

Ferritin L-subunit Gene Mutation and Hereditary Hyperferritinaemia Cataract Syndrome: A Case Report and Literature Review

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Case Report

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Abstract

Background: 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. Most of the mutations are point mutations located in the upper stem and the conserved hexanucleotide of the hairpin structure of IRE, only a few mutations are deletions.

Case presentation: 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. DNA sequencing analyses identified a heterozygous c.-167C>T mutation in the 5' untranslated region (UTR) of the *FTL* gene. Her daughter and granddaughter were also confirmed to have the same genetic mutation.

Conclusion: HHCS should be considered in the differential diagnosis of hyperferritinemia, especially in the presence of normal serum iron concentration and transferrin saturation. 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, so as to avoid unnecessary liver biopsy and venesection.

Introduction

Hereditary hyperferritinaemia–cataract syndrome (HHCS) is a rare autosomal dominant genetic disease characterized by significantly raised serum ferritin, bilateral congenital cataracts, but there were no other laboratory indicators of increased iron load in the body (normal or low transferrin saturation and serum iron), no increased iron load in the liver and other parenchymal organs, and no evidence of inflammation or tumor [1–5].

It is currently believed that the pathogenesis of HHCS is mainly due to the mutation in the segment of Iron Response Element (IRE), which is the critical sequence of the stem-loop motif that located in the 5' untranslated region (UTR) of the ferritin L-subunit (*FTL*) gene [6]. This region can affect the binding affinity of IRE binding protein to IRE and deregulate the expression of the L ferritin, resulting in an increased synthesis of L ferritin. The excessive ferritin subsequently accumulated in tissues and serum, leading to hyperferritinemia, L-ferritin deposition in the lens and the early onset of bilateral cataracts [7–13]. Kröger et al reported that the lens opacities of patients with HHCS consisted of a lot of L ferritin [14]. Mumford and colleagues found that the level of ferritin in the lens of patients with HHCS was 10-fold higher than that in the control group [15]. The severity of cataracts is related to the levels of serum ferritin [16] and the clinical severity of HHCS (including serum ferritin levels and cataract severity) is related to the location of the IRE mutation [17, 13].

The main clinical manifestations of HHCS are bilateral cataract and elevated serum ferritin level. Usually, bilateral cataract may be the only recognizable phenotypic manifestation [18]. 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 [5]. Family history of hyperferritinemia and cataracts are important diagnostic indicators of HHCS. Genetic analysis of *FTL* gene is a simple procedure that can confirm the diagnosis [19]. Accurate diagnosis of HHCS can avoid unnecessary phlebotomy 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. In addition, we have reviewed all the mutations of *FTL* gene in reported cases of HHCS until now, in order to provide experience for accurate diagnosis of similar patients.

Case Report

The patient was a 73-year-old woman, and the overall condition was fairly 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 since 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 found her ferritin was elevated (2500 ng/ml, reference value 24–336 ng/ml) during a routine health check-up 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) and total iron binding capacity (TIBC) (51.25 umol/L, reference value 48.3–68.0 umol/L) were all normal. Evaluation of magnetic resonance imaging (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, Sanger sequencing was performed to identify the mutations of the *FTL* gene in the peripheral blood of patients, including all point mutations, small insertions, and small deletions. Genomic DNA was extracted from peripheral blood using the commercially available kits. The IRE of the *FTL* gene in the 5'-UTR was amplified by standard polymerase chain reaction (PCR) using Taq polymerase. PCR amplification was performed using the following primer pair: forward, 2F: 5'-GGGCTGAGACTCCTATGTGC-3', reverse, 2R: 5'-GGTTGGTTGGCAAGAAGGAG-3'. Sequence analysis of PCR products was performed on Illumina Novaseq6000 sequencing platform. A

heterozygous sequence variant (c.-167C > T, chr19:49468598) was identified in the 5' UTR of the L-ferritin mRNA in the patient (Fig. 1). Her daughter and granddaughter were also confirmed to have the same genetic mutation.

Family history was significant in that the patient's mother also had early onset cataract. One of her younger brothers was diagnosed with congenital cataract at the age of 10 and underwent cataract surgery at the age of 19. The patient's daughter and granddaughter 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 nonaffected daughter. No member of this family had previously had genetic counseling. The family pedigree is outlined in Fig. 2.

