

Early-Onset Juvenile SLE Associated With a Novel Mutation in Protein Kinase C δ

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Juvenile systemic lupus erythematosus (jSLE) is rare before 5 years of age. Monogenic causes are suspected in cases of very early onset jSLE particularly in the context of a family history and/or consanguinity. We performed whole-exome sequencing and homozygosity mapping in the siblings presented with early-onset jSLE. A novel homozygous missense mutation in protein kinase C delta (c.1294G>T; p.Gly432Trp) was identified in both patients. One patient showed a marked clinical response and resolution inflammation with rituximab therapy. This report demonstrates the clinical importance of identifying monogenic causes of rare disease to provide a definitive diagnosis, help rationalize treatment, and facilitate genetic counseling.

Systemic lupus erythematosus (SLE) is a complex, severe, chronic, and sometimes life-threatening disease. Many factors contribute to the development of juvenile SLE (jSLE), including genetics, immune dysfunction, and environmental factors.¹ jSLE is rare before 5 years of age, and where this occurs monogenic causes should be considered, particularly if there is a family history of SLE or consanguinity. There is now an ever-expanding list of monogenic causes of SLE (Table 1), and many present very early in life.²⁻⁶ We describe 2 siblings who presented with early-onset jSLE in whom we identified a homozygous missense mutation in the *PRKCD* gene. This report demonstrates the clinical importance of identifying monogenic causes of rare disease to provide a rapid and definitive diagnosis, help rationalize treatment, and facilitate genetic counseling.

CASE

The index case presented at the age of 12 months with scarring alopecia,

rash affecting the scalp, and a photosensitive malar rash (Fig 1A). She also had hepatosplenomegaly and bruising of the skin (Fig 1B) and erythematous, nonpruritic, vasculitic rash affecting the hands and feet (Fig 1 C and D). Oral mucosa was normal. Other features were mild monoarthritis of the knee for >2 months (clinically not typical of septic arthritis and hence joint not aspirated) and an episode of acute onset of fever, epistaxis, rectal bleeding, and pancytopenia (hemoglobin 10 g/L, white blood cells 3060 cells per milliliter, neutrophil count 1540 cells per milliliter, lymphocyte count 1010 cells per milliliter, platelet count 87 200 cells per milliliter) at the age of 3 years. Additional investigations showed elevated inflammatory markers (elevated erythrocyte sedimentation rate 125 mm/hour and C-reactive protein 30 mg/L), positive antinuclear antibody 1:320, anti-double stranded DNA at 37 (normal < 10), and positive anti-extractable nuclear antigens

abstract



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Dr Nanthapaisal designed the study, carried out the analyses, and drafted the initial manuscript; Dr Omoyinmi, Ms Murphy, and Dr Standing coordinated and supervised data analyses and reviewed and revised the manuscript; Dr Eisenhut coordinated data collection and reviewed the manuscript; Dr Eleftheriou and Prof Brogan conceptualized and designed the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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TABLE 1 Monogenic Causes of SLE

