

Hereditary Hyperferritinemia-Cataract Syndrome

Prevalence, Lens Morphology, Spectrum of Mutations, and Clinical Presentations

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Objectives: To provide a comprehensive description of the clinical presentations, cataract morphology, and molecular basis of hereditary hyperferritinemia-cataract syndrome (HHCS) in 4 Australian pedigrees and to estimate its prevalence.

Methods: All known cases of HHCS in southeastern Australia were ascertained. Family members provided a medical history and underwent physical examination, lens photography, and venipuncture for measurement of serum ferritin levels and DNA extraction. Sequence analysis of the iron-responsive element of the ferritin light chain on chromosome 19q13.3-qter was performed.

Results: We investigated 26 affected individuals from 5 Australian pedigrees. Two pedigrees with HHCS ascertained independently were subsequently found to form 1 large kindred carrying the mutation A40G. The minimum estimated prevalence of HHCS is 1/200 000. One pedigree had the mutation G32C. Among 2 smaller pedigrees studied, one carried a novel mutation (C39A), and the other was identified through the 2-year-old proband with cataract but no positive family history. The latter case was shown to be due to a de novo mutation (G32U). All cataracts were highly distinctive in morphology, consisting of slowly pro-

gressive flecks, vacuoles, and distinctive crystalline deposits scattered predominantly in the lens cortex but also in the nucleus. Eight of 18 affected individuals examined have required cataract extraction to date. No other identified clinical manifestations of HHCS were delineated.

Conclusions: Cataract morphology in HHCS is highly distinctive. Longitudinal observation demonstrated slow progression of the cataracts. This study highlights that, although HHCS is an autosomal dominant condition, the diagnosis should be considered even in sporadic cataract of typical morphology. Furthermore, individuals with unexplained hyperferritinemia should be referred for ophthalmological assessment, as the cataract may be asymptomatic but lead to a correct diagnosis of HHCS.

Clinical Relevance: Progressive cataracts of highly distinctive morphology are an important feature of HHCS. Evaluation for this type of cataract may be of diagnostic value in patients with unexplained hyperferritinemia. Hereditary hyperferritinemia-cataract syndrome can be a cause of cataracts in pediatric patients even in the absence of any positive family history.

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HEREDITARY hyperferritinemia-cataract syndrome (HHCS) (Mendelian Inheritance in Man 600886)¹ is a recently described syndrome of autosomal dominant inherited cataract associated with elevated levels of serum ferritin but otherwise normal iron studies and hematological parameters. The original reports¹⁻³ described pedigrees in which unexplained hyperferritinemia in the absence of iron overload appeared to segregate in an autosomal dominant fashion with "congenital cataracts." The cataracts were originally described as nuclear.⁴ A common feature in some presentations was an erroneous diagnosis of hereditary hemochromatosis followed by inappropriate venisection, which

led to rapid onset of iron deficiency anemia. Linkage studies mapped HHCS to an interval of chromosome 19q13, confining the genes for the light chain of ferritin (*FTL*) and also for the major intrinsic protein of lens fiber membrane (*MP19*).⁵ Subsequently, a point mutation A to G in the highly conserved CAGUGU motif in the iron-responsive element (IRE) in the 5' non-coding region of the ferritin light chain gene was identified in a French pedigree.² This mutation leads to a high level of poorly regulated expression of L-ferritin. It was speculated that excess production of ferritin in tissue is responsible for the hyperferritinemia and that intracellular accumulation of ferritin leads to cataract.⁶ A series of 11 different point mutations and 4 small deletions in the IRE of the ferritin light chain mes-

senger RNA have subsequently been shown to cause HHCS by preventing binding of the inhibitory iron regulatory protein to the IRE stem loop structure, leading to constitutively expressed high-level ferritin light chain translation independent of iron stores.⁷⁻¹⁶ Thus, affected individuals typically exhibit dramatically elevated serum ferritin levels in the absence of iron overload.

Cataract is the only known feature of the syndrome leading to symptoms¹⁷; however, only scant references to the ophthalmic manifestations of HHCS have been made in the literature. Ferritin is known to be expressed normally in the lens and has been postulated to play a role as an antioxidant. Mumford et al¹⁸ performed an analysis of a lens from a patient with HHCS obtained by means of extracapsular cataract extraction and found that the ferritin levels in the lens tissue were approximately 10-fold higher than in lens material from control subjects. This confirmed an earlier finding of an analysis of emulsified lens material obtained at the time of cataract surgery.¹⁹

Chang-Godinich et al²⁰ recently described cataracts in a father and son with HHCS. The visual acuity (VA) was normal, and neither had required surgery. It was not possible for the authors to determine whether the cataracts in their patients were progressive or static. No attempt has been made in the literature to estimate the proportion of hereditary cataract accounted for by HHCS. In this report, we have ascertained all known cases of HHCS in southeastern Australia (population, 5.5 million). A detailed descriptive and photographic account of the ophthalmic features in 18 affected individuals from 4 HHCS pedigrees is given, highlighting a distinctive cataract morphology that may be diagnostically useful. We diagnosed on the basis of lens morphology alone a sporadic case of HHCS in a 2-year-old child who was initially seen with accommodative esotropia. Analysis of a recently published population-based ascertainment of congenital cataract from our group indicates that HHCS is not commonly diagnosed in infants with congenital cataracts,²¹ and this is supported by the current study. Herein we estimate prevalence and describe the associated range of clinical presentations, lens morphology, ophthalmic management, and mutation spectrum of HHCS in our population.

