskeletal involvement	42 (73.7)	18 (75.0)	14 (73.7)	74 (74.0)	0.992
Neurological involvement	24 (42.1)	5 (20.8)	13 (68.4)	42 (42.0)	0.007*
Renal involvement	20 (35.1)	11 (45.8)	6 (31.6)	37 (37.0)	0.568
Gastrointestinal involvement	17 (29.8)	4 (16.7)	5 (26.3)	26 (26.0)	0.467
Lung involvement	15 (26.3)	7 (29.2)	3 (15.8)	25 (25.0)	0.567
Cardiovascular involvement	12 (21.1)	5 (20.8)	6 (31.6)	23 (23.0)	0.614
Recurrent infections	26 (45.6)	4 (16.7)	6 (31.6)	36 (36.0)	0.042
pSDI median (IQR)	3 (1–6)	1.5 (0–4)	5 (3–7)	3 (1–6)	0.013*‡
Mortality	10 (17.5)	1 (4.2)	5 (26.3)	16 (16.0)	0.128

P values were reported using the χ^2 test and the Kruskal-Wallis's test.
*Considered statistically significant (p<0.017) adjusted significance level after Bonferroni correction.
†Significant difference between Caucasians and Arabs (p<0.001) and between Caucasians and Persians (p<0.001), adjusted for multiple comparisons in post-hoc analysis.
‡Notable differences between Persians and Arabs (p=0.022) and significant between Caucasians and Persians (p=0.006), adjusted for multiple comparisons in post-hoc analysis.
pSDI, Paediatric Systemic Disease Index.

were included; 63% were female. The median age at disease onset was 24 months (IQR 7–60). Demographic and clinical characteristics, along with disease outcomes, are summarised in table 1. The majority of patients were of Arab descent (57%), followed by Caucasian (24%) and Persian (19%). Consanguinity was significantly higher in Persian (100%) and Arab (91.2%) patients compared with Caucasian patients (0%) (p<0.001). Family history of lupus was most frequent among Arab patients (61.4%) compared with other ethnic groups (p=0.004).

Clinical and laboratory manifestations

Our cohort exhibited a broad and heterogenous spectrum of clinical manifestations (online supplemental S.1). Constitutional symptoms were common, with recurrent fever reported in 75% of patients and growth failure in 45%. Mucocutaneous involvement was observed in 84% of cases, including manifestations such as recurrent oral ulcers, discoid rash and scarring alopecia. Musculoskeletal symptoms were also prevalent, with arthritis occurring in 74% of patients. Neurological involvement was noted in 42%, presenting as recurrent headaches, seizures or lower limb spasticity; this was most frequent among Persian patients (68.4%, p 0.007). Renal involvement was identified in 37 patients (37%); of whom 19 had renal impairment (elevated serum creatinine and/or reduced age-adjusted estimated glomerular filtration rate (eGFR)). Among these, 30 patients (81.1%) had biopsy-confirmed lupus nephritis. According to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification,[15 17] proliferative lupus nephritis (class III or IV) was observed in 15 patients, membranous lupus nephritis (class V) in seven and combined proliferative and membranous lupus nephritis (class III/IV+V) in another seven patients. Additionally, one patient had focal segmental glomerulosclerosis. Lung involvement was seen in 25 patients, of whom 18 had chronic lung infiltrates characterised by diffuse interstitial infiltration without a specific distribution pattern, and 10 demonstrating nodular or cavitary lesions. Documented recurrent infections occurred in 36% of patients, with bacterial infection being the most frequent. Nine patients experienced more than one type of infection, with a higher (though not statistically significant) frequency among Arabs (45.6%) compared with Caucasians (16.7%) (p=0.042) (table 1).

