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Sutural cataract associated with a mutation in the ferritin light chain gene (FTL) in a family of Indian origin

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Purpose: The molecular characterization of 27 members of an Indian family, with 13 members in four generations, affected with Y-sutural congenital cataract.

Methods: Detailed family history and clinical data were collected. A genome-wide scan by two-point linkage analysis using more than 400 microsatellite markers in combination with multipoint lod score and haplotype analysis was performed. Mutation screening was carried out in the candidate gene by bi-directional sequencing of amplified products.

Results: A maximum two-point lod score of 6.37 at θ=0.00 was obtained with marker D19S879. Haplotype analysis placed the cataract locus to a 5.0 cM region between D19S902 and D19S867, in close proximity to the L-ferritin light chain gene (FTL) on chromosome 19q13.3. Hematological tests in two affected individuals showed very high levels of serum ferritin without iron overload leading to the diagnosis of hyperferritinemia-cataract syndrome. Mutation screening in FTL identified a G>A change at position 32 (c.-168G>A) in a highly conserved 3 nucleotide motif that forms a loop structure in the iron responsive element (IRE) in the 5’-untranslated region (5’-UTR). This nucleotide alteration was neither seen in any unaffected member of the family nor found in 50 unrelated control subjects.

Conclusions: The present study is the first report of a Y-sutural congenital cataract mapping to 19q13.3. The mutation observed in FTL in this family highlights the phenotypic heterogeneity of the disorder in relation to the genotype as the identical mutation (32 G>A) has previously been reported in two Italian families with entirely different phenotypes. It is also the first report of hereditary hyperferritinemia-cataract syndrome in a family of Indian origin.

Congenital cataract is a clinically and genetically highly heterogeneous eye lens disorder. Its incidence is estimated to be 2.2 to 2.49 per 10,000 live births [1,2]. One-third of the cases show a positive family history [3], usually suggesting an autosomal dominant mode of inheritance [4,5]. It may occur as an isolated eye anomaly or as a part of a multisystem syndrome.

Lenses sutures are the lines at anterior and posterior poles of the embryonic lens nucleus where growing secondary fiber cells from the equator migrate and meet. Sutures start to appear at the eighth to ninth weeks of fetal life. The addition of more cell layers till birth forms the suture plane with a symmetrical Y-pattern and a symmetrical inverted Y-pattern at respective anterior and posterior sections of the lens [6]. After birth, suture formation becomes complex and irregular due to fundamental changes that occur in the lens fibers differentiation [7]. Abnormal development of sutures has been found to be associated with specific types of cataracts [8]. A cataract is classified as sutural when the opacity affects the whole or part of either one or both sutures of the lens. So far, sutural cataract, in association with other lens opacities, has been mapped at 1p36 [9], 3q (BFSP2) [10-12], 15q [13], 16q22 (HSF-4) [14], 17q (CRYBA1) [15], 22q (CRYBB1, CRYBB2) [16,17], and in syndromal cases at 14q13-21 (craniofacial-dysplasia syndrome) [18] and on the X chromosome (Nance-Horan syndrome gene, NHS) [19].

Hereditary hyperferritinemia-cataract syndrome (HHCS; OMIM 600886) is an autosomal dominant disorder characterized by early onset bilateral nuclear cataract in association with a manyfold increase in L-ferritin levels in blood serum and in tissues such as lymphocytes, liver, and lenses in the absence of iron overload [20-22]. Under normal conditions, synthesis of ferritin is regulated at the translational level by iron availability. During low iron status, high affinity interaction between trans-acting iron regulatory proteins (IRPs) and the iron responsive element (IRE) in the 5’-untranslated region (5’-UTR) of L-ferritin mRNA prevents iron sequestration by blocking ferritin translation. In cases of abundant cellular iron availability, formation of 4Fe-4S clusters within IRPs inhibits their binding to the IRE and allows abundant ferritin translation [20,22-24]. So far, 28 different mutations have been found in the 5’-UTR of the L-ferritin gene, resulting in reduced affinity for IRPs and hence increased synthesis of L-ferritin.

We came across a four generation family affected with bilateral congenital cataract at the Dr. Daljit Singh Eye Hos-
A genome-wide scan by two-point linkage analysis using more than 400 microsatellite markers and further multipoint and haplotype analysis placed the cataract locus within a 5.0 cM region between markers D19S902 and D19S867 on chromosome 19q13. Since **FTL** lies within the mapped interval, and because of its association with HHCS, hematological tests were performed in two patients. These indicated high levels of ferritin in the serum without iron overload. Sequencing of **FTL** showed a G>A change in the 5'-UTR at position 32 from the transcription start site, in a highly conserved three-nucleotide motif that forms the IRE bulge. This is the first report of HHCS in a family of Indian origin.

