

CASE REPORT

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Compound heterozygous *LPIN2* pathogenic variants in a patient with Majeed syndrome with recurrent fever and severe neutropenia: case report

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Abstract

Background: Majeed syndrome is a rare, autosomal recessive autoinflammatory disorder first described in 1989. The syndrome starts during infancy with recurrent relapses of osteomyelitis typically associated with fever, congenital dyserythropoietic anemia (CDA), and often neutrophilic dermatosis. Mutations in the *LPIN2* gene located on the short arm of chromosome 18 have been identified as being responsible for Majeed syndrome.

Case presentation: We report an 8-month-old boy, who presented with recurrent fever, mild to moderate anemia, and severe neutropenia. Erythrocyte sedimentation rate and C-reactive protein were elevated. Molecular testing identified a paternal splicing donor site variant c.2327 + 1G > C and a maternal frameshift variant c.1691_1694delGAGA (Arg564Lysfs*3) in *LPIN2*.

Conclusions: Only a few cases with *LPIN2* mutation have been reported, mainly in the Middle East with homozygous variants. Our patient exhibited a mild clinical phenotype and severe neutropenia, different from previous reports.

Keywords: Majeed syndrome, Fever, Neutropenia, Autosomal recessive

Background

Majeed syndrome is a rare, autosomal recessive autoinflammatory disorder first described in 1989. The syndrome starts during infancy with recurrent relapses of osteomyelitis typically associated with fever, congenital dyserythropoietic anemia (CDA), and often neutrophilic dermatosis. Mutations in the *LPIN2* gene, located on the short arm of chromosome 18, have been identified as being responsible for Majeed syndrome. Here we report what we believe to be the first case of Majeed

syndrome in a Chinese individual. This case is of variable severity.

Case presentation

Clinical information

This Chinese 8-month-old boy presented at the age of 6 months with recurrent fever lasting for 5–7 days, recurring every 3–7 days. Sometimes he had a slight cough. He had no physical pain or movement problems. He had no rash or other symptoms. The infant was born full term. The delivery was normal delivery with a birth weight of 3.0 kg. His parents had a non-consanguineous marriage. There was a neonatal history of jaundice. The boy had mild pallor when he was admitted to our hospital. He had no lymphadenopathy or hepatosplenomegaly. Blood routine examination showed severe neutropenia (380–400/mm³) with normal white blood cell count, microcytic anemia (hemoglobin 85–95 g/L), and

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slight thrombocytosis. The boy had an elevated erythrocyte sedimentation rate (79 mm/h) and C-reactive protein (39 mg/L, normal < 8 mg/L). Immunoglobulin and lymphocyte subsets were found to be normal. Rheumatoid factors were negative. Antinuclear antibody was positive with a titer of 1:80, while the anti-ds DNA antibody was negative. Antineutrophil cytoplasmic antibodies showed mild elevated anti-MPO antibody (30.2 RU/ml) and negative anti-PR3 antibody. Thyroid function was normal. Serum iron and transferrin levels were low, which indicated iron-deficiency anemia. Bone marrow hemocytology revealed myeloproliferation cells, and the proportion of myelocyte was decreased because of the granulocytosis. Red blood cells were active and tended to proliferate. Metarubricytes dominated with small, hollow, and distorted mature erythrocytes. Blood and bone marrow puncture specimens were cultured for bacteria and fungi and showed no growth. Results of viral serologic studies were also negative. Lymphocyte interferon release assay was negative. Abdominal ultrasound scan gave normal findings. Cardiac ultrasound showed no abnormalities. Chest CT showed no interstitial or parenchymal infiltration. Because he had no limb pain, the patient did not undergo an MRI scan.

