Genetic heterogeneity in Chinese children with systemic lupus erythematosus

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Abstract

Objective

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease with extreme clinical heterogeneity and significant differences between populations. Here, we performed whole exome sequencing (WES) in 52 children with SLE from China.

Methods

The patients all fulfilled the 2012 SLICC criteria for the classification of SLE. Patients were enrolled if they met one of the following criteria: 1. age of disease onset under 5 years; 2. family history of autoimmune disease; 3. syndromic SLE; and 4. complicated conditions, such as life-threatening and refractory SLE.

Results

52 out of 281 newly diagnosed pSLE patients met the inclusion criteria. We identified causative mutations in 12 patients in five different genes: SLC7A7, NRAS, TNFAIP3, PIK3CD, and IDS. The age of onset was under five years in eight patients (8/15, p=0.003) with mutations. Two of 5 patients had a family history of autoimmune disease, with family members developing different autoimmune diseases. Causal mutations were identified in five patients who presented with syndromic SLE (5/5 p=0.000) and in another five patients who presented with primary immunodeficiency diseases (5/5, p=0.000). Causal mutations were detected in 12 of 36 patients with SLEDAI scores>14 (12/36, p=0.023) and in 9 of 17 patients with haematological and renal involvement (9/17, p=0.048).

Conclusion

We revealed a significant fraction of monogenic SLE aetiologies using WES (12/52, 23.1%). WES should perform in patients with very early onset SLE (<5 years of age), syndromic SLE, severe SLE (SLEDAI score>14), family history of autoimmune disease, primary immunodeficiency disease and renal and haematological involvement.

Key words

children, genetic heterogeneity, monogenic, systemic lupus erythematosus, whole exon sequencing

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Introduction

Systemic lupus erythematosus (SLE; OMIM 152700) is a highly heterogeneous disease and is considered a prototype of systemic autoimmune diseases; SLE is characterised by differences in autoantibody profiles, serum cytokines, and multisystem involvement commonly affecting the clinical manifestations of the skin and the musculoskeletal, renal, and haematological systems (1, 2). Disease features range from mild manifestations, such as arthritis or rash, to life-threatening end-organ manifestations, such as glomerulonephritis or thrombosis, and it is difficult to predict which manifestations will affect a given patient (3, 4). When SLE commences in an individual under 18 years of age, it is commonly referred to as paediatric SLE (pSLE). pSLE accounts for approximately 10–20% of all patients with SLE. Disease onset in paediatric SLE most frequently occurs between the ages of 12 and 18 years, is uncommon before the age of 10 years and is very rare before 5 years (5, 6). pSLE exhibits a more abrupt onset with higher rates of organ involvement, a more aggressive clinical course, more rapid damage accrual, and greater lifetime morbidity and mortality than adult-onset SLE (aSLE) (7, 8). These differences between pSLE and aSLE may be due to variations in biology or genetics (9). Genome-wide association studies (GWASs) have identified more than 100 risk loci associated with SLE susceptibility (10, 11). Recently, whole exome sequencing (WES) and whole genome sequencing (WGS) have facilitated the identification of rare monogenic variants associated with SLE and lupus-like phenotypes with high penetrance (12-14). To date, more than 40 single gene mutations causing SLE/lupus-like syndromes have been discovered in humans with recessive and/or dominant modes of inheritance (14-16). Examples include genes important for complement deficiency (*e.g.* C1Q), apoptosis (*e.g.* FAS), nucleic acid degradation (*e.g.* DNASE1), nucleic acid sensing (*e.g.* RNASEH2A), and type I interferon (IFN) overproduction (*e.g.* TREX1) (15-17). Although monogenic lupus is rare, research on this disease can help to elucidate its pathogenesis. The long-term goal is to better explain SLE heterogeneity, to correlate genotype and phenotype and to develop a more personalised treatment strategy.

A systematic investigation of the genes for pSLE in China has never been performed; therefore, we conducted WES in 52 children with SLE, with the children coming from 22 provinces and autonomous regions in China. We discuss novel clinical insights gained from the genetic findings in each case, summarise the current knowledge of monogenic forms of SLE, and suggest clinical features that may alert clinicians to suspect monogenic aetiology and bioinformatics technicians to focus on candidate genes in SLE patients.

Materials and methods

The study was approved by the Ethics Committee at the Children's Hospital of Fudan University, Shanghai, China (ekyy-2011-091). All the patients' parents provided written informed consent for enrolment in this study.

