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

CURRENT STATUS: ACCEPTED

BMC Medical Genetics

jun liu
beijing children's hospital

Xu-Yun Hu
Beijing children's Hospital

Zhi-Peng Zhao
Beijing children's Hospital

Ruo-Lan Guo
Beijing children's Hospital

Jun Guo
Beijing children's Hospital

Wei Li
Beijing Children's Hospital

Chan-Juan Hao
Beijing children's Hospital

Bao-Ping Xu

Corresponding Author

ORCiD: https://orcid.org/0000-0002-9765-0098

DOI: 10.21203/rs.2.11655/v1

SUBJECT AREAS
Medical Genetics

KEYWORDS
Majeed syndrome, fever, neutropenia, autosomal recessive
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 the Majeed syndrome.

Case presentation

We report a 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 studies identified a paternal splicing donor site variant c.2327+1G>C and a maternal frameshift variant c.1691_1694delGAGA (Arg564Lysfs*3)in LPIN2.

Conclusions

Up to now, 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, distinct from previously reported.

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 the Majeed syndrome. Here we report, to our knowledge, the first case of Majeed syndrome in individual of Chinese heritage and with variable severity.

Case presentation

Clinical information

This Chinese 8-month old boy presented at the age of 6 month with recurrent fever lasting for 5-7 days and recurrent every 3-7 days. Sometimes he had a slight cough. He had no physical pain or movement problems. He had no rash and other symptoms. The infant was born at full term, normal
delivery with a birth weight of 3.0Kg. His parents were not consanguineous marriages. There was a neonatal history of jaundice. The boy had mild pallor when he was admission to our hospital. He had no lymphadenopathy or hepatosplenomegaly. Blood routine examination showed severe neutropenia (0.38-0.40 ×10^9/L) with normal white blood cell count, microcytic anemia (hemoglobin 85-95g/L) and slight thrombocytosis. The boy had elevated erythrocyte sedimentation rate (79mm/h) and C-reactive protein (39mg/L, normal<8mg/L). Detection of immunoglobulin and lymphocyte subset were 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 revealed with mild elevated anti-MPO antibody (30.2RU/ml) and negative anti-PR3 antibody. Measurement of Thyroid Function was normal. Serum iron and transferrin were decrease, which indicated iron-deficiency anemia. Bone marrow hemocytology revealed myeloproliferative, the proportion of myelocyte was decreased in the granulocytosis; Red blood cell is proliferous and active, metarubricyte was dominated with small, hollow and distorted mature erythrocyte. Blood and bone marrow puncture specimens had been cultured for bacteria and fungi, and had showed no growth. Results of viral serologic studies also had been 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.

**Molecular genetic studies**

After obtaining informed consent, we isolated DNA from peripheral blood samples obtained from the patient and parents by using the Gentra Puregene Blood Kit (QIAGEN, Hilden, Germany). Whole exome library was captured by SureSelect Human All Exon Kit (Agilent Technologies, Santa Clara, America) 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 TGex (tgex-app.genecards.cn). Variants were classified following the ACMG/AMP standards and guidelines\(^1\).

Putative pathogenic variants were confirmed by Sanger sequencing.

**Results And Discussion**

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 is not reported in dbSNP, 1000 genome, ESP, ExAC or gnomAD databases, indicating it is very rare in normal population. This variant was first reported in a Arabic family, the proband was a 3-year-old girl with Majeed Syndrome [2]. This variant was predicted to disarrange the donor site and caused exon 17 deletion or intron 17 insertion either entirely or partly. c.1691_1694delGAGA located in exon 12, leading 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 was not 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 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. Up to now, 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 which plays important roles in controlling the metabolism of fatty acids at different levels. The function of LPIN2 is not well known. According to pervious 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 PPARGC1A and therefore, regulate lipid metabolism [10,11]. Homozygous knock our Lpin2 in mice displayed increase in mean platelet volume,
red blood cell distribution width and lymph nodes, decrease in mean corpuscular hemoglobin, bone mineral density and content. They also had abnormal circulating phosphate level, hydrometra, and preweaning lethality with incomplete penetrance. *LPIN2* has 19 exons and three lipin domains located in N-terminal, middle and C-terminal, respectively (Fig. 2). Lipin domains are highly conserved in lipin proteins, in which when mutated in mice lead to fatty liver dystrophy.

Here we report, to our knowledge, the first case of Majeed syndrome in individual of Chinese heritage and with variable severity. Our patient exhibited a mild clinical phenotype, distinct from previously reported cases (Table1). He had recurrent fever, 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 whose presented at the age of 2 months with recurrent episodes of high fever and irritability. At the age of 9 months, these episodes started to be associated with periarticular swellings with hotness, tenderness and limitation of movement. Therefore, the symptoms and signs of our patient’s need to be observed continuously. Our patient had severe neutropenia from 6 months and his absolute neutrophil count was 0.38-0.40×10^9/L. This phenotype has been reported in few cases. Mosawi reported an Arabic female with Majeed syndrome who had mild neutropenia (1.08×10^9/L) in the neonatal period. RAO reported a 15-year-old boy with Majeed syndrome complicated by mild neutropenia. Those cases suggest that neutropenia may be part of the phenotype. More cases are needed to be observed to confirm this phenotype.