METHODS

PATIENTS AND EXAMINATION

All known cases of HHCS in southeastern Australia were ascertained by liaison with specialist hematologists and ophthalmologists. Four pedigrees with different ferritin light chain IRE mutations were studied in detail. All available family members provided medical and ophthalmic history and underwent physical examination, lens photography, and venipuncture for serum ferritin levels, iron studies, and DNA extraction.

Ophthalmological examination included best corrected VA (BCVA) at a viewing distance of 6 meters (20 feet), slitlamp examination of the anterior segment, and dilated fundus examination. Lens photography was performed under direct illumination and retroillumination. Selected cases were chosen for Scheimpflug photography to document precisely the location of lens opacities. A 2-year photographic follow-up was performed in selected cases to examine progression of these cataracts.

Written informed consent was obtained in all participating individuals, and the project was conducted in accordance with the declaration of Helsinki and subsequent revisions.

MUTATION SCREENING

Genomic DNA was extracted from mononuclear cells isolated from peripheral blood samples following standard protocols. The DNA from available family members was screened for sequence changes in the L-ferritin IRE with bidirectional direct sequencing of polymerase chain reaction–amplified product containing the IRE and using an ABI Prism BigDye kit (Terminator Cycle Sequencing Ready Reaction Kit; PerkinElmer, Foster City, Calif). Descriptions of the primers and conditions have been previously published elsewhere.¹⁹

RESULTS

Clinical details of available patients from each pedigree are summarized in the **Table**.

PEDIGREE 1

This large pedigree came to our attention independently in 2 branches and, consequently, there are 2 index cases. Our genealogical and molecular investigation established that they were in fact part of 1 large pedigree (**Figure 1A**).

Branch 1A

The index case (family member III:2) was first examined at 44 years of age. He complained of a gradual decline in his VA during the past 2 years and of glare symptoms. He had been known to have cataracts since 1 year of age, which had previously been attributed to maternal x-ray exposure. His BCVA was 20/30 OD and 20/40 OS. Results of slitlamp examination showed a distinctive appearance of scattered central and peripheral cystic flecks in the cortex and nucleus (**Figure 2**). He had recently been diagnosed as having type 2 diabetes mellitus, but results of the fundus examination were normal. He was concurrently undergoing investigation by the hematology service for a high serum ferritin level of 3200 µg/L (reference range, 15-300 µg/L) with normal serum iron and transferrin saturation levels. The combination of diabetes mellitus, bronze skin complexion, and hyperferritinemia led to a provisional diagnosis of hemochromatosis. The patient was treated initially with therapeutic venesection. Subsequently, results of genetic testing for hemochromatosis mutations (C282Y and H63D mutation in the *HFE* gene) were negative, and a liver biopsy specimen showed no evidence of iron overload.

It was then discovered that his 19-year-old daughter (IV:3) had cataracts, diagnosed at 4 years of age. Ophthalmic examination disclosed a BCVA of 20/30 OU and bilateral cataracts of appearance similar to those of the father. Her serum ferritin level was 1299 µg/L, and *HFE* gene mutation analysis for hemochromatosis was negative. Therapeutic venesection was commenced at the same time as for her father, but iron deficiency developed rapidly. Venesection was then ceased in both father and daughter. During the next 2 years, she was increasingly

Clinical Information and Ferritin Levels of Affected Individuals

Family Members	Age at Diagnosis of Cataract	Visual Symptoms	Preoperative VA		Cataract Surgery	Age at Cataract Surgery, y	Postoperative VA		Ferritin Level, µg/L
			OD	OS			OD	OS	
Pedigree 1A									
III:2 (index)	1 y	Decreased VA, glare	20/30	20/40	Bilateral	44	20/20	20/20	3200
II:2	61 y	NA	NA	NA	Bilateral	62	NA	NA	2298
II:3	NA	NA	20/30	20/30	Nil				1456
II:7	NA	NA	NA	NA	Nil				1987
III:4	13 y	Asymptomatic	20/30	20/30	Nil				1845
IV:1	18 y	Decreased VA, glare	20/30	20/40	Bilateral	22	20/20	20/20	1210
IV:2	12 y	Asymptomatic	20/16	20/16	Nil				1092
IV:3	4 y	Decreased VA, glare	20/40	20/20	Bilateral	19	20/20	20/20	1299
IV:4	10 y	Asymptomatic	20/16	20/30	Nil				1280
Pedigree 1B									
III:8 (index)	23 y	Glare	NA	NA	Nil				1690
II:10	18 y	Minimal glare	20/30	20/40	Nil				5996
Pedigree 2									
V:1 (index)	9 wk	Initially asymptomatic, then decreased VA	NA	NA	None (considering surgery)				2000
IV:2	3 y	R, Photophobia; L, decreased VA	20/60	20/120	Yes L, waiting for R	34 (L)	NA	20/25	2400
III:3	NA	NA	NA	NA	Bilateral	9	NA	NA	2898
II:2	NA	NA	NA	NA	Bilateral	NA	NA	NA	
Pedigree 3									
II:1 (index)	28 y	Decreased VA	20/60	20/40	Bilateral	45	20/20	20/30	1652
III:2	5 y	Reading difficulty; optometrist noted lens opacity	20/40	20/40	Nil				1594
Pedigree 4									
II:1 (index)	2 y	Photophobia	20/50	20/50	Considered for surgery	>8			1554

Abbreviations: L, left eye; NA, not available; nil, no surgery; R, right eye; VA, visual acuity.

