

**Research Article****Monogenic systemic lupus erythematosus associated with DNASE1 gene mutation: a case report and literature review**

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**Abstract**

A retrospective analysis of the clinical features and genetic test results of a child with monogenic systemic lupus erythematosus (SLE) associated with a mutation in the deoxyribonuclease 1 (DNASE1) gene who presented to the First People's Hospital of Jingzhou City, Hubei Province in July 2021. The child was a female, 1 year and 5 months old, with recurrent fever, facial erythema, lupus-like rash on the trunk, positive for anti-nuclear and anti-Sm antibodies, and whole exon sequencing results suggested that the SLE susceptibility gene DNASE1, chr16:3705860, had a G>A mutation at locus c.158, and generation sequencing family verification presumed that the heterozygous mutation originated from the mother. This mutation has not been reported in China and expands the spectrum of pathogenic variants in SLE in China.

**Key words:** Systemic lupus erythematosus; monogenic lupus; DNASE1

**Introduction**

Systemic lupus erythematosus (SLE) in children is an autoimmune disease that can involve multiple systems, and its pathogenesis is genetically related, with single mutations causing the disease being extremely rare [1]. No cases of SLE associated with mutations in the deoxyribonuclease 1 (DNASE1) gene have been reported in China, and only four cases have been reported abroad [2-3]. One case of monogenic SLE in a young child associated with DNASE1 mutation was diagnosed in our hospital through clinical features, autoantibody examination and genetic testing, and the diagnosis and treatment of this case are reported below.

**Case Presentation**

A female child, 1 year and 5 months old, was admitted to our department on July 31, 2021, because of "a generalized rash found for more than 20 days with fever for more than 4 hours". The child had red masses of erythema on the trunk and extremities for more than 20 days without any obvious cause, no itching or pain, no significant relief of rash without special treatment, and fever appeared 4 hours before admission. Physical examination: body temperature 38°C, acute

disease face, dark red spots on the upper limbs, superficial vesicles, dryness, scaling, peripheral papules, papules, scaling and erythema visible on the fingertips, back and feet bilaterally (Figure 1A, Figure 1B), past history: the child has been hospitalized 8 times for recurrent infections since the age of 8 months, and is currently growth retarded and malnourished. The child's aunt has a history of systemic lupus erythematosus. She denied previous history of recurrent rash and oral ulcers, and denied family history of hereditary disease. Ancillary examinations: routine blood: WBC 10.91\*10<sup>9</sup>/L, N% 45.04%, RBC 4.98\*10<sup>12</sup>/L, HGB 124g/L, PLT 182\*10<sup>9</sup>/L. Hypersensitivity CRP <0.50mg/L. ESR: 23mm/h. Liver enzymes and cardiac enzymes: ALT 194U/L, AST 353U/L, LDH CTnI 117.40pg/ml. renal function and electrolytes were normal. T lymphocyte subsets: CD3+ 47.59%, CD3+CD4+ 29.07%, CD3+CD8+ 14.72%, CD3-CD19+ 25.62%, CD3 (CD16+ /CD56+) 20.01%, CD3+CD4+/CD3- CD8+ 1.97. Complement C3 and C4 were normal. Urine routine: weakly positive for protein. Blood culture was negative. Electrocardiogram: sinus rhythm with T-wave changes in some leads. Ultrasound of heart, liver, gallbladder and spleen showed no abnormality. Chest CT: multiple infectious lesions in both lungs.

