INVITED EDITORIAL
The Genetics of Cataract: Our Vision Becomes Clearer

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The article by Shiels et al. (1998 [in this issue]), describing a mutation in the human connexin50 gene (*GJA8*) in individuals with the autosomal dominant zonular pulverulent cataract (CAE1), represents a milestone for human genetics. The *CAE1* locus was initially linked with the Duffy blood-group locus by Renwick and Lawler (1963), and in 1968 the Duffy blood-group locus was assigned to chromosome 1 (Donahue et al. 1968), making *CAE1* the first human disease locus to be assigned to a human autosome. The likelihoods reported by Renwick were estimated by use of a computerized algorithm and were the first to be analyzed in this fashion.

In his commentary in 1970, "Eyes on Chromosomes," Renwick credits the potential for surgical treatment of congenital cataracts, one of the first serious genetic conditions for which effective therapy was available, with stimulating the pioneering work of ophthalmologists such as Nettleship and Usher (Renwick 1970). Congenital cataracts often are dominantly inherited and do not reduce reproductive fitness, so large families suitable for mapping studies are available. However, until recently genetic analysis of cataracts has lagged behind that of retinal degenerations and other ophthalmologic diseases.

Following the initial localization of the *CAE1* locus, additional genetic studies of congenital cataract demonstrated the challenges arising from genetic heterogeneity, which still confront investigators today. Renwick and Lawler (1963) reanalyzed data from Mohr on the Marner cataract (CAM), which has a variable phenotype overlapping that of CAE1, and excluded this locus from the Duffy region. In 1973 Hammerstein and Scholtz and in 1978 Huntzinger et al. also excluded from the Duffy region the loci for phenotypically similar cataracts. Conneally et al. (1978) confirmed the linkage to the Duffy region in one of seven families studied.

With more efficient genetic markers, nine new cataract loci have been described (table 1). Of these, the cataracts in two families map near the Duffy region, the cataracts in three families map to the γ-crystallin cluster at 2q33-q35, and the cataracts in two families map near haptoglobin, at 16q22. The remaining six loci have each been described in a single family. It has been estimated that there are 30 loci responsible for autosomal dominant cataracts in man (Ehling 1991). That there are already 22 cataract loci mapped in mice suggests that this might be a low estimate. A gene for recessive cataracts has been localized to the Ii blood-group locus (Ogata et al. 1979), where it is associated with the "I" phenotype in Japanese and some Caucasians, and the Nance-Horan syndrome has been mapped to Xp21-22 (Stambolian et al. 1990). Finally, a number of chromosomal abnormalities, genetic syndromes, and metabolic diseases are associated with cataract (Hejtmancik et al. 1995).

CCA1 and CCA2, which map to chromosomes 17 and 22, respectively, are both cerulean cataracts, and CAE1, CCL, CAM, and CZP, which map to loci on chromosomes 1, 2, 16, and 13, respectively, are all nuclear or nuclear lamellar (zonular) with some variations—that is, they are sometimes pulverulent or have a sutural or cortical component. This demonstrates the power of linkage studies to distinguish the pathogenesis of a phenotypically similar family of diseases. On the other hand, cataracts within a single family can show remarkable phenotypic variation (Scott et al. 1994).

Crystallins and Lens Transparency

Understanding cataract would be impossible without knowledge of the biology of the lens. In 1894, Morner first described the crystallins as heterogeneous structural proteins found at high concentrations in the lens, and the first crystallin (δ-) was cloned in 1979. The lens crystallins constitute 80%–90% of the soluble protein and, in most species, constitute three main families, called "ubiquitous" crystallins. α-Crystallins can be induced by stress (Klemenz et al. 1991) and function as molecular chaperones (Horwitz 1993). β- and γ-crystallins, which share a common two-domain structure composed of four extremely stable torqued β-pleated sheets termed "Greek key" motifs, are related to the stable spore-coat proteins (Lubsen et al. 1988) and to the tumor sup-

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Table 1

Mapped Human Cataract Loci

Locus (Phenotype)	MIM Number	Chromosome	Morphology	Gene	No. of Families	Reference
CAE1 (CZP1, Duffy linked)	116200	1q21-q25	Zonular pulverulent	Connexin50 (*GJA8*)	2	Renwick and Lawler (1963)
CAM (Marner, CTM)	116800	16q22	Variable (progressive central and zonular nuclear, anterior polar, or stellate)		2	Eiberg et al. (1988)
CCL (Coppock like)	123660	2q33q35	Nuclear lamellar (Coppock like), aculeiform, variable nuclear	γE-crystallin	3	Lubsen et al. (1987)
CCA1 (cerulean-blue dot)	115660	17q24	Cerulean (nuclear and cortical)		1	Armitage et al. (1995)
CCV (Volkmann)	115665	1p36	Variable (progressive central and zonular with sutural component)		1	Eiberg et al. (1995)
CCZS-LSB (zonular sutural)	600881	17q11-q12	Variable nuclear lamellar with sutural component	Near βA3-crystallin	1	Padma et al. (1995)
CTAA2 (anterior polar)	601202	17p13	Anterior polar		1	Berry et al. (1996)
CCA2 (cerulean-blue dot)	601547	22q	Cerulean	βB2-crystallin	1	Kramer et al. (1996)
CZP	601885	13	Zonular pulverulent	Near connexin6 (*GJA3*)	1	Mackay et al. (1997)

