Cataract, which can be defined as any opacity of the crystalline lens, results when the refractive index of the lens varies significantly over distances approximating the wavelength of the transmitted light. This variation in the refractive index can result from changes in lens cell structure, changes in lens protein constituents, or both. Cataracts are generally associated with breakdown of the lens microarchitecture. Vacuole formation can cause large fluctuations in optical density, resulting in light scattering. Light scattering and opacity also can occur if there are significant concentrations of high-molecular-weight protein aggregates, roughly 0.1 nm or more in size. The short-range, ordered packing of the crystallins, which make up more than 90% of soluble lens proteins, is important for the maintenance of lens crystallins in a homogeneous phase.

 Defined by age at onset, a congenital or infantile cataract is visible within the first year of life; a juvenile cataract occurs within the first decade of life; a presenile cataract occurs before age 45 years; and senile or age-related cataract, thereafter. The boundaries between different types of cataract are approximate; for example, some investigators would consider juvenile cataracts to occur before 20 years of age and age-related cataracts to occur after 60 years of age. In addition, subtle cataracts might not be seen for years after they occur, especially if they are asymptomatic. The age at onset of a cataract does not necessarily indicate its etiology. Congenital cataracts may be hereditary or secondary to a noxious intrauterine event (eg, rubella). Cataracts associated with a systemic or genetic disease may not occur until the second or third decade (eg, cataracts associated with retinitis pigmentosa). Even age-related cataracts, generally thought to be due to multiple insults accumulated over many years, have a genetic component, making certain individuals more vulnerable to the environmental insults.

It seems likely that when mutations in crystallins or other lens proteins are sufficient in and of themselves to cause protein aggregation they usually result in congenital cataract, while if they merely increase susceptibility to environmental insults, such as light, hyperglycemic, or oxidative damage, they might contribute to age-related cataract. Thus, hereditary congenital cataracts tend to be inherited in a mendelian fashion with high penetrance, while age-related cataracts tend to be multifactorial, with both multiple genes and environmental factors influencing the phenotype. This makes them significantly less amenable to genetic and biochemical study.

**CONGENITAL CATARACT**

Hereditary cataracts are estimated to account for between 8.3% and 25% of congenital cataracts. The lens alone may be involved, or lens opacities may be associated with other ocular anomalies, such as microphthalmia, aniridia, other anterior chamber developmental anomalies, or retinal degenerations. Cataracts may also be part of multisystem genetic disorders, such as chromosome abnormalities, Lowe syndrome, or neurofibromatosis type 2. In some cases this distinction is blurred. In-
Hereditary cataracts may be isolated in some individuals and associated with additional findings in others, as in the developmental abnormality anterior segment mesenchymal dysgenesis, resulting from abnormalities in the PITX3 gene.6

Hereditary mendelian cataracts may be inherited as autosomal dominant (most frequent), autosomal recessive, or X-linked traits. Phenotypically identical cataracts can result from mutations at different genetic loci and may have different inheritance patterns, while phenotypically variable cataracts can be found in a single large family.7 There are several classification systems that have been developed based on the anatomical location of the opacity. In an attempt to deal with congenital cataract, Merin and Crawford2 have proposed a system based on morphological classification. Summarized very briefly, the cataract is classified as total (mature or complete), polar (anterior or posterior), zonular (nuclear, lamellar, or sutural), and capsular or membranous.

AGE-RELATED CATARACT

In age-related cataracts, the lens is clear during infancy and remains clear until sometime after 45 years of age when progressive opacities begin to form in the lens. These opacities almost certainly result at least in part from the cumulative damage of environmental insults on lens proteins and cells. Lens proteins are known to undergo a wide variety of alterations with age, and many of these are accelerated in the presence of oxidative, osmotic, or other stresses. These stresses are themselves known to be associated with cataracts. In the case of lens crystallins, these include proteolysis, an increase in disulfide bridges, deamidation of asparagine and glutamine residues, racemization of aspartic acid residues, phosphorylation, nonenzymatic glycosylation, and carbamylation. Many of these changes have been found to be increased in cataractous lenses and to be induced in vitro or in model systems by the same stresses epidemiologically associated with cataracts.8

