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CASE REPORT

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Ferritin L-subunit gene mutation and hereditary hyperferritinaemia cataract syndrome (HHCS): a case report and literature review

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ABSTRACT

Objectives: Hereditary hyperferritinaemia cataract syndrome (HHCS) is an autosomal dominant disease characterized by high serum ferritin levels and juvenile bilateral cataracts. It is often caused by mutations in the iron response element (IRE) of the ferritin L-subunit (FTL) gene. Here, we report a 73-year-old woman who presented to clinic with persistently elevated serum ferritin and family history of juvenile bilateral cataracts in four generations.

Methods: Exome sequencing was used to identify the mutation of the FTL gene. Moreover, Sanger sequencing was performed to validate the mutation in the proband. We also reviewed the FLT gene mutations in published HHCS cases to provide experience for accurate diagnosis of similar patients.

Results: A heterozygous mutation at position +33 (c.-167C > T, chr19:49468598) of the FTL gene was identified in the patient.

Discussion: HHCS should be considered in the differential diagnosis of hyperferritinemia, especially in the presence of normal serum iron concentration and transferrin saturation.

Conclusion: For patients with unexplained hyperferritinemia and bilateral cataracts who have experienced early vision loss, the establishment of genetic counseling is essential to diagnose other family members who are at risk in time.

Abbreviations: FTL: ferritin L-subunit; HHCS: hereditary hyperferritinaemia cataract syndrome; IDT: integrated DNA technologies; IRE: iron response element; IRP: iron regulatory proteins; MRI: magnetic resonance imaging; SNV: single nucleotide variant; UTR: untranslated region

KEYWORDS

L-ferritin; cataract; hereditary hyperferritinaemia cataract syndrome; mutation

Background

Serum ferritin is a water-soluble protein that contains about 23% iron. It is mainly composed of the L-subunit and a few H subunits, which is roughly equivalent to the total iron storage of the human body. Therefore, serum ferritin is often used to determine the level of stored iron in the body. Hereditary hyperferritinaemia cataract syndrome (HHCS) is a rare autosomal dominant genetic disease characterized by significantly raised serum ferritin, bilateral congenital cataracts, but the transferrin saturation and serum iron in the body are normal or high, no increased iron load in the liver and other parenchymal organs, and no evidence of inflammation or tumor [1].

It is currently believed that the pathogenesis of HHCS is mainly the mutation in the segment of Iron Response Element (IRE) that located in the 5′ untranslated region (UTR) of the ferritin L-subunit (FTL) gene, which is the critical sequence of the stem-loop motif [2]. This region can affect the binding affinity of Iron Regulatory Proteins (IRP) to IRE and deregulate the expression of the L-Ferritin, resulting in increased synthesis of L-Ferritin. The excessive ferritin subsequently accumulated in serum and crystalline lens, leading to hyperferritinemia and the early onset of bilateral cataracts [3]. Mumford and colleagues found that the level of ferritin in the lens of affected individuals was 10-fold higher than that in the normal group [4]. The severity of cataracts is related to the levels of serum ferritin and the clinical severity of HHCS (i.e. serum ferritin levels and cataract severity) is related to the location of the IRE mutation [2,5].

The clinical manifestations of HHCS are bilateral cataracts with elevated serum ferritin level, and bilateral cataract may be the only recognizable phenotypic manifestation [6]. However, many clinicians often fail to identify and diagnose HHCS. They just treat the patient as a pure cataract patient and even perform eye surgery on the patient without checking the serum ferritin concentration, ignoring the genetic characteristics of the disease [7]. Family history of hyperferritinemia and cataracts are important diagnostic indicators of HHCS. Genetic analysis of the FTL gene is a simple procedure that can confirm the diagnosis [8]. Accurate diagnosis of HHCS can avoid unnecessary

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phlebectomy therapy and focus attention on early cataract detection in high-risk offspring.

Here, we report a Chinese female with HHCS associated with a heterozygous mutation at position +33 (c.-167C > T, chr19:49468598) in the FTL gene. The version of the human genome used for chr19:49468598 position is hg19. '+33' refers to the traditional nomenclature, where the number of the mutational position is counted from the transcription initiation site as +1; in opposition to the official HGVS nomenclature considering +1 the A in the ATG of the starting codon (c.-167C > T). In addition, we have reviewed all the mutations of the FTL gene in reported cases of HHCS until now, in order to provide experience for accurate diagnosis of similar patients.