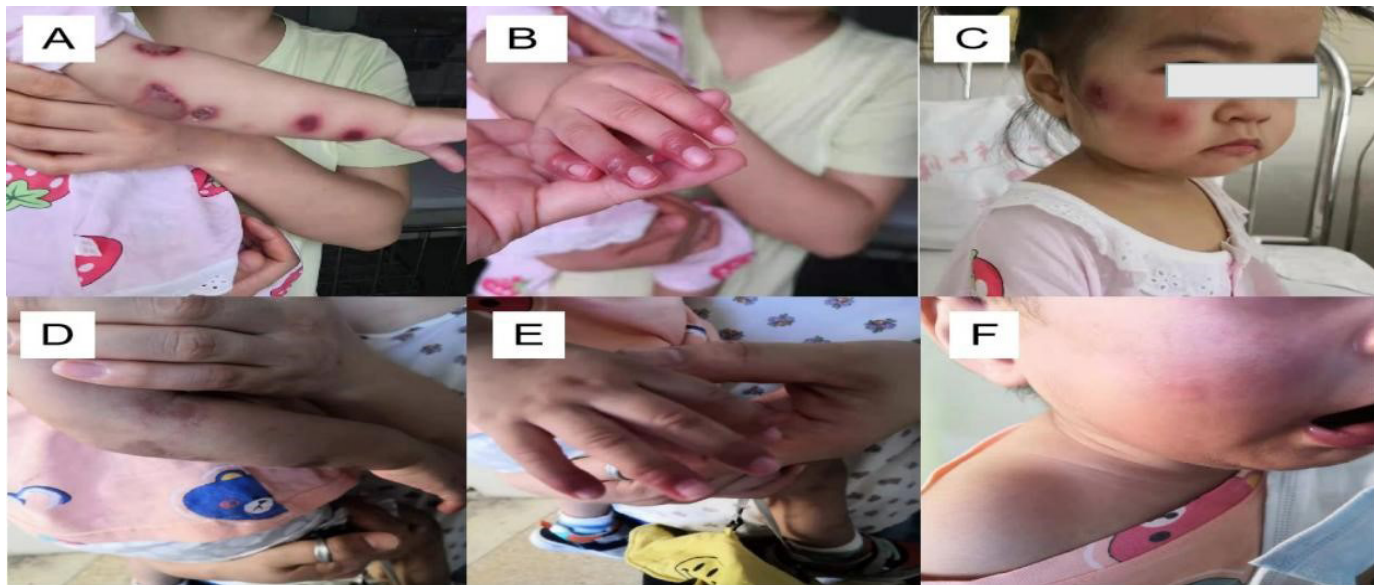
She was given symptomatic treatment such as anti-infection, liver protection, and myocardial nutrition, etc. The routine blood tests and CRP did not show any significant abnormality, but she still had recurrent fever, and the erythema of bilateral fingers and fingers, back and feet did not fade significantly. New erythema appeared on the right cheek (Figure 1C) with right eyelid edema, positive for anti-nuclear and anti-Sm antibodies. She was diagnosed with SLE and was treated with oral prednisone (5 mg/dose, 2 times/day). The fever gradually improved and the rash faded. Given the young age and early onset of the disease, monogenic lupus was considered a high probability, and the results of the perfect whole exome reanalysis returned: gene name: DNASE1, chromosomal locus: chr16:3705860, nucleotide change: c.158G > A, ACMG variant rating: unknown significance, associated disease: SLE susceptibility. One generation sequencing genealogical verification: heterozygous mutation at position chr16:3705860 in the prior witness and mother, and wild type in the father at this locus (Figure 2). hematocrit was normal and the rash faded significantly at our hospital on September 20 (Figure 1D, Figure 1E, Figure 1F).

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Received: July 28, 2022

Published: August 15, 2022

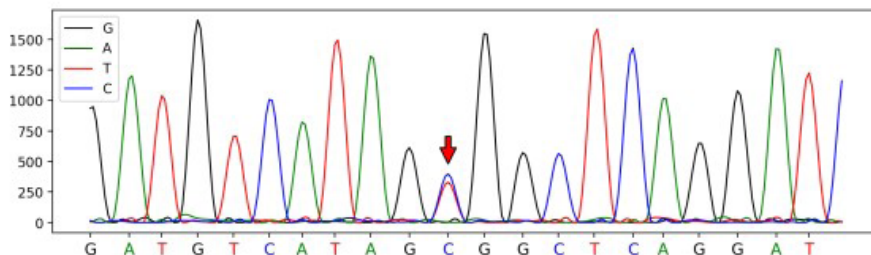
**Citation:** Tang Ling-ling, Pan Yan, Liu Shan, Fan Qi-hong . Monogenic systemic lupus erythematosus associated with DNASE1 gene mutation: a case report and literature review. *Int Clin Img and Med Rew.* 2022; 2(5): 1093.



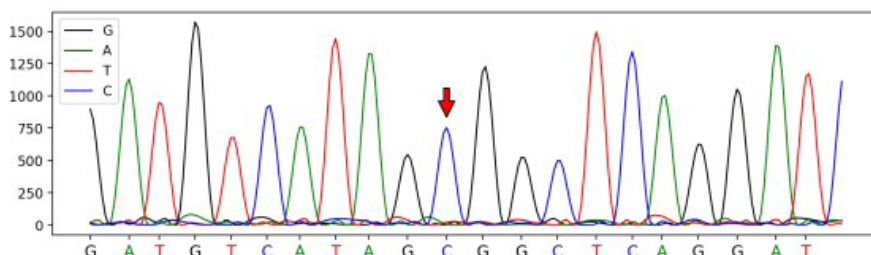
**Figure 1: Systemic skin lesions**  
A: dark red spots on the upper extremities with superficial vesicles, dryness and scaling adherence; B: erythema on the fingertips; C: erythema on the cheeks.  
The rash on the upper limbs (D), fingers (E) and cheeks (F) faded significantly at our follow-up examination on September 20.