**Conclusions**

Majeed syndrome is an autosomal recessive, autoinflammatory disorder. It characterized by CRMO and CDA. Our patient exhibited a mild clinical phenotype, distinct from previously reported cases.

**Abbreviations**

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

**Declarations**

**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

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

Competing interests
The authors declare that they have no competing interests.

Funding
Not applicable.

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, C JH, JL and XYH conceived the study. ZPZ, RLG, JG and WL collected the data and designed the analysis. JL wrote the first draft of the paper. BPX reviewed and approved the final report.

Acknowledgements
We thank all the people who have been involved in our study.

Author details
1 China National Clinical Research Center of Respiratory Diseases, Respiratory Department of Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing 100045, China.

2 Beijing Key Laboratory for Genetics of Birth Defects, Beijing Pediatric Research Institute; Genetics and Birth Defects Control Center, National Center for Children’s Health; MOE Key Laboratory of Major Diseases in Children; Beijing Children's Hospital, Capital Medical University, Beijing 100045, China

3 Henan Key Laboratory of Pediatric Inherited & Metabolic Diseases, Henan Children's Hospital, Zhengzhou Hospital of Beijing Children's Hospital, Zhengzhou, China.

References
1. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24.

2. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, Munnich A, Lyonnet S, Majeed HA, El-Shanti H. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). J Med Genet. 2005;42:551-7.

3. Al-Mosawi ZS, Al-Saad KK, Ijadi-Maghsoodi R, El-Shanti HI, Ferguson PJ. A splice site mutation confirms the role of LPIN2 in Majeed syndrome. Arthritis Rheum. 2007;56:960-4.

4. Herlin T, Fiirgaard B, Bjerre M, Kerndrup G, Hasle H, Bing X, Ferguson PJ. Efficacy of anti-IL-1 treatment in Majeed syndrome. Ann Rheum Dis. 2013;72:410-3.

5. Rao AP, Gopalakrishna DB, Bing X, Ferguson PJ. Phenotypic Variability in Majeed Syndrome. J Rheumatol. 2016;43:1258-9.

6. Monies D, Abouelhoda M, AlSayed M, Alhassnan Z, Alotaibi M, Kayyali H, Al-Owain M, Shah A, Rahbeeni Z, Al-Muhaizea MA, et al. The landscape of genetic diseases in Saudi Arabia based on the first 1000 diagnostic panels and exomes. Hum Genet. 2017;136:921-9.

7. Moussa T, Bhat V, Kini V, Fathalla BM. Clinical and genetic association, radiological findings and response to biological therapy in seven children from Qatar with non-bacterial osteomyelitis. Int J Rheum Dis. 2017;20:1286-96.

8. Omoyinmi E, Standing A, Keylock A, Price-Kuehne F, Melo GS, Rowczenio D, Nanthapisal S, Cullup T, Nyanhete R, Ashton E, et al. Clinical impact of a targeted next-generation sequencing gene panel for autoinflammation and vasculitis. PLoS One. 2017;12:e0181874.

9. Marzano AV, Ortega-Loayza AG, Ceccherini I, Cugno M. LPIN2 gene mutation in a patient with overlapping neutrophilic disease (pyoderma gangrenosum and aseptic abscess syndrome). JAAD Case Rep. 2018;4:120-2.

10. Donkor J, Zhang P, Wong S, O’Loughlin L, Dewald J, Kok BP, Brindley DN, Reue K. A conserved
serine residue is required for the phosphatidate phosphatase activity but not the transcriptional coactivator functions of lipin-1 and lipin-2. J Biol Chem. 2009;284:29968-29978.

11. Gropler MC, Harris TE, Hall AM, Wolins NE, Gross RW, Han X, Chen Z, Finck BN. Lipin 2 is a liver-enriched phosphatidate phosphohydrolase enzyme that is dynamically regulated by fasting and obesity in mice. J Biol Chem. 2009;284:6763-72.

12. Majeed HA, Al-Tarawna M, El-Shanti H, Kamel B, Al-Khalaileh F. The syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia. Report of a new family and a review. Eur J Pediatr. 2001;160:705-10.

Table
Due to technical limitations, Table 1 is only available as a download in the supplemental file section.

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

Figures
Figure 1

Pedigrees of PLIN2 mutation family and Sanger sequencing
Distribution of variants in exonic location of LPIN2 and domain structure of the Lipin2 protein. Structure of the protein is shown in the upper row with crucial domains drawing approximately to scale. Structure of the LPIN2 is shown in the lower row. Two structures are linked by dashed line to indicate exonic locations of respective domains. Variants above (red) are reported in this study. Variants below (black) are previously reported in literature.

c.2327+1G>C was already reported by Al-Mosawi (2007)

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

table 1.xlsx