Familial hemophagocytic lymphohistiocytosis type 2 in a female Chinese neonate: A case report and review of the literature

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Abstract

BACKGROUND
Familial hemophagocytic lymphohistiocytosis type 2 (FHL2) is a rare genetic disorder presenting with fever, hepatosplenomegaly, and pancytopenia secondary to perforin-1 (PRF1) mutation. FLH2 has been described in Chinese but usually presents after 1 year old. We describe a female Chinese neonate with FHL2 secondary to compound heterozygous PRF1 mutation with symptom onset before 1 mo old. We review Chinese FHL2 patients in the literature for comparison.

CASE SUMMARY
A 15-d-old female neonate was referred to our hospital for persistent fever and thrombocytopenia with diffuse petechiae. She was born to a G5P3 mother at 39 wk and 4 d via cesarean section secondary to breech presentation. No resuscitation was required at birth. She was described to be very sleepy with poor appetite since birth. She developed a fever up to 39.5°C at 7 d of life. Leukocytosis, anemia, and thrombocytopenia were detected at a local medical facility.

CONCLUSION
A literature review identified 75 Chinese FHL2 patients, with only five presenting in the first year of life. Missense and frameshift mutations are the most common PRF1 mutations in Chinese, with 24.8% having c.1349C>T followed by 11.6% having c.65delC. The c.658G>C mutation has only been reported once in the literature.
literature and our case suggests it can be pathogenic, at least in the presence of another pathogenic mutation such as c.1066C>T.

Key Words: Hemophagocytic lymphohistiocytosis; Familial hemophagocytic lymphohistiocytosis; Perforin-1; Neonate; Compound heterozygous; Case report

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Core Tip: We report the case of a newborn infant with familial hemophagocytic lymphohistiocytosis who had clinical manifestations by the age of 7 d. The genetic test revealed a compound heterozygous mutation of c.658G>C (p.Gly220Arg) and c.1066C>T (p.Arg356Trp). The two mutations carried by the index cases were not commonly seen variants in Chinese PRF1 mutations. The clinical manifestation of our case strongly suggests that c.658G>C (p.Gly220Arg) is also a pathogenic variant.

INTRODUCTION

Familial hemophagocytic lymphohistiocytosis (FHL), a type of hemophagocytic lymphohistiocytosis (HLH), is a rare disorder of the immune system presenting with excessive inflammatory syndrome caused by activated T cells and histiocytosis, which affects almost all ages with 70%-80% presenting in the first year of life[1]. Its clinical manifestations include fever, pancytopenia, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia, hepatitis, neurological symptoms, etc[2]. FHL can be divided into five subtypes (FHL1 to 5) according to the causative genetic mutation. The pathogenic genes of FHL1 remain unknown, while PRF1, UNC13D, STX11, and STXBp2 are specific genes for type 2 to 5, respectively[3]. Nearly 58% of all reported FHL patients have PRF1 gene mutations, with more than 100 FHL2 cases with identified PRF1 variants reported so far[4]. Here we report a case of FHL2 initially presenting with recurrent fever and jaundice by 1 wk of life secondary to a compound heterozygous PRF1 mutation. PRF1 gene mutations in the Chinese population are also reviewed.

CASE PRESENTATION

Chief complaints

A 15-day-old female neonate was referred to our hospital for persistent fever starting from the age of 7 d and thrombocytopenia with diffuse petechiae.

History of present illness

The patient was born to a G5P2 mother at 39 wk and 4 d via cesarean section secondary to breech presentation. No resuscitation was required at birth. She was described to be very sleepy with poor appetite since birth. She developed a fever up to 39.5°C at 7 d of life. Leukocytosis, anemia, and thrombocytopenia were detected at a local medical facility.

History of past illness

No resuscitation was required at birth.