Molecular genetic studies

After obtaining informed consent, we isolated DNA from peripheral blood samples obtained from the patient and parents using the Genra Puregene Blood Kit (Qiagen, Hilden, Germany). Whole exome library was captured by a SureSelect Human All Exon Kit (Agilent Technologies, Santa Clara, CA, USA) according to the manufacturer's instructions. Target regions were sequenced and aligned to the GRCh37/hg19 human reference sequence. Variants were annotated and filtered by TGen (tgex-app.genecards.cn). Variants were classified following the ACMG/AMP standards and guidelines [1]. Putative pathogenic variants were confirmed by Sanger sequencing.

Discussion and conclusions

After sequencing, we identified a paternal splicing donor site variant c.2327 + 1G > C and a maternal frameshift variant c.1691_1694delGAGA (Arg564Lysfs*3) in *LPIN2* (NM_014646.2, Fig. 1). c.2327 + 1G > C has not been reported in dbSNP, 1000 genome, ESP, ExAC, or gnomAD databases, indicating it is very rare in normal populations. This variant was predicted to disarrange the donor site according to Human Splicing Finder (www.umd.be/HSF3/HSF.shtml) and caused exon 17 deletion or intron 17 insertion either entirely or partly. This variant was first reported in an Arabic family. The proband was a 3-year-old girl with Majeed syndrome [2]. The author predicted this variant could produce an R776S change followed by 65 amino acids prior to encountering a stop

codon in intron 17. c.1691_1694delGAGA, located in exon 12, led to premature termination codon at position 3 amino acids after mutation. It is expected to produce a truncated protein or lead to early degradation of mRNA through the mechanism of nonsense-mediated decay. This variant has not been reported in dbSNP, ESP, or 1000 genome databases. The frequency in ExAC database was 0.000008236, suggesting that the frequency was extremely low. Both variants were classified as pathogenic variants according to ACMG/AMP guidelines.

Majeed syndrome is a rare autosomal recessive disorder characterized by chronic recurrent multifocal osteomyelitis (CRMO). This is an early-onset disorder with a lifelong course and congenital dyserythropoietic anemia (CDA) that presents as hypochromic, microcytic anemia during the first year of life and ranges from mild to severe enough to render the patient transfusion dependent. Some individuals also develop a transient inflammatory dermatosis, often manifesting as Sweet syndrome (neutrophilic skin infiltration). It is often accompanied by recurrent fever. The diagnosis is based on clinical findings and molecular genetic testing of *LPIN2*, the only gene in which pathogenic variants are known to cause Majeed syndrome. Only a few cases with *LPIN2* mutation have been reported, mainly in the Middle East with homozygous variants [2–9].

LPIN2 encodes a phosphatidate phosphatase that plays important roles in controlling the metabolism of fatty acids at different levels. The function of *LPIN2* is not well known. According to a previous study, it acts as a magnesium-dependent phosphatase, converting phosphatidic acid to diacylglycerol in the biosynthesis of triglycerides, phosphatidylcholine, and phosphatidylethanolamine. It can also act as a nuclear transcriptional coactivator of PPAR γ C1A and so regulate lipid metabolism [10, 11]. Homozygous knock out *Lpin2* mice displayed increases in mean platelet volume, red blood cell distribution, and lymph nodes and decreases in mean corpuscular hemoglobin, bone mineral density, and overall bone mass. They also had abnormal circulating phosphate level, hydrometra, and preweaning lethality with incomplete penetrance. *LPIN2* has 19 exons and 3 lipin domains located in N-terminal (amino acid: 1–108), middle (amino acid: 469–561), and C-terminal (amino acid: 677–831), respectively (Fig. 2). Lipin domains are highly conserved in lipin proteins and lipin homologues from *Saccharomyces cerevisiae* (Smp2, PAH1) and *Schizosaccharomyces pombe* (Ned1) and the function of these domains was still unclear. Mutations on lipin domains in mice lead to fatty liver dystrophy.