**METHODS**

**Family description:** The index case, a five-year-old child, was diagnosed as having bilateral sutural cataract (Figure 1). The family history revealed 13 affected members in four generations (Figure 2). The detailed ophthalmological examination, which included slit lamp examination and photography of affected lenses, performed on 27 members of the family, revealed 13 members who were bilaterally affected (some had a history of cataract extraction in childhood) and 14 individuals (including four spouses) who were unaffected.

**Phenotype description:** In all affected individuals the opacities were confined to the Y-sutures (Figure 1). However, this sutural cataract was peculiar in appearance as the opacities were flat and wide, nonuniform in width, and appeared to be composed of small round and oval segments, superimposed upon each other near the edges. It appeared like a pile of coins. This coin-like character was seen in the primary Y-sutures and in its divisions. Both anterior and posterior lesions were similar in appearance. In optical sections, the location of the opacities was Y-sutural as both the anterior and posterior inverted Y-sutures are severely affected. No nuclear component is involved, and there is no opacity evident in the cortex of the lenses. The opacity appears to be made up of a compilation of coins.
ties was between the nucleus and the surrounding cortex, at some distance from the anterior and posterior capsules. There were no additional opacities in the lens. The nucleus and the periphery were clear. In short, this phenotype may be described as a Y-sutural cataract composed of coin-like segments.

**Genotyping and linkage analysis:** Informed consent was obtained from each individual studied. This study was approved by the ethics review board of the Guru Nanak Dev University, consistent with the provisions of the Declaration of Helsinki. Blood was drawn and DNA isolated by standard methods. A genome-wide search with more than 400 microsatellite markers (Genethon linkage map) [25] was done on DNA samples of all 27 ophthalmologically examined individuals (13 affected and 14 unaffected, including four spouses). Microsatellites were amplified in singleplex reactions by touchdown PCR (MJ-Research, Watertown, MA) using fluorescent-labeled primers following standard methods. Polymerase chain reaction (PCR) products were pooled and denatured at 95 °C for 1 min and electrophoresed on 96-capillary automated DNA sequencers (MegaBACE 1000, Amersham, Freiburg, Germany). Genotyping was done with the use of the software Genetic Profiler version 1.5 (Amersham). Autosomal dominant inheritance with a disease gene frequency of 0.0001 and complete penetrance of the trait was assumed. Recombination frequencies were considered equal between males and females. Two-point linkage analysis was carried out with MLINK from the LINKAGE program package [26], and multipoint analysis was carried out using Genehunter [27]. Autosomal dominant inheritance was assumed with a reduced penetrance of 98% and a phenocopy rate of 0.5%.

**Hematological tests:** After informed consent was obtained, fresh blood was drawn from two affected individuals (II:9, III:12; Figure 2) and sent to the Clinical Reference Laboratory (SRL Ranbaxy, Mumbai Maharashtra (MH), India) for measuring serum ferritin, serum iron, total iron binding capacity (TIBC), and transferrin levels.

**Mutation analysis:** Four pairs of primers (Table 1) were designed from intronic regions to amplify the coding regions and splice sites of *FTL* (GenBank NM_000146.3 and NC_000019.8). Genomic DNA from two affected and one unaffected individuals were amplified. Amplification was carried out in 25 μl reactions containing 100 ng genomic DNA, 10 pmoles each of forward and reverse primers, 200 μM dNTP, 10X PCR buffer, 1.5 mM MgCl₂, and 0.25 U Taq DNA polymerase (AmpliTaq Gold; ABI, Foster City, CA). Amplification conditions consisted of an initial denaturation step at 95 °C for 5 min, followed by 35 cycles consisting of a denaturation step at 95 °C for 45 s, annealing step for 30 s at 57 °C, and an extension at 72 °C for 45 s, followed by a final extension step at 72 °C for 10 min. PCR products were purified using a PCR product purification kit (QIAquick: Qiagen, Valencia, CA). Purified PCR products were sequenced bidirectionally using the ABI BigDye™ Terminator Cycle Sequencing Ready Reaction Kit version 3.1 (ABI) for a 10 μl final volume, containing 5.0 μl purified PCR product, 4.0 μl BigDye Terminator ready reaction mix and 3.2 pmoles of primers. Cycling conditions were 95 °C for 2 min, 25 cycles at 95 °C for 30 s, 52 °C for 15 s, and 60 °C for 4 min. The sequencing reaction products were purified by the isopropanol precipitation method (ABI protocol), suspended in 10 μl of formamide (Hi-Di-Formamide; ABI), denatured at 95 °C for 5 min, and electrophoresed on an ABI 3100 Genetic Analyzer. Sequencing results were assembled and analyzed using the SeqMan II program of the Lasergene package (DNA STAR Inc., Madison, WI).