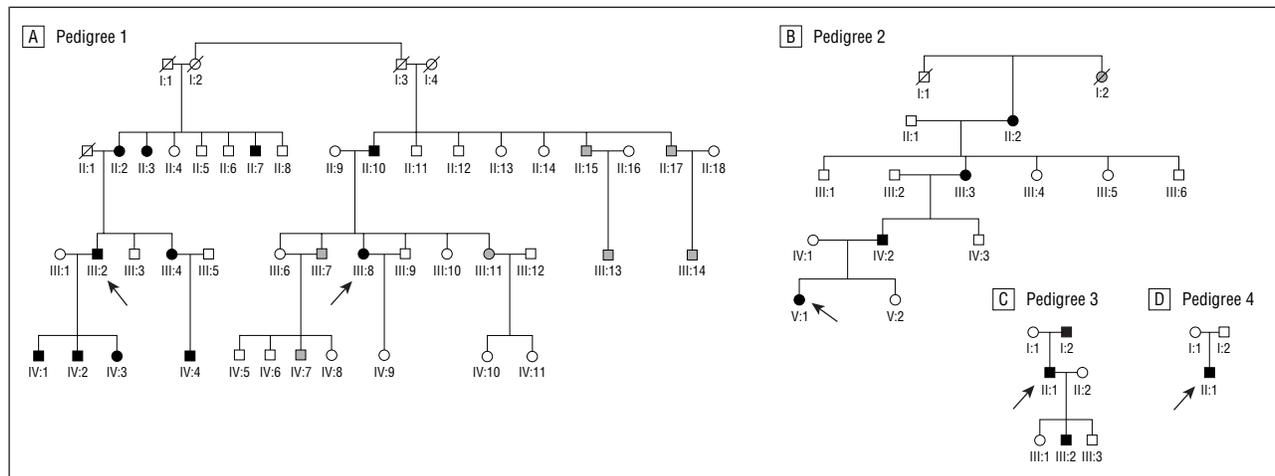


Figure 1. Family information of the 4 Australian pedigrees with hereditary hyperferritinemia-cataract syndrome (HHCS). Solid shapes indicate confirmed HHCS; shaded shapes, cataract diagnosed but unavailable for ferritin study; blank shapes, no cataract; arrows, index cases; squares, male family members; circles, female family members; and slashes, deceased.

troubled by glare symptoms, and her VA deteriorated. Cataract extraction was performed bilaterally, and her postoperative BCVA was 20/20 OU.

Further investigation of the rest of the pedigree showed that the mother (II:2), a maternal aunt and uncle (II:3 and II:7), the sister (III:4), the nephew (IV:4), and 2 sons (IV:1 and IV:2) of the index case were all affected with cataract and hyperferritinemia (range, 1092-3200 µg/L). No other ophthalmic or clinical

manifestations were noted. All affected individuals were unaware of their elevated serum ferritin level before our study. With the exception of family member IV:2, all the cataracts had a similar appearance. Family member II:2 had undergone 1 previous cataract extraction; the other eye showed cataract with similar distinctive scattered flecks and crystalline deposits of a cataract, and also moderate nuclear sclerosis.

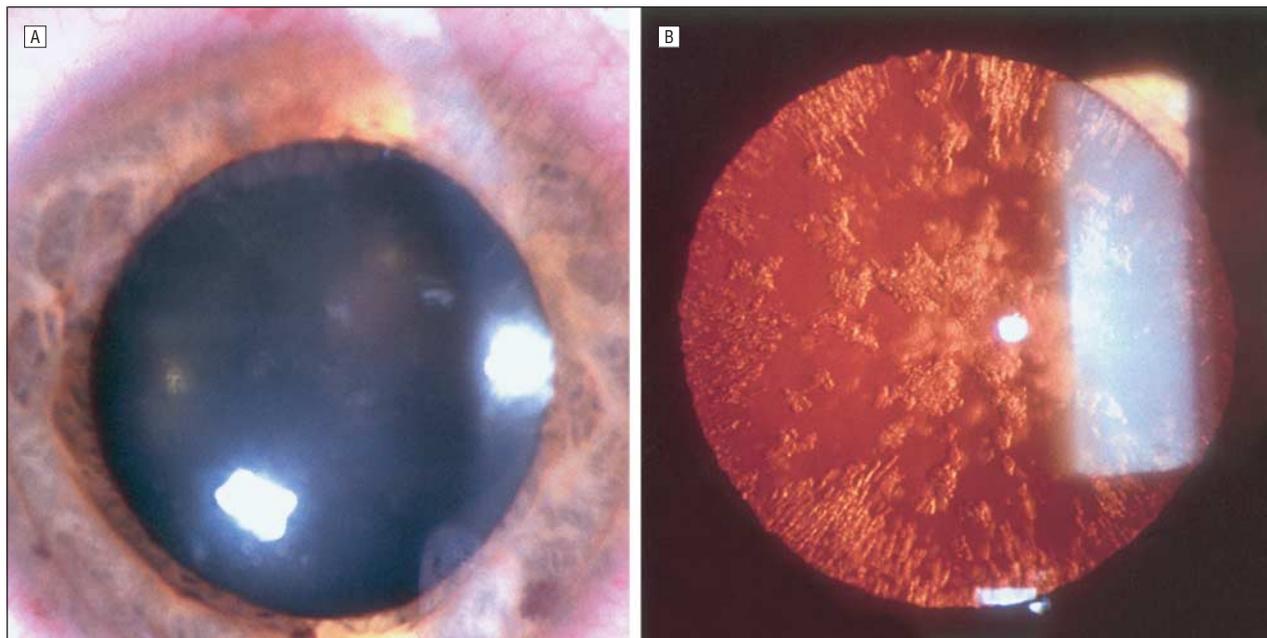


Figure 2. Slitlamp photography using direct illumination (A) and retroillumination (B) of the index case (family member III:2) of pedigree 1A shows a distinctive cataract with scattered central and peripheral cystic flecks in the cortex and nucleus.