Literature review

We identified 97 cases from all the English literatures that reported HHCS from 1995 to 2020 via PubMed. The current case is the second reported case of HHCS in China. Since first reported by Girelli *et al.* in 1995 [4], a series of point mutations and short deletions of L-ferritin related to HHCS have been reported. Table 1 shows that a total of 33 single nucleotide transitions and 5 nucleotide deletions have been reported as of February 2021. Among them, the single nucleotide transition most frequently reported is 40 A > G. In addition, most mutations have been reported only once. Mutations causing HHCS in the predicted IRE structure of L-ferritin are presented in Fig. 3. 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, indicating that these parts are critical for an efficient interaction of IRE and IRP.

The main clinical manifestations of the majority of individuals diagnosed with HHCS are long-term serum ferritin elevation and juvenile cataracts, while serum iron and transferrin saturation are normal. The severity of cataracts in HHCS patients is largely controlled by the binding interaction between IRE and iron regulatory proteins (IRP), and depends on the extent to which the genetic mutation changes the structure of the binding site itself [10]. Brooks *et al.* reported that cataract in patients with HHCS was caused by a large amount of small opacities, mainly in the lens cortex, which is a ferritin crystal that diffracts light [8]. Often, the symptoms of cataracts can be ameliorated by surgery.

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

Mutation type	Location based on nucleotide change	Location based on FTL cDNA nomenclature	Times of reports	Reference
SNP	40 A > G	c.-160 A > G	17	[20–26, 3, 27–29, 19, 30–34]
SNP	39 C > T	c.-161 C > T	10	[35, 26, 28, 36, 37, 29, 19, 38, 15, 39]
SNP	32 G > T	c.-168 G > T	8	[9, 3, 29, 19, 40–42, 39]
SNP	33 C > T	c.-167 C > T	7	[43, 8, 19, 44, 45, 39, 46]
SNP	32 G > C	c.-168 G > C	7	[47, 3, 48, 29, 10, 19, 49]
SNP	32 G > A	c.-168 G > A	7	[17, 26, 42, 49, 50, 39, 51]
SNP	29 C > G	c.-171 C > G	2	[52, 45]
SNP	51 G > C	c.-149 G > C	2	[53, 18]
SNP	41 G > C	c.-159 G > C	2	[54, 55]
SNP	24 T > C	c.-176 T > C	2	[56, 57]
SNP	36 C > A	c.-164 C > A	2	[19, 15]
SNP	22 T > G	c.-178 T > G	2	[17, 56]
SNP	39 C > G	c.-161 C > G	2	[58, 59]
SNP	43 G > A	c.-157 G > A	1	[39]
SNP	36 C > T	c.-164 C > T	1	[13]
SNP	52 G > C	c.-148 G > C	1	[13]
SNP	46 T > G	c.-154 T > G	1	[60]
SNP	39 C > A	c.-161 C > A	1	[3]
SNP	18 C > A	c.-182 C > A	1	[56]
SNP	26 T > G	c.-174 T > G	1	[56]
SNP	47 G > C	c.-153 G > C	1	[61]
SNP	48 G > T	c.-152 G > T	1	[61]
SNP	37 A > C	c.-163 A > C	1	[62]

Mutation type	Location based on nucleotide change	Location based on FTL cDNA nomenclature	Times of reports	Reference
SNP	36 C > G	c.-164 C > G	1	[63]
SNP	37 A > G	c.-163 A > G	1	[63]
SNP	18 C > T	c.-182 C > T	1	[37]
SNP	47 G > A	c.-153 G > A	1	[29]
SNP	50 C > A	c.-150 C > A	1	[64]
SNP	14 C > G	c.-186 C > G	1	[54]
SNP	7 C > G	c.-193 C > G	1	[25]
SNP	49 A > C	c.-151 A > C	1	[25]
SNP	10 C > T	c.-190 C > T	1	[63]
SNP	16 C > T	c.-184 C > T	1	[63]
Deletion	38_39delAC	c.-162-161delAC	2	[37, 29]
Deletion	42_57del16	c.-158_143del16	2	[65, 29]
Deletion	-	c.-220_196del25	1	[66]
Deletion	10_38del29	c.-190_162del29	1	[67]
Deletion	22_27del6	c.-178_173del30	1	[68]
SNT: single nucleotide transition.				