Patients

All new patients were admitted to our center (Children's Hospital of Fudan University) from January 2011 to June 2019. The patients all fulfilled the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of SLE [18]. Demographic data, clinical manifestations, laboratory and histopathological findings, treatment, and outcome were documented. Patients were enrolled if they met one of the following criteria: 1. age of disease onset under 5 years; 2. family history of rheumatoid disease, including SLE, juvenile idiopathic arthritis, and Sjögren's syndrome; 3. syndromic SLE (additional comorbidities); and 4. complicating conditions, such as life-threatening or organ-threatening presentation or refractory SLE.

DNA sequencing

Genomic DNA was extracted and purified from peripheral leukocytes in whole-blood samples by a DNA isolation kit (Qiagen, Hilden, Germany). WES analysis and bioinformatic analy-

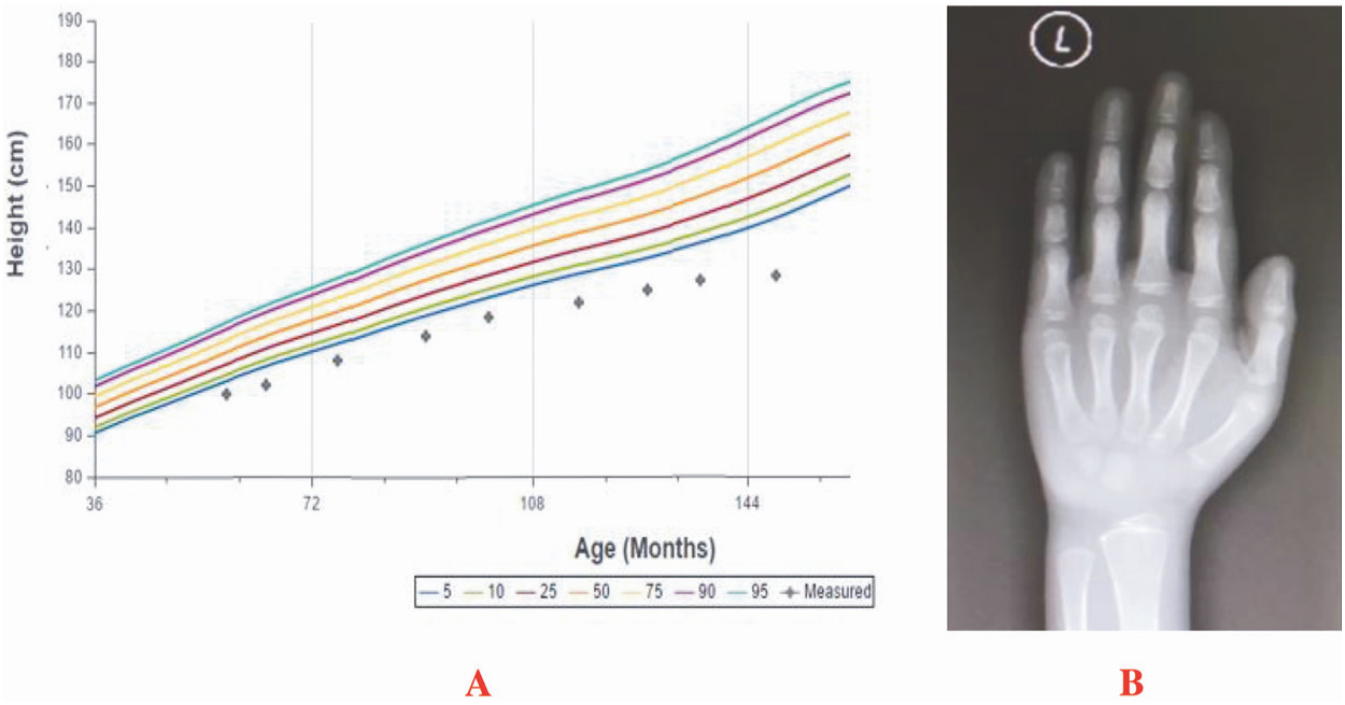

Fig. 1. Growth curve and bone age for patient 1. **A**: growth retardation, **B**: Bone age is 2.5 years at the age of 13 years.