Gene	Locus	Inheritance	Clinical Features	Onset of SLE or SLE-like Features, y	SLE or SLE-like Features	Specific Treatment ^a	Ref. Nos.
Complement cascade				1–40		Fresh-frozen plasma, hematopoietic stem cell transplant	6–9
<i>C1QA</i>	1p36.12	AR	SLE, ICD, RI		Mucocutaneous and renal involvement, positive ANA, anti-dsDNA, extractable nuclear antigen antibodies, increased cardiovascular risk		
<i>C1QB</i>	1p36.12	AR	SLE, ICD, RI				
<i>C1QC</i>	1p36.11	AR	SLE, ICD, RI				
<i>C1R</i>	12p13	AR	SLE, ICD, RI	<1	Mucocutaneous, neurologic, and renal involvement	—	10
<i>C1S</i>	12p13	AR	SLE, ICD, RI	<1	Mucocutaneous and renal involvement, autoimmune thyroiditis, autoimmune hepatitis	—	11–12
<i>C2</i>	6p21.3	AR	SLE, RI, undifferentiated connective tissue disease, vasculitis, Sjögren syndrome	>10	Mucocutaneous, hematologic, and renal involvement, arthritis	—	1–13–15
<i>C4</i>	6p21.3	AR	SLE, ICD, RI, rheumatoid arthritis	2–40	Mucocutaneous, hematologic, and renal involvement, vasculitis	—	16
<i>TREX1</i>	3p21.31	AD	SLE, familial chilblain lupus, retinal vasculopathy with cerebral leukodystrophy	4–adulthood	Cold-induced chilblain lupus, photosensitive rash, hematologic and neurologic involvement, arthralgia or arthritis	—	17–19
<i>RNASAH2A</i>	19p13	AR	AGS1	<1	Cold-induced chilblain lupus	—	18–19
<i>RNASAH2B</i>	13q14	AR	AGS2	<1	Cold-induced chilblain lupus	—	18–19
<i>RNASAH2C</i>	11q13	AR	AGS3	<1	Cold-induced chilblain lupus	—	18–19
<i>SAMHD1</i>	20q11	AR	AGS5	<1	Cold-induced chilblain lupus	—	18–19
		AD	Familial chilblain lupus		Cold-induced chilblain lupus	—	20
<i>ADAR</i>	1q21.3	AR	AGS6	<1	Cold-induced chilblain lupus	—	21
<i>DNASE1</i>	16p13.3	AD	Sporadic SLE	9–13	Systemic lupus, Sjögren syndrome, high ANA	—	5
<i>DNASE1L3</i>	3p14.3	AR	Familial SLE	2–12	Mucocutaneous and renal involvement, positive ANCA, and anticardiolipin antibodies	—	22
<i>PRKCD</i>	3p21.31	AR	Familial SLE	<5	Cutaneous vasculitis, hematologic involvement, positive ANA and dsDNA antibodies	—	23
<i>ACPS5</i>	19p13.2	AR	Spondyloenchondrodysplasia, skeletal dysplasia, delayed development, intracranial calcification, immune dysregulation	<1–15	Hematological and renal involvement, positive ANA	—	24
<i>SLC7A7</i>	14q11.2		Lysinuric protein intolerance with some cases of SLE	>10	Renal involvement, vasculitis, hemophagocytic lymphohistiocytosis	—	25–26
<i>IFIH1</i>	2q24.2	AD	SLE with immunoglobulin A deficiency, RI, limb spasticity	6–12	Arthritis, cutaneous vasculitis, hematologic involvement, positive ANA and dsDNA antibodies, secondary antiphospholipid syndrome	—	4
<i>TMEM173</i>	5q31.2	AD	Familial SLE	2–20	Arthritis, cutaneous vasculitis, hematologic and pulmonary involvement, positive ANA	—	27

AD, autosomal dominant; AGS, Aicardi–Goutières syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; AR, autosomal recessive; dsDNA, double-stranded DNA; ICD, immune complex disease; RI, recurrent infection.

^a All reported treatments described are case reports.



FIGURE 1

A, A 3-year-old with early-onset SLE caused by homozygous mutation of *PRKCD* manifesting with alopecia and rash affecting the scalp and face, with sparing of the nasolabial folds. B, Hepatosplenomegaly and bruising from thrombocytopenia. C, D, Erythematous, nonpruritic, vasculitic rash affecting the palms and soles.

(ribonucleoprotein, Smith and ribosomal P protein). Complement assays were normal: C1q 42 mg/L (normal range 50–250 mg/L), C3 0.66 g/L (normal range 0.75–1.65 g/L), C4 0.1 g/L (normal range 0.14–0.54 g/L); functional classic complement pathway assay activity was 75% (normal > 40%), and functional alternative complement pathway assay activity was 99% (normal > 10%). Renal function and transaminase levels were entirely normal.

The pedigree of the family is shown in Fig 2A. She was the second child of consanguineous parents (first cousins once removed, ie, the father was the child of the mother's first cousin) originally from Pakistan. The 5-year-old sister of the index case had identical symptoms and signs, which started at the age of 12 months. Her parents were initially healthy, although the mother subsequently developed SLE during her third pregnancy. It manifested as mild cutaneous malar rash and arthralgia but no evidence

of pancytopenia or other organ involvement.

Both siblings were received a diagnosis of familial SLE, with fulfillment of 6 out of 11 of the American College of Rheumatology classification criteria: malar rash, photosensitivity, arthritis, hematologic disorder, immunologic disorder, and positive antinuclear antibody.²⁸ Both patients were initially treated in the first instance with pulse methylprednisolone (30 mg/kg for 3 days followed by oral prednisolone 2 mg/kg per day), hydroxychloroquine (5 mg/kg per day), and azathioprine (2 mg/kg per day). However, over the next 6 months both children progressively deteriorated with pancytopenia, with a platelet count in the range of 60 000 to 84 000 cells per milliliter. Both siblings demonstrated only a transient response to additional pulses of intravenous methylprednisolone and intravenous immunoglobulin (2 g/kg, for persistent thrombocytopenia). Therefore, rituximab (750 mg/m²,

repeated 2 weeks later) was given to the index case, which resulted in a rapid and sustained (13 months at the time of writing) clinical improvement, with complete normalization of the full blood count and normalization of inflammatory markers. Rituximab (at the same dosage) was then given to the older sibling, who unfortunately developed anaphylaxis during the second infusion, although still B-cell depleted successfully, and remains in clinical remission 12 months later.