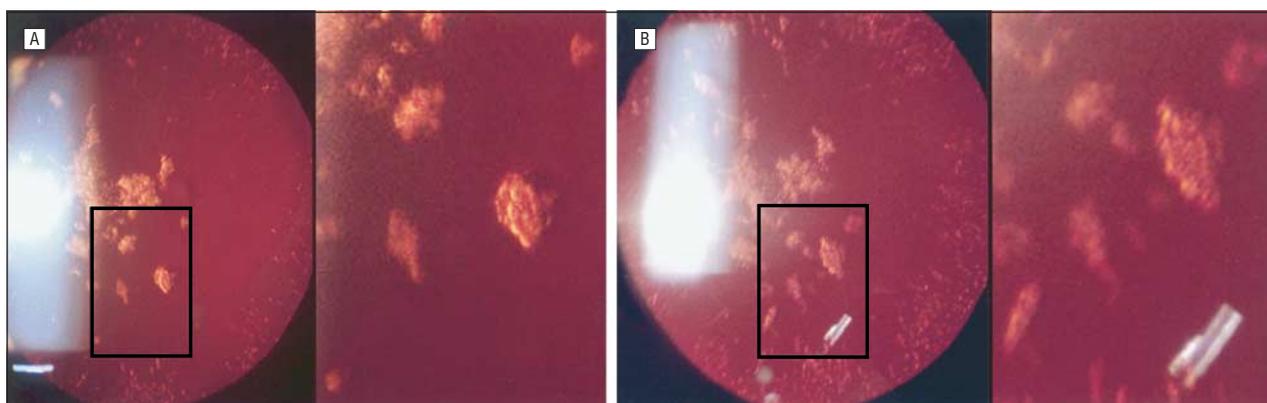


Figure 3. Retroillumination cataract appearance in family member IV:4 of pedigree 1 at 10 (A) and 12 (B) years of age shows increase in the size and number of crystalline aggregates.

Family member IV:2 had a clear lens in the right eye and a small single fleck in the left eye of uncertain significance at 12 years of age. Examination at 14 years of age showed no change in the lens appearance. His serum ferritin level was 1092 $\mu\text{g/L}$. By contrast, case IV:4 had a ferritin level of 1280 $\mu\text{g/L}$, and at 10 years of age had striking central crystalline lens opacities with clear lens between granules and myriad fine dotlike opacities peripherally. Review 2 years later showed progression of the lens opacities with enlargement of individual deposits and the appearance of new dotlike opacities, especially in the periphery (**Figure 3**).

Branch 1B

The index case (family member III:8) is a 35-year-old woman who was examined by a hematologist (H.F.S.) after a pulmonary embolus during pregnancy. She had a history of investigation for iron overload that included a liver biopsy, but results of genetic testing for hemo-

chromatosis were negative. Her presenting complaint of postpartum fatigue was associated with a hypochromic microcytic anemia but with a persistently elevated ferritin level (1500-2000 $\mu\text{g/L}$) and a low serum iron level with low transferrin saturation. She underwent extensive investigation, including bone marrow aspiration, results of which showed no stainable iron. Her symptoms of fatigue resolved with iron replacement. An ophthalmic history of bilateral cataract diagnosed at 23 years of age was noted, and further inquiry disclosed a strong family history of cataract (in family members II:15, II:17, III:7, III:11, III:13, III:14, and IV:7). The diagnosis of HHCS was subsequently made. The index case and her father (II:10) were available for examination. Both had the distinctive lens appearance of scattered axial and peripheral flecks and crystalline deposits most striking on retroillumination. Neither case had required cataract surgery, although other family members had.

Clinical descriptions of the other 7 family members with cataract were obtained from the treating rural

