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Autosomal Dominant Cataract: Intrafamilial Phenotypic Variability, Interocular Asymmetry, and Variable Progression in Four Chilean Families

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Abstract

PURPOSE—To document intrafamilial and interocular phenotypic variability of autosomal dominant cataract (ADC).

DESIGN—Prospective observational case series.

METHODS—We performed ophthalmologic examination in four Chilean ADC families.

RESULTS—The families exhibited variability with respect to morphology, location with the lens, color and density of cataracts among affected members. We documented asymmetry between eyes in the morphology, location within the lens, color and density of cataracts, and a variable rate of progression.

CONCLUSIONS—The cataracts in these families exhibit wide intrafamilial and interocular phenotypic variability, supporting the premise that the mutated genes are expressed differentially in individuals and between eyes; other genes or environmental factors may be the bases for this variability. Marked progression among some family members underscores the variable clinical course of a common mutation within a family. Like retinitis pigmentosa, classification of ADC will be most useful if based on the gene and specific mutation.

Infantile Cataracts are an important and treatable cause of visual impairment in infancy. In emerging countries, prevalence may be greater because of higher birth and consanguinity rates, or increased incidence of intrauterine infections. The causes include intrauterine embryopathies and genetic defects. The most common form of “hereditary” cataracts is autosomal dominant, which has been classified on the bases of the morphology, size, color, and location of the opacities in the lens, or the name of the author.

Autosomal dominant cataracts (ADC) exhibit high penetrance; 24 loci have been mapped and 15 genes identified by linkage and mutational analyses. The same phenotype may be caused by mutations of different genes; conversely, the identical mutation of a gene has been reported to cause different cataracts in different families. Pulverulent cataract express variability with

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respect to location and density within family members.^{1,2} Asymmetry of ADC has been documented in one family.³ Ionides and associates⁴ reported 16 ADC families with a consistent cataract morphology within each family except one. In previous publications, textual descriptions and photographs are limited; in those with detail, there is consistency within the family with respect to density and morphology of the cataract.

Because some investigators combine families for gene mapping studies, and because textual descriptions of cataracts have not documented clinical variability, we describe four ADC families and document wide intrafamilial phenotypic variability and asymmetry among affected members.

The study conformed to the tenets of the Declaration of Helsinki. The Spanish protocol and informed consent was approved by the institutional research board of the University of Colorado. All subjects agreed to participate. We clinically studied four ADC Chilean families.

Members of families affected with ADC51 (Figure S1) had cataracts in variable locations within the lens and of different densities; we documented interocular asymmetry of density and location within the lens (307) (Figure 1; figures are representative) and progression (305, 404) (Figures 2 and S4). Morphology varied with nuclear opacities, posterior subcapsular cataracts, and combinations in others; one individual had a dense white cataract (305).

Two family members affected with ADC52 demonstrated differences in the morphologic characteristics and location within the lens of the cataract (312, 313; Figure S5).

In patients with ADC53, we documented differences in the cataract location within the lens (311, 313, 403, 425), density of similar (311 and 323, 403 and 417) and disparate opacities (311, 313, 403, 417), morphology (311, 313, 403, 425), and color (410) among affected members. The morphology and density were the same in each eye. Cataracts included embryonal cataract of varying densities, pulverulent cortical opacities, posterior star-shaped subcapsular cataract with pulverulent opacities in the cortical or embryonal regions, and dense embryonal (Figure 3) cataracts. Significant variability was demonstrated (Figures S6 through S9). Although some affected individuals described progression, we do not have documentation to support this.

Members of ADC54 families exhibited significant variability in the morphology and density of the opacities. One individual had opacities of different color (217); others underscored significant differences in morphology and density (217, 320, 410) (Figures S10 and S11).

Most authors report a consistent morphology among members of a family and between eyes of an individual; phenotypic variability of ADC within the affected members of a family has been less commonly reported.^{1-3,5-7} On careful review of photographic figures in gene mapping studies, we conclude that documentation of intrafamilial phenotypic variability is rare. Interocular phenotypic variability has been documented in one family.³

On the basis of the dramatic morphologic differences and positional variability within the lens in these four Chilean families, we believe such phenotypic variability is common in ADC. The scarcity of documentation in the modern era may reflect the few numbers of phakic-affected members in some families, smaller family sizes in some countries, and printing costs. The bases for variability are speculative and may relate to expression patterns of the protein, alternative effects of the mutation at the protein product level, and the effect of other genes among family members or between two eyes of an individual.

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FIGURE 1.

Family ADC51 with autosomal dominant cataract (ADC). A relatively dense nuclear opacity in one eye (Top) and minimal pulverulent opacity in the posterior subcapsular region in the other (Bottom) in a 32-year-old woman (307). This individual demonstrates interocular variability in the location within the lens and differences in morphology and differences in density among individuals within a family.

FIGURE 2.