Personal and family history

The parents were healthy and not blood-related. The elder sister was 13 years old in good health. Another brother died at the age of 3 mo, without known etiology but...
manifested with recurrent fever and jaundice. The mother also experienced two spontaneous abortions. One aunt had chronic thrombocytopenia and anemia without an established diagnosis.

**Physical examination**

Physical examination upon admission revealed hypotonia with poor response to stimuli. Extensive bruises and petechia, pallor, and a soft but flat anterior fontanelle were noticed. She had mild shallow tachypnea without retraction or rales. Her heart rate was 150 per minute without a murmur. Her abdomen was soft but distended with palpable margins of the liver while the tip of the spleen reached 3.5 cm below the costal margin.

**Laboratory examinations**

Abdominal ultrasound showed gallbladder edema, and moderate amount of abdominal and pelvic effusion. Hemogram showed pancytopenia with a hemoglobin level of 77 g/L, platelet count of $11 \times 10^9/L$, and white blood cell count of $2.7 \times 10^9/L$ with 10.4% neutrophils and 78.5% lymphocytes. Serum ferritin level was 16322.60 ng/mL. Bone marrow examination showed hemophagocytic histiocytes; NK cell killing activity was decreased, and soluble interleukin-2 receptor (sCD25) was 12702 pg/mL. We also detected an elevated D-dimer, abnormal coagulation profile, alanine aminotransferase 1041.0 IU/L, aspartate aminotransferase 2390.0 IU/L, and negative Epstein-Barr virus detection (DNA < 400 copies/mL).

**GENETIC WORK-UP**

A genetic study showed compound heterozygous PRF1 mutation involving c.658G>C (p.Gly220Arg) and c.1066C>T (p.Arg356Trp). The diagnosis of FHL2 was thus established. Trio-clinical exome sequencing was performed on the extended family members for the purpose of genetic counselling after approval from the hospital ethical committee. Written consent was obtained from the parents for reporting this case. Peripheral blood was collected into an EDTA tube, and genomic DNA was extracted after gene fragmentation, amplification and purification, and library construction; the targeted sequence was captured by the Illumina MiSeq high-throughput sequencing platform, covering approximately 4200 known HLH genes. The reference sequence was the hg19 genome, the reliable mutation spectrum was obtained after the invalid mutations were filtered through biological information analysis, and the suspected pathogenic mutations selected after the hazard prediction analysis of the mutation sites. Sanger verification was carried out. The amplified products were sequenced by ABI 3500 analyzer.

Polyphen_2[5], SIFT[6], and Mutation Taster[7] online analysis platform were used to predict the biological hazardous variants, search public SNP databases for variant sites, check the incidence frequency of variant sites in the normal population, and curate the output determined according to the "ACMG Genetic Variation Classification Standards and Guidelines "(ACMG) Rating[8] for the variation. Mega 7.0 software was used to conduct conservative analysis of the variant sites. Swiss-model online analysis platform (https://swissmodel.expasy.org/) was used to search for the three-dimensional PRF1 protein structure. Protein structure was obtained from the PDB protein structure database (http://www.rcsb.org/) and DeepView software was used for visual display and analysis to obtain the result after optimization.

Results obtained from Sanger sequencing confirmed the father and paternal grandfather were heterozygous for c.658G>C mutation while the mother and maternal grandmother were heterozygous for c.1066C>T mutation (Figure 1A and B). The distribution frequency of c.658G>C in the ExAC database was 0.00005, and the frequency of c.1066C>T was zero. Both mutation sites had been reported in ClinVar and HGMD databases. According to the "ACMG Genetic Variation Classification Standards and Guidelines"[9], c.658G>C is rated as possible pathogenic while c.1066C>T is rated as a pathogenic variant. Judging from our index case with her very early onset clinical presentation, the c.658G>C may be classified as a pathogenic variant, at least in the presence of another pathogenic variant.