We here report the first case of Majeed syndrome in the individual of Chinese heritage and with variable severity. Our patient exhibited a mild clinical phenotype, unlike in previously reported cases (Table 1). He had

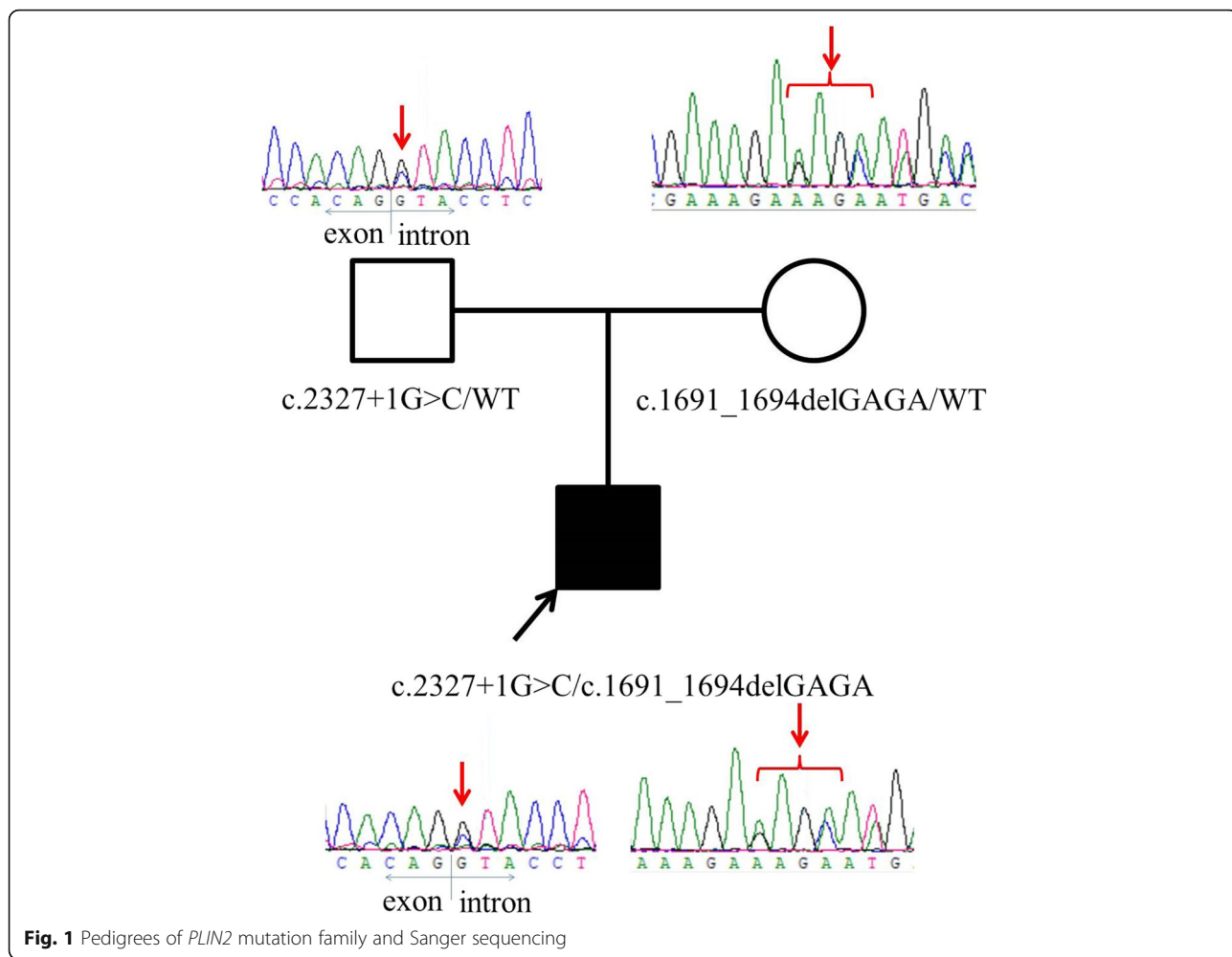


Fig. 1 Pedigrees of *PLIN2* mutation family and Sanger sequencing

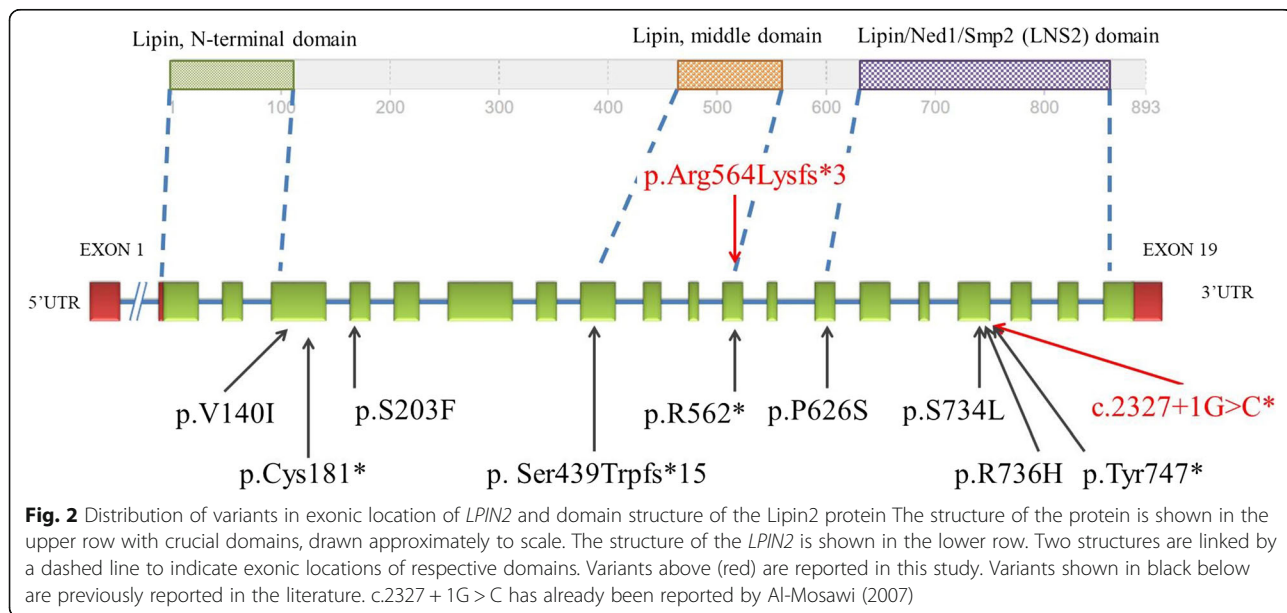


Fig. 2 Distribution of variants in exonic location of *LPIN2* and domain structure of the Lipin2 protein. The structure of the protein is shown in the upper row with crucial domains, drawn approximately to scale. The structure of the *LPIN2* is shown in the lower row. Two structures are linked by a dashed line to indicate exonic locations of respective domains. Variants above (red) are reported in this study. Variants shown in black below are previously reported in the literature. *c.2327 + 1G > C* has already been reported by Al-Mosawi (2007)

Table 1 Fourteen patients with Majeed syndrome: clinical course and laboratory investigations

