

## Identification of a novel mutation in complement receptor 2 in Chinese familial systemic lupus erythematosus

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### ABSTRACT

**Objectives:** This study aims to analyze the relationship between complement receptor 2 (CR2) gene mutation and the clinical phenotype in Chinese familial systemic lupus erythematosus (SLE).

**Patients and methods:** A total of one Chinese familial SLE patients (median age: 30.25 years; range, 22 to 49 years) were included between January 2017 and December 2018. The clinical features and diagnoses of familial SLE patients were analyzed using whole-exome sequencing (WES) of genomic deoxyribonucleic acid (DNA) samples. Sanger sequencing was used to verify candidate mutations detected in the examined family.

**Results:** The mother and her three daughters were diagnosed with SLE. The clinical characteristics showed that the patient and her mother were diagnosed with lupus nephritis. The eldest daughter had decreased renal function and lower serum albumin levels. Immunological index analysis showed that all four patients were positive for anti-SSA and antinuclear antibody (ANA), but that only the second daughter was positive for anti-double-stranded DNA (dsDNA). Complement 3 (C3) was significantly decreased in all patients, while evaluation of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) showed that the second and third daughters had mild active SLE. The mother and eldest daughter were treated with prednisolone combined with cyclophosphamide, while the other two daughters were treated with prednisolone alone. The WES and Sanger sequencing analyses revealed an unreported missense T>C mutation c.2804 in the 15<sup>th</sup> exon of the CR gene in all four patients.

**Conclusion:** We identified a novel c.2804 (exon 15) T>C mutation in the CR gene of Chinese familial SLE. This mutation was previously reported, suggesting that the CR gene c.2804 (exon 15) T>C mutation is the probable cause of SLE in this family.

**Keywords:** Complement receptor 2, mutation, sequencing, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is an autoimmune disease with a variety of clinical manifestations that can affect various bodily organs and tissues.<sup>1</sup> The incidence of SLE varies from 0.3/100,000 person-years to 23.2/100,000 person-years worldwide, and women are more frequently affected by age and ethnic group.<sup>2</sup> The etiology of SLE has not been well understood; genetic constitution, environmental triggers, and hormone milieu have been reported to contribute to disease development and activity.<sup>3</sup>

The pathogenesis of SLE is complex, involving the innate and adaptive immune systems, autoantibodies, and immune complexes, as well as the complement system.<sup>4</sup> In addition, different genetic and environmental factors are involved in its disease pathogenesis.<sup>5</sup>

Cumulating evidence shows that genetic factors play a central role in SLE. Previous studies have shown that lupus susceptibility is related to genetic factors, and several susceptibility sites

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have been clearly identified.<sup>6,7</sup> However, current genetic research cannot explain the entirety of SLE heritability, and other associated gene susceptibilities remain largely unknown.<sup>8</sup> Clinical observations indicate that complement activation is a core process in human SLE, with approximately 75% of SLE patients showing low C3 and C4 levels, particularly when renal is involved.<sup>9</sup>

Human complement receptor 2 (CR2) is encoded by a single gene with 20 exons located on chromosome 1q32.2.<sup>10</sup> A previous study demonstrated that CR2 could bind C3 degradation products during complement activation,<sup>10</sup> suggesting that CR2 might play an essential role in immunity.<sup>11</sup> Additional studies showed that polymorphisms of the CR2 gene were associated with osteonecrosis in SLE<sup>12</sup> and that polymorphisms such as rs3813946, rs1048971, and rs17615 were associated with lupus susceptibility in Caucasian and Chinese lupus patients.<sup>13</sup>

Next-generation sequencing technologies have been widely used for sequencing exomes, transcriptomes, and genomes,<sup>14</sup> particularly in the mutant landscape of genetic diseases.<sup>15,16</sup> In this study, we aimed to report the analysis of familial SLE by whole-exome sequencing (WES) and the discovery of a novel c.2804 (exon 15) T>C mutation in the CR2 gene.