<table>
<thead>
<tr>
<th>Exon</th>
<th>Sequence (5’-3’)</th>
<th>PCR product size (bp)</th>
<th>Annealing temperature (°C)</th>
</tr>
</thead>
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<tr>
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<td>CCTATGCTCCCGGACTGCTA</td>
<td>549</td>
<td>57</td>
</tr>
<tr>
<td>1A</td>
<td>GTAAAGAGGGGCAGGTTCC</td>
<td>385</td>
<td>57</td>
</tr>
<tr>
<td>2F</td>
<td>GAAGTGCTGCTCCTCTGGCTCCTT</td>
<td>361</td>
<td>57</td>
</tr>
<tr>
<td>2A</td>
<td>GAGACGGGTCGCGAGATGTTGAT</td>
<td>445</td>
<td>57</td>
</tr>
<tr>
<td>3F</td>
<td>GGCTCAGAGCTGGGAGGACGTTGGA</td>
<td>385</td>
<td>57</td>
</tr>
<tr>
<td>3A</td>
<td>TCCCTTCCAGGCTCCTTCTGTAAG</td>
<td>250</td>
<td>57</td>
</tr>
<tr>
<td>4F</td>
<td>TGTGTTTGGAGTTAGG</td>
<td>445</td>
<td>57</td>
</tr>
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Shown are primers for PCR (polymerase chain reaction) and sequencing of *FTL*.

<table>
<thead>
<tr>
<th>Marker</th>
<th>IMD</th>
<th>LOD Scores at 0</th>
<th>LOD Scores at 0</th>
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<td></td>
<td></td>
<td>0.00 0.001 0.01 0.05 0.10 0.15 0.20 0.30 0.40</td>
<td></td>
</tr>
<tr>
<td>D19S902</td>
<td>2.7</td>
<td>2.5 1.34 1.89 1.53 1.18 0.94 0.73 0.55 0.42</td>
<td>D19S970</td>
</tr>
<tr>
<td>D19S879</td>
<td>2.8</td>
<td>2.5 1.49 0.86 0.64 0.45 0.30 0.20 0.15 0.10</td>
<td>D19S974</td>
</tr>
<tr>
<td>D19S604</td>
<td>3.0</td>
<td>2.5 1.49 0.86 0.64 0.45 0.30 0.20 0.15 0.10</td>
<td>D19S974</td>
</tr>
<tr>
<td>D19S902</td>
<td>2.7</td>
<td>2.5 1.49 0.86 0.64 0.45 0.30 0.20 0.15 0.10</td>
<td>D19S970</td>
</tr>
</tbody>
</table>

This table summarizes the two-point LOD scores for chromosome 19q13.3 around the *FTL* locus. The highest observed LOD score was 6.37 at θ=0.0 for marker D19S879. Intermarker distances (IMD) are based on the Genethon linkage map [25].
RESULTS

Linkage analysis: In a genome-wide scan using more than 400 markers, we initially obtained positive two-point lod scores of 1.977 at \( \theta = 0.001 \) with marker D19S178 and of 3.201 at \( \theta = 0.000 \) with marker D19S246. Further analysis with more markers in this region on chromosome 19 gave a maximum lod score of 6.37 at \( \theta = 0.000 \) with marker D19S879 (Table 2). Multipoint analysis carried out with more markers from this region also supported the linkage with the same maximum lod score of 6.37 with D19S879 (data not shown).

Haplotype analysis: Haplotypes were constructed for the markers analyzed on chromosome 19 (Figure 2). Recombination events were detected in affected individuals II:2, III:8, and IV:1. Individual II:2 was recombinant at marker D19S902, individual III:8 was found to be recombinant at marker D19S902, while individual IV:1 was found to be recombinant at marker D19S879, as seen in his mother and grandmother, and markers telomeric to D19S867. Cosegregation was observed in all affected individuals for markers D19S879 and D19S604, indicating that the disease locus lies in this interval. The cataract locus was thus mapped to a 5.0 cM region between D19S902 and D19S867, which corresponds to a region on chromosome 19q13.3.