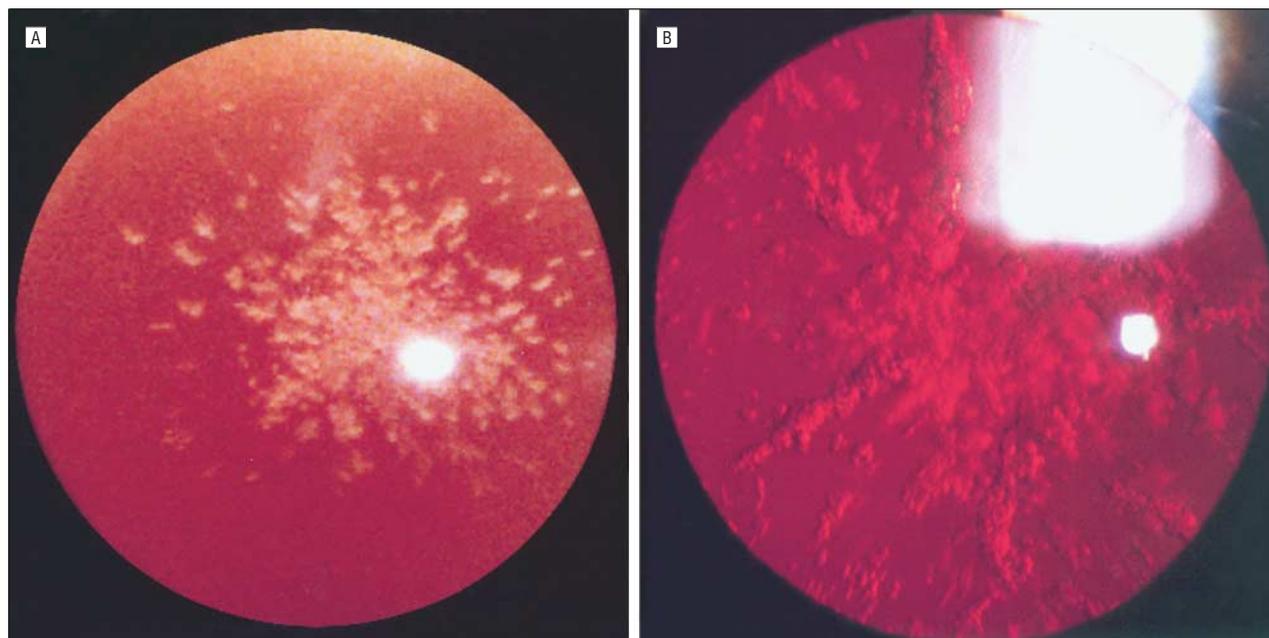


Figure 4. Retroillumination photograph of the index case of pedigree 2 (family member V:1) at 3 (A) and 16 (B) years of age shows progression of the cataract.

ophthalmologist (M.G.T.), and the cataracts were described as bilateral central vacuolated opacities in the cortex and central nucleus. No other family members had been aware of hyperferritinemia or had undergone hematological investigations.

Blood samples and DNA were available from 11 affected individuals from pedigree 1. Sequencing of the L-ferritin IRE showed that all affected individuals were heterozygous for the previously reported A-to-G point mutation at position +40 relative to the translation start site.^{1,2,14} An additional 7 individuals were known to be affected by early-onset cataract typical of HHCS but were unavailable for study.

PEDIGREE 2

The index case (family member V:1; Figure 1B) was noted to have bilateral cataract at 9 weeks of age. It was initially described as “triradiate” by the pediatrician. She had significant myopia with astigmatism resulting in left amblyopia, which was treated with patching. The BCVA was 20/30 OD and 20/60 OS at 3 years of age, and slitlamp examination revealed dense bilateral cataract with central and peripheral cystic flecks (**Figure 4A**). The subject was subsequently found to have hyperferritinemia at 16 years of age when she was undergoing investigation for postviral fatigue, and a high serum ferritin level of 2000 µg/L was noted; hemochromatosis has been excluded. At a recent review at 16 years of age, the cataracts showed definite progression compared with the appearance at 3 years of age (Figure 4B), and cataract surgery is planned in the near future.

Her father (IV:2), grandmother (III:3), and great-grandmother (II:2) all had bilateral cataract from an early age and have subsequently been found to have hyperferritinemia. The father was diagnosed as having bilateral cataract at 3 years of age, when he had decreased VA;

astigmatism was noted and he was prescribed glasses. The VA gradually deteriorated to 20/120 OS, and left cataract extraction was performed at 34 years of age. He is presently troubled by photophobia in the right eye, which has the typical distinctive scattered flecklike appearance similar to that of his daughter. He is currently on the waiting list for a right cataract extraction. His ferritin level was 2400 µg/L, leading to investigations including a liver biopsy, the results of which excluded hemochromatosis. The grandmother (III:3) had bilateral cataract surgery at 9 years of age. At 55 years of age, she underwent investigation for an elevated serum ferritin level (2898 µg/L); results of liver ultrasonography and *HFE* gene study were normal.

Sequencing of the IRE of the L-ferritin gene in the 4 affected family members disclosed heterozygosity for a previously described G-to-C point mutation at position 32.^{15,22}

PEDIGREE 3

A family of Italian descent underwent investigation after the identification of a 45-year-old man with a history of bilateral cataract and hyperferritinemia in the absence of iron overload as the proband (family member II:1; Figure 1C). His cataracts were diagnosed at 28 years of age, but he gave a history of photophobia and glare symptoms since childhood. He noticed gradual deterioration in his vision in the 6 years before the index visit. On examination, his VA was 20/60 OD and 20/40 OS. Axial lens opacities were noted, with the presence of central cortical vacuoles with mild nuclear involvement of similar appearance. He underwent bilateral cataract extraction. He was incidentally found to have hyperferritinemia in 1989 on a test performed at the time of blood donation. Subsequently, he underwent investigation for hemochromatosis, but results of *HFE* gene studies were