## PATIENTS AND METHODS

This retrospective study was conducted at Three Gorges Hospital, Department of Nephrology between January 2017 and December 2018. A total of one Chinese familial SLE patients (median age: 30.25 years; range, 22 to 49 years) were enrolled in this study.

### WES and deoxyribonucleic acid (DNA) sequence analysis

Genomic DNA was extracted from the peripheral blood of the patients using the QIAamp Blood DNA Mini Kit (QIAGEN S.p.A, Milano, Italy) according to the manufacturer's instructions. The whole-exome library was constructed using the IDT xGen<sup>®</sup> Exome Research Panel V1.0 (IDT, Iowa, USA) and sequenced on an Illumina Nova Seq 6000 series sequencer (Illumina, USA), with a sequencing coverage of

the target sequence that was  $\geq 99\%$ . For mutation annotation and pathogenicity prediction, the raw data were cleaned and compared with the National Center for Biotechnology Information's Human Reference Genome (HG19) using the BWA software package. Synonymous changes and single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF)  $\geq 5\%$  were removed (<http://www.ncbi.nlm.nih.gov/projects/SNP>). Non-synonymous changes were filtered using the SIFT software (<http://sift.jcvi.org>). Analysis of the function of mutated genes, their relationship to disease, and the interpretation of sequencing variations were based on guidelines from the American College of Medical Genetics and Genomics and the As Association for Molecular Pathology.

### Mutation confirmed by Sanger sequencing

Sanger sequencing was used to verify suspected pathogenic mutations. The polymerase chain reaction (PCR) products were sequenced using ABI 3730XL and analyzed using the DNASTAR software.

## RESULTS

### The clinical characteristics of the familial SLE

The baseline characteristics of the four family members, including the patient's mother (Ia, mother), IIa (eldest daughter), IIb (middle daughter), and IIc (youngest daughter), are listed in Table 1 and Figure 1a. The proband patient (IIa, eldest daughter) was a 26-year-old woman who visited our department and reported a history of SLE. The mother and three daughters were all diagnosed with SLE according to the European League Against Rheumatism (EULAR) SLE 2012 criteria.<sup>17</sup> The patient and her mother had lupus nephritis. Patient's mother and she had mild hypertension. The proteinuria in the mother was nephritic proteinuria, while the proband patient showed nephrotic proteinuria. The patients all showed a mild decrease in estimated glomerular filtration rate (eGFR) and low serum albumin levels. Our laboratory findings showed that all four patients were positive for the anti-SSA and anti-nuclear (ANA) antibodies, but the titers of ANA varied among the four patients. All patients showed hypocomplementemia, with titers of the

**Table 1.** Baseline information of the familial SLE

	Ia	Ila	Ilb	Ilc
Sex	Female	Female	Female	Female
Age (year)	49	26	24	22
Hypertension (mmHg)	143/95	145/107	118/72	NO
Disease history	1 year	1 month	1 year	1 year
White blood cell ( $\times 10^9/L$ )	14.56	14.89	5.53	4.35
Hemoglobin (g/L)	132	122	123	136
Platelet ( $\times 10^9/L$ )	330	273	204	246
Creatinine ( $\mu\text{mol/L}$ )	58	97.9	62.7	44
Albumin (g/L)	38	26.3	47.4	43.7
eGFR ( $\text{mL}/\text{min}/1.73 \text{ m}^2$ )	95.84	59.57	101.26	155.10
Uric acid ( $\mu\text{mol/L}$ )	330.6	430.4	493.3	326
Urea ( $\mu\text{mol/L}$ )	3.72	7.12	4.07	3.13
24-h urine protein (g/24h)	0.02	3.73g	0.05	0.03
SSA	Positive	Positive	Positive	Positive
ANA titer	1:320	1:100	1:320	1:640
dsDNA	Negative	Negative	Positive	Negative
Serum C3 (g/L)	0.37	0.86	0.57	0.62
Serum C4 (g/L)	7.54	4.40	14	0.14
SLEDAI score	8	9	10	12
Renal biopsy	NA	IV	NA	NA
Therapy	Prednisone + cyclophosphamide	Prednisone + cyclophosphamide	Prednisone	Prednisone