The homology analysis indicates that Gly220 and Arg356 are highly conserved between different species (Figure 1C), and the structure simulation indicates that c.658G>C (p.Gly220Arg) mutation makes Arg220 collide with Arg55 and Ser56, which affects the second level of Arg55. The c.1066C>T mutation breaks the hydrogen bond between Trp356 and Leu197, Asp354, Pro355, and the steric hindrance of the benzene
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Figure 1 Gene sequencing results of the index case and some family members. A: Sanger sequencing revealed that the child had a compound heterozygous mutation of PRF1 gene consisting of c.658G>C (p.Gly220Arg) and c.1066C>T (p.Arg356Trp); B: The paternal grandfather and father were heterozygous for c.658G>C (p.Gly220Arg) while the maternal grandmother and mother were heterozygous for c.1066C>T (p.Arg356Trp). The healthy sister did not carry any perforin-1 (PRF1) gene mutation. The eldest brother died at the age of 3 mo, more than 13 years ago, with recurrent fever and jaundice without diagnosis. C: Protein alignment shows that both Gly220 and Arg356 are highly conserved among many animal species; D: Gly220Arg mutation causes molecular collision between Arg220, Arg55, and Ser56 (the pink dotted line in the white box), and Arg356Trp mutation causes hydrogen bond breaks between Trp356, Leu197, Asp354, and Pro355 (green dashed line in the orange box). Both mutations change the conformation of PRF1 protein and decrease the protein function.
FINAL DIAGNOSIS
FHL2.

TREATMENT
Our patient received only supportive treatment, including vitamin K1 injection, transfusions, anti-infective therapy, and hepatoprotective medications such as glycyrrhizin and glutathione. Unfortunately, hematopoietic stem cell transplantation (HSCT) was refused by the family due to financial difficulty.

OUTCOME AND FOLLOW-UP
Our patient passed away at the age of 3 mo at home with fever and jaundice.

LITERATURE SEARCH
Wanfang database, CNKI full-text database, and Pubmed database were used for our literature search. Keywords of "PRF1", "Perforin 1", "Familial Hemophagocytic Lymphohistiocytosis type 2", "Hemophagocytic Lymphohistiocytosis type 2" were used as the input and search for "Lymphohistiocytosis" and "Hemophagocytic Lymphohistiocytosis" to obtain the reported PRF1 gene mutation in the Chinese population.

Results from literature search
We identified a total of 75 Chinese FHL2 patients with complete clinical phenotype and genotype reported between 2000 and 2020 (Table 1). The age of onset ranged between 45 days and 56 years, with only six (8%) presenting before the age of 1 year. There were 43 males and 32 females (1.34:1). Overall, 56 PRF1 gene mutations were identified. The hotspot mutation sites were c.1349C>T (24.8%), c.65delC (11.6%), and c.503G>A (9.3%); the main type of mutations was missense mutations (72%), followed by frameshift mutations (24%)[3,10-23].

DISCUSSION
FHL is a kind of HLH with an autosomal or X-linked recessive genetic mutation that is commonly present in infants or young children. About 90% of the children are younger than 2 years old, and the incidence is about 0.12 per 100,000[24]. Our literature review showed that only 8% (6/75) of Chinese FHL2 cases, excluding this reported case, were younger than 1 year old, which is in sharp contrast to the literature. However, we cannot exclude the possibility of reporting bias. The prognosis is known to be worse with a younger age of presentation. The main clinical features are persistent fever, hepatosplenomegaly, pancytopenia, increased ferritin level, and decreased NK cell activity[25], which can be detected in 20%-73% of the patients at initial clinical presentation. Patients with FHL may also present with neurological symptoms, including seizures, facial paralysis, gait instability, or even coma. It is worth noting that FHL is more susceptible to neurologic involvement than the non-familial HLH[11,19].