Discussion And Conclusion

In this report, we described a Chinese family diagnosed with HHCS who were identified a heterozygous c.-167C > T mutation in the 5' UTR of the *FTL* gene. This mutation has also been reported to be associated with HHCS previously in several other pedigrees [43, 8, 19, 44, 45, 39, 46].

According to a study by Australian scholars, the prevalence of HHCS in the population is at least 1/20,000 [3]. Since the first case of HHCS in China reported in 2020 [33], our case is the second identified case. This may be due to the fact that the actual incidence of the disease in the Chinese population is relatively low, 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 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 [3]. Unfortunately, since the patient had undergone cataract surgery before diagnosis, we were unable to obtain the photos of patient's eye before surgery.

HHCS should be considered in the differential diagnosis of hyperferritinemia, especially in the presence of normal serum iron concentration and transferrin saturation. Serum ferritin levels can be effectively used to screen suspicious families for this condition. For patients with 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, so as to avoid unnecessary procedural biopsy and phlebotomy, the latter would make the patients develop iron-deficient anemia rapidly, without any improvement in the elevated serum ferritin. We recommend that patients with cataracts at young age should routinely test serum ferritin levels. 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. For example, early genetic diagnosis can be used for screening the offspring with pathogenic mutations in test-tube baby so as to prevent the disease from being inherited.

Abbreviations

HHCS

Mantle cell lymphoma; IRE:Iron Response Element; *FTL*:Ferritin L-subunit; UTR:Untranslated region; MRI:Magnetic resonance imaging; PCR:Polymerase chain reaction; IRP:Iron regulatory proteins; SNT:Single nucleotide transition.

Declarations

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Authors' contributions

Yun-Fan Yang and Ting Lin performed the studies and writing of the manuscript. Xin-Chuan Chen revised the manuscript. All authors read and approve the final manuscript.

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Availability of data and materials

All relevant data and materials are included in this publication.

Ethics approval and consent to participate

Informed consent was obtained from the patient and the study protocol conforms to the declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