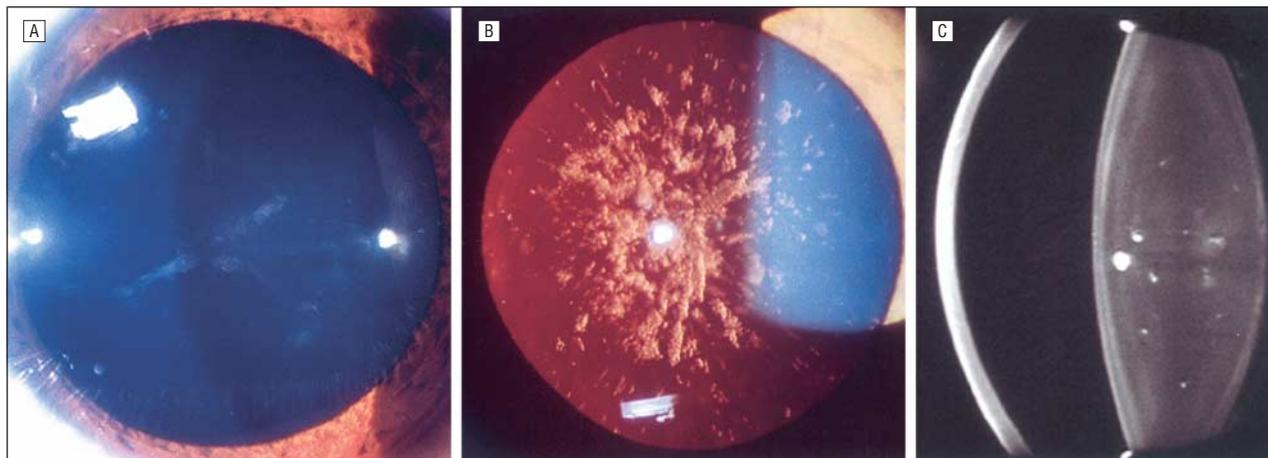


Figure 5. Images of family member III:2 of pedigree 3 using direct illumination (A), retroillumination (B), and Scheimpflug photography (C) show the distinctive central and peripheral opacities distributed in the cortex and nucleus.

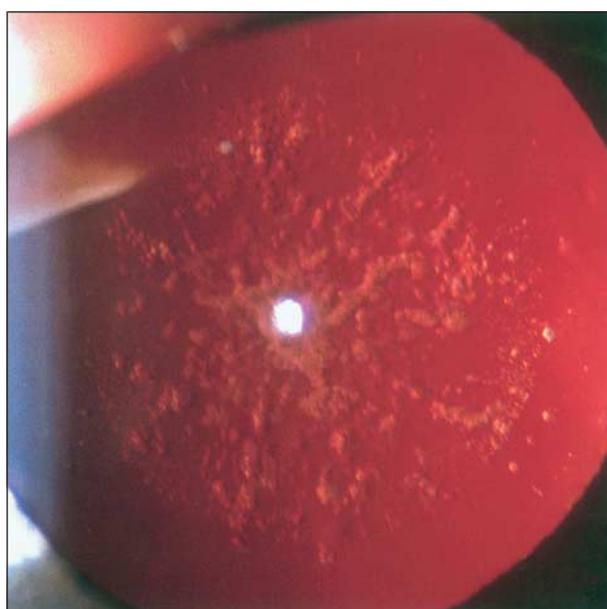


Figure 6. Retroillumination slitlamp photography of the index case (family member II:1) of pedigree 4.

normal and the liver biopsy specimen showed no evidence of iron overload.

His son (III:2) was referred to an optometrist at 5 years of age for difficulty reading the blackboard. Astigmatism and bilateral lens opacities were noted. The BCVA was 20/30 OU. The lens had widespread cortical vacuolated opacities with mild nuclear involvement (**Figure 5A** and B), similar to the father's lens appearances. Scheimpflug images confirmed cortical and nuclear distribution (**Figure 5C**). The serum ferritin level was 1594 $\mu\text{g/L}$. He has been observed for longer than 7 years, and his VA has remained stable. His lens opacity has increased with more peripheral vacuolation. A younger sibling (III:3) had normal ferritin levels and no cataract.

Sequencing of the IRE of the L-ferritin gene in the 2 affected members disclosed heterozygosity for a mutation unique to this family at position 39 (C to A). The unaffected members of the family did not carry the mutation. Although the parents of the index case in Italy were

unavailable for examination, it is noteworthy that both individuals were said to be free of cataract, and results of serum ferritin analysis were also normal.

PEDIGREE 4

An 8-year-old boy (family member II:1; **Figure 1D**) had been followed up by an ophthalmologist for accommodative esotropia and incidental findings of bilateral cataract of unusual morphology; both conditions had been documented to be present since 2 years of age. The lens findings were described as sutural lens opacities initially, which then progressed to a widespread fine fleck-like appearance scattered through the cortex and nucleus and involving the visual axis and periphery with a vaguely radial distribution (**Figure 6**). The boy complained of photophobia. There was no family history of cataract, and examination of the parents and siblings revealed no cataract. The lens morphology of the index case was noted by one of us (J.E.E.) to be similar to that of the pedigrees previously described in this report. Iron studies were performed, which showed a high ferritin level of 1554 $\mu\text{g/L}$ in the presence of normal serum iron levels and transferrin saturation. Results of genetic testing for hemochromatosis were negative. Over time, his VA has deteriorated from 20/30 to 20/50 OU, and cataract surgery is under consideration.

Sequence analysis of the IRE of the L-ferritin gene in the proband showed a de novo mutation (G to U at position 32). The rest of the family members had normal serum ferritin levels and normal L-ferritin IRE sequence. Mendelian inheritance of 12 microsatellite markers on 8 chromosomes established the biological relationships in the pedigree, confirming that this is indeed a de novo mutation (data not shown). This represents, to our knowledge, the first reported case of HHCS diagnosed solely on the basis of cataract morphology alone.