Case presentation

The proband was a 73-year-old woman (II-3 in Figure 1), and her overall condition was good. According to the patient, she had poor vision from childhood. At the age of twelve, she was diagnosed with congenital cataracts, with visual acuity 6/10 in the left eye and 7/10 in the right eye. She began to have blurred vision in both eyes at the age of 40. When she was 68 years old, the loss of her visual acuity progressed, and visual acuity was 5/10 in the left eye and 4/10 in the right eye. Then she underwent ultrasound phacoemulsification and intraocular lens implantation under topical anesthesia. After the surgery, her visual acuity recovered to 8/10 in the left eye and 7/10 in the right eye, with eyeglasses for correction. She was found to have elevated serum ferritin (2500 ng/ml, reference value 24–336 ng/ml) during a routine health checkup at the age of 71. Then the patient began to review serum ferritin regularly.

In August 2020, she visited the outpatient department of Hematology of West China Hospital for further assessment due to persistently raised serum ferritin. Repeated examination indicated that her serum ferritin concentration was significantly increased (1652 ng/ml, reference value 24–336 ng/ml). Further laboratory examination indicated that, except for a slight decrease in transferrin (2.26 g/L, reference value 2.5–4.3 g/L), other iron metabolism parameters including soluble transferrin receptor (1.16 mg/L, reference value: 0.76–1.76 mg/L), serum iron (22.4 umol/L, reference value: 7.8–32.2 umol/L), total iron-binding capacity (TIBC) (51.25 umol/L, reference value: 48.3–68.0 umol/L) and transferrin saturation (43.7%, reference value: 20%~55%) were all normal. Evaluation of magnetic resonance imaging