Laboratory findings are summarised in table 2. Investigations revealed elevated inflammatory markers and positive ANA levels in the majority of patients, with

Table 2 Laboratory findings of 100 patients with monogenic lupus

Parameters	Arab No.=57 (%)	Caucasian No.=24 (%)	Persian No.=19 (%)	Overall No.=100 (%)	P value
Positive Coombs test	37/54 (68.5)	9/17 (52.9)	2/17 (11.8)	48/88 (54.6)	<0.001*
Abnormal APR	52/55 (94.6)	21/24 (87.5)	14/19 (73.7)	87/98 (88.8)	0.045
Renal impairment	13/52 (25.0)	4/12 (33.3)	2/19 (10.5)	19/83 (22.9)	0.284
Transaminitis	9/55 (16.4)	3/23 (13.0)	8/19 (42.1)	20/97 (20.6)	0.034
Hyperserotonaemia	3/55 (5.5)	1/24 (4.2)	NA	4/79 (5.1)	0.81
Low C3, C4	33/57 (57.9)	15/24 (62.5)	5/19 (26.3)	53/100 (53.0)	0.033
Low CH50	23/30 (76.7)	NA	16/19 (84.2)	39/50 (78.0)	0.135
Low C1q	20/31 (64.5)	NA	5/5 (100.0)	25/37 (67.6)	0.100
Hypogammaglobulinaemia	22/52 (42.3)	7/24 (29.2)	2/19 (10.5)	31/95 (32.6)	0.037
ALI	14/32 (43.8)	1/1 (100.0)	1/3 (33.3)	16/36 (44.4)	0.495
ANA (≥1:80)	55 (96.5)	20 (83.3)	19 (100.0)	94 (94.0)	0.035
Anti-ds-DNA	37 (64.9)	15 (62.5)	8 (42.1)	60 (60.0)	0.205
Anti-Smith	26 (45.6)	2 (8.3)	2 (10.5)	30 (30.0)	<0.001*
Anti-SSA (Ro)	23 (40.4)	4 (16.7)	6 (31.6)	33 (33.0)	0.116
Anti-SSB (La)	17 (29.8)	3 (12.5)	1 (5.3)	21 (21.0)	0.038
Anti-RNP	18 (31.6)	0 (0.0)	1 (5.3)	19 (19.0)	0.001*
APL	30 (52.6)	7 (29.2)	7 (36.8)	44 (44.0)	0.119

P values were reported using the χ^2 test.
*Considered statistically significant (p<0.017) adjusted significance level after Bonferroni correction.
ALI, abnormal lymphocyte immunophenotyping; Anti-ds-DNA, anti-double-stranded DNA antibody; Anti-RNP, anti-ribonucleoprotein antibody; Anti-Smith, anti-Smith antibody; Anti-SSA (Ro), Anti-Sjögren's syndrome antibody A (Ro); Anti-SSB (La), Anti-Sjögren's syndrome antibody B (La); APL, antiphospholipid antibodies; APR, acute phase reactants; C3, C4, complement components 3 and 4; CH50, total haemolytic complement (classical pathway activity); C1q, complement component 1q.

variable frequencies of extractable nuclear antigens, including anti-ds-DNA, anti-SSA and anti-SSB antibodies. Notably, anti-Smith and anti-RNP antibodies, along with low serum C1q levels, were significantly more prevalent in Arabs compared with Caucasian and Persian patients (p<0.001 and p=0.001, respectively). In contrast, low serum total haemolytic complement (CH50) levels were predominantly observed in Persian patients. It is worth noting that CH50 data are not available for Caucasian patients.

Imaging studies were performed on a subset of the cohort. Chest CT was conducted in 49 patients, of whom 10 (20.4%) demonstrated abnormal findings, including interstitial lung disease with nodular and cavitary lesions. A brain MRI was performed at different centres, only in patients with neurological manifestation (n=46) and revealed non-specific abnormalities such as brain atrophy, vasculopathy, white matter changes and basal ganglia calcification (online supplemental S.2).