WORKUP FOR SUSPECTED MONOGENIC SLE

All experimental work was performed with ethical approval (ethics number 08H071382) and with written informed consent from all participants. Both patients were screened via conventional Sanger sequencing for known monogenic causes of SLE for *TREX1*, *SAMHD1*, *C1qA*, *C1qB*, and *C1qC*, all of which were negative (wild-type). Homozygosity mapping was therefore performed in both patients and both parents (see Supplemental Materials). Whole-exome sequencing (WES) was subsequently performed only in the index case (see Supplemental Materials). These studies revealed a homozygous missense mutation (c.1294G>T; p.Gly432Trp) in the *PRKCD* in the index case (see Supplemental Materials for more details), subsequently confirmed via Sanger sequencing. The c.1294G>T substitution is a novel mutation not yet annotated in the single nucleotide polymorphism database, the ClinSeq database,²⁹ 6500ESP,³⁰ or the 1000 Genomes Project databases.³¹ This homozygous c.1294G>T mutation was also confirmed in her affected sister via Sanger sequencing (Fig 2B). Her currently asymptomatic 1-year-old brother was also homozygous for the same mutation. As expected, both parents were confirmed to be

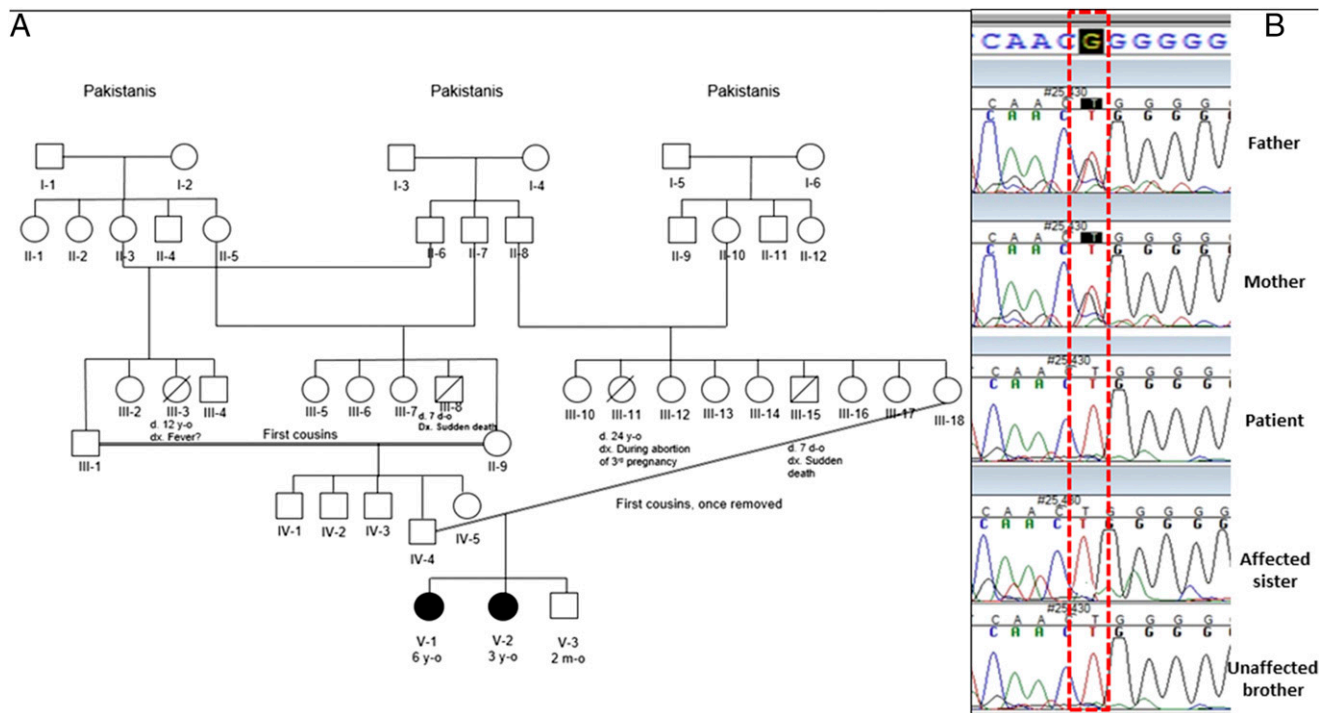


FIGURE 2

A, Pedigree of the family. The index case is V-2; the affected sister is V-1. B, Sanger sequencing chromatogram of *PRKCD* at position c.1294 (in the red-dashed box). The reference base in wild type is G shown above the chromatogram. The chromatogram shows a heterozygous pattern with 2 peaks of T and G in parents, and a homozygous T in patient, affected sister, and unaffected brother. (T is red and G is black.)

heterozygous carriers of the same mutation.