As a possible example, crystallins are the major soluble structural proteins in the lens and in humans comprise 3 major classes encoded by multiple genes, the α-, β-, and γ-crystallins. As the β- and γ-crystallins slowly accumulate damage over the lifetime of an individual, they lose the ability to participate in normal intermolecular interactions, and even to remain in solution. As these crystallins begin to denature (lose their native structure) and precipitate (come out of solution), they are bound by the α-crystallins, which have a chaperonelike activity.9 That is, binding by α-crystallins maintains solubility of βγ-crystallins and reduces light scattering, but in general, the α-crystallins appear not to renature their target proteins and release them into the cytoplasm, as do true chaperones. Rather, they hold them in complexes that, while soluble, increase in size as additional damaged protein is bound over time until they themselves begin to approach sizes sufficient to scatter light.9 Eventually, the available α-crystallin is overwhelmed by increasing amounts of modified βγ-crystallin and the complexes precipitate within the lens cell, forming the insoluble protein fraction that is known to increase with age and in cataractous lenses. Whether proteins in the insoluble fraction become insoluble on complete or partial denaturation, as would be implied by the schema described earlier, or whether they simply become less soluble because of modifications that leave their protein fold largely intact is not known currently. However, it seems clear from numerous mouse models of cataract that the presence of large amounts of unstable or precipitated protein does damage to the lens cell and contributes to cataracts not only directly through light scattering by protein aggregates but eventually also through disruption of cellular architecture.10 Similarly, mutations that disrupt intracellular homeostasis of lens cells can damage their constituents over time and contribute to age-related cataract, as discussed later for galactokinase.

While congenital cataracts can be particularly threatening to vision and up to one half of all congenital cataracts are inherited, they affect relatively few individuals in comparison with age-related cataracts, which are responsible for blinding 17 million persons, causing just less than half of all blindness worldwide.11 Cataracts are the leading cause of low vision in the United States,11 and cataract surgery is the most frequently performed surgical procedure in the United States, undergone by about 5% of the American population older than 40 years. Because of its demographics, it has been estimated that delaying the development of cataract by 10 years would decrease the need for cataract surgery by about 45%.12 Age-related cataract is associated with a number of environmental risk factors, including cigarette smoking or chronic exposure to wood smoke, obesity or elevated blood glucose levels, poor infantile growth, exposure to UV light, and alcohol consumption.13 Conversely, antioxidant vitamins seem to have a protective effect, although this has not been borne out by all studies.14

Epidemiological evidence supports the importance of genetic factors in the pathogenesis of age-related cataract.13,16 The Lens Opacities Case-Control Study17 and the Italian-American Cataract Study Group18 support a role for family history as a risk factor in cortical, mixed nuclear and cortical, and posterior subcapsular cataracts. The Framingham Offspring Eye Study18 showed that individuals with an affected sibling have a 3-fold increased risk of having a cataract. The Beaver Dam Eye Study19 suggested that a single major gene could account for as much as 35% of nuclear and up to 75% of cortical cataract variability. The twin eye study20 demonstrated a significant genetic influence on age-related cataract, with heritability accounting for 53% to 58% of the liability for cortical cataract and 48% of the risk for nuclear cataract.

CURRENT APPROACHES AND TOOLS

Genetic causes of congenital cataracts have been identified by a combination of linkage analysis and screening candidate genes for mutations. Linkage analysis, a powerful tool to sort out the different genetic loci that can cause human...
cataracts, localizes mutant genes causing inherited cataracts to a specific chromosomal region by comparing their inheritance patterns with those of known genetic markers. Most cataract loci currently have been identified using microsatellite markers, although single nucleotide polymorphisms (SNPs) are rapidly gaining favor. Both approaches remain useful. New analytical approaches using homozygosity mapping methods to identify genomic regions identical by descent promise to be increasingly useful in studying rare autosomal recessive cataracts from isolated populations. While it has been estimated that there are 30 autosomal dominant congenital cataract loci in man, the number of identified loci is currently approaching that with no obvious sign of plateauing. Obviously, much work remains to be done in understanding inherited congenital cataracts.

Age-related cataract loci generally have been studied using a combination of model-based and model-free linkage analysis and association studies. Because the late age at onset often precludes studying multiple generations of a single family, the cataracts are often variable in severity and even appearance, and the mode of inheritance is complex, age-related cataracts are significantly more difficult to study than congenital cataracts. However, progress is beginning to be made by association studies on candidate genes and model-free linkage analysis, as described later.