Treatment and outcomes

All patients received systemic corticosteroids and immunosuppressive therapy, including both conventional and biologic disease-modifying antirheumatic drugs (DMARDs). Among the biologic DMARDs, rituximab was administered to 26 patients, belimumab to 26 and Janus kinase (JAK) inhibitors to 10 patients (online supplemental S.3). In a subset of cases, sequential therapy with rituximab followed by belimumab was implemented to achieve better disease control. Despite therapy, most patients experienced cumulative organ damage. The median accrual damage index (pSDI) was 3 (IQR 1–6), with the most frequently affected domains being growth and skin, followed by neurological and renal systems. 16 patients (16%) died due to severe multiorgan involvement compounded by serious infections.

Molecular genetics

Genetic analysis of 100 patients with monogenic lupus revealed a diverse spectrum of pathogenic or likely pathogenic mutations spanning multiple immunological pathways (figure 1). The most prominent cluster involved defects in the complement cascade, accounting for over one-third of all cases (35 patients). Among these, 26 patients harboured homozygous mutations in *C1Q* genes, including 20 in *C1QA*, all carrying bi-allelic pathogenic or likely pathogenic variants. The two most common of these were the missense c.470G>A (p.Gly157Asp) and the nonsense c.622C>T (p.Gln208*) mutations. Additional homozygous variants were identified in *C1QC in* four patients, and two each in *C1QB* and *C1S*, consistent with autosomal recessive inheritance. Rare variants were also identified in *C3*, *C4A*, *C8B* and *CR1*, further highlighting

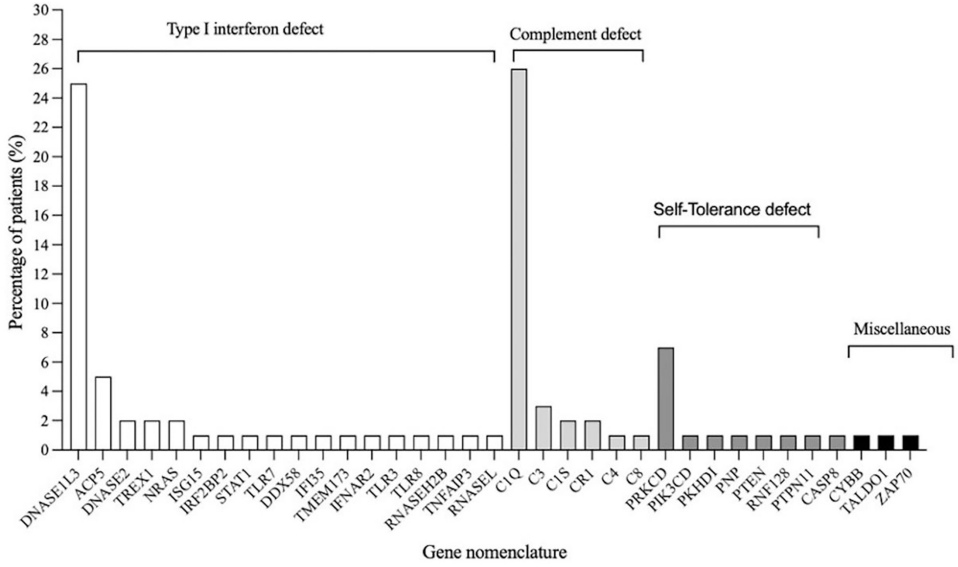

Figure 1 Identified genetic defects and pathways involved in a cohort of 100 patients.

the contribution of early complement deficiencies in disease pathogenesis (online supplemental S.4).

Genes in the type I IFN signalling pathway represented the largest single functional category, with mutations found in 48 patients. *DNASE1L3* emerged as the most frequently affected gene within this group, with 25 patients carrying pathogenic mutations, of whom 18 had homozygous variants, while the remainder were either compound heterozygous or carried a single heterozygous mutation (for which the other allele was likely outside our NGS methodology), in the context of a history of affected siblings. Figure 2 provides a schematic representation of protein-coding mutations in the *C1Q* subunits and *DNASE1L3* as observed in this cohort.