Our index case had a very early onset, by the age of 7 d, and was the youngest one in the reported Chinese cases. Although there was no proof that the deceased eldest brother was also a case of FHL2, his clinical presentation was highly suggestive of another case of FHL2. The pancytopenia, splenomegaly, increased serum ferritin, and decreased NK cell activity detected by the age of 15 d in our reported case were typical for FHL. Although there was no clinically evident neurologic involvement, the diagnosis of FHL could be established by fulfilling the criteria of HLH-2004 guidelines[25].

Five subtypes of FHL have been identified. Except for FHL1, which has no precise gene location being identified, each subtype is caused by its respective gene mutation such as PRF1, UNC13D, STXI1, and STXBP2[11]. Mutations involving PRF1 and
Table 1 Cases of familial hemophagocytic lymphohistiocytosis reported in Chinese population

| Case | Age of onset | Gender | Variant | Amino acid change(s) | Type of mutation | Ref. |
|------|--------------|--------|---------|----------------------|------------------|------|
| 1    | 6 yr         | M      | c.C1066T| p.R356W              | Missense mutation| [10] |
| 2    | 19 yr        | M      | c.C1349T| p.T450M              | Missense mutation|      |
| 3    | 27 yr        | M      | c.65delC| p.S618N              | Missense mutation|      |
| 4    | 11 yr        | M      | c.T172C | p.S558P              | Missense mutation|      |
| 5    | 9 yr         | F      | c.C1066T| p.R356W              | Missense mutation|      |
| 6    | 17 yr        | F      | c.A380G | p.N127S              | Missense mutation|      |
| 7    | 20 yr        | F      | c.G503A | p.T450M              | Missense mutation|      |
| 8    | 1 yr         | F      | c.G673T | p.R225W              | Missense mutation|      |
| 9    | 2 mo         | M      | c.G984A | p.W328X              | Nonsense mutation|      |
| 10   | 6 yr         | F      | c.G1349T| p.T450M              | Missense mutation|      |
| 11   | 3 yr         | M      | c.G503A | p.T450M              | Missense mutation|      |
| 12   | 2 yr         | F      | c.1090_1091delCT| p.T364fsX93 | Frameshift mutation|      |
| 13   | 1 yr         | F      | c.C10T  | p.R4C                | Missense mutation|      |
| 14   | 10 yr 9 mo   | M      | c.65delC| p.P22RfsX29          | Frameshift mutation|      |
| 15   | 14 yr        | M      | c.G503A | p.S618N              | Missense mutation|      |
| 16   | 13 yr        | M      | c.G503A | p.S618N              | Missense mutation|      |
| 17   | 3 yr         | M      | c.G503A | p.S618N              | Missense mutation|      |
| 18   | 24 yr        | M      | c.C1005A| p.S535R              | Missense mutation|      |
| 19   | 26 yr        | M      | c.1419delC| p.T740fsX5 | Frameshift mutation|      |
| 20   | 1 yr 6 mo    | F      | c.1083_1094del| p.361_365del | Frameshift mutation| [11] |
| 21   | 4 yr 11 mo   | F      | c.1349C>T| p.T450M              | Missense mutation|      |
| 22   | 9 yr         | F      | c.1349C>T| p.T450M              | Missense mutation|      |
| 23   | 1 yr 9 mo    | M      | c.65delC| p.P22RfsX29          | Frameshift mutation|      |
| 24   | 7 yr         | M      | c.C10T  | p.R4C                | Missense mutation| [12] |
| 25   | 6 yr         | M      | p.V50L  | p.V50L               | Missense mutation|      |
| 26   | 4 yr         | M      | C1465A>T| p.R489W              | Missense mutation|      |
| ID | Age | Gender | Mutation Details | Functional Impact |
|----|-----|--------|------------------|------------------|