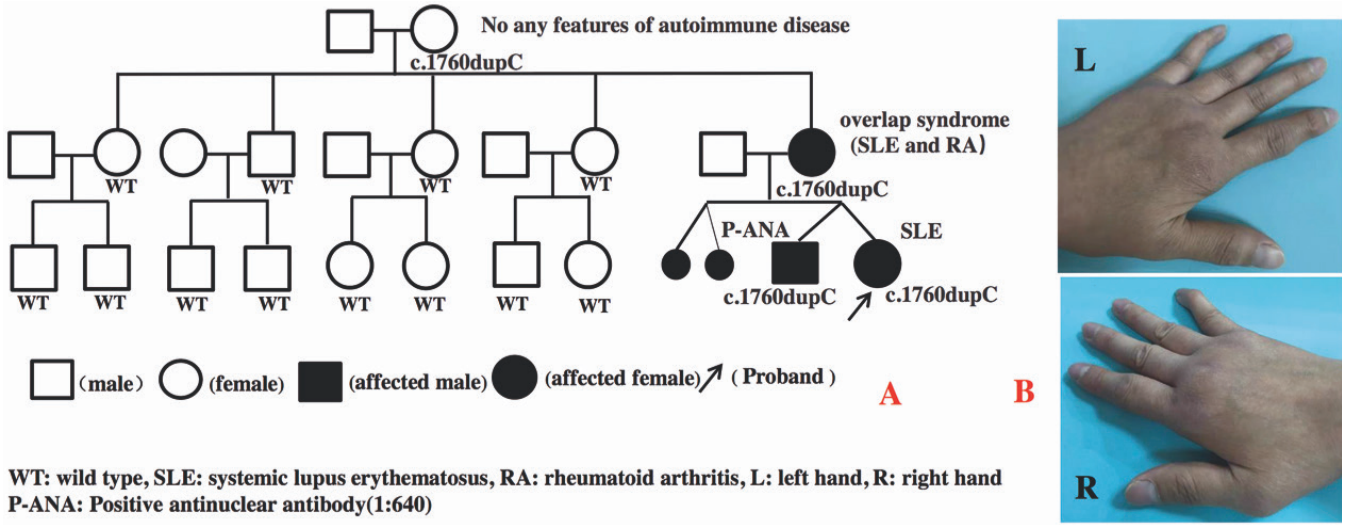

Fig. 2. A: Spectrum of family of patient 10; **B**: Patient's mother of deformities in the interphalangeal joints.

sis were performed in patient families as previously described (19). Only genes listed in OMIM (Online Mendelian Inheritance in Man: https://www.omim.org/) were considered to be candidate causative genes. Variants identified by WES analysis were confirmed by Sanger sequencing. The deleteriousness of the selected variants was subsequently predicted by various bioinformatics programs (SIFT, Polyphen2, and NetGene2, respectively), and the variants were retained if their changes to the resulting proteins were damaging.

Statistical analysis

Statistical analyses were performed using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) v. 22 and Microsoft Excel (Microsoft Office 2016 v. 16.0; Microsoft Corporation, Redmond, WA, USA). We used descriptive statistics, including the mean and standard deviation, to describe the study population as appropriate. Categorical variables are expressed as percentages (numbers). A p-value ≤ 0.05 was considered to be significant.

Results

Clinical characteristics

From January 2011 to June 2019, 281 new cases of childhood-onset SLE were diagnosed in our center. Fifty-two out of 281 newly diagnosed patients from 51 unrelated families met the inclusion criteria. There were 32 (57.1%) females and 20 males. The age of onset was under 5 years in 15 patients, between 5 and 12 years in 30 patients, and more than 12 years in 7 patients. Seven patients not only presented with SLE but also lymphoproliferation, such as hepa-

Table I. Demographic, clinical and immunological characteristics of the 52 SLE patients.

Characteristic	
Female gender, n (%)	32 (61.5%)
Age at diagnosis, mean ± SD	7.1 ± 3.7 yrs
Clinical manifestations, n (%)	
Mucocutaneous involvement	28 (53.8%)
Malar rash	20 (38.5%)
Photosensitivity	18 (34.6%)
Discoid rash	16 (30.7%)
Oral ulcers	15 (28.8%)
Arthritis	13 (25.0%)
Serositis	8 (15.4%)
Nephritis	33 (63.5%)
CNS involvement	7 (13.5%)
Haematological involvement	38 (73.1%)
Immunological manifestations, n (%)	
ANA positive	52 (100.0%)
Anti-dsDNA positive	30 (57.7%)
Anti-Sm positive	11 (21.2%)
Lupus anticoagulant positive	10 (19.2%)
IgG/IgM anticardiolipin positive	6 (11.5%)
IgM/IgG anti-B2GPpositive	8 (15.4%)
Low level of complement	37 (71.2%)

SD: standard deviation; CNS: central nervous system; ANA: antinuclear antibodies; anti-DsDNA: anti-double stranded DNA antibodies; anti-Sm: anti-Smith antibody; anti-B2GP: anti-beta 2 glycoprotein.

tomegaly and/or splenomegaly, and/or lymphadenectasis. One of these seven patients also presented with recurrent sinopulmonary infections, $CD4^+$ lymphopenia, EBV viraemia and elevated serum IgM before diagnosis of SLE. Five patients presented with syndromic SLE. Of these patients, four presented with recurrent vomiting and episodes of diarrhoea after weaning, poor feeding, aversion to protein-rich food, and failure to thrive. The other patient presented with short stature and abnormal bone age (see Fig 1). Fourteen patients had a family history of autoimmune disease (n=12) and non-autoimmune disease (n=2). Of these 14 patients, seven patients had a family history of SLE, and family members developed different autoimmune diseases in two patients' families. One family was reported before (20), and the other was first described in the study (Fig. 2). Thirty-six patients were assessed with SLEDAI scores greater than 15. Four patients presented with refractory SLE. Both renal and haematological involvement were found in 17 patients. The clinical and laboratory characteristics of the patients are summarised in Table I.