COMMENT

Hereditary hyperferritinemia-cataract syndrome is the first genetic disorder known to result from regulatory mutations affecting translation. As such, it presents a novel

mechanism of cataract formation. In the literature, primarily hematology publications, the clinical presentation of affected pedigrees has been dominated by investigation of unexplained hyperferritinemia in the absence of iron overload. Our data support the contention that affected individuals have often been misdiagnosed as having hemochromatosis, but we show for the first time that the cataract morphology alone in HHCS is sufficiently characteristic to arouse strong suspicion of the diagnosis, and may even be pathognomonic, and that HHCS is in the differential diagnosis of infantile cataract, even in the absence of any positive family history of hyperferritinemia or cataract. We also present data confirming that factors other than the IRE mutation must contribute to the timing of the onset and severity of cataract and clearly document clinical evidence of cataract progression in this syndrome.

EPIDEMIOLOGY

No information in the literature estimates the prevalence of HHCS. One study in Switzerland that examined ferritin levels in 15 of 135 individuals with early-onset cataract found no cases of HHCS, implying a very low prevalence in their population.²³ Our study found 5 pedigrees (subsequently shown to be 4) and a total of 26 affected individuals with characteristic HHCS cataract and documented mutations in southeastern Australia (population, 5.5 million). This indicates a minimum prevalence of approximately 1/200 000. This figure would be an underestimate because (1) serum ferritin level is not routinely measured by ophthalmologists investigating cataracts (including congenital cataracts), and there is generally a low awareness of the condition among ophthalmologists, and (2) mutations reportedly exist that lead to lesser magnitudes of hyperferritinemia, which may result in clinically insignificant cataract.⁶

To further investigate the incidence of HHCS in our population with pediatric cataract, we reviewed our database of congenital and pediatric cataract that includes the previous 25 years.^{21,24} One case among 342 nonfamilial congenital cataracts was diagnosed with HHCS in this series. One index case child in 1 of the 30 autosomal dominant cataract pedigrees in this series was diagnosed as having HHCS. None of the 6 patients with HHCS younger than 25 years in pedigrees 1, 2, and 3 were found in the database of 421 congenital or infantile cataracts, but were included in the pedigrees in which the cataracts of the index case were diagnosed in adolescence or later. In our updated database, including cases in this report, there are now 4 of 40 autosomal dominant cataract pedigrees with HHCS. This indicates that HHCS less commonly is first seen as congenital or infantile cataract, but more likely as childhood or adolescent cataract. The index cases in pedigrees 2 and 4 were listed in our original database. The index case of pedigree 2 indicates that cataract may be present in this condition as early as 9 weeks of age.

To assess whether hyperferritinemia could be responsible for other autosomal dominant cataract pedigrees, we measured serum ferritin levels in affected individuals from 5 additional large cataract pedigrees among

the 30 with early-onset autosomal dominant cataract in our original series. None had hyperferritinemia. Ferritin levels were not measured routinely in patients with congenital and infantile cataracts, and thus there is the possibility of undiagnosed HHCS cases in our database. However, it is our clinical impression that cataract morphology similar to that of pedigree 3 was very uncommon in this age group, and HHCS more typically is seen as an entity separate from congenital and infantile cataract, with distinctive lens morphology.

CLINICAL PRESENTATIONS

The most striking visual complaint in affected individuals was glare symptoms that tended to be noted in the second decade of life, but sometimes earlier. These were particularly manifest in bright sunlight or when driving at night. Many individuals were severely photophobic at the time of slitlamp examination or lens photography. In all cases in our study, the severity of glare symptoms exceeded the loss of VA. Those requiring surgery had often experienced documented deterioration of BCVA from 20/20 to 20/40 or worse over time.

It is difficult to judge the age at onset of the cataract. Girelli et al⁶ described an infant who had hyperferritinemia from birth but no lens opacity when seen at birth and 1 month and 1 year of age. In our study, of the 3 individuals who were diagnosed at a young age (family members V:1 in pedigree 2, III:2 in pedigree 3, and II:1 in pedigree 4), 2 had their cataracts diagnosed as an incidental finding at ocular examination for other problems (accommodative esotropia and astigmatism). Furthermore, we have documented mild lens opacity as early as 9 weeks of age (family member V:1 in pedigree 2), but have also seen a patient with one clear lens and a single small fleck in another lens at 14 years of age (family member IV:2 in pedigree 1). The symptoms are usually of a vague nature with gradual onset, and we have also seen an individual remaining asymptomatic (family member IV:4 in pedigree 1) at 10 years of age, despite obvious cataract. Another individual (family member II:10 in pedigree 1) remained phakic with obvious cataract but free of symptoms at 62 years of age.

The level of serum ferritin did not appear to correlate well with cataract severity in our series. In pedigree 1, family members IV:2 and IV:4 had comparable serum ferritin levels but very different lens opacity. This variability cannot be explained on the basis of the specific IRE mutation, as they both have the same A40G mutation. It is therefore likely that factors independent of the mutation and serum ferritin levels are involved in the timing of onset and severity of cataract.