Other notable findings included bi-allelic pathogenic variants in *ACP5*, *DNASE2* and *ISG15*, as well as heterozygous mutations in *TMEM173*, *TLR3*, *TLR7*, *TLR8*, *PIK3CD* and several additional genes. These findings were consistent with autosomal dominant or X-linked modes of inheritance. A somatic NRAS c.38G>A (p.Gly13Asp) mutation was identified in one patient, supporting the emerging role of somatic mosaicism in lupus pathogenesis.[18]

Genes involved in self-tolerance and lymphocyte regulation were implicated in 15 patients. *PRKCD* was the most frequently affected gene in this category. Additional pathogenic variants of interest included heterozygous mutations in *PTEN* and *PTPN11*, as well as a hemizygous mutation in *RNF128*.

Finally, two patients carried mutations in genes not classically associated with lupus but involved in broader immune regulation. These included a homozygous nonsense mutation in *CYBB* and a heterozygous missense variant in *ZAP70*. While their significance in lupus remains uncertain, these findings may point towards underlying immune dysregulation or tolerance-breaking mechanisms.

The distribution of genetic pathways appeared to vary among ethnic groups within this cohort. Complement deficiencies were more frequently observed in Persian patients (63.2%) compared with Arab (35.1%) and Caucasian (12.5%) patients. Conversely, type I IFN pathway defects were more common in Caucasian patients (79.2%) than in Arabs (38.6%) and Persians (36.8%) patients. Figure 3 illustrates the distribution of genetic pathways in relation to ethnicity.

Overall, the most frequently mutated genes in this cohort were *C1Q* (26%) and *DNASE1L3* (25%). The majority of patients (69%) had homozygous mutations, while 28% had heterozygous, 2% had compound heterozygous and 1% had hemizygous mutations.

Genotype and phenotype association

A wide spectrum of mutations was identified across the cohort; however, the majority were attributable to mutations in *DNASE1L3*, representing the IFN signalling pathway, and *C1Q*, representing the complement system. Accordingly, genotype-phenotype correlation analyses were primarily focused on these two immunological pathways.

Comparison of clinical features and autoantibody profiles between patients with mutations affecting the complement or IFN signalling pathways vs those with other genetic mutations revealed several statistically significant differences (tables 3 and 4).

Patients with complement gene mutations, predominantly *C1Q*, exhibited significantly higher rates of neurological involvement and developmental delay (60.0% vs 32.3%, p=0.007), an association that remained significant in multivariable analysis (OR=3.7; 95% CI 1.32 to 10.59; p=0.013). These patients were also more likely to have mucocutaneous lesions and musculoskeletal involvement, though these associations did not achieve statistical significance. Recurrent infections were significantly more frequent in this group (57.1% vs 24.6%, p=0.001), with increased odds in the adjusted model (OR=3.7; 95% CI 1.29 to 10.68; p=0.015). Serologically, they demonstrated