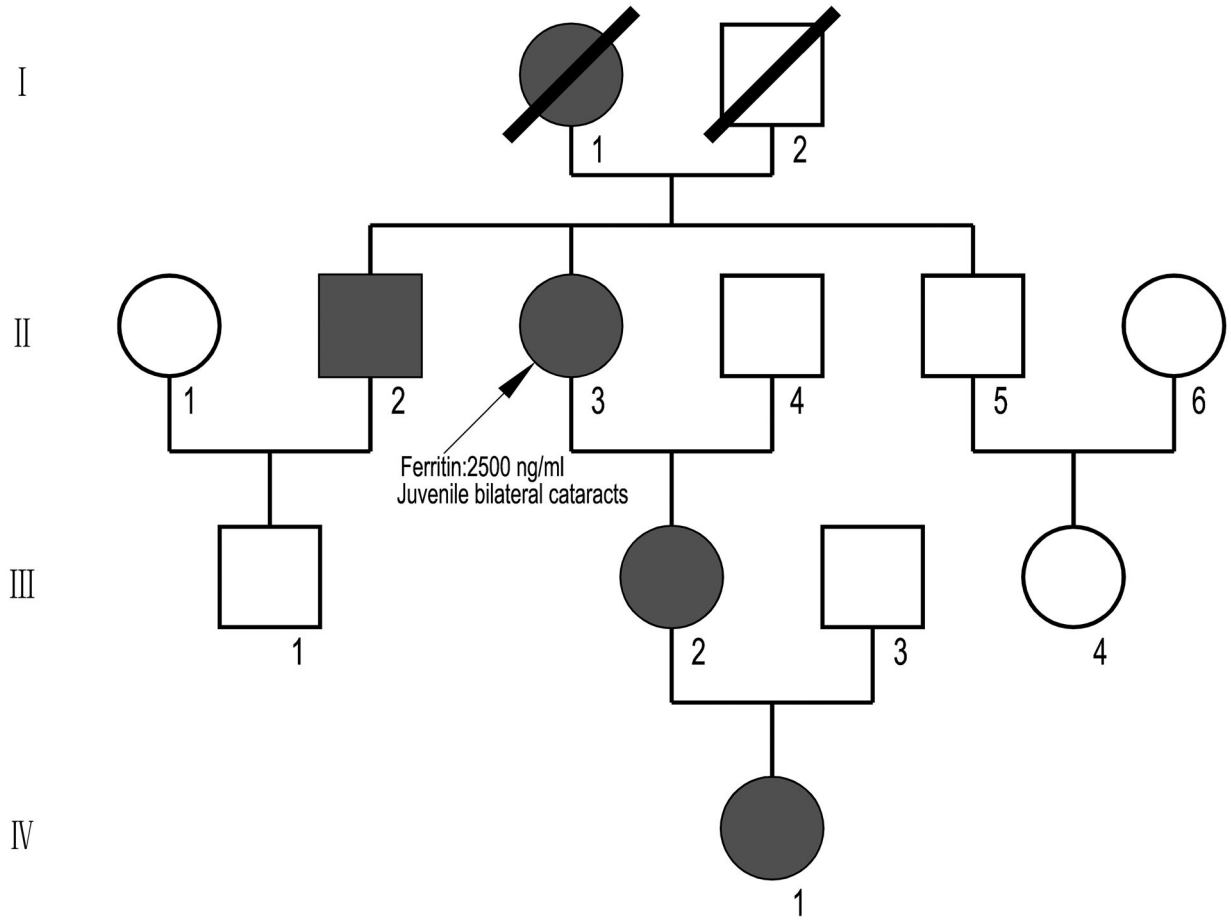

Figure 1. A four-generation family pedigree with HHCS. The proband is shown arrowed. Circles denote female family members and squares male family members. Black symbols indicate individuals with HHCS. Open symbols indicate non-affected individuals.

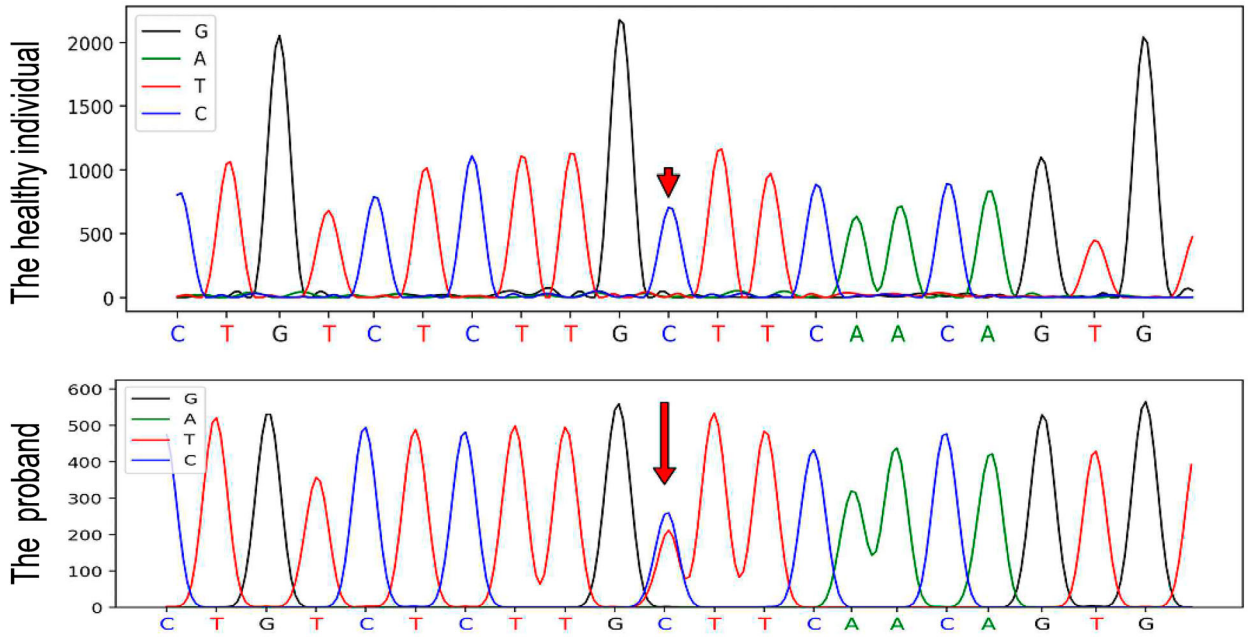

Figure 2. DNA sequence of the L-ferritin gene encompassing the c.-167C > T mutation in the proband and in a healthy individual. The mutation is indicated by red arrow.

(MRI) of the heart and liver showed no evidence of parenchymal iron overload. She had no other aetiologies such as malignancy, inflammation, obesity, and alcohol abuse that could cause hyperferritinemia. Consequently, genetic testing was carried out on the patient.