pressor A1M1 (Ray et al. 1997). The α-crystallins are synthesized early in lens development, as the lens vesicle pinches off from the surface ectoderm. Synthesis of the βγ-crystallins increases as anterior epithelial cells move laterally and then into the lens nucleus, elongating and losing their nuclei to form lens fiber cells.

The lens crystallins provide cellular cytoplasm consistent with lens transparency, which requires that the refractive index must be relatively constant over distances approximating the wavelength of the transmitted light (Delaye and Tardieu 1983). This requires maintenance of a high degree of short-range order among the lens crystallins. In addition, because fiber cells in the central lens nucleus lose their nuclei during development, the crystallins in these cells do not turn over. Since most are at least as old as the individual in whose eyes they reside, crystallins must be extremely stable proteins.

The classical view of crystallins as lens-specific proteins that allow lens transparency was shaken by the description of taxon-specific, or enzyme, crystallins; these are closely related or identical to enzymes expressed at low concentrations in nonlens tissues, as well as at high concentrations in the lens. Recently some members of the α- and βγ-crystallins were also shown to be expressed outside the lens (Head et al. 1995; Kantorow et al. 1997). Finally, α- and βB2-crystallins have autokinase activity (Kantorow and Piatigorsky 1994; Kantorow et al. 1997), further blurring the distinction between the enzyme crystallins and the ubiquitous crystallins.

Lens transparency also requires a variety of noncrystallin proteins. Catalase, the glutathione redox cycle, and the mercaptopuric pathway are critical for maintenance of a reducing environment in the lens (Spector 1995). The lens cytoskeleton supports cellular architecture, especially the beaded filament, which appears to be unique to the lens and which may interact with α-crystallin (Carter et al. 1995). Membrane proteins such as MP-26 and aquaporins in thin junctions and the connexins and N-cadherin in gap junctions provide osmoregulation and help to maintain the intracellular environment (Gruijters et al. 1987). Finally, developmental regulation by factors such as Pax-6 is critical for formation of the lens architecture (Cvekl and Piatigorsky 1996). Each component of these systems would be a candidate for causing hereditary cataract.

Initial insights into the genetic causes of cataract came from animal models, mostly mice. Of the mutations associated with animal models of cataract, four are in crystallin genes, and four more are in membrane proteins—three in MP-26 and one in MP-19 (table 2). The mutations characterized so far confirm the importance of membrane proteins, which modulate exchange of ions and metabolites between lens fibers, epithelial cells, and

Table 2

Animal Models of Cataract

Model	Protein	Mutation	Mechanism	Reference
Philly mouse	βB2-crystallin	12-bp In-frame deletion	Disrupts tertiary structure	Chambers and Russell (1991)
ELO mouse	γE-crystallin	Frameshift	Frameshift	Cartier et al. (1992)
13/N guinea pig	ζ-Crystallin	Splice error	6-Amino-acid deletion from skipped exon	Rodriguez et al. (1992)
Cat3 mouse	γ-Crystallin	Unknown	Decreased γ-crystallin mRNA	Santhiya et al. (1995)
Fraser mouse	MP-26	Splice error	Carboxy terminus replaced by long terminal repeat sequence	Shiels and Bassnett (1996)
LOP mouse	MP-26	A55P	Disrupts targeting to membrane	Shiels and Bassnett (1996)
To3 mouse	MP-19 (myelin precursor)	G15V	Disrupts first α-helical transmembrane	Steele et al. (1997)
Hf1 mouse	MP-26	76-bp In-frame deletion	In-frame deletion of exon 2 (55 amino acids)	Chepelinsky et al. (1997)

the extracellular space. The existence of a second group of mutations reemphasizes the importance of the lens crystallins in the maintenance of lens transparency. All the crystallin mutations characterized to date are predicted to disrupt the tertiary structure of the given crystallin, precipitating from solution with it any associated crystallins. In addition, there are a number of genetically engineered mouse models with cataract resulting either from abnormalities of development (Lang et al. 1987; Perez-Castro et al. 1993), immunity (Egwuagu et al. 1994; Geiger et al. 1994), growth (Mahon et al. 1987; Eva et al. 1991; Griep et al. 1993), cytoskeleton (Capetanaki et al. 1989; Bloemendal et al. 1997), membrane transport (Dunia et al. 1996), or lens crystallins (Brady et al. 1997) or from proteolysis of lens proteins (Mitton et al. 1996). Although some of these results are difficult to interpret precisely, they do suggest cellular systems that might be involved in hereditary human cataract, generally consistent with but extending other studies of animal and human cataracts.