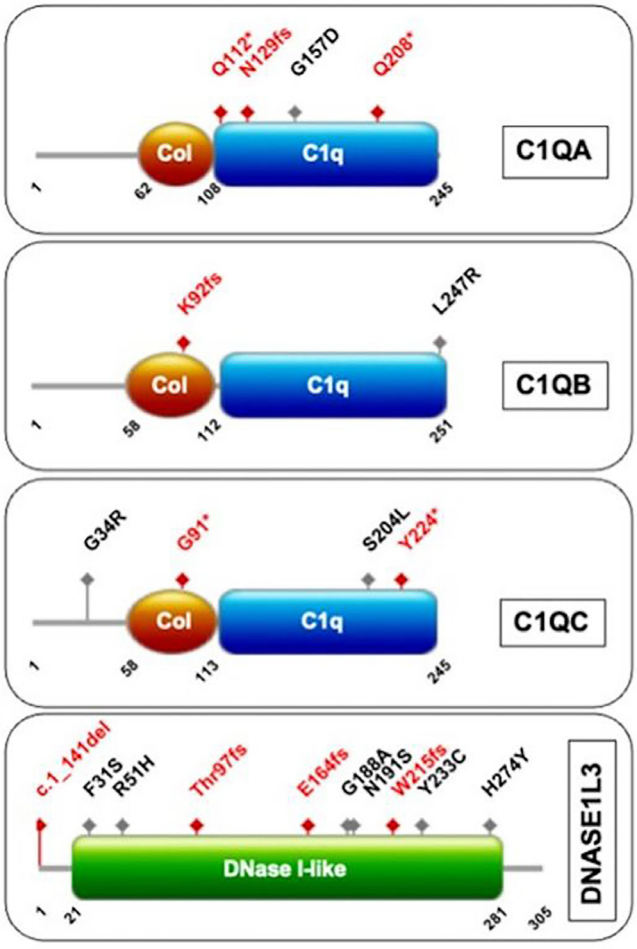

Figure 2 Schematic representation of protein-coding mutations in *C1Q* subunits and *DNASE1L3*, as identified in a cohort of monogenic lupus patients. Each schematic shows the respective protein with annotated functional domains (coloured shapes), and amino acid positions are indicated along the bottom axis. Mutations are positioned above the protein structure, with truncating variants in red and missense variants in black.

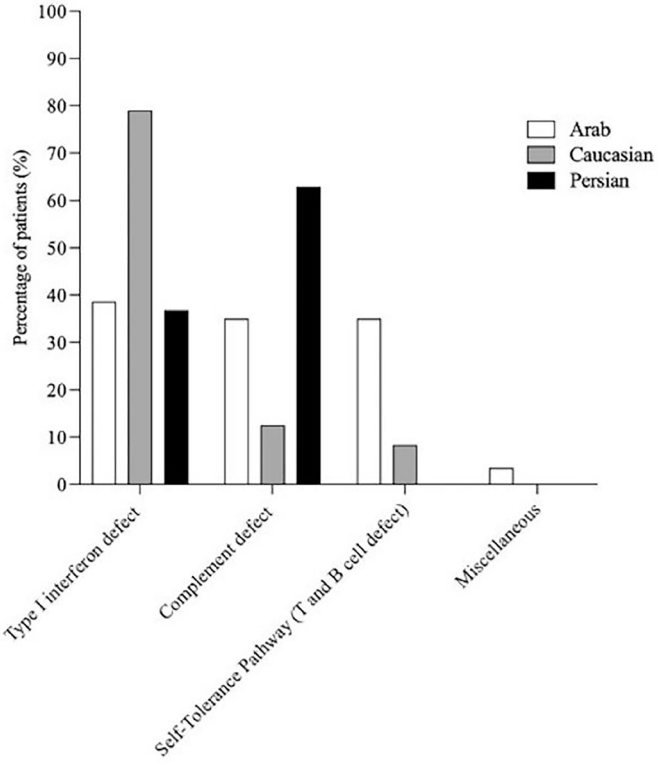

Figure 3 Distribution of genetic pathways in relation to ethnicity. Complement defect is more common in Persian patients (63.2%) compared with Arab (35.1%) and Caucasian (12.5%) patients. Type I interferon defect is significantly higher in Caucasian patients (79.2%) than in Arabs (38.6%) and Persians (36.8%) (p=0.001).

a higher prevalence of specific autoantibodies, particularly anti-Smith (45.7% vs 21.5%, p=0.012), anti-SSA (Ro) (62.9% vs 16.9%, p<0.001) and anti-SSB (La) antibodies (37.1% vs 12.3%, p=0.004). The strongest independent association was observed with anti-SSA positivity (OR=19.6; 95% CI 3.41 to 113.05; p=0.001). Additionally, complement deficiency was associated with an increased damage index in the univariable analysis, as reflected by a higher pSDI median score (5 vs 2; p=0.029). However, there was no significant association with mortality.

In contrast, patients with mutations in the IFN signalling pathways, primarily *DNASE1L3*, were significantly less likely to experience recurrent infections (18.8% vs 51.9%, p=0.001), a finding that remained robust in multivariable analysis (OR=0.3; 95% CI 0.11 to 0.77; p=0.013). While these patients also showed a lower frequency of neurological symptoms, the differences were not statistically significant. Serologically, they were less likely to test positive for anti-Smith (14.6% vs 44.2%, p=0.001), anti-SSA (12.5% vs 51.9%, p<0.001) and anti-SSB antibodies (8.3% vs 32.7%, p=0.003) in the univariable analysis. Notably, no significant associations were observed between IFN signalling pathway mutations and clinical outcomes or mortality (table 4).