OVERVIEW OF CATARACT GENETICS

Congenital Cataract

Cataracts can be isolated or can occur in association with a large number of metabolic diseases and genetic syndromes. Isolated congenital cataracts tend to be highly penetrant mendelian traits, with autosomal dominant more common than autosomal recessive cataracts. Currently, as listed in the Table, there are about 34 genetic loci to which isolated or primary cataracts have been mapped, although the number is constantly increasing. Of these, 8 are associated with additional abnormalities, mostly as part of developmental syndromes. These tend to result from mutations in genes encoding transcriptional activators, and most of these have been identified by sequencing candidate genes in patients with developmental abnormalities. Two notable exceptions are the αB-crystallin gene, mutations in which can cause either isolated cataracts or cataracts associated with myopathy, and the ferritin gene, which causes the hereditary hyperferritinemia-cataract syndrome (Table). While in some cases (eg, some α- and β-crystallin mutations) inherited congenital cataracts are associated with microcornea and even microphakia, with the exception of heat shock transcription factor 4 (HSF4), most inherited cataracts caused by mutations in growth or transcription factors are associated with extralenticular abnormalities.

Of the mapped loci for isolated congenital or infantile cataracts, more than 20 have been associated with mutations in specific genes. Of the families with cataract for whom the mutant gene is known, about half have mutations in crystallins and about a quarter have mutations in connexins, with the remainder largely split between the genes for HSF4, aquaporin 0 (AQP0, MIP), and beaded filament structural protein 2 (BFSP2). Inheritance of the same mutation in different families or even the same mutation within the same family can result in radically different cataract morphologies and severities. This suggests that additional genes or environmental factors might modify the expression of the primary mutation associated with the cataracts. Conversely, cataracts with similar or identical clinical manifestations can result from mutations in quite different genes.

Specific Genes Implicated in Congenital Cataracts

Examination of the genes implicated in congenital cataracts provides insight into those biological pathways important for lens transparency and homeostasis as well as being of some clinical interest. Mutations in the α-crystallin gene have been implicated both in autosomal recessive cataracts, which are associated with a chain termination mutation near the beginning of the protein, and in autosomal dominant cataracts, which are associated with nonconservative missense mutations. The chain termination mutation would be expected to cause loss of function of the mutant protein without affecting protein synthesized from the normal gene, suggesting that half the normal levels of α-crystallin can provide sufficient chaperonelike activity and structural crystallin packing to establish and maintain lens transparency. These findings are consistent with data from knockout mice in which the αA-crystallin gene is disrupted. In these mice, the lenses are somewhat smaller in size and develop cataracts associated with the presence of inclusions containing αB-crystallin. The occurrence of dominant cataracts with the missense mutations suggests that the mutant αA-crystallin protein exerts a deleterious effect that actively damages the lens cell or its constituent proteins, or inhibits the function of the remaining normal α-crystallin, rather than acting through loss of chaperone function as the recessive cataract appears to do.

Because αA- and αB-crystallins are found in the lens associated into large multimeric complexes and function similarly in vitro, one might expect that mutations in αB-crystallin would have a similar effect to those in αA-crystallin, at least in the lens. However, the first human mutation reported in αB-crystallin was associated with desmin-related myopathy and only “discrete” cataracts. This was a missense mutation that reduced αB-crystallin chaperone activity dramatically, causing aggregation and precipitation of the protein under stress. The myopathy associated with this mutation is probably related to the expression of αB-crystallin, but not αA-crystallin, in muscle cells, where it binds and presumably stabilizes desmin. Similarly, an αB-crystallin knockout mouse exhibits myopathy without cataracts. In contrast, a deletion in the αB-crystallin gene resulting in a frameshift and expression of an aberrant 184 amino acid protein causes autosomal...
dominant cataracts in the absence of myopathy. This seems more similar to the dominant αA-crystallin- associated cataract, with the aberrant protein likely to have a toxic effect on the lens cells.