Whole exome sequencing

An average of 11.8 Gb of raw sequence data was generated with 93.62× depth of exome target regions for each individual as paired-end 150 base pair reads. A total of 92.1% of the raw date sequencing quality was above Q30. The coverage of at least 10× and 20× of the target regions was 99.68% and 97.62%, respectively. We identified causative mutations in 12 patients (12/52, 23.1%) in five different genes: SLC7A7 (n=4), NRAS (n=4), TNFAIP3 (n=2), PIK3CD (n=1), and IDS (n=1). Three compound heterozygous mutations and one homozygous mutation in the SLC7A7 gene were detected in four patients (Table II). The same heterozygous c.38 A>G mutation (p.G13C) in the *NRAS* gene were identified in four patients. Two *de novo* mutations, c.559C>T and c.1760dupC in the TNFAIP3 gene, were found in two patient families. Another two heterozygous mutations, c.820G>C in the *IDS* gene and c.3061G>A in the *PIK3CD* gene, were detected in two patients. No mutations in other genes associated with primary complement deficiency were identified in all patients. The genotypes and phenotypes of the 12 patients with mutations are summarised in Table II. The *p*-values for gene mutations between groups in children with SLE are summarised in Table III. Five patients with mutations had a family history (5/14, χ^2 score=0.89, *p*-value=0.346). Two out of 5 patients had a family history of autoimmune disease, in which members developed different autoimmune diseases (Fig. 2).

Sanger sequencing

All mutations were confirmed by Sanger sequencing in 12 families. Using DNA extracted from somatic cells (nails and buccal mucosa) in patients with *NRAS* mutations, *NRAS* exon 1 was amplified by PCR, and then the products were cloned. Mutated alleles were observed less frequently in the buccal mucosa and nails (42.8 and 8.8%, respectively) than in the blood (52.0%) in one patient. Similar results were found in three other patients (21). All mutations were checked in mutation databases on human populations, such as ExAC Browser (http://exac.broadinstitute.org/), 1000 Genomes (http://www.internationalgenome.org/), and HGMD (http://www.hgmd.cf.ac.uk/ac/index.php). Three mutations, c.1085T>C (p.L362P) in the SLC 7A7 gene, c.1760dupC in the TNFAIP3 gene, and c.820G>C (p.E274Q) in the IDS gene were not found in the above mutation databases.

Functional prediction

The missense mutations p.L362P and p.E274Q were assessed via SIFT and PolyPhen-2 for their potential to disrupt protein function (Fig. 3).

Discussion

SLE is a prototype autoimmune disease with extreme clinical heterogeneity and

Table II. *p*-value for gene mutations between groups in children with SLE.

Groups	less than 5 years (n=15)	5–12 years (n=30)	more than 12 years (n=7)	family history (n=14)	Syndromic SLE (n=5)	PID (n=5)	SLEDAI score >14 (n=36)	haematological and renal involvement (n=17)
Positive (n)	8	4	0	5	5	5	12	9
χ^2	8.61	3.72	1.16	0.89	13.96	13.96	5.18	3.90
p-value	0.003	0.051	0.28	0.346	0.000	0.000	0.023	0.048

PID: primary immunodeficiency disease.

Table III. Phenotypes and genotypes in 12 SLE patients with a single gene mutation.