Hematological analysis: The candidate gene FTL lies within the mapped critical interval and is pathogenetically involved in HHCS. Therefore, we performed hematological analyses in two affected individuals II:9 and III:12 (Figure 2). They showed very high serum ferritin levels (2283.1 and 1638.7 \( \mu \)g/l, respectively; Table 2) in comparison to the control levels (range: 22-322 \( \mu \)g/l). Serum iron, TIBC, and its relative saturation, serum transferrin, and transferrin saturation levels were within normal range in patient II:9. In patient III:12, the levels of TIBC were slightly higher and the transferrin saturation lower than in the controls. These findings indicated that these individuals had HHCS.

Mutation analysis: Sequencing of FTL in two affected individuals (II:9 and III:12) showed a heterozygous change G>A (Figure 3) at position 32 from the transcription start site (c.-168G>A). This position belongs to the IRE in the 5'-UTR of FTL. All other affected family members tested also showed this nucleotide change. This alteration was neither seen in any unaffected member of the family nor found in 50 unrelated

| Table 3. Hematological data of the cataract patients investigated |
|------------------|----------------|----------------|----------------|----------------|
| Patient ID | Serum iron levels (µg/dl) | Total iron binding capacity (µg/dl) | Transferrin saturation (%) | Serum transferrin levels (µg/dl) | Serum ferritin levels (µg/dl) |
| 73 | 76 | 249.0 | 325 | 23.4 | 261 | 2283.1 |
| 85 | 37 | 377.0 | 414 | 8.9 | 307 | 1638.7 |
| Range | 35-140 | 130-375 | 245-400 | 13-45 | 200-400 | 22-322 |

Shown here are the serum iron, total iron binding capacity, transferrin saturation, and serum ferritin levels in patients with congenital cataract. Very high levels of serum ferritin (1638.7 and 2283.1 \( \mu \)g/l) were observed in patients as compared to the reference range.

Figure 3. DNA sequence of a part of ferritin light chain polypeptide in an unaffected and an affected individual. Electropherogram showing a part of the IRE (iron responsive element) sequence of FTL (ferritin light chain polypeptide) in an unaffected (forward and reverse strands) and an affected family member (forward and reverse strands; individuals III:3 and IV:1). A heterozygous change G>A in the 5'-untranslated region (5'-UTR) at position 32 from the transcription start (c.-168G>A) is indicated by arrows.
control subjects (data not shown). Apart from this, a known polymorphic change, TTG to CTG in codon 55 in exon 2 of FTL (both coding for leucine), was observed in affected and unaffected individuals (data not shown).

**DISCUSSION**

This study is the first report of a Y-sutural congenital cataract mapping to 19q13.3. The opacities were present bilaterally since birth in the affected members who underwent cataract surgery during the first decade of life. Both Y-sutures were severely affected without involvement of any other lens components. The lens nucleus, cortex, and periphery were clear.

Two affected individuals, in whom hematological tests were undertaken, showed very high levels of serum ferritin without iron overload, indicating HHCS. This was confirmed by mutation screening in FTL showing a disease-causing G>A mutation in the 5'-UTR at position 32 of exon 1 in all affected individuals. This mutation, also known as the Pavia-1 mutation, has been reported in two Italian families in association with nuclear and bilateral cataracts, respectively [24,28]. The Indian family described here with an identical mutation differs from the Italian families in having an entirely different cataract phenotype, in the age of cataract onset, and in the levels of serum ferritin. To our knowledge, this is the first report of HHCS in a family of Indian origin, after previous reports of HHCS from Europe, Australia, and the USA.

So far, at least 28 mutations have been reported in the 5'-UTR of FTL; some occurred in the loop (5'-CAGUG-3' at positions 39 to 43), while others affected the bulge (5'-UGC-3' at positions 31 to 33) or stem of the IRE. Most of these mutations alter the structure of the IRE thus either abolishing or significantly decreasing the affinity binding of IRPs. This results in constitutive upregulation of L-ferritin in the serum and body tissues [29,30]. It has been reported that nucleotide 32G is important for IRE function in vivo and for high affinity RNA-protein interaction in vitro [31]. On the basis of a thermodynamic analysis, it has been revealed that mutations in the IRE either change its stability and secondary structure or disrupt the IRP-IRE recognition site [32].