Family ADC51 with ADC. Dense white cataract in the phakic left eye of a 30-year-old woman (305). By history, the cataract had progressed rapidly. Hospital records indicate that she had a visual acuity of 20/30 with a posterior subcapsular cataract in each eye at age 13 years and a total cataract on the right eye at age 17 years. After cataract surgery on her right eye at age 23 years, she had a visual acuity of 20/20 in her left eye; we concluded she had significant progression of the opacities. Neither eye had nystagmus under monocular conditions, and no strabismus was noted. This individual demonstrates interocular differences in progression of opacity and, among individuals within a family, differences in location within the lens, morphology, and density.

FIGURE 3.

Family ADC53 with ADC. (Top) The most mildly affected ADC53 individual, a 6-year-old boy (417), had few white spherical opacities in the anterior and posterior cortex. (Bottom) Dense embryonal cataract in the right eye of a 27-year-old man (311). These individuals demonstrate differences in location within the lens, morphology, and density among family members.

FIGURE S1.
Pedigrees of families ADC51 and ADC52 with autosomal dominant cataracts (ADC).

FIGURE S2.
Pedigree of family ADC53 with ADC.

FIGURE S3.
Pedigree of family ADC54 with ADC.

FIGURE S4.

Family ADC51 with ADC. Phakic eye of a 9-year-old girl (404) with minimal pulverulent opacities in the cortex and a dense posterior subcapsular cataract. She was described as having a dense white cataract in the opposite eye at birth and underwent lensectomy early in life. This individual demonstrates interocular differences in density of opacity and, compared with other individuals in the family, variable location within the lens, morphology, and density.

FIGURE S5.

Family ADC52 with ADC. (Top) Left eye with dense, posterior subcapsular circular plaques with defined margins and otherwise clear lens in a 20-year-old woman (312). (Bottom) Right eye with posterior subcapsular cataract with poorly defined borders and white, punctate opacities in the peripheral lens in the 19-year-old female sibling (313); vacuoles were evident below the anterior capsule. These sisters demonstrate differences in morphology and location of opacities within the lens among individuals within a family. The opacities were symmetric, and neither of the sisters had nystagmus.

FIGURE S6.

Family ADC53 with ADC. (Top) Pulverulent opacities in the embryonal region in a 42-year-old (323); the center of the “shell” appears to be clear. (Bottom) Dense embryonal cataract in the right eye of a 27-year-old (311). These male cousins demonstrate differences in density of cataracts of similar morphology and, as compared with other affected family members, differences in morphology, density, and location within the lens.

FIGURE S7.

Family ADC53 with ADC. White pulverulent and snowball-like opacities in the cortical region and a dense, star-shaped opacity at the level of the posterior capsule in a 43-year-old man (313). This individual demonstrates differences in morphology, density, and location of cataract within the lens as compared with other members of the family.

FIGURE S8.

Family ADC53 with ADC. (Top) The most mildly affected individual, a 6-year-old boy (417), had few white spherical opacities in the anterior and posterior cortex. (Bottom) Similar morphology and location within the lens but the opacities are denser in this 5-year-old girl (403). These individuals demonstrate differences in density of cataracts of similar morphology and, compared with others in the family, differences in location within the lens, density, and morphology.

FIGURE S9.

Family ADC53 with ADC. (Top) Mild, bluish pulverulent opacities in the embryonal nuclear and cortical regions in a 5-year-old girl (410); the opacities were densest in a disk-shaped configuration at the level of the posterior subcapsular region. (Bottom) Pulverulent white opacities in a disk-shaped configuration at the level of the posterior subcapsular region and cortical spokelike opacities in a 21-year-old man (425). These individuals demonstrate differences in color and density of similar opacities (disk shaped) and, compared with others in the family, differences in location within the lens and morphology.

FIGURE S10.

Family ADC54 with ADC. (Top) Dense embryonal nuclear opacities extending anteriorly to a polar cataract and mild microcornea (diameter 10 mm) in the right eye of a 53-year-old man (217). (Bottom) Left eye of patient 217. The opacity in his right eye was denser and yellow as compared with the left. This individual demonstrates interocular differences in color and, compared with others in the family, differences in location within the lens, color, density, and morphology.

FIGURE S11.

ADC54. (Top) Fine embryonal punctate opacities in the only phakic eye of a 39-year-old man (308). The minimal cataract supports the premise that the aphakic eye had a denser cataract before surgery. (Center) Dense embryonal and nuclear cataract in left eye of a 27-year-old man (327). Nystagmus was detected in early visual deprivation, unilateral aphakia, and a dense cataract in the phakic eye. (Bottom) A small, dense embryonal nuclear opacity in a 6-year-old boy (410). This younger individual had relatively small but dense embryonal opacities. These individuals of varying ages underscore differences in density of cataracts of similar morphology and location within the lens and, as compared with other affected members of the family, differences in location within the lens, density, and morphology.