Case	Gender	Age at onset (y)	Clinical manifestations	Immunologic manifestations (positive)	Gene	Nucleotide change	Amino acid change	Type of mutation	Mutation origin	Family history
1	F	4.9	Fever, haematological and renal involvement	ANA, anti-dsDNA, and SSA	SLC7A7	NM_001126106 c.625+1G>A	-	Hom	P and M	LPI
2	F	6.1	Fever, arthritis, CNS involvement	ANA, anti-dsDNA, anti-Sm, SSA, Coombs' test, and low complement	SLC7A7	c.625+1G>A c.235G>A	- p.G79R	Het Het	P M	No
3	M	6.1	Haematological, renal and CNS involvement	ANA, SSA , SSB, Coombs' test, and low complement	SLC7A7	c.625+1G>A c.1085T>C	- p.L362P	Het Het	P M	ITP
4	F	2.6	Haematological involvement	ANA, Coombs' test, and low complement	SLC7A7	c.1387delG c.1215G>A	p.V463Cfs56 p.W405X	Het Het	P M	LPI
5	M	1.5	Fever, arthritis, rash haematological and renal involvement	ANA, and anti-dsDNA,	NRAS	NM_002524 c.38G>A	p.G13D	Het	D	No
6	M	4.0	Haematological and renal involvement	ANA, anti-dsDNA, anti-nucleosome, MPO, lupus anticoagulant, and low complement	NRAS	c.38G>A	p.G13D	Het	D	No
7	M	3.0	Rash, haematological and renal involvement	ANA, anti-dsDNA, anti-Sm, Coombs' test, lupus anticoagulant and low complement	NRAS	c.38G>A	p.G13D	Het	D	No
8	F	1.2	Fever, haematological and renal involvement	ANA Coombs' test, and low complement	NRAS	c.38G>A	p.G13D	Het	D	No
9	F	7.0	Fever, hydropericardium, haematological, and renal involvement	ANA, SSA, MPO, p-ANCA, anticoagulant antibody, and low complement	TNFAIP3	NM_006290 c.559C>T	p.Q187X	Het	P	IBD-AR
10	F	2.2	Rash and haematological involvement	ANA, SSA and low complement	TNFAIP3	c.1760dupC	p.P587Pfs*85	Het	M	OS (SLE, RA)
11	M	10.0	Fever, haematological and renal involvement	ANA, anti-dsDNA, and Coombs' test.	PIK3CD	NM_005026 c.3061G>A	p.E1021K	Het	D?	No
12	M	4.5	Rash, haematological and renal involvement	ANA, Coombs' test, lupus anticoagulant and low complement	IDS	NM_00202 c.820G>C	p.E274Q	Het	D	No

P: paternal; M: maternal; D: *de novo*; OS: overlap syndrome; ITP: idiopathic thrombocytopenic purpura.

significant differences between populations (22). In this report, we describe a cohort of patients who had phenotypic heterogeneity. However, the clinical and laboratory data in all patients fulfilled four 2012 SLICC criteria for the classification of SLE (18). The average age at onset was 5.0 years (range from 1.2 to 10.0 years). In our study, we identified causative mutations in 12 patients (12/52, 23.1%) in five different genes: SLC7A7 (n=4), NRAS (n=4), TNFAIP3 (n=2), PIK3CD (n=1), and IDS (n=1). No mutations in other genes, including genes associated with primary complement deficiency, were identified in all patients.

SLE pathogenesis can be split into two distinct processes: (1) loss of tolerance to self-antigen and generation of autoantibodies and (2) pathogenic autoantibodies and immune complexes that result in inflammation and tissue damage and organ failure (23, 24). Five patients presented with syndromic SLE. Although four patients presented with recurrent vomiting and episodes of diarrhoea after weaning, poor feeding, aversion to protein-rich food, and failure to thrive, their parents did not pay attention to them. The patients were admitted to our centre because of the SLE phenotype. We performed WES for these patients due to the above symptoms, which could not be explained by inflammation. WES revealed three compound heterozygous mutations and one homozygous mutation in the SLC7A7 gene in these four patients (see Table II). Solute Carrier Family 7 Member 7 (SLC7A7) is a protein coding gene. Lysinuric protein intolerance (LPI) is a rare autosomal recessive disease caused by mutations in the SLC7A7 gene encoding the cationic amino-acid transporter subunit y+LAT1. Autoimmunity and immunological abnormalities have been observed in patients with LPI, including SLE (25, 26). Metabolic derangement may cause immunological abnormalities in LPI. Therefore, when multisystem involvement is observed in LPI patients, SLE should be considered a rare complication. One SLE patient