To date, mutations in three genes have been associated with human autosomal dominant cataract. In humans, the γE-crystallin gene is a pseudogene, having an inactive promoter and a termination mutation in the second exon (which would form the first globular domain of the protein). In the Coppock-like cataract, base changes in the promoter of the ιγE-crystallin gene increase expression of the truncated product 10-fold, to ~30% of the level of γD-crystallin, the first human disease associated with reactivation of a pseudogene (Brakenhoff et al. 1994). Similarly, in the autosomal dominant cerulean cataract localized to chromosome 22, βB2-crystallin is truncated because of a nonsense mutation at the beginning of exon 6, which encodes the fourth Greek key motif (Litt et al. 1997). Presumably, both these gene products fold improperly, disturbing the supramolecular organization of the remaining crystallins and eventually becoming unstable in solution, leading to opacity. Now, in this issue of the *Journal,* Shiels et al. provide a convincing rationale for a cataract occurring as a result of aberrant intercellular transport of small molecules, because of mutation of a highly conserved proline in the gap-junction protein connexin50. Since a large part of the metabolic activity of the lens resides in the anterior epithelium, with the resulting requirement that metabolites be transferred to the nuclear fiber cells, the lens would be particularly susceptible to such a lesion. Because human lens material is not always easily obtainable, final confirmation of these mutations as causative may have to await transgenic expression of the mutant molecules. However, Gong et al. (1997) have recently shown that disruption of connexin46, which associates in the same gap-junction plaques with connexin50, causes cataract in mice, providing strong support for a causative role of connexin50 in the CAE1 cataract.

In general, cataracts can be envisioned as falling into two groups. One group involves disruption of lens development and uncontrolled cell division, leading to the loss of cellular order in the lens and to light scattering. A second group results from aberrations of the lens crystallins or the intracellular environment, disrupting the ability of the crystallins to interact in a close and orderly fashion and causing them to aggregate or to precipitate and scatter light. These two processes are not necessarily mutually exclusive. Anterior epithelial cells that fail to differentiate into lens fibers are unlikely to synthesize appropriate concentrations of crystallins. Furthermore, there is suggestive evidence that at least some crystallins may be necessary for normal fiber-cell differentiation (Graw 1996). Finally, osmotically induced cataracts (e.g., sugar cataracts) lead not only to abnormalities of the crystallins but also to formation of blebs and vac-

uoles that would disrupt the optical properties of the lens, in a fashion similar to cellular disarray.

The Genetics of Age-Related Cataract

Although congenital cataracts are relatively easy to study, most visual morbidity in Western populations comes from age-related cataract. We would like to be able to extrapolate our experience with congenital cataracts to age-related cataracts. Currently, the only firm information on the causes of age-related cataract comes from epidemiological studies implicating exposure to UV light (Rosmini et al. 1994) and exposure to cigarette or wood smoke (during cooking) (Shalini et al. 1994). Although there are some tantalizing data suggesting that autoimmunity (Singh et al. 1995) or abnormal cell division (Liu et al. 1994) contributes to age-related cataract, oxidative damage is currently held to be the most common cause of age-related cataract.

Simplistically stated, a variety of environmental insults, including exposure to UV light, osmotic perturbation, and direct oxidative stress, have been shown to threaten the reducing environment normally maintained in the lens (Spector 1995). In addition to damaging membranes and DNA, with time the cumulative damage resulting from oxidative stress destabilizes the lens crystallins, which partially denature. These are initially bound by α-crystallin, which serves as a chaperone, to protect the lens cells from damaged proteins. However, α-crystallin cannot renature proteins and release them in the fashion of a true chaperone but, rather, holds them in large soluble aggregates. In time the "buffer capacity" of α-crystallin is overcome, and large masses of insoluble crystallins precipitate from solution, leading to opacity. Candidate genes that contribute to age-related cataract include not only those capable of causing congenital cataracts but also genes encoding enzymes that protect the lens from oxidation or other types of environmental insults.

Dissecting the mechanisms of age-related cataract promises to be challenging, and identifying the specific genes involved may depend on completion of an expressed sequence map of the human genome, to provide candidate genes in risk regions. Although this task seems daunting, it is no greater than that faced by geneticists 2 or 3 decades ago as they began to map Mendelian traits. In 1970 Renwick estimated that "samples from 200 suitable individuals for 20 markers would probably be adequate for picking up about 50% of the markers 'close enough' to the disease locus" (Renwick 1970, p. 239), giving an overall success rate of ~1/4. A knowledge of the genetic contribution to age-related cataract will allow more-accurate epidemiological studies, targeted at genetic subpopulations with increased risk for the specific environmental factor under study. Together, a combination of clinical-epidemiological and genetic studies will allow both presymptomatic prediction of risk for development of age-related cataract and rational design and application of measures to prevent or delay the onset of age-related cataract.

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