After obtaining informed consent, the peripheral blood sample was drawn from the proband. DNA was extracted using the commercially available kits. Integrated DNA Technologies (IDT) capture kits, Kapa Library Construction Kit was employed for seizing and gathering the patient DNA in exon regions. Exome sequencing using Illumina Novaseq6000 sequencing machine was performed to detect gene mutations in the proband, including all point mutations, small insertions, and small deletions. DNA analysis detected a mutation in the IRE region of the FTL gene (c.-167C > T, chr19:49468598).

Sanger sequencing using ABI 3730 Genetic Analyzer machine was performed to validate the mutation in the proband. PCR amplification was performed using the following primer pair: forward, 2F: 5′-GGGCTGAGACTCCTATGTGC-3′, reverse, 2R: 5′-GGTTGGTTGGCAAGAAGGAG-3′.

We found a heterozygous sequence variant converting C to T at chr19:49468598 (c.-167C > T) in the FTL gene in the patient (Figure 2). The mutation is reported to be related to HHCS in the HGMD

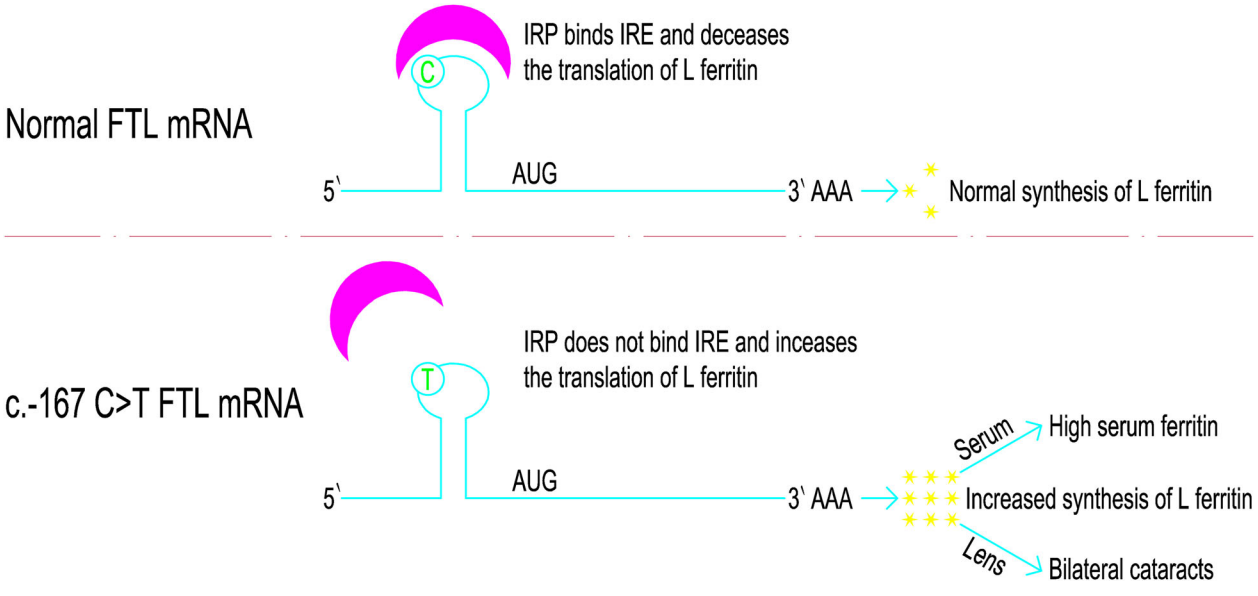

Figure 3. Mechanism of HHCS caused by c.-167C > T mutation in the FTL gene.

Table 1. An overview of all mutations causing HHSC (as of September 2021).