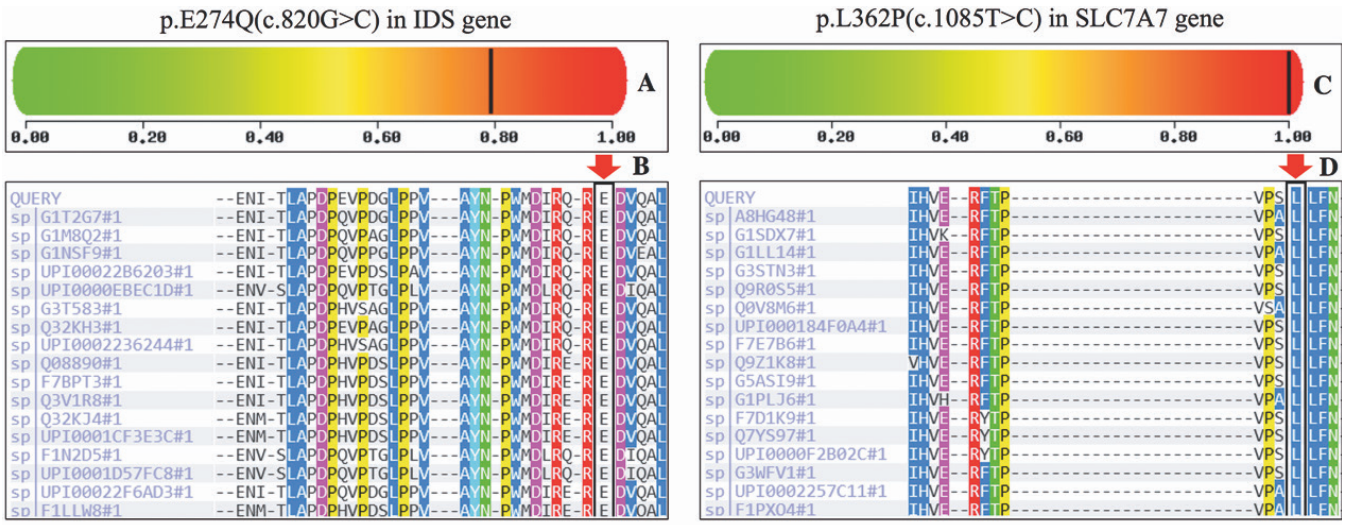

Fig. 3. Functional prediction for two mutation by PolyPhen-2.
A: This mutation is predicted to be possibly damaging with a score of 0.792 (sensitivity: 0.85; specificity: 0.93);
B: Alignment of the mutated p.E274Q IDS protein with different species shows the complete conservation of the amino acid by arrow;
C: This mutation is predicted to be probably damaging with a score of 1.000 (sensitivity: 0.00; specificity: 1.00);
D: Alignment of the mutated p.L362P SLC7A7 protein with different species shows the complete conservation of the amino acid by arrow.

presented with short stature and abnormal bone age (Fig. 1), which could not be explained by inflammation. WES revealed a *de novo* c.820G>C (p.E274Q) mutation in the IDS gene in the patient. This mutation is ~~also~~ damaging for the IDS protein, as predicted by the PolyPhen and MutationTaster software. Diseases associated with IDS include lysosomal storage disease and mucopolysaccharidosis type II (MPS II). MPSI II has been reported in both a child and an adult with SLE (27, 28). Two rare disorders were simultaneously diagnosed in one patient, but there is no known association between the IDS gene and connective tissue disorders of any sort. Thus, further research is warranted. Five out of 52 patients who underwent gene testing presented with syndromic SLE. However, all of the patients were found to have causal mutations (5/5, χ^2 score=13.96, *p*-value=0.000). We also recommend that gene testing be performed in patients with syndromic SLE, as reported previously (29).

SLE has familial aggregation. The concordance rate in monozygotic twins (24%) is approximately 10-fold higher than in dizygotic twins (2%) (30, 31). In our study, 14 patients had a family history of autoimmune disease (n=12) and non-autoimmune disease (n=2). However, only 5 out of 14 patients with a family history were found to have causal mutations (p=0.346). Interestingly, no pathogenic mutations in genes associated with monogenic SLE were detected in seven patients with a family history of SLE, whereas causal mutations in the SLC7A7 gene were identified in three patients with a family history of LPI or ITP and in the TNFAIP3 gene in two patients whose family members developed different autoimmune diseases (Table II and Fig. 2). One family with the TNFAIP3 gene mutation was reported in our previous study (20), and the other with the c.1760dupC (p.P587Pfs*85) mutation was first reported in this study. The mutation is a novel and frameshift mutation. The patient's mother with c.1760dupC presented with overlap syndrome (SLE and rheumatoid arthritis, Fig. 2), and her brother had positive ANA (1:640) and no features of autoimmune disease. However, the patient's grandmother with c.1760dupC did not have any autoimmune diseases. Incomplete penetrance may explain this phenomenon. Therefore, we should pay more attention to patients with a family history of different autoimmune diseases.