DISCUSSION

Monogenic lupus is typically characterised by early-onset disease and severe clinical manifestations, and a strong association with a positive family history, particularly in populations with high rates of consanguinity.[9] Numerous pathogenic and novel genetic variants have been implicated in monogenic lupus and lupus-like disorders.[1 2 19] While several reports have described the clinical and laboratory features of monogenic lupus, highlighting unique phenotypes based on underlying genetic defects, comprehensive genotype-phenotype correlation studies remain limited.[19–21] Various terms have been used in the literature to describe this clinical entity, including early-onset SLE, monogenic SLE, SLE-like phenotype, lupus-like disease, lupus-like syndrome, familial SLE and Mendelian lupus. However, standardised diagnostic criteria for monogenic lupus have not yet been established. In addition, a variety of monogenic predisposing conditions, particularly inborn errors of immunity, have been associated with lupus manifestations, underscoring

Table 3 Univariable associations between genotype and organ phenotypes in monogenic lupus

	Complement defect			Self-tolerance (T and B cell defect)			Type I interferon defect		
	Yes 35 (%)	No 65 (%)	P value	Yes 15 (%)	No 85 (%)	P value	Yes 48 (%)	No 52 (%)	P value
Organ involvement									
Mucocutaneous	31 (88.6)	53 (81.5)	0.360	11 (73.3)	73 (85.9)	0.222	40 (83.3)	44 (84.6)	0.861
Musculoskeletal	29 (82.9)	45 (69.2)	0.138	9 (60.0)	65 (76.5)	0.180	35 (72.9)	39 (75.0)	0.812
Neurological	21 (60.0)	21 (32.3)	0.007*	3 (20.0)	39 (45.9)	0.061	17 (35.4)	25 (48.1)	0.200
Gastrointestinal	12 (34.3)	14 (21.5)	0.166	3 (20.0)	23 (27.1)	0.566	11 (22.9)	15 (28.9)	0.499
Renal	10 (28.6)	27 (41.5)	0.200	4 (26.7)	33 (38.8)	0.369	21 (43.8)	16 (30.8)	0.179
Lupus nephritis	10 (28.6)	20 (30.8)	0.819	4 (26.7)	26 (30.6)	0.760	16 (33.3)	14 (26.9)	0.485
Lung	8 (22.9)	17 (26.2)	0.717	4 (26.7)	21 (24.7)	0.872	13 (27.1)	12 (23.1)	0.644
Cardiovascular	10 (28.6)	13 (20.0)	0.331	2 (13.3)	21 (24.7)	0.335	11 (22.9)	12 (23.1)	0.985
Recurrent infections	20 (57.1)	16 (24.6)	0.001*	6 (40.0)	30 (35.3)	0.726	9 (18.8)	27 (51.9)	0.001*
Antibodies									
ANA (≥1:80)	34 (97.1)	60 (92.3)	0.332	13 (86.7)	81 (95.3)	0.195	45 (93.8)	49 (94.2)	0.919
Anti-ds-DNA	17 (48.6)	43 (66.2)	0.087	12 (80.0)	48 (56.5)	0.086	30 (62.5)	30 (57.7)	0.624
Anti-Smith	16 (45.7)	14 (21.5)	0.012*	7 (46.7)	23 (27.1)	0.127	7 (14.6)	23 (44.2)	0.001*
Anti-SSA (Ro)	22 (62.9)	11 (16.9)	<0.001*	5 (33.3)	28 (32.9)	0.976	6 (12.5)	27 (51.9)	<0.001*
Anti-SSB (La)	13 (37.1)	8 (12.3)	0.004*	4 (26.7)	17 (20.0)	0.559	4 (8.3)	17 (32.7)	0.003*
APL	13 (37.1)	31 (47.7)	0.311	10 (66.7)	34 (40.0)	0.055	20 (41.7)	24 (46.2)	0.652
Outcomes									
pSDI, median (IQR)	5(1–7)	2(0–5)	0.029	1(0–4)	3(1–6)	0.048	2(1–6)	3(1–6)	0.524
Mortality	7 (20.0)	9 (13.9)	0.423	4 (26.7)	12 (14.1)	0.222	5 (10.4)	11 (21.2)	0.143