Most mutations described in the βγ-crystallins would be expected to cause major abnormalities in the

Table. A Gene Map of Nonsyndromic Cataract

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Locus/Gene (MIM)</th>
<th>DNA Change</th>
<th>Protein Change</th>
<th>Mode of Inheritance</th>
<th>Cataract Phenotype</th>
<th>Associated Phenotype</th>
</tr>
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<tbody>
<tr>
<td>1p36</td>
<td>CCV (115665)</td>
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<td>AD</td>
<td>Progressive lamellar</td>
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<tr>
<td></td>
<td>CTPP1 (116600)</td>
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<td>AD</td>
<td>Posterior polar</td>
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<td></td>
<td>AD</td>
<td>Total</td>
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<td>1p32</td>
<td>FOXE3 (601094)</td>
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<td>Anterior segment ocular dysgenesis</td>
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<td>1p13.3</td>
<td>GSTM1 (138350)</td>
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<td>C</td>
<td>Age-related (Japanese, Iranian)</td>
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<td>None</td>
<td></td>
<td>C</td>
<td>Age-related cortical (Estonian)</td>
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<td>GJA8 (600897)</td>
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<td>Nuclear</td>
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<td></td>
<td>c.T131A</td>
<td>p.V44E</td>
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<td>Total</td>
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<tr>
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<td></td>
<td></td>
<td>Microcornea, mild myopia</td>
<td></td>
</tr>
<tr>
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<td>c.T741G</td>
<td>p.I247M</td>
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<td></td>
<td>AD</td>
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<td></td>
<td>AD</td>
<td>Nuclear</td>
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<tr>
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<td></td>
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<td>AR</td>
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<td>2p12</td>
<td>CNNP (607304)</td>
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<td>p.T5P</td>
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<td>p.C42fs</td>
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<td>CRYGD (123690)</td>
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<td></td>
<td>AD</td>
<td>Cerulean</td>
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<tr>
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<td></td>
<td></td>
<td>AD</td>
<td>Flaky silicilike nuclear</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>AD</td>
<td>Coral-like</td>
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<tr>
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<td></td>
<td>AD</td>
<td>Fasiculiform</td>
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<tr>
<td></td>
<td>c.G176A</td>
<td>p.R58/59H</td>
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<td>AD</td>
<td>Nuclear golden crystal</td>
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<td>c.G470A</td>
<td>p.W156/157X</td>
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<tr>
<td>3p11.23-pter</td>
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<td>3p11.3-p22.3</td>
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<td>3q21.3-p22.3</td>
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<td>3q25-qter</td>
<td>CRYGS (123730)</td>
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<td>Cortical progressive</td>
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<tr>
<td>3q25-qter</td>
<td>GCC7 (600429)</td>
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<td>?</td>
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<td>6p12-q12</td>
<td>ARCC1 (609028)</td>
<td>c.Y1A1 (601533)</td>
<td>p.R514G</td>
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<td>9q13-q22</td>
<td>CAAR (605749)</td>
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<td>9q13-q22</td>
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<td>AR</td>
<td>Adult-onset cortical pulverulent, progressive nuclear, and posterior subcapsular</td>
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<td>10p25</td>
<td>c.650delG</td>
<td>p.S13N</td>
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<td>AD</td>
<td>Anterior cortical</td>
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<td>11p13</td>
<td>PAX6 (607108)</td>
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<td>S353X</td>
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<td>Lamellar anterior capsular, posterior subcapsular</td>
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<td>AD</td>
<td>Corneal dystrophy</td>
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<td></td>
<td>g.IVS4a-3T&gt;C</td>
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<td></td>
<td>AD</td>
<td>Peripheral corneal opacity, glaucoma, nystagmus</td>
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</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Locus/Gene (MIM)</th>