author	Gender	Age at onset/diagnosis	Clinical features	Laboratory tests	Genetic testing	others
Mosawi [2]	F	10 m/3 y	CRMO	ESR 66–96 mm/h CRP 30 mg/L Neutropenia (750/mm ³) Hb 7.5–9.5 g/dL	c.2327 + 1G > C	Fever Dyserythropoietic anemia Neutropenia
Ferguson [3]	F	–	CRMO	–	c.2201C > T p.s734 L	Mild fever Microcytosis Sweet syndrome Relative with psoriasis
	M	–	CRMO	–	c.2201C > T p.s734 L	Mild fever Microcytosis Sweet syndrome Relative with psoriasis
	M	–	CRMO	–	c.2201C > T p.s734 L	Mild fever Microcytosis Relative with psoriasis
	M	–	CRMO	–	c.2201C > T p.s734 L	Mild fever Microcytosis Sweet syndrome Relative with psoriasis
	–	–	CRMO	–	c.540_541delAT p.(Cys181*)	High fever Microcytosis Frequent blood transfusion pustulosis
	–	–	CRMO	–	c.540_541delAT p.(Cys181*)	High fever Microcytosis Frequent blood transfusion
Herlin [4]	M	6 m/29 m	CRMO	ESR 92 mm/h CRP 19.6 mg/L Hb 9.7 g/dL	c.1316_1317delCT P.(Ser439Trpfs*15)	Dyserythropoietic anaemia
	M	3 m/13 m	CRMO	ESR 96 mm/h CRP 23.7 mg/L Hb 9.0 g/dL	c.1316_1317delCT P.(Ser439Trpfs*15)	Dyserythropoietic anemia Fever
Rao [5]	M	2 y/15 y	CRMO	ESR 53–140 mm/h Hb 7.9–9.9 g/dL Neutropenia (2840–4230/mm ³)	c.2241_2243delinsGG	Mild neutropenia Dyserythropoietic Anemia
	M	8 y/13 y	Milder CRMO	ESR 45 mm/h Hb 11.2 g/dL	c.2241_2243delinsGG	Mild anemia
Moussa [6]	M	6 m/5y	CRMO	ESR14-92 mm/h CRP < 5-14 mg/L Hb9.7–12.1 g/dL	c.2327 + 1G > C p.s734 L	No skin lesions Mild anemia
	F	4 y/14 y	CRMO	ESR20–68 mm/h CRP < 5–59 mg/L Declining Hb to 8 g/dL at age 15 years	c.2327 + 1G > C p.s734 L	No skin lesions Idiopathic scoliosis Rheumatic fever Dyserythropoietic anemia
Roy [13]	M	–	CRMO	High inflammatory	c.2207 G > A p.R736H	Microcytic anaemia

recurrent fever and mild to moderate hypochromic and microcytic anemia without severe CRMO. He had no physical pain, swelling, or movement disorders. Majeed reported a Palestinian Arab boy who presented at the age of 2 months with recurrent episodes of high fever and irritability [12]. At the age of 9 months, these episodes began to be associated with periarticular swellings with heat, tenderness, and limitation of movement. Therefore, the patient's signs and symptoms need to be

observed continuously. Our patient had severe neutropenia from the age of 6 months, and his absolute neutrophil count was 380–400/mm³. This phenotype has been reported in few cases. Mosawi reported an Arabic female with Majeed syndrome who had mild neutropenia (1080/mm³) in the neonatal period [3]. RAO reported a 15-year-old boy with Majeed syndrome complicated by mild neutropenia [5]. Those cases suggest that neutropenia may be part of the phenotype. More cases must be

studied to confirm this phenotype. Treatment with IL-1 blockade was reported in Majeed syndrome [13]. Our patient did not use IL-1 blockade because of his age and the mildness of his phenotype.

Majeed syndrome is an autosomal recessive, autoinflammatory disorder. It is characterized by CRMO and CDA. Our patient had the compound heterozygous LPIN2 pathogenic variant and exhibited a mild clinical phenotype, unlike in previously reported cases.

Abbreviations

CDA: Congenital dyserythropoietic anemia; CRMO: Chronic recurrent multifocal osteomyelitis; CRP: C-Reactive protein

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Authors' contributions

All of the authors had access to the full dataset (including the statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of the data analysis. BPX, CJH, JL and XYH conceived the study. ZPZ, RLG, JG and WL collected the data and designed the analysis. JL and XYH wrote the first draft of the paper. BPX reviewed and approved the final report. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants or their legal representatives signed informed consent and the study was approved by the Ethics Committee of Beijing Children's Hospital Affiliated to Capital Medical University.

Consent for publication

The patient's parents had written informed consent to publish this information.

Competing interests

The authors declare that they have no competing interests.

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