Mutation type	Location based on traditional nomenclature	Location based on HGVS nomenclature	Times of reports	References
SNV	40 A > G	c.-160 A > G	17	[1,8–10,12,14,16,20,22,25,26,34,42,44,47,55,57,59]
SNV	39 C > T	c.-161 C > T	10	[4,8,11,22,26,29,31,34,38,53]
SNV	32 G > T	c.-168 G > T	8	[1,7,8,34,37,39,50,53]
SNV	32 G > A	c.-168 G > A	8	[5,22,34,50–54]
SNV	33 C > T	c.-167 C > T	8	[8,12,34,35,45,53,56,58,59]
SNV	32 G > C	c.-168 G > C	7	[1,3,8,19,27,34,51]
SNV	36 C > A	c.-164 C > A	3	[4,8,34]
SNV	22 T > G	c.-178 T > G	3	[5,31,36]
SNV	29 C > G	c.-171 C > G	2	[15,45]
SNV	51 G > C	c.-149 G > C	2	[6,18]
SNV	41 G > C	c.-159 G > C	2	[23,41]
SNV	24 T > C	c.-176 T > C	2	[36,48]
SNV	39 C > G	c.-161 C > G	2	[30,43]
SNV	18 C > T	c.-182 C > T	2	[5,31]
SNV	43 G > A	c.-157 G > A	1	[53]
SNV	36 C > T	c.-164 C > T	1	[2]
SNV	52 G > C	c.-148 G > C	1	[2]
SNV	46 T > G	c.-154 T > G	1	[46]
SNV	39 C > A	c.-161 C > A	1	[1]
SNV	18 C > A	c.-182 C > A	1	[36]
SNV	26 T > G	c.-174 T > G	1	[36]
SNV	47 G > C	c.-153 G > C	1	[40]
SNV	48 G > T	c.-152 G > T	1	[40]
SNV	37 A > C	c.-163 A > C	1	[49]
SNV	36 C > G	c.-164 C > G	1	[24]
SNV	37 A > G	c.-163 A > G	1	[24]
SNV	47 G > A	c.-153 G > A	1	[34]
SNV	34 T > C	c.-166 T > C	1	[34]
SNV	50 C > A	c.-150 C > A	1	[33]
SNV	14 C > G	c.-186 C > G	1	[23]
SNV	7 C > G	c.-193 C > G	1	[20]
SNV	49 A > C	c.-151 A > C	1	[20]
SNV	10 C > T	c.-190 C > T	1	[24]
SNV	16 C > T	c.-184 C > T	1	[24]
SNV	90 C > T	c.-110 C > T	1	[24]
SNV	49 A > G	c.-151 A > G	1	[60]
SNV	56 A > T	c.-144 A > T	1	[61]
SNV	-	c.-216C > A	1	[62]
SNV	33 C > A	c.-167 C > A	1	[63]
SNV	37 A > T	c.-163 A > T	1	[64]
Insertion-deletion	18_26 delCGGGTCTGT insAGGGGCCGG	c.-182_-174 delCGGGTCTGT insAGGGGCCGG	1	[36]
Insertion-deletion	47_48delGGinsCT	c.-153_-152 delGGinsCT	1	[40]
Deletion	38_39delAC	c.-162-161delAC	2	[31,34]
Deletion	42_57del16	c.-158_143del16	2	[34]
Deletion	156 delT	c.-44delT	1	[24]
Deletion	32_35delGCTT	c.168_165delGCTT	1	[65]
Deletion	36_42del7	c.-164_158del7	1	[66]
Deletion	39 delC	c.-161delC	1	[67]
Deletion	-	c.-220_196del25	1	[17]
Deletion	10_38del29	c.-190_162del29	1	[32]
Deletion	22_27del6	c.-178_173del6	1	[21]

professional database. Her daughter and granddaughter were also confirmed to have the same genetic mutation. Figure 3 represents the mechanism of HHCS caused by c.-167C > T mutation of the FTL gene.

Family history was significant in that the patient's mother (I-1) also had early onset cataract. One of her younger brothers (II-2) was diagnosed with a congenital cataract at the age of 10 and underwent cataract surgery at the age of 19. The patient's daughter (III-2) and granddaughter (IV-1) also suffered from eye problems at the age of 12, and were confirmed to have the same genetic mutation as the patient. The affected brother of the patient had a 35-year-old son who had no eye problems. The remaining healthy brother had a non-affected daughter. No member of this family had previously had genetic counseling. The family pedigree is outlined in Figure 1.

Literature review

We identified 115 cases that reported HHCS from 1995 to 2021 via PubMed using a combination of the keywords 'Hereditary hyperferritinaemia cataract syndrome', 'L-Ferritin', and 'Cataract'. The current case is the second reported case of HHCS in China. Since first reported in 1995, a series of point mutations and short deletions of L-ferritin related to HHCS have been reported [9–57]. Table 1 shows that a total of 34 single nucleotide transitions (SNT) and 5 nucleotide