<th>DNA Change</th>
<th>Protein Change</th>
<th>Mode of Inheritance</th>
<th>Cataract Phenotype</th>
<th>Associated Phenotype</th>
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<tbody>
<tr>
<td>11q22.1-q23.2</td>
<td>CRYAB (123590)</td>
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<td>p.R120G</td>
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<td>Myopathy</td>
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<td></td>
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<td>c.G418A</td>
<td>p.D140N</td>
<td>AD  Lamellar</td>
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<td></td>
<td></td>
<td>c.450delA</td>
<td>p.K150fs</td>
<td>AD  Posterior polar</td>
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<td>12q13-q14</td>
<td>MIP (154050)</td>
<td>c.A401G</td>
<td>p.E134G</td>
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<td></td>
<td>c.A413G</td>
<td>p.T138R</td>
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<td>GJA3 (121015)</td>
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<td>p.V28M</td>
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<td>p.F32L</td>
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<td>p.W45S</td>
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<td>c.A188G</td>
<td>p.N63S</td>
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<tr>
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<td>c.G226A</td>
<td>p.R76H</td>
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<tr>
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<td></td>
<td>c.C226G</td>
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<td>AD  Total</td>
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<td>c.A563C</td>
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<tr>
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<td>c.1137insC</td>
<td>p.S380fs</td>
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<td>CHX10 (142993)</td>
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<td>p.R2000/P</td>
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<td>Microphthalmia, iris coloboma, dislocated lens</td>
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<td>p.A20D</td>
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<td>c.C358T</td>
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<td>c.G524C</td>
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<td>g.IVS5-9del5bp</td>
<td>t[5,16]</td>
<td>AR  ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16q22-q23</td>
<td>MAF (177075)</td>
<td>c.G863C</td>
<td>p.R288P</td>
<td>AR  Cortical (lamellar) nuclear pulverulent</td>
<td>Peters anomaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>g.IVS3-1G [1G]</td>
<td></td>
<td>AD  Central saccular sutural</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17q11.2-q12</td>
<td>CRYBA3/A1 (123610)</td>
<td>g.IVS3 + 1G [A]</td>
<td>AD  Zonular suture-sparing</td>
<td>Nuclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17q24</td>
<td>GALK1 (604313)</td>
<td>c.C293T</td>
<td>p.A198V</td>
<td>?  Age-related (Asian)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17q24</td>
<td>CCA1 (115660)</td>
<td>25*</td>
<td>AD  Cerulean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19q13.4</td>
<td>FLI (134790)</td>
<td>5IRE†</td>
<td>AD  Nuclear</td>
<td></td>
<td></td>
<td>Hyperferritinemia-catarract syndrome</td>
</tr>
<tr>
<td>19q13.4</td>
<td>LIM2 (154045)</td>
<td>c.T313G</td>
<td>p.F105V</td>
<td>AR  Puncher cortical suture</td>
<td></td>
<td>Microcornea, microphthalmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c.C145T</td>
<td>p.R49C</td>
<td>AD  Central nuclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c.C346T</td>
<td>p.R116C</td>
<td>AD  Zonular central nuclear, cortical, posterior subcapsular</td>
<td>Microcornea, microphthalmia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>g.IVS12 + 4A [G]</td>
<td>t[5,16]</td>
<td>AR  Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22q11.2</td>
<td>CRYBB1 (609929)</td>
<td>c.G658T</td>
<td>p.G220X</td>
<td>AD  Central spheroidal</td>
<td></td>
<td>Microcornea, microphthalmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c.T757C</td>
<td>p.X253R</td>
<td>AD  Nuclear cortical riders</td>
<td></td>
<td>Microcornea, microphthalmia</td>
</tr>
<tr>
<td>22q11.2</td>
<td>CRYBB2 (123620)</td>
<td>c.C463T</td>
<td>p.Q155X</td>
<td>AD  Cerulean</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>g.IVS3-1G [1G]</td>
<td></td>
<td>AD  Central spheroidal</td>
<td></td>
<td>Microcornea, microphthalmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c.G453T</td>
<td>p.W151C</td>
<td>AD  Central nuclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CRYBB3 (123630)</td>
<td></td>
<td>AD  Central nuclear</td>
<td></td>
<td>Microcornea, microphthalmia</td>
</tr>
<tr>
<td>Xp22</td>
<td>CXN (NHS?) (300457)</td>
<td>c.T242C</td>
<td>p.L69P</td>
<td>AR  Congenital lamellar</td>
<td></td>
<td>Microcornea, microphthalmia</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ASMD, anterior segment mesenchymal dysgenesis; BOR, branchiootorenal dysplasia syndrome; bp, base pair; C, complex; fs, frameshift; IRE, iron response element; MIM, Mendelian Inheritance in Man number; XL, X-linked; ?, morphology of the cataract is in doubt.