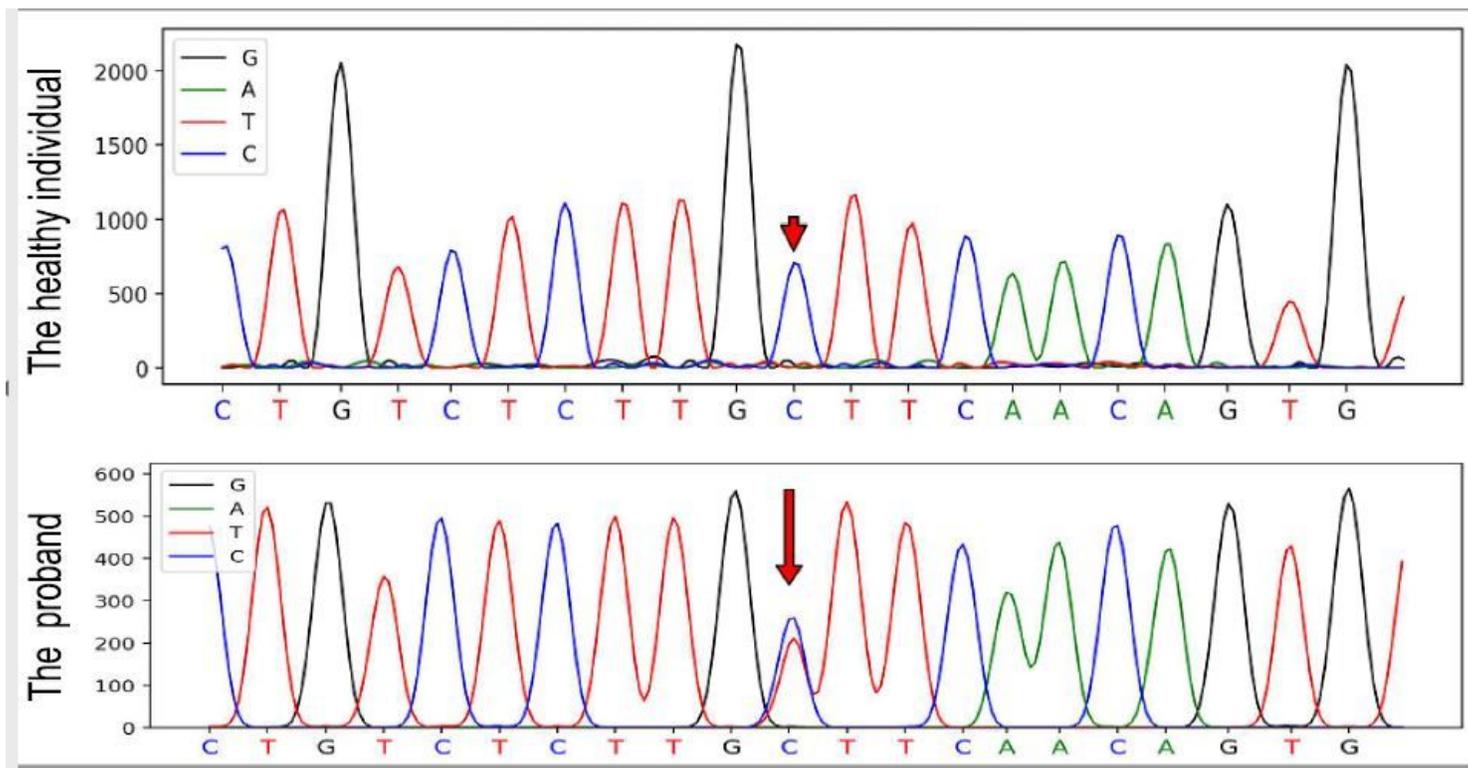


Figure 1

Sequence analysis of the FTL from a healthy individual and the proband. a heterozygous c.-167 C>T mutation in the proband DNA was depicted by red arrow.