Several of our patients underwent investigation for hyperferritinemia of unexplained etiology. In the index cases for pedigrees 1, 2, and 3, a provisional diagnosis of hereditary hemochromatosis had been made in the past but was not supported by the normal results of serum iron and transferrin saturation measurements and genetic testing for hemochromatosis. All of these patients had normal liver biopsy findings, and all had undergone earlier inappropriate venisection leading to iron deficiency anemia before the correct diagnosis of HHCS was

made. The initial findings in these cases are similar to those in the single other large series in the hematology literature.⁶ As awareness of HHCS is increased among clinicians, it would be expected that additional cases will be diagnosed. Because there has been a paucity of information in ophthalmology literature on HHCS, and because it is not yet featured in any textbooks, most ophthalmologists remain unaware of it. We have shown that the diagnosis in pedigree 4 was based on lens morphology alone, even in the absence of a positive family history. This is, to our knowledge, the first case of HHCS to be diagnosed in this way, and we would expect further diagnoses by ophthalmologists as a result of this study.

CATARACT MORPHOLOGY

Cataract morphology in HHCS was initially described as a congenital nuclear cataract.²⁵ This now seems inadequate and incorrect. Mumford et al¹⁸ described the cataract as central sutural opacity within the lens, with cortical opacities extending radially. Girelli et al⁶ described 2 cataract morphologies of pulverulent and sunflower cataract, but their photographs actually appear to correspond to different stages of cases observed in our study.

In the 18 cases in which we have performed detailed examination and photography, the morphology of the cataract was highly distinctive and consistent in appearance, although clearly variable in age at onset and severity. In all cases, there was the appearance of axial and peripheral white flecks and small crystalline aggregates. Other opacities were small cortical vacuoles that were translucent but easily visible on retroillumination. In less advanced cases on wide dilation, there were myriad numbers of very small, white, round dots in the peripheral cortex with larger flecks axially. Family member IV:4 from pedigree 1 exhibited the peripheral small white dots and, in addition, the larger central crystalline deposits that are reminiscent of the corneal opacities seen in granular dystrophy (Figure 3). In the early stages, the axial lens and far periphery seemed to be involved first. With progression of visual symptoms, the midperiphery of the lens became involved. In each case, there were discrete opacities with clear lens between, and the opacities were best visualized with retroillumination. Slitlamp analysis disclosed a predominance of opacities in the cortical layers, but in every case there were discrete opacities in the nucleus also; this finding was verified by the Scheimpflug images (Figure 5C). The distribution is likely to be relevant to the pathogenesis in this condition. There was a tendency in some cases of cortical aggregates to coalesce into spokes with a radial orientation, hence the previous description of a sunflower shape.

Several older individuals had typical nuclear sclerosis in addition to the findings described. It is unclear whether this represents an acceleration of age-related nuclear sclerosis or is an unrelated and incidental finding. No individual younger than 40 years was found to have significant nuclear sclerosis. There were no posterior subcapsular cataract changes in the patients with HHCS. When the index case of pedigree 4 was 2 years of

age, the cataract was described as sutural. In their cases of HHCS, Mumford et al¹⁸ also described a patient aged 10 months with sutural opacities. The index case of pedigree 2 had infantile cataracts described by a pediatrician as triradiate. These descriptions imply that the earliest changes may indeed be sutural. However, none of the older individuals exhibited well-defined sutural opacities, although the widespread nature of the opacity could act to obscure such findings.

PROGRESSION OF CATARACT

The previous short description of HHCS cataracts in the ophthalmic literature did not determine whether cataracts in HHCS are static or progressive. The absence of HHCS cases from our database of early-onset congenital cataract and the presence of multiple individuals with progressive decline in BCVA requiring surgery after the second decade of life argue strongly that HHCS cataracts are progressive in nature. This is proved by 2-year serial lens photography of individual IV:4 of pedigree 1 (Figure 3) and of 13-year serial photography of individual V:1 of pedigree 2 (Figure 4), in which increased numbers of crystalline deposits are noted centrally and peripherally.

MUTATION SPECTRUM

We have identified a large Australian kindred of Irish descent (pedigree 1) first seen as 2 smaller pedigrees in which affected individuals are heterozygous for the single base substitution A40G of the L-ferritin IRE. This mutation has been well documented in several populations ("Paris 40").^{1,2,14,26} Pedigree 2 is of English descent with the G32C mutation.^{15,22} Analysis of a second smaller pedigree of Italian descent disclosed the presence of a mutation (C39A) in 2 affected individuals.⁷ The parents of the index case were said to be free of cataract and had normal serum ferritin levels. This could not be confirmed, as they were unavailable for study, but raised the possibility of de novo mutation, a mechanism that has been reported in a single case of HHCS previously.¹⁰ We have formally proved this mechanism in pedigree 4, in which a single base substitution (G to U) at position 32 of the IRE of the L-ferritin gene was demonstrated in the index case but absent in the parents and an unaffected sibling.⁷ Correct paternity was established using 12 microsatellite markers on 8 chromosomes, confirming that this case indeed represents a de novo mutation.

Our results add to the genetic heterogeneity of HHCS and reflect the importance of the stem-loop region of the IRE in the genesis of the hyperferritinemia. Furthermore, the confirmation of a de novo mutation in pedigree 4 and the strong likelihood of that mechanism in pedigree 3 raise the possibility that this may be a more common cause of HHCS than hitherto appreciated.

As the awareness of HHCS increases and ferritin analysis is performed more often in this context, it is expected that ophthalmologists may encounter the condition more frequently. Our study indicates that the cataract appearance is sufficiently characteristic to be diagnostically useful. Patients with unexplained hyper-

ferritinemia clearly need hematological evaluation. It is suggested that such patients should also be examined by an ophthalmologist, as the appearance of the cataract may be useful in establishing a correct diagnosis of HHCS. Furthermore, our findings indicate that the typical HHCS cataract may be present, despite the absence of any symptoms or positive family history.

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