*This cataract is not listed in Online MIM and thus is independently referenced.
†Mutations located in the 5' IRE.
protein structure, presumably resulting in an unstable protein that precipitates from solution and serves as a nidus for additional protein denaturation and precipitation, eventually resulting in cataract formation. These include missense mutations, insertions changing the reading frame and causing expression of aberrant peptides with premature termination, and splice mutations, as presented in the Table. Although phenotypes can vary significantly, mutations in γ-crystallins tend to produce nuclear or zonular cataracts, consistent with their high level of expression in the lens nucleus. Presumably, central nuclear cataracts reflect high-level expression of the mutant gene early in lens development, while zonular cataracts reflect synthesis somewhat later and for a limited period, resulting in a shell of opaque cells surrounded internally and externally by relatively clear lens. The cataract phenotypes reported with mutations in the β-crystallins are somewhat more varied, ranging in different families from zonular pulverulent with or without involvement of the sutures to cuneiform cataracts. The association of identical mutations in βB2-crystallin in different families with nuclear lamellar Coppock-like and cuneiform cataracts emphasizes the importance of modifying genes in the phenotypic expression of these mutations.

Recently, 2 mutations in γD-crystallin, R36S and R58H, have been shown not to alter the protein fold, but rather to alter the surface characteristics of the protein. This, in turn, lowers the solubility and enhances the crystal nucleation rate of these mutants so that they precipitate out of solution, in at least 1 case actually forming crystals in the lens. In a third mutation in γD-crystallin, R14C, the protein also maintains a normal protein fold but is susceptible to thiol-mediated aggregation. These results emphasize that crystallins need not undergo denaturation or other major changes in their protein folds to cause cataracts.

The hyperferritinemia-cataract syndrome is a recently described disorder in which cataracts are associated with hyperferritinemia without iron overload. Ferritin L (light chain) levels in the lens can increase dramatically to levels approaching that of a crystallin. The molecular pathology lies in the ferritin L iron-responsive element, a stem loop structure in the 5′ untranslated region of the ferritin messenger RNA. Normally, this structure binds a cytoplasmic protein, the iron regulatory protein, which then inhibits translation of ferritin messenger RNA. Mutation of this structure and overexpression of ferritin by loss of translational control in the hyperferritinemia-cataract syndrome results in crystallization of ferritin in the lens, similar to that described earlier for the R36S and R58H γ-crystallin mutations, and the appearance of bread crumb–like opacities in the cortex and nucleus. This emphasizes the requirement that crystallins or other proteins must be exceptionally soluble to be expressed at such high levels in the lens without causing dysfunction.

Connexins 46 and 50 are constituents of gap junctions, on which the avascular lens depends for nutrition and intercellular communication. At least 1 cataract-associate mutation in the connxin 50 gene, the P88S missense mutation in the second transmembrane domain, has been shown to result in a connexin that fails to form functional gap junctional channels. Incorporation of even a single mutant protein molecule into a gap junction in Xenopus oocytes inhibits channel function. Mutant connexin 46 proteins are also associated with cataracts. Two mutant connexins, with an N63S missense mutation in the first extracellular domain and a frameshift mutation at residue 380, which causes read-through into the 3′ untranslated region until an in-frame stop codon 90 nucleotides downstream from the wild-type stop codon, also fail to form intercellular channels in paired Xenopus oocytes. However, these mutant connexins are unable to participate in gap junction formation at all and thus do not inhibit channel function by products of the normal gene. Mutations in both connexin 46 and connexin 50 produce phenotypically similar autosomal dominant nuclear and especially zonular pulverulent cataracts.

Lamellar and polymorphic cataracts have been associated with missense mutations in the AQP0 (MIP) gene. One mutation, E134G, is associated with a nonprogressive congenital lamellar cataract, and the second, T138R, is associated with multifocal opacities that increase in severity throughout life. Both of these mutations appear to act by interfering with normal trafficking of AQP0 to the plasma membrane and thus with water channel activity. In addition, both mutant proteins appear to interfere with water channel activity by normal AQP0, consistent with a dominant negative mechanism for the autosomal dominant inheritance of the cataracts.