We identified a somatic activating *NRAS* mutation (c.38 A>G, p.G13C) in four patients at levels ranging from 8.8% to 42.8% in variant tissues, and the mutation was absent from their parents. BCL-2-Interacting Mediator of Cell Death (BIM) levels in peripheral blood mononuclear cells (PBMCs) from four patients were markedly reduced, whereas those in the control were normal. These four patients not only presented with SLE but also lymphoproliferation, such as hepatomegaly and/or splenomegaly, and/or lymphadenectasis. The patients were diagnosed with RAS-associated autoimmune leukoproliferative disease (RALD) based on lymphoproliferation, autoimmune cytopenia, and without a defect in FAS-dependent apoptosis or an increase in peripheral αβ-DNT cells. This finding has been published (21). A heterozygous mutation, c.3061G>A (p.E1021K), in the PIK3CD gene was detected in a patient who presented with recurrent sinopulmonary infections, $CD4^+$ lymphopenia, lymphadenopathy, EBV viraemia and elevated serum IgM before the diagnosis of SLE. The patient was also reported in our previous study (32). Primary immunodeficiency diseases (PIDs) were diagnosed in four patients with somatic *NRAS* mutations and one patient with PIK3CD gene mutations. Initially, PIDs and autoimmune diseases (ADs) were considered independent or even polar opposites. However, due to genetic advances and a greater understanding of the pathophysiological processes involving T-cell development, immune tolerance, T-cell

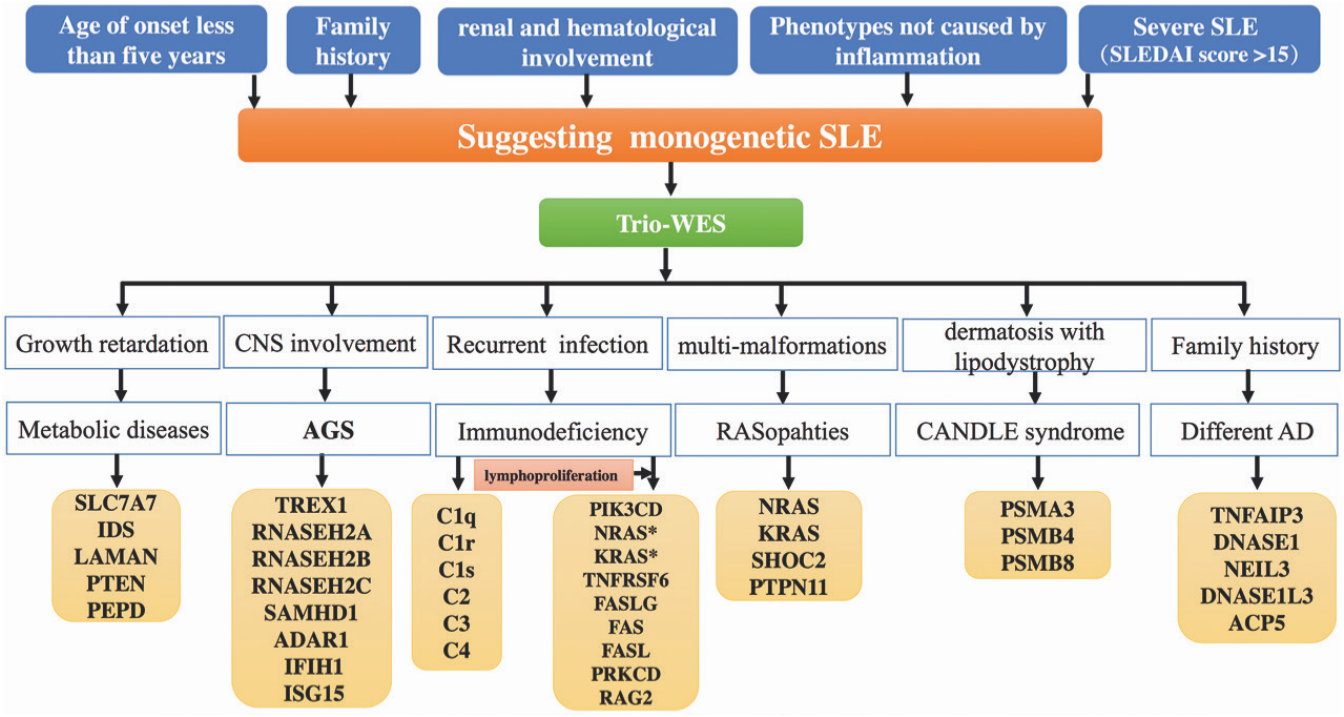

Fig. 4. Flow chart of gene testing and analysis for pSLE. AD: autoimmune diseases, AGS: Aicardi-Goutières syndrome; CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CNS: central nervous system. *somatic mutation.

signaling, complement pathway and inflammation, they are now accepted as interconnected processes that share some common mechanisms (33, 34). Patients with PIDs have an increased susceptibility to infectious diseases and noninfectious complications, including allergies, malignancies and ADs, with the latter being the first manifestation of PIDs in several cases (32, 35). Five patients with PID all had causal mutations (5/5, χ^2 score=13.96, *p*-value=0.000) in our study. Thus, we should monitor children with SLE for PIDs.