P values were reported using the χ^2 test for categorical variables and Kruskal-Wallis for the pSDI.
*Considered statistically significant (p<0.017) adjusted significance level after Bonferroni correction.
Anti-dsDNA, anti-double-stranded-DNA; Anti-SSA (Ro), anti-Sjögren's syndrome antibody A (Ro); Anti-SSB (La), anti-Sjögren's syndrome antibody B (La); APL, antiphospholipid antibodies; pSDI, Paediatric Systemic Disease Index.

the clinical heterogeneity and phenotypic overlap of this group of disorders.[9 14 21] Based on current evidence, monogenic lupus can be tentatively defined as the presence of lupus manifestations in individuals with immune dysregulation attributable to a pathogenic or likely pathogenic variant in a single gene.[15 22] In this multicentre international study, we present one of the largest cohorts of patients with genetically confirmed monogenic lupus. Our primary aim was to validate previously reported genotype-phenotype associations and identify novel pathogenic variants, particularly in high consanguineous populations. Remarkably, 83% of patients in our cohort were products of consanguineous marriage, reinforcing the known link between consanguinity and autosomal

Table 4 Multivariable logistic regression: genetic-phenotypic associations in monogenic lupus

	Complement defect		Type I interferon defect	
	OR (95% CI)	P value	OR (95% CI)	P value
Neurological Involvement	3.7 (1.32 to 10.59)	0.013*	†	†
Recurrent infections	3.7 (1.29 to 10.68)	0.015*	0.3 (0.11 to 0.77)	0.013*
Anti-Smith	0.7 (0.2 to 2.62)	0.625	0.5 (0.17 to 1.71)	0.292
Anti-SSA (Ro)	19.6 (3.41 to 113.05)	0.001*	0.2 (0.03 to 0.9)	0.038
Anti-SSB (La)	0.2 (0.04 to 1.45)	0.120	1.5 (0.21 to 10.28)	0.705

P values were reported using multivariable logistic regression.
*Considered statistically significant (p<0.017) adjusted significance level after Bonferroni correction.
†Not significant association by univariable associations.
Anti-SSA (Ro), anti-Sjögren's syndrome antibody A (Ro); Anti-SSB (La), anti-Sjögren's syndrome antibody B (La).

recessive monogenic lupus. Notably, there was an average diagnostic delay of approximately 3 years from disease onset, underscoring the ongoing challenge in timely recognition of these rare disorders.

Our findings confirm the genetic heterogeneity of monogenic lupus, with the most frequently affected pathways being the complement cascade, especially mutations in *C1Q*, followed by *DNASE1L3*. The distribution of genetic pathways varied across ethnic groups within our cohort, suggesting possible ethnic influences on the underlying genetic architecture of monogenic lupus. Consistent with earlier reports, our cohort exhibited early disease onset and multi-organ involvement. The broad clinical spectrum spanned constitutional, mucocutaneous, musculoskeletal, neurological, renal, pulmonary and immunological domains, underscoring the systemic and complex nature of monogenic lupus.

Interestingly, anti-ds-DNA antibodies were infrequently detected, whereas other autoantibodies such as anti-Smith and anti-SSB were more commonly observed. Infections were a significant complication, affecting 40% of patients, while disease-related mortality was substantial, with 16% of the cohort succumbing to severe disease and associated infections.