Beaded filaments are a type of intermediate filament unique to the lens fiber cells. They are made up of Bfsp1 (also called CP115 or filensin) and Bfsp2 (also called CP49 or phakinin), highly divergent intermediate filament proteins that combine in the presence of α-crystallin to form the appropriate beaded structure. Cataracts in 3 families have been associated with mutations in Bfsp2. In 1 family, the cataracts were associated with a non-conservative missense mutation in exon 4 substituting a tryptophan for an evolutionarily conserved arginine in the central rod domain of the protein. A deletion resulting in the loss of Glu233 in this protein has also been associated with cataracts. These cataracts are nuclear or nuclear lamellar, with some involvement of the sutures, consistent with fiber cell-specific expression of the beaded filament proteins.

HSF4 is a member of the heat-shock transcription factor family, which regulates expression of heat-shock proteins, including lens αB-crystallin, in response to elevated temperature and other stress stimuli (eg, oxidation). Mutations in HSF4 have been associated with autosomal dominant and recessive cataracts. The dominant cataracts were initially seen in early childhood and were described as lamellar, including the historically important Marner cataract family, whereas the recessive cataracts had a congenital onset and ranged in severity from nuclear with some cortical involvement to total lens opacities. Interestingly, the
dominant mutations in HSF4 lie within the α-helical DNA-binding domain, whereas the recessive mutations lie outside this highly conserved functional domain.

Age-Related Cataract

Linkage Studies. In addition to epidemiological evidence implicating genetic factors in age-related cataract, a number of inherited cataracts with postinfantile age at onset or progression of the opacity throughout life have been described. Mutations in BFSP2 can cause juvenile cataracts, the Marner and Volkmann cataracts can be progressive, mutations in AQP0 (MIP) and γC-crystallin can cause progressive cataracts, and the CAAR locus is linked to familial adult-onset pulverulent cataracts. These all suggest that for at least some genes, a mutation that severely disrupts the protein or inhibits its function might result in congenital cataracts inherited in a highly penetrant mendelian fashion, while a mutation that causes less severe damage to the same protein or impairs its function only mildly might contribute to age-related cataracts in a more complex multifactorial fashion. Similarly, mutations that severely disrupt the lens cell architecture or environment might produce congenital cataracts, while others that cause relatively mild disruption of lens cell homeostasis might contribute to age-related cataract.

In contrast to congenital cataracts, mapping and identification of genes for age-related cataract is still in its infancy. The first genome-wide scan, using model-free linkage analysis of affected sib pairs, has contained approximately 400 positional candidate genes and likely includes the loci for Volkman cataract, posterior polar cataract, and total cataract. The potential susceptibility loci on 1q31 and 2q33 lie near the connexin 50 gene and the γ-crystallin gene cluster, respectively, suggesting the possibility that genes linked with autosomal dominant congenital cataracts may also contribute to age-related cataract. The difficulties in carrying out linkage studies of age-related cataracts are reflected in the multiple chromosomal regions possibly implicated, in the relatively low likelihood that each one is significant, and in the large sizes of most of the regions and the correspondingly large numbers of genes they contain.

Association Studies. Galactosemic cataracts provide an interesting example of mutations severely affecting a gene, causing early-onset cataracts, while milder mutations simply decreasing its activity contribute to age-related cataracts. Deficiencies of galactokinase (GALK1) and galactose 1-phosphate uridyltransferase and severe deficiencies of uridine diphosphate 1-4 epimerase cause cataracts as a result of galactitol accumulation and subsequent osmotic swelling. The latter 2 are also associated with vomiting, failure to thrive, liver disease, and mental retardation, if untreated, while the cataracts in galactokinase deficiency are isolated. Intriguingly, galactosemic cataracts initially are reversible both in human patients and in animal models. In 2001, a novel variant of galactokinase, the “Osaka” variant with an A198V substitution, was shown to be associated with a significant increase in bilateral cataracts in adults. It results in instability of the mutant protein and is responsible for mild galactokinase deficiency, leaving about 20% of normal levels. This variant allele frequency occurs in 4.1% of Japanese individuals overall and 7.1% of Japanese individuals with cataracts. The allele was also present in 2.8% of Korean individuals but had a lower incidence in Chinese individuals and was not seen in black or white individuals from the United States. This and other GALK1 variants appeared to be absent from northern Italian individuals with age-related cataract, suggesting that the genetic contributions to cataract might vary in different populations. However, decreased activity of galactokinase consistent with heterozygous deficiency was found in 3 of 39 white subjects, confirming the importance of galactokinase activity for maintenance of lens transparency over time. Similar results were also seen for galactose 1-phosphate uridyltransferase activity in 3 of 45 subjects.