**验证位点 : DNASE1,c.158G>A, 染色体位置 : chr16:3705860**

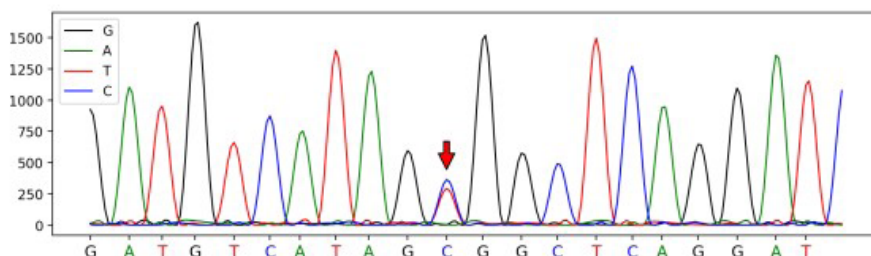
**先证者 : 在 chr16:3705860 位置存在杂合突变**



**父亲 : 在 chr16:3705860 位置为野生型**



**母亲 : 在 chr16:3705860 位置存在杂合突变**



**Figure 2: Next generation sequencing family validation diagram**

## Discussion

SLE is an autoimmune disease characterized by excessive autoantibody production, immune complex deposition and multi-organ involvement, and its etiology and pathogenesis are still unclear and may be due to the interaction of genetic, environmental and immune activation, with genetic factors playing an important role in the pathogenesis of SLE [4]. In recent years, with the development of genetic testing technology, more and more single genes have been found to be closely associated with susceptibility to SLE, especially in early-onset, familial and rare cases of SLE [5], and more than 30 single genes have been reported to be associated with SLE [6], such as TREX1, STING, DNASE1, DNASE1L3, etc. [7-8]. In 2011, French scholars Alexandre Belot et al. first introduced the concept of monogenic lupus, which is a general term for a class of diseases in which heterozygous or pure mutations in a single gene cause abnormalities or deletions in the associated nucleic acid or protein it encodes, resulting in clinical manifestations of lupus-like manifestations such as rash, nephritis, and pneumonia [9]. The main mechanisms that have been reported for the pathogenesis of monogenic lupus are complement defects, impaired immune tolerance of T and B lymphocytes, abnormal apoptosis and nucleic acid degradation, and overproduction of interferons [6].

DNA nucleases play an important role in the maintenance of immune tolerance and in the recognition and clearance of DNA from foreign pathogens, and mutations in any of the genes encoding DNA nucleases can lead to impaired immune tolerance and abnormal accumulation of DNA degradation products, thereby inducing autoimmune disease. DNASE1 is an endonuclease widely present in blood and urine, and animal studies have found that DNASE1 gene knockout mice eventually develop a lupus-like phenotype with antinuclear antibodies and glomerulonephritis [10]. No cases of SLE with DNASE1 mutations have been reported in China, but four cases of SLE with DNASE1 mutations have been reported abroad (two cases with G>A mutation at exon 2, site 172, one case with deletion at exon 2, 46\_72, and one case with G>A mutation at site 1760 combined with T>C mutation at site 1785), all of which exhibited high titers of antinucleosomal antibodies and also detected DNASE1 mutations are a very rare lupus gene mutation, and a UK cohort study of 170 SLE patients with genetic sequencing did not identify DNASE1 mutations [11]. The mechanism by which DNASE1 mutations contribute to the pathogenesis of SLE is unclear and may be related to DNASE1 deletion leading to extracellular nucleic acid. These nucleic acids are recognized by DNA sensors such as toll-like receptors (TLR7 and TLR9), which in turn promote the production of type I interferons, and may also be associated with reduced DNASE1 enzyme activity following DNASE1 mutations [2,9]. The girl was 1 year and 5 months old with recurrent fever, lupus-like rash, positive antinuclear and anti-Sm antibodies, meeting four of the 1997 American College of Rheumatology revised SLE classification criteria (buccal erythema, discoid erythema, positive anti-Sm antibodies, and abnormal antinuclear antibody titers), and a clear clinical diagnosis of SLE. DNASE1, an SLE susceptibility gene, was later detected by whole exome sequencing. chr16:3705860, G > A mutation at locus c.158, confirmed the diagnosis of monogenic SLE, and the heterozygous mutation was presumed to originate from the mother by generation sequencing family lineage verification. The heterozygous

mutation in the DNASE1 gene at c.158 is the first case of SLE in a child with SLE, and we hypothesize that the mutation in this locus leads to a reduction in DNASE1 activity, resulting in the development of a lupus-like phenotype. Considering that the detection of DNASE1 protein may be interfered by hormones and that there is controversy in the foreign literature as to whether DNASE1 mutations play a role through reduced DNASE1 enzyme activity [12], we did not measure DNASE1 activity further and further studies are needed to verify the correlation between the two.

## Conclusion

For children with early-onset SLE, emphasis should be placed on the adoption and promotion of gene sequencing technologies, which can screen for risk genes and identify new susceptibility genes in children with SLE and provide a theoretical basis for the development of targeted biological agents for SLE.

## Funding

This work was supported by Hubei Pediatric Alliance Medical Research Project(HPAMRP202117).

## Conflict of Interest

Authors had no conflicts of interest to declare.

## Patient consent

Obtained.

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