DISCUSSION

PRKCD is located on chromosome 3p21.31. It encodes protein kinase C δ (PKC δ), a member of serine/threonine kinase family that plays a role in apoptosis and proliferation of cells.³² PKC δ is also known to play a role in B-cell negative selection³³ and has been shown to prevent proliferation of B and T cells in response to stimulation in the mouse model.³⁴ PKC δ -deficient mice were found to have features of SLE including anti-double strand DNA autoantibodies, glomerulonephritis with immunoglobulin G containing immune complex deposition, and lymphocyte infiltration in multiple organs.^{34,35}

The p.Gly432Trp mutation affects the protein kinase activity domain, which is located between amino acid

349 and 603.³⁶ Thus, this mutation is likely to cause a loss of function of the kinase activity of PKC δ . The p.Gly432Trp mutation is predicted to be deleterious in pathogenicity prediction algorithms (Supplemental Table 2). One limitation of our study was that we did not perform any functional experiments to assess protein expression or function or detailed B cell immunotyping (for various practical reasons, including limited access to clinical samples). However, we suggest that the clinical features are explained by the mutations we identified in *PRKCD*, particularly because WES did not identify any other plausible genetic cause.

Mutation of *PRKCD* (p.Gly510Ser) has previously been identified as the cause of early-onset jSLE by Belot et al²³ in 3 children of consanguineous unions. Mutations identified were shown to cause reduction of PKC δ expression and phosphorylation activity, and

transfected lymphoblastoid cell lines were found to be resistant to apoptosis, reversible by coexpression of nonmutant protein. In the Belot study, primary B cells from patients and heterozygous carriers also exhibited a higher proliferation rate than wild-type individuals after stimulation of the B-cell receptor, CD40, and Toll-like receptor 9 compared with wild-type B cells.

Rituximab, a monoclonal antibody against CD20 present on pre-B and mature B lymphocytes, was (fortuitously) the optimal therapeutic drug of choice in these patients because of the possible immunologic defects in B cells caused by the mutation in *PRKCD*. Because 1 sibling developed anaphylaxis to rituximab, other B-cell targeted therapies such as ofatumumab (an alternative fully humanized monoclonal antibody against CD20)³⁷ or belimumab (a fully humanized monoclonal antibody against B-lymphocyte

stimulator)³⁸ are being considered for future treatment.³⁹ Alternatively, it is possible that hematopoietic stem cell transplantation may ultimately be needed, although to the best of our knowledge it has not yet been performed in SLE caused by mutations in *PRKCD* (A. Belot, MD, PhD, personal communication, 2016).

Interestingly the mother, who is a heterozygous carrier of the mutation, developed SLE during pregnancy with her third child. The combined contribution of heterozygous carriage and hormonal changes occurring during pregnancy may be responsible for the new onset of SLE during pregnancy.⁴⁰ The youngest brother, aged 18 months at the time of writing, also has the homozygous mutation and is thus far asymptomatic but will be closely monitored for the development of symptoms.

CONCLUSIONS

We have described a rare monogenic form of jSLE caused by a novel but damaging homozygous mutation affecting the active region of *PRKCD*. Identification of this additional disease-causing variant of *PRKCD* provides additional supportive evidence for this gene to be included in routine genetic screening for suspected monogenic SLE. Securing this molecular diagnosis not only provided us with a definitive diagnosis but also explained the dramatic and complete therapeutic response to B-cell depletion (despite failing other therapies) and will direct the choices made for future treatment options. Because the list of monogenic causes of SLE is increasing (Table 1), next-generation sequencing offers the opportunity to screen all known genetic causes rapidly, and for a fraction of the cost of conventional sequencing, and should be considered in all cases of early-onset (<5 years) jSLE,

particularly for consanguineous families.

ABBREVIATIONS

jSLE: juvenile systemic lupus erythematosus
 PKCδ: protein kinase C δ
 ROH: runs of homozygosity
 SLE: systemic lupus erythematosus
 SNP: single nucleotide polymorphism
 WES: whole-exome sequencing

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