The GALK1 results fit well with the known influence of hyperglycemia on age-related cataract, probably with an oxidative component. That these cataracts result from polyol accumulation is suggested by work in galactosemic dogs and transgenic and knockout mice. Dogs have aldose reductase levels similar to those in humans and when made hyperglycemic readily develop sugar cataracts that are prevented by aldose reductase inhibitors. Mice, which have very low aldose reductase activity in the lens, are naturally resistant to sugar cataracts, either galactosemic or hyperglycemic. However, on transgenic expression of aldose reductase, mice readily develop cataracts, especially when the galactokinase or sorbitol dehydrogenase gene is deleted. Consistent with these animal data are the recent findings that susceptibility to cataracts as a diabetic complication in humans is associated with specific allele Z of the microsatellite polymorphism at the 5′ end of the aldose reductase gene.

CLINICAL IMPLICATIONS AND GENETIC COUNSELING

Congenital cataracts can lead to permanent blindness by interfering with the sharp focus of light on the retina and resulting in failure to establish appropriate visual cortical synaptic
connections with the retina. Prompt diagnosis and treatment can prevent this. Understanding the biology of the lens and the pathophysiology of selected types of cataract can yield insight into the process of cataractogenesis in general and provide a framework for the clinical approach to diagnosis and therapy.

Evaluation

After establishing the significance and classifying the cataract by type, the evaluation of a cataract consists of a careful assessment of its effect on the vision and function. The first assessment in small children (0-3 years of age) is usually carried out by observation fixing and following and by covering alternate eyes and observing the response. Covering the eye with good vision will cause more fretting, objecting, and crying. More accurate assessment is provided by specialized testing including visually evoked cortical responses, preferential looking, or the forced-choice method. With older children, subjective tests, including identification of the illiterate E or Allen cards (picture-differentiating tests), are used. Finally, once the alphabet is learned, conventional acuity testing by a log minimum angle of resolution Early Treatment of Diabetic Retinopathy Study or Snellen chart may be used.

Cataracts may be visualized in a variety of ways. When viewed with a hand light, a cataract may appear as white pupillary opacity (leukocoria). Direct ophthalmoscopy is useful to evaluate the effect on visual function following the principle that if the examiner can see the optic nerve and macula, the patient can probably see out. One can visualize a lens opacity silhouetted in the red reflex using either direct illumination or retroillumination. The definitive description of a lens opacity depends on a slitlamp biomicroscopic examination through a widely dilated pupil, allowing for direct illumination and retroillumination with appropriate magnification to visualize the lens opacity and define its clinical features. Photographs are useful to document the features and progression of the cataract, especially in a research setting.

Differential Diagnosis and Diagnostic Tests

The differential diagnosis of a hereditary congenital cataract includes (1) Prenatal causes including virus or other infectious disease; this is more common in developing countries. Rubella directly involves the lens, whereas other infectious agents (toxoplasmosis, mumps, measles, influenza, chickenpox, herpes simplex, herpes zoster, cytomegalovirus, and echovirus type 3) result in ocular inflammation (uveitis). Depending on the clinical setting, these can be screened for by a variety of cultures and other tests including TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) titer. (2) Developmental abnormalities associated with prematurity. These may be associated with low birth weight, birth anoxia, or central nervous system involvement leading to seizures, cerebral palsy or hemiplegia, and retinopathy of prematurity. (3) Perinatal-postnatal problems, such as hyperglycemia and hypocalcemia, can cause cataracts. These are associated with signs of diabetes and tetany, respectively, and can be screened for by serum chemistries. (4) Association with other ocular abnormalities, including anterior chamber abnormalities (eg, Reiger syndrome or anomaly, primary hyperplastic vitreous, aniridia, retinopathies such as retinal dysplasia, Norrie disease, and microphthalmia). (5) Association with multisystem abnormalities, including TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) titer. Lastly, communication between health care professionals, therapists, and teachers combined with counseling of patients is very important in the treatment of young patients with cataract and their families.

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