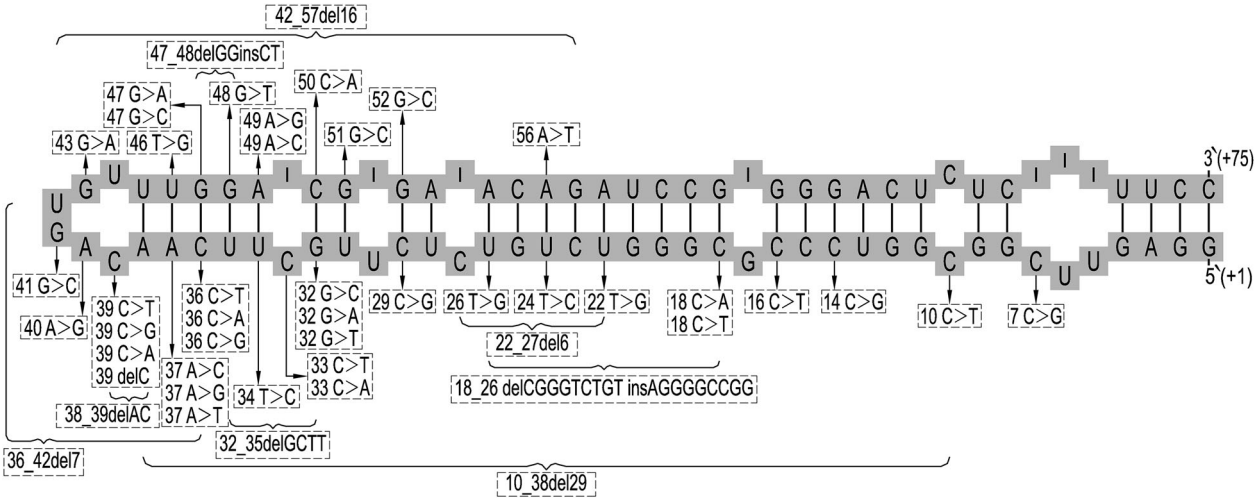

Figure 4. Mutations causing HHCS in the predicted secondary structure of the IRE. The nucleotide deletions are represented by brackets, and the single nucleotide variants are denoted by black arrows. Genetic variants are reported following the traditional nomenclature.

deletions have been reported as of September 2021. Among them, the single nucleotide transition most frequently reported is +40A > G (c.-160A > G in the HGVS nomenclature). Mutations causing HHCS in the predicted IRE structure of L-ferritin are presented in Figure 4. It can be seen from the figure that most of the mutations that cause HHCS are at the upper stem and the conserved hexanucleotide of the hairpin structure of IRE.

Discussion

In this report, we described a Chinese family affected with HHCS who was identified a heterozygous c.-167C > T mutation in the 5′ UTR of the FTL gene. HHCS is inherited in an autosomal dominant manner, and this heterozygous mutation is in line with the inheritance pattern of the disease. This mutation has also been reported to be associated with HHCS previously in several other pedigrees [8,12,35,45,53,56,58].

According to a study by Australian scholars, the prevalence of HHCS in the population is at least 1/20,000 [1]. Since the first case of HHCS in China was reported in 2020 [55], our case is the second identified case. This may be due to the relatively low actual incidence of the disease in the Chinese population, or it may be that the understanding of the disease is still insufficient, and the rate of missed diagnosis and misdiagnosis is still high.

As the increase of L-Ferritin in affected individuals is due to the dysregulation of L-Ferritin synthesis and has nothing to do with the body iron storage, there is no real iron overload in HHCS patients. In our case, the level of serum iron and TIBC was normal and MRI of liver and heart showed no evidence of iron overload. Patients with HHCS often develop cataracts at a young age. Just as in our case, the proband, her daughter, granddaughter and younger brother all started to develop cataracts around the age of twelve. The typical cataract of HHCS has unique morphological features, which are characterized by progressive white spots along the axial and surrounding areas, accompanied by small crystal aggregates [1]. Unfortunately, since the patient had undergone cataract surgery before diagnosis, we were unable to obtain the photos of patient's eye before surgery.

Conclusion

HHCS should be considered in the differential diagnosis of hyperferritinemia. Serum ferritin levels can be effectively used to screen suspicious families for this condition. We recommend that patients with cataracts at young age should check their serum ferritin levels routinely. On the other hand, individuals with unexplained high level of serum ferritin should be referred for ophthalmological consultation. In summary, although HHCS is a rare disorder, clinicians should be aware of it in order to avoid unnecessary treatment to deplete iron, as well as enable patients to conduct appropriate genetic counseling and more appropriate management.

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Disclosure statement

None of the authors has a potential conflict of interest to disclose.

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Ethical approval

The study protocol conforms to the World Medical Association Declaration of Helsinki.

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