Importantly, our analysis revealed distinct genotype-phenotype associations. Patients with *C1QA* mutations demonstrated a more severe disease phenotype, marked by higher rates of recurrent infections, developmental delay, neurological manifestations and mucocutaneous lesions. These patients were also more likely to test positive for anti-Smith, anti-SSA and anti-SSB antibodies. Multivariable analysis further identified spasticity and anti-SSA antibody positivity as features significantly associated with *C1QA* mutations. Conversely, *DNASE1L3* mutations were associated with a comparatively milder clinical course, characterised by lower rates of neurological involvement and infections, though ocular involvement was more common in this group.

A detailed evaluation of treatment strategies is beyond the scope of this study.[23–25] While no therapies are specifically approved for monogenic lupus or interferonopathies, off-label use of conventional biologic DMARDs—particularly B-cell depleting therapies and JAK inhibitors—was common in our cohort, with a subset of patients requiring sequential or combination regimens.

The main strength of this study lies in its focus on genotype-phenotype correlations in a relatively large, genetically diverse and well-characterised cohort of patients. The multicentre design enabled the inclusion of individuals from a range of ethnic backgrounds and geographic regions, enhancing the generalisability of the findings. Nonetheless, several limitations should be acknowledged. Patient selection bias may have influenced the representation of genotypes and phenotypes, as participating centres varied in the number of enrolled patients and the depth of available data. In addition, the multicentre design resulted in heterogeneity in genetic testing approaches across and within centres. The study also did not systematically evaluate the full spectrum of rare or novel variants, thereby limiting the comprehensiveness of genotype-phenotype association analyses. Finally, formal assessment of treatment response using standardised disease activity indices was not feasible due to the retrospective design and the long study period spanning more than 25 years, resulting in incomplete and non-comparable disease activity data.

CONCLUSION

This study presents the most extensive international data on genotype-phenotype associations in children with monogenic lupus. The disease manifestations observed ranged from mild features to severe, life-threatening organ involvement. These findings emphasise the value of genetic testing in early diagnosis and risk stratification and support its role in guiding clinical management and genetic counselling based on individual genetic profiles.

Author affiliations
[1]Pediatric Rheumatology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[2]Alfaisal University College of Medicine, Riyadh, Saudi Arabia
[3]Children's Medical Center, Tehran, Iran (the Islamic Republic of)
[4]Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran (the Islamic Republic of)
[5]School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran (the Islamic Republic of)
[6]Golestan Rheumatology Research Center, Golestan University of Medical Sciences, Gorgan, Iran (the Islamic Republic of)
[7]Saint Petersburg State Pediatric Medical University, Sankt Peterburg, Russian Federation
[8]Department of Pediatrics, Prince Sultan Medical Military City, Riyadh, Saudi Arabia
[9]UOC Reumatologia e Malattie Autoinfiammatorie, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[10]DINOGMI, University of Genoa, Genoa, Italy
[11]King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia
[12]Department of Child Health, Royal Hospital, Muscat, Oman
[13]King Fahad Hospital, Jazan, Saudi Arabia
[14]Security Forces Hospital in Riyadh, Riyadh, Saudi Arabia
[15]Department of Pediatrics, Al-Quds University, Abu Dis, Palestine, State of
[16]Department of Translational Genomics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

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Contributors Conceptualisation: SMA-M and AAlSa; methodology: SMA-M, AAlSa and RA; collecting data: AAlSa, NM, VZ, MK, AAs, SV, MM, SAA, MY, AAlh and SA-S; formal analysis: (SMA-M, AAlSa, RA, AMA); writing—original draft preparation: SMA-M, RA and AMA; critically revised for important intellectual content: SMA-M, AAlSa, RA, AMA, NM, VZ, MK, AAlso, AAs, SV, MG, MM, SAA, MY, AAlh and SA-S. SMA-M is the guarantor.

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parents at the time of blood extraction as part of standard medical care. Data were collected anonymously from patient records, ensuring confidentiality, and with no personally identifiable information included.

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ORCID iDs
Sulaiman M Al-Mayouf https://orcid.org/0000-0003-0142-6698
Mikhail Kostik https://orcid.org/0000-0002-1180-8086
Mada Yateem https://orcid.org/0000-0003-0504-0266

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