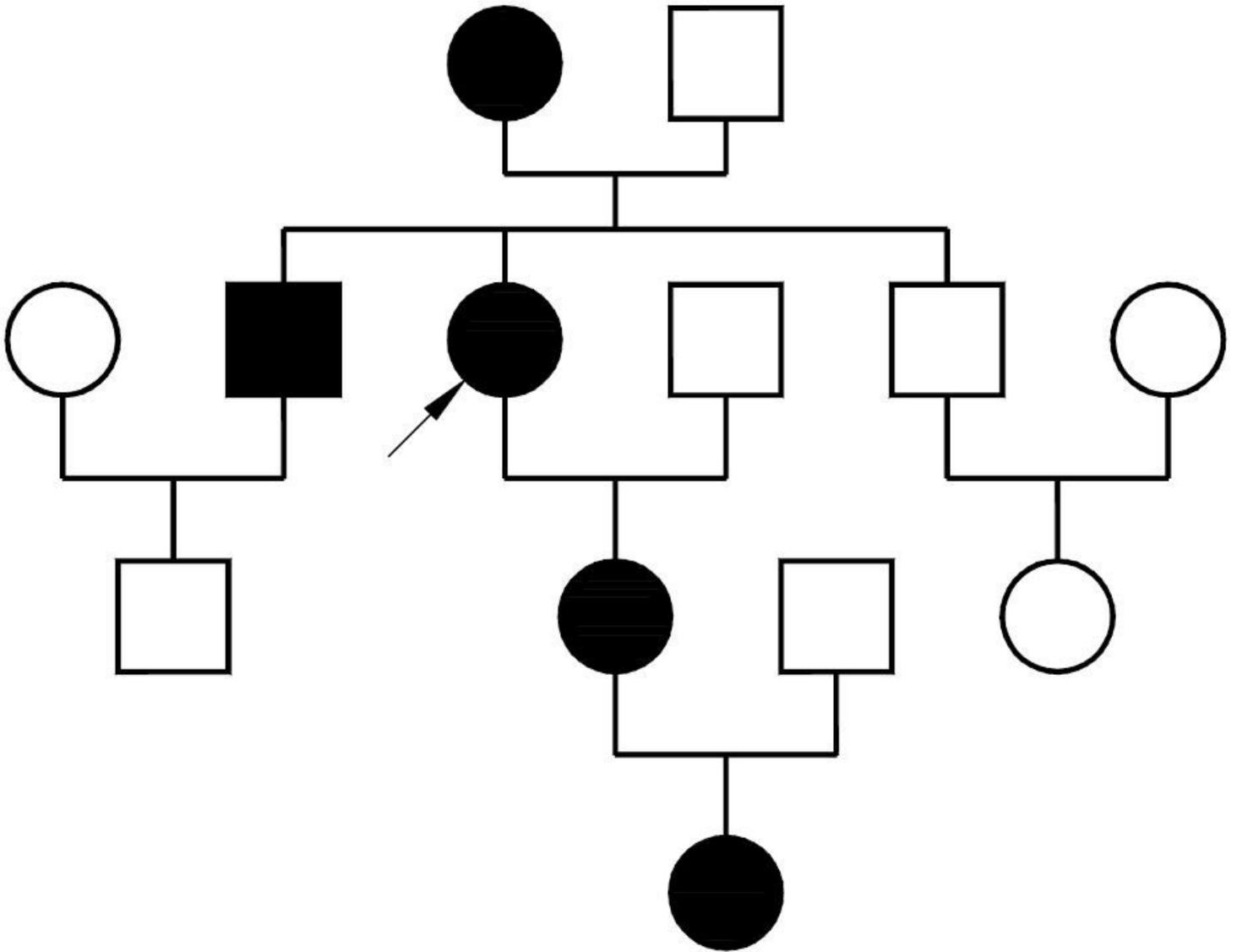


Figure 2

The family pedigree. The proband is shown arrowed. Circles denote female family members and squares male family members. Black symbols indicate individuals with hyperferritinaemia-cataract syndrome. Open symbols indicate non-affected individuals.

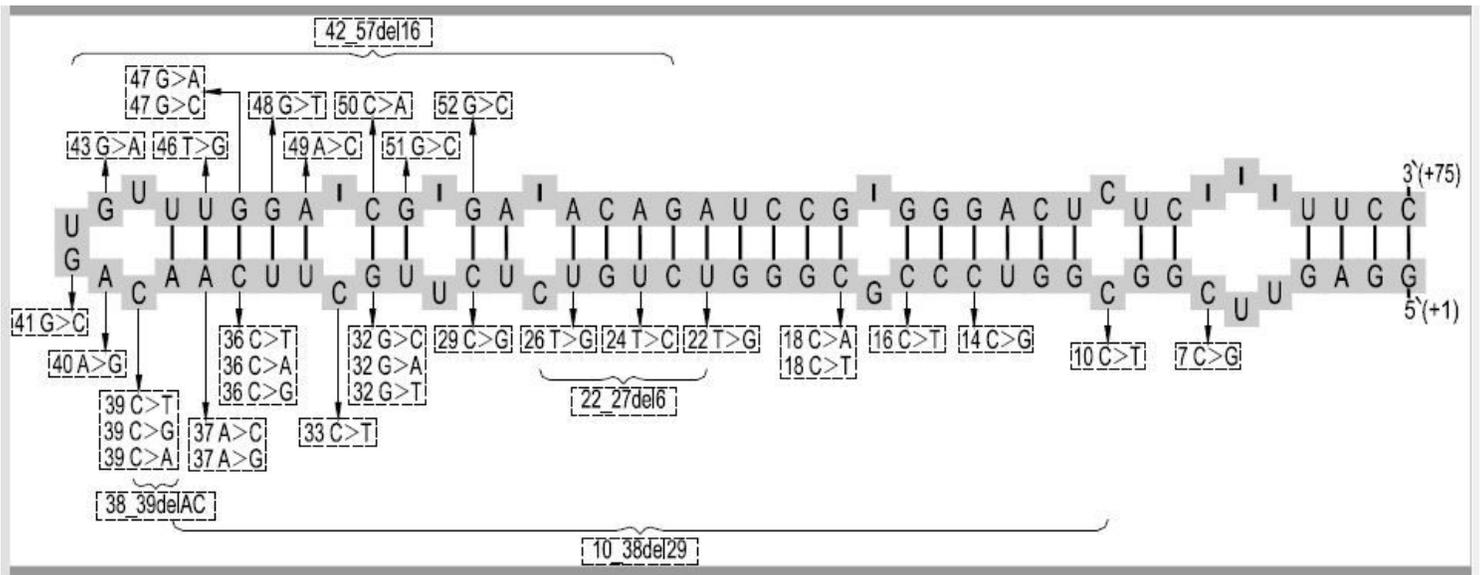


Figure 3

Mutations causing HHCS in the predicted secondary structure of the IRE. The nucleotide deletions are represented by brackets, and the single nucleotide transitions are denoted by black arrows.