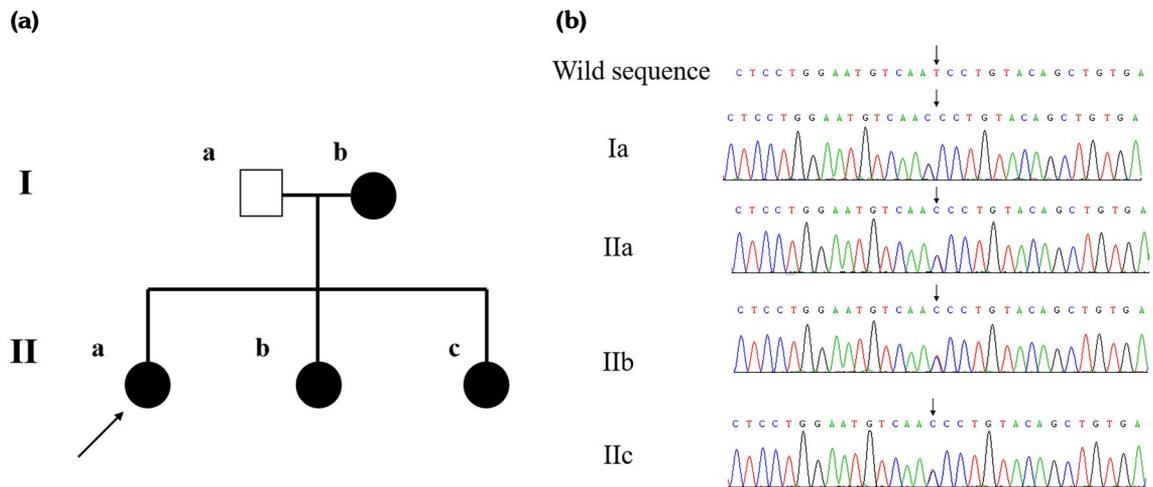
SLE: Systemic lupus erythematosus; eGFR: Estimated glomerular filtration rate; SSA: Sjögren syndrome type A; ANA: Anti-nuclear; dsDNA: Anti-double-stranded deoxyribonucleic acid; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

ANA and anti-SSA antibodies (+++). One of the patient's sisters showed anti-double-stranded DNA (dsDNA) positivity, while the other three patients were negative for this phenotype. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was calculated based on symptoms. Renal biopsy showed that the proband patient had lupus nephritis IV according to the 2003 International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Classification of lupus nephritis (LN) (Figure 2).<sup>18</sup>