pSLE is rare, with a reported incidence of 0.3-0.9 per 100, 000 children per year and a prevalence of 3.3–24 per 100 000 children (36). Disease onset in paediatric SLE most frequently occurs between the ages of 12 and 18 years, is uncommon before the age of 10 years and is very rare before 5 years (6, 37). Early-onset SLE may reveal monogenic pathologies (6, 29). Our findings revealed causal mutations in 8 out of 15 patients under five years of age (8/15, χ^2 score=8.61, *p*-value=0.003), 4 out of 30 patients between 5-12 years of age (4/30, χ^2 score=3.72, *p*-value=0.051), and 0 out of 7 patients more than 12 years old. Our results also suggest that early-onset SLE may suggest a genetic aetiology. In addition to the susceptibility of SLE itself, several genotype-phenotype analyses have shown that the specific phenotypes of SLE can also be influenced by genetic factors (29, 38). This rare variant of SLE generally presents with early onset severe disease, especially affecting the kidneys and central nervous system (39, 40). However, our findings revealed that 9 out of 17 patients with renal and haematological involvement had causal mutations (9/17, χ^2 score=3.9, *p*-value=0.048). Our results revealed that SLE with renal and haematological involvement may suggest a genetic aetiology. The SLE Disease Activity Index (SLEDAI) is the most widely used disease activity measure in international multicenter trials (41). An SLEDAI score greater than 14 suggests severe disease activity. There were 36 patients with SLEDAI scores greater than 14 in our study, including all 12 patients with causal mutations (12/36, χ^2 score=5.18, *p*-value=0.023). Therefore, severe SLE should also be on the alert for a genetic aetiology.

The first monogenic SLE cases to be identified were inherited complement deficiencies, which predisposed patients to lupus due to impaired tolerance and aberrant clearance of apoptotic bodies and immune complexes (42). The first familial cases of SLE in children due to C1 deficiency were described in the 1970s (43). Lupus-like manifestations have been associated with inherited deficiencies in many classical pathway complement components, including C1q, C1r, C1s, C2, C3, C4A, and C4B (44-47). It is estimated that the prevalence of autoimmunity with lupus-like manifestations is 90% in C1q deficiency, 65% in C1r-C1s deficiency, 10% in C2 deficiency and 75% in C4 deficiency (48). Genetic defects in the complement system are the most common cause of monogenic SLE in America and Europe (29, 44, 47). However, no defects in the complement were found in our study, suggesting genetic heterogeneity in different races. Characteristically, these patients with complement defects develop at an early age, and many have severe cutaneous involvement and severe and recurrent infections with high mortality. Immunologically, most C1q-deficient patients had normal C3 and C4 levels, positive ANA, and extractable nuclear antigen antibodies (ENA; especially

anti-Ro/SSA) and a low frequency of positive anti-dsDNA. Twenty-five and 30 out of 52 patients had low levels of C3 and C4 and positive anti-dsDNA in our study, respectively. These patients' manifestations are different from those in patients with inherited complement deficiencies. Therefore, our study revealed genetic heterogeneity in children with SLE.

An increasing number of candidate genes associated with SLE have been identified, but genetic mutations that cause the disease in a Mendelian fashion account for only a small percentage of SLE cases; although the gene sequencing cost is gradually decreasing, it is relatively high in developing countries, especially in underdeveloped countries. Therefore, WES cannot be performed for every patient with SLE by physician. Optimal use of WES in pSLE requires an understanding of who should be considered for testing and when it should be performed to maximise clinical utility and cost-effectiveness. We recommend that monogenic SLE should be suspected in patients with very early onset SLE (<5 years of age), syndromic SLE, severe SLE (SLEDAI score >14), family history of autoimmune disease, and renal and haematological involvement (Fig. 4). Paediatricians or rheumatologists of children should pay more attention to different candidate genes based on phenotypes (Fig 4). For instance, patients with complement deficiency always present with early onset, recurrent pyogenic infections, cutaneous rash, and glomerulonephritis, but a low rate of anti-dsDNA and gene complement deficiency should be suspected in patients with these features.

Conclusions

Our findings show a significant detection rate for monogenic aetiologies using WES and reveal broad genetic heterogeneity in clinically complex cases of pSLE. These results highlight the importance of genetic diagnosis, especially for children with very early onset SLE (<5 years of age), syndromic SLE, severe SLE (SLEDAI score >14), family history of autoimmune disease, and renal and haematological involvement. Pursuing WES as part of the diagnostic approach in specific cases of pSLE (Fig. 4) provides opportunities for an accurate and early aetiology-based diagnosis that can improve clinical management. An unbiased genetic screening of larger cohorts of patients with diverse clinical manifestations is needed to better estimate the prevalence of monogenic aetiology for paediatric SLE.

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