| 27 | 25 yr | M | c.65delC | p.P22fsX29 | Frameshift mutation |
| 28 | 13 yr | F | c.916G>A | p.G306S | Missense mutation |
| 29 | 8 yr | M | c.1349C>T | p.T450M | Missense mutation |
| 30 | 48 yr | M | c.916G>A | p.G306S | Missense mutation |
| 31 | 2 yr 2 mo | F | c.10C>T | p.R4C | Missense mutation |
| 32 | 8 yr 5 mo | F | c.1349C>T | p.T450M | Missense mutation |
| 33 | 5 yr 2 mo | M | c.305C>T | p.C102F | Missense mutation |
| 34 | 14 yr 5 mo | F | c.503G>A | p.S168N | Missense mutation |
| 35 | 5 yr 2 mo | F | c.503G>A | p.S168N | Missense mutation |
| 36 | 45 D | F | c.65delC | p.P22fsX29 | Frameshift mutation |
| 37 | 13 yr 8 mo | F | c.1349C>T | p.T450M | Missense mutation |
| 38 | 2 mo | M | c.1349C>T | p.T450M | Missense mutation |
| 39 | 4 yr | F | c.133G>A | p.K285del | Frameshift mutation |
| 40 | 4 yr 2 mo | F | c.1349C>T | p.T450M | Missense mutation |
| 41 | 3 yr | F | c.1349G>A | p.T364fsX93 | Frameshift mutation |
| 42 | 5 mo | F | c.673C>T | p.T364fsX93 | Frameshift mutation |
| 43 | 4 yr 11 mo | F | c.853_855delAAG | p.K285del | Frameshift mutation |
| 44 | 10 mo | F | c.1349C>T | p.T450M | Missense mutation |
| 45 | 11 yr 3 mo | M | c.1349C>T | p.T450M | Missense mutation |
| 46 | 6 yr | F | c.133G>A | p.K285del | Frameshift mutation |
| 47 | 8 mo | M | c.562C>G | p.P188A | Missense mutation |
| 48 | 1 yr | M | c.916G>A | p.R33H | Missense mutation |
| 49 | 1 yr | M | c.65delC | p.P22fsX29 | Frameshift mutation |
| 50 | 1 yr | M | c.65delC | p.P22fsX29 | Frameshift mutation |
| No. | Age | Gender | cDNA Change | Protein Change | Mutation Type |
|-----|------|--------|-------------|---------------|--------------|
| 51  | 2 yr | M      | c.1349C>T   | p.T450M       | Missense     |
| 52  | 2 yr | M      | c.1103T>A   | p.L368Q       | Missense     |
| 53  | 3 yr | M      | c.1349C>T   | p.T450M       | Missense     |
| 54  | 3 yr | M      | c.634T>C    | p.Y212H       | Missense     |
| 55  | 3 yr | F      | c.1481T>A   | p.C497X       | Nonsense     |
| 56  | 4 yr | M      | c.1103T>A   | p.L368Q       | Missense     |
| 57  | 4 yr | M      | c.634T>C    | p.Y212H       | Missense     |
| 58  | 5 yr | M      | c.1349C>T   | p.T450M       | Missense     |
| 59  | 6 yr | M      | c.394G>A    | p.G132R       | Missense     |
| 60  | 6 yr | F      | c.445G>A    | p.G149S       | Missense     |
| 61  | 9 yr | M      | c.1349C>T   | p.T450M       | Missense     |
| 62  | 10 yr 9 mo | F   | c.503G>A   | p.S168N       | Missense     |
| 63  | 19 yr | M      | c.1066C>T   | p.R356W       | Missense     |
| 64  | 56 yr | M      | c.65delC    | p.P22RfsX29   | Frameshift   |
| 65  | 18 yr | F      | c.1168C>T   | p.R390X       | Nonsense     |
| 66  | 19 yr | M      | c.1349C>T   | p.T450M       | Missense     |
| 67  | 18 yr | M      | c.1349C>T   | p.T450M       | Missense     |
| 68  | 18 yr | M      | c.172T>C    | p.S58P        | Missense     |
| 69  | 27 yr | M      | c.1083_1094del | p.361_365del | Frameshift   |
| 70  | 18 yr | F      | c.65delC    | p.P22RfsX29   | Frameshift   |
| 71  | 18 yr | M      | c.65delC    | p.P22RfsX29   | Frameshift   |
| 72  | 18 yr | F      | c.1349C>T   | p.T450M       | Missense     |
| 73  | 18 yr | F      | c.380A>G    | p.N127S       | Missense     |
| 74  | 15 yr | M      | c.380A>G    | p.N127S       | Missense     |
| 75  | 15 yr | M      | c.853_855delAAG | p.K285del    | Frameshift   |
| 76  | 15 yr | M      | c.853_855delAAG | p.K285del    | Frameshift   |
| 77  | 15 yr | M      | c.1349C>T   | p.T450M       | Missense     |
| 78  | 15 yr | M      | c.1349C>T   | p.T450M       | Missense     |