### Mutational analysis

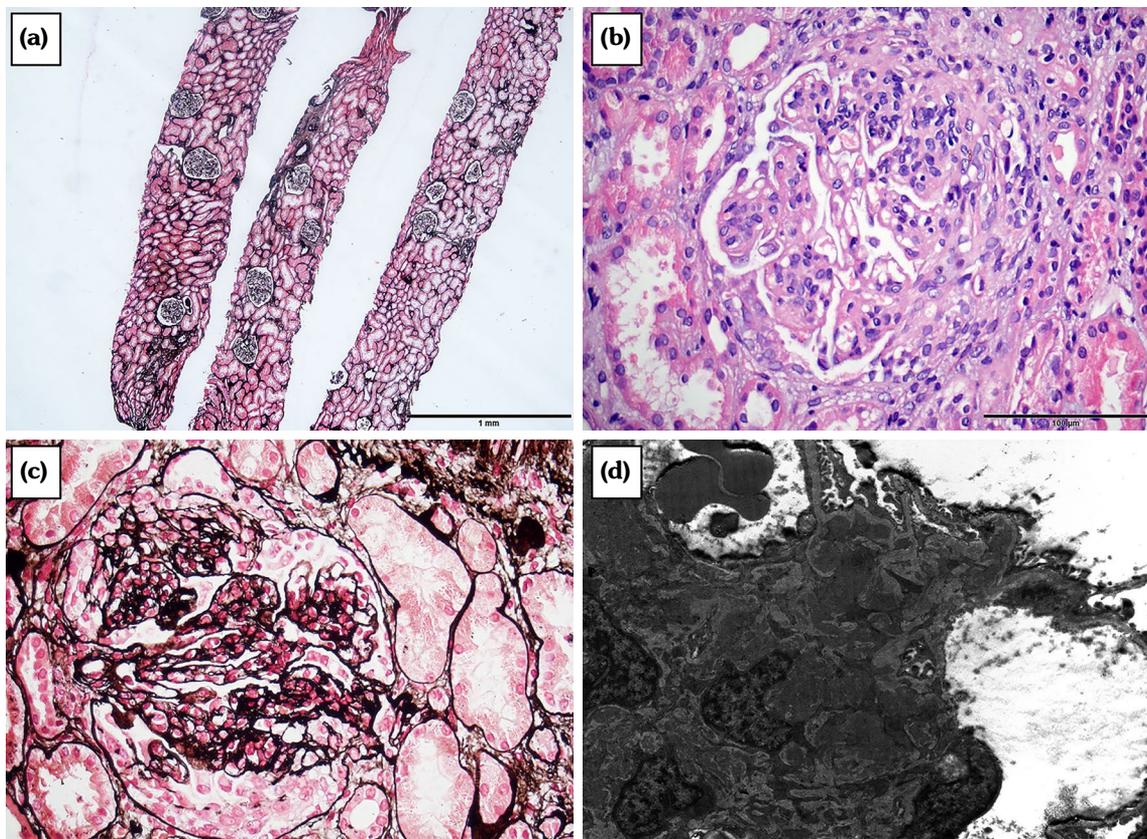
Using WES, there were about 41,130 variants in common among the mother and her three daughters, two gene mutations have been identified, ITGB3 with c.1960 (exon12) G>A mutation (reference sequence GenBank accession no. NM\_000212). However, the ITGB3 mutation is inconsistent with the clinical manifestations of the patients. Another mutation

is CR2 (reference sequence GenBank accession no. NM\_001006658.2). This is a currently unreported nonsense mutation, characterized by a 2804 T>C nucleotide change (Figure 1b). Thus, the peptide isoleucine at site 935 was replaced by threonine (I935T) in the CR2 protein (Table 2). The PROVEAN test showed that the p. I935T mutation was deleterious (-2.75), and PolyPhen2 analysis predicted that the p. I935T mutation was most likely damaging, with scores of 0.63 and 0.516 in the HumDiv and HumVar models, respectively. ProtParam computed the instability index (II) of the CR2 protein to be 77.98, which classifies the protein as unstable, although the p. I935T substitution did not change the aliphatic or instability index (II). Mutation tasker software hazard prediction showed a score of 0.998, indicating that it is predicted to be disease-causing. The Mendelian Clinically Applicable Pathogenicity (M-CAP) Score and Sorting Intolerant from Tolerant (SIFT) prediction also



**Figure 1.** Genomic analysis of the familial SLE patients. **(a)** A detailed family history of SLE patients evaluated in this study. **(b)** A novel c.2804 T>C mutation of the CR2 gene in the mother and the three daughters evaluated in this study.

SLE: Systemic lupus erythematosus.