Cazzola et al. [24] tried to establish a relationship between the identified mutations, the serum-ferritin levels, and the severity of the cataract. They observed that mutations within the IRE loop sequence resulted in the highest ferritin levels (1200-2700 µg/l) with severe cataracts (marked loss of visual acuity in the first decade with some individuals requiring cataract surgery). Mutations in the IRE bulge caused mild cataract (visual acuity corrected with the use of appropriate eye glasses) with ferritin levels being in the range of 950-1900 µg/l. The nucleotide changes in the lower stem of the IRE resulted in lowest levels of ferritin (350-650 µg/l) with asymptomatic cataract (no effect on visual acuity). These findings were confirmed by Mumford et al. [22], who showed

<table>
<thead>
<tr>
<th>Nucleotide change</th>
<th>Origin of family</th>
<th>Serum ferritin (µg/l)</th>
<th>Cataract diagnosis</th>
<th>Cataract type/severity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>32G&gt;C</td>
<td>USA</td>
<td>793-2350</td>
<td>Childhood</td>
<td>Bilateral*</td>
<td>[38]</td>
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<td>32G&gt;C</td>
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<td>18 months</td>
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<td>[39]</td>
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<td>2000-2898</td>
<td>9 weeks</td>
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<tr>
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<td>Mild cataract*</td>
<td>[31]</td>
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<td>734-1362</td>
<td>3-40 years</td>
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<td>[34]</td>
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<td>2 years</td>
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<td>[41]</td>
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<tr>
<td>32G&gt;A</td>
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<td>950-1900</td>
<td>Childhood</td>
<td>Nuclear (severe cataract)</td>
<td>[24]</td>
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<tr>
<td>32G&gt;A</td>
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<td>1100-1275</td>
<td>7-18 years</td>
<td>Bilateral*</td>
<td>[28]</td>
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<tr>
<td>32G&gt;A</td>
<td>India</td>
<td>1638-2283</td>
<td>At birth</td>
<td>Severely affected Y-sutural, without nuclear opacities</td>
<td>Present study</td>
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<tr>
<td>33C&gt;T</td>
<td>Spain</td>
<td>989-1770</td>
<td></td>
<td>Mild bilateral cataract during 1st decade, except in proband</td>
<td>[33]</td>
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<tr>
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<td>9-18 years</td>
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<td>1000</td>
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<td>[42]</td>
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</table>

This table shows the identified mutations in the bulge region of the iron responsive element (IRE) in the 5' UTR (untranslated region) of FTL (ferritin light chain polypeptide) in relation to origin of family, serum ferritin levels, age at diagnosis of cataract, and its phenotype. In the “Nucleotide change” column, the numbering starts from the transcription start site (GenBank NM_000146.3). The asterisk indicates that no exact phenotype of opacity was described by the authors.
that mutations near the apex of the IRE resulted in higher serum ferritin concentrations and denser cataracts, and by Balas et al. [33], who observed mild cataracts associated with mutations in the bulge region. However, not all mutations reported in this region follow a simple genotype-phenotype correlation (Table 4).

Balas et al. [33], Girelli et al. [34], and Perez de Navalera et al. [35] reported that lens opacities in their HHCS patients were not detectable at birth and manifested in an age-dependent manner. In the present family, lens opacities were prominent since birth, with both Y-sutures being severely affected. The patients needed early cataract surgery within their first decade of life.

A 5-20 fold higher accumulation of L-ferritin in serum and tissues has been observed in HHCS cases, which has no evident effect on the body iron status but is often associated with early onset cataract. Two mechanisms have been proposed for this association of cataract with hyperferritinemia. A change in the L- and H-subunit ratio of ferritin composition may cause an increase in free iron and reactive oxygen, resulting in oxidative damage of the lens and cataract formation. Alternatively, cataract may be the result of lens protein aggregation caused by intracellular ferritin. Thus, Brooks et al. [36] reported light diffracting deposits of ferritin crystals in HHCS cataractous lenses, and Mumford et al. [37] found that HHCS lenses contain crystalline deposits of L-ferritin. However, Levi et al. [21] reported that ferritin in HHCS lenses was readily soluble without forming any aggregates in vitro and suggested that ferritin precipitation is not the primary cause of lens opacity.

In summary, large intragenic heterogeneity and phenotypic variability with respect to severity and type of cataract, age of onset, and serum ferritin levels has been observed in HHCS. This is illustrated in our patients and in those from two Italian families [24,28]. They share the same FTL mutation (32G>A) but show clear differences in the type of cataract, the age of onset, and the serum ferritin levels. Thus, apart from the pathogenetic mutation, other genetic or even environmental factors must play a significant role in disease manifestation. The analysis of serum ferritin levels is therefore mandatory in individuals with congenital cataract to establish the correct diagnosis HHCS.

ACKNOWLEDGEMENTS

We wish to thank the patients and their relatives for their cooperation. This work was in part supported by grant number DBT/B7/IC/71/89/Pt sanctioned to JRS, INI 331 from BMBF to KS, and SR/FT/L-91 from DST to VV.

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