[22] [23]
UNC13D are more pathogenic than STX11 and STXBP2, as shown in studies involving Italian, Turkish, and Korean cohorts[20]. PRF1 is a gene located in the 10q21-22 region containing three exons. The encoded human perforin protein precursor is mainly expressed in cytotoxic T lymphocytes (CTL) and NK cells, which plays an important role in immune regulation. Patients who carry PRF1 gene defects are vulnerable to infections, autoimmune diseases, and malignant tumors[26,27].

The PRF1 gene mutations reported in Chinese are different from those of other ethnic groups. We identified that c.1349C>T is the most common PRF1 mutation in Chinese FHL2 patients, accounting for 24.8% of all reported cases, followed by the c.65delC mutation, which accounts for 11.6%. The distribution of variants is in sharp contrast to that reported in Turkish patients with the most prevalent one (approximately 74%) being the c.1122G>A (p.W374X), a variant not reported in Chinese FHL2 patients. About one-third of Japanese FHL2 patients have c.1090-1091delCT variant that only occurs in 2% of Chinese FHL2 cases. The hotspot mutation in Chinese FHL2 is in the protein kinase C conserved region 2. This domain is the key region for PRF1 protein to initiate membrane perforation and to maintain cytotoxic activity. The conformational change of the mutated PRF1 reduces the cytotoxic activity of the protein and causes disease[28]. Our case is the second one with c.658G>C (p.Gly220Arg), which has not been confirmed as a pathogenic variant at this moment. However, our patient's rapid progressive manifestation strongly suggests the c.658G>C (p.Gly220Arg) is a true pathogenic variant, at least in the presence of another known pathogenic variant.

FHL2 is a rapidly progressing immune disorder with a high mortality rate if not treated. Most untreated patients will die of severe infection or have multiple organ dysfunction syndrome. FHL2 treatment is by supportive measures and chemotherapy until allogeneic HSCT can be available[25]. A recent comprehensive study of the HLH-94/2004 treatment regimens showed an overall response rate of 72.7% (complete response rate of 55.5%) and a 3-year overall survival rate of 74.7%, with an overall incidence of side effects at 18.2%. Although chemotherapy can temporarily alleviate the symptoms, it cannot eliminate the genetic basis of immune deficiency. HSCT is generally considered the curative treatment for FHL. Studies have shown that patients who fail the transplantation can still have long-term survival[24]. Our patient received only supportive treatment, including vitamin K1 injection, transfusions, anti-infective therapy, and hepatoprotective medications such as glycyrrhizin and glutathione. Unfortunately, HSCT was refused by the family due to financial difficulty. Our patient passed away at the age of 3 mo at home with fever and jaundice.

CONCLUSION

In summary, we report the case of a newborn infant with FHL2 who had clinical manifestations by the age of 7 d. The genetic test revealed a compound heterozygous mutation of c.658G>C (p.Gly220Arg) and c.1066C>T (p.Arg356Trp). The two mutations carried by the index cases were not commonly seen in Chinese PRF1 mutations. The clinical manifestation of our case strongly suggests that c.658G>C (p.Gly220Arg) is also a pathogenic variant.

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