**Figure 2.** Patient renal pathology results of proband patient. **(a)** A total of 16 glomeruli were acquired, and two glomeruli were global sclerotic (PAS staining,  $\times 40$ ). **(b)** Focal segmentations of mesangial cells and mild mesangial matrix hyperplasia, and a cellular fibroid crescent formation (H&E staining,  $\times 400$ ). **(c)** A small amount of granular eosinophilic protein deposition was observed in the mesangial area of the kidney (PAS staining,  $\times 400$ ). **(d)** An electron-dense deposition was observed in the mesangial and subendothelial area of the kidneys of familial SLE patients.

SLE: Systemic lupus erythematosus.

**Table 2.** CR2 mutation of the familial SLE

Patient	Gene	Variance types	Nucleic acid mutation	Amino acid variation
Ia	CR2	heterozygous	c.2804 (exon 15) T>C	p.I935T(p.Ile935Thr)
Ila	CR2	heterozygous	c.2804 (exon 15) T>C	p.I935T(p.Ile935Thr)
Ilb	CR2	heterozygous	c.2804 (exon 15) T>C	p.I935T(p.Ile935Thr)
Ilc	CR2	heterozygous	c.2804 (exon 15) T>C	p.I935T(p.Ile935Thr)

SLE: Systemic lupus erythematosus.

**Table 3.** Previous reports of CR2 gene mutation and association with disease

Gene	Molecular consequence	Nucleic acid mutation	Amino acid variation	Clinical significance
CR2	Synonymous variant	c.375C>T	p.Asn125=	Likely benign
CR2	Missense	c.524C>T	p.Pro175Leu	Conflicting interpretations of pathogenicity
CR2	Synonymous variant	c.624C>A	p.Pro208=	Benign
CR2	Synonymous variant	c.624C>G	p.Pro208=	Benign
CR2	Missense	c.641G>A	p.Arg214His	Likely benign
CR2	Synonymous variant	c.999G>A	p.Gly333=	Likely benign
CR2	Splice site	c.1225+1G>C		Pathogenic
CR2	Synonymous variant	c.1395A>G	p.Gln465=	Benign
CR2	Synonymous variant	c.1458T>C	p.Phe486=	Likely benign
CR2	Synonymous variant	c.1617C>T	p.Thr539=	Benign
CR2	Missense	c.1622G>T	p.Ser541Ile	Benign
CR2	Missense	c.1676G>A	p.Gly559Glu	Conflicting interpretations of pathogenicity
CR2	Synonymous variant	c.1776G>A	p.Leu592=	Benign
CR2	Missense	c.1916G>A	p.Ser639Asn	Benign
CR2	Missense	c.1987T>C	p.Ser663Pro	Benign
CR2	Missense	c.2006A>G	p.His669Arg	Likely benign
CR2	Missense	c.2012G>A	p.Arg671His	Benign
CR2	Nonsense	c.2297G>A	p.Trp766Ter	Pathogenic
CR2	Synonymous variant	c.2352T>C	p.Ile784=	Benign
CR2	Synonymous variant	c.2445A>G	p.Gly815=	Benign
CR2	Missense	c.2611G>T	p.Val871Leu	Likely benign
CR2	Synonymous variant	c.2649T>C	p.Gly883=	Benign
CR2	Missense	c.2654G>A	p.Arg885His	Likely benign
CR2	Synonymous variant	c.2844G>A	p.Glu948=	Benign/Likely benign
CR2	Missense	c.3185C>A	p.Ala1062Glu	Benign
CR2	Synonymous variant	c.3189-8_3189-7delCT		Benign

showed a genetic damaging effect. Based on the above prediction software, the mutation c.2804 (exon 15) T>C in CR2 is likely pathogenic. We also searched the ClinVar database and found that a total of 74 variations were reported for CR2.

However, most of them were likely benign or not clinically significant, with only a few classified as pathogenic (Table 3). Therefore, our analysis has added a new pathogenic variation to CR2 that is correlated with symptoms of familial SLE.

## DISCUSSION

Systemic lupus erythematosus has a strong genetic predisposition in human patients and animal models.<sup>18</sup> The genetic basis of SLE has been established using genome-wide association studies (GWAS),<sup>19</sup> which have indicated that the genes responsible for regulating immune regulation pathways are mainly involved in SLE.<sup>20,21</sup> Recent studies have shown that the CR2 gene encodes complement receptor (CR)1 and CR2. CR2 is a 145 kDa glycoprotein that plays a crucial role in regulating normal immunity. For instance, it activates B cells by combining with B cell receptors to target the follicular dendritic cell antigen.<sup>22</sup> A previous report showed that CR2 was expressed in B cells<sup>23</sup> and that changes in CR2 expression had different effects on disease presentation in autoimmune animal models.<sup>24</sup> Moreover, CR2 knockout mice had a severe defect in their humoral response to T-dependent antigens.<sup>25</sup>

Both CR1 and CR2 have been reported to play a role in the development of SLE. Abnormal CR1 and CR2 function may be associated with the production of autoantibodies by altering the action of other SLE susceptibility genes.<sup>26</sup> In CR1/CR2 deficient mice, low levels of IgG3 rheumatoid factor (RF) and total serum IgG3 were observed, while significantly higher levels of IgA were observed in the glomeruli.<sup>27</sup>

Currently, SLE, like most common human illnesses, is recognized as a polygene disease with complex genetic susceptibility. A large number of gene polymorphisms have been associated with SLE susceptibility;<sup>28,29</sup> however, some researchers have hypothesized that SLE may be a mono-gene disease, as a complete deficiency in C1, C2, and C4 can cause SLE,<sup>30</sup> although other genes have also been implicated in single-gene lupus, which provides a valuable insight into the course of the very complex disease.<sup>31</sup> Familial SLE was first reported in 1961,<sup>32</sup> with more cases reported over time.<sup>33</sup> Wang et al.<sup>34</sup> analyzed the clinicopathological characteristics of familial SLE patients and found that compared to sporadic subjects, familial subjects had a higher prevalence of fever, rash, and arthritis, but lower platelet counts. However, another study reported no significant differences in the clinical and serological manifestations between familial

and non-familial SLE.<sup>35</sup> Compared to the non-familial cohort, the familial SLE group had poorer SLEDAI scores at the beginning of diagnosis.<sup>36</sup> In our case study, we found a slight difference in serological manifestations and SLEDAI scores among the four SLE patients. In addition, only one patient developed lupus nephritis. Therefore, the link between CR2 and different phenotypes requires further study.

With its rapid development, second-generation sequencing technology has been applied to study several biological problems. It can quickly sequence entire genomes and be scaled up to target genomic regions for deep sequencing.<sup>37</sup> Frangou et al.<sup>38</sup> used next-generation ribonucleic acid (RNA) sequencing technology to investigate the pathogenesis of SLE by comparative transcriptome analysis of the spleen and kidneys of lupus-prone and healthy mice. Sandling et al.<sup>39</sup> identified coding single-nucleotide variations (SNVs) in novel candidate risk sites for adolescent SLE by targeting next-generation sequencing. Next-generation sequencing can also identify micro RNA (miRNA)-based biomarker panels for lupus nephritis.<sup>40</sup> As a result, next-generation sequencing technologies with high throughput and accuracy provide a powerful tool for identifying genomic mutations in autoimmune diseases.<sup>41</sup>

In conclusion, our study identified a novel CR2 gene mutation by next-generation sequencing in close family members with familial SLE. These findings provide evidence that CR2 contributes to the pathogenesis of SLE and this new disease-associated mutation site may provide new clues to the underlying molecular mechanisms of SLE.

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**Ethics Committee Approval:** The study protocol was approved by the Institute of Three Gorges Hospital Ethics Committee (No. 2017-002-01). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from all patients and/or their family members.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Collected the data and drafted the paper: Y.W.T.; Conceived the idea and revised the paper: Y.L.

**Conflict of Interest:** The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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