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Reply to Veromann

To the Editor:

We thank Dr. Siiri Veromann (Veromann 2002 [in this issue]) for the interest shown in our article (Berry et al. 2001). Dr. Veromann has highlighted the fact that it is difficult to explain why a mutation in *CRYAB* should give rise to a discrete opacity at the posterior pole of the lens, since α-crystallin continues to be synthesized throughout life. Dr. Veromann suggests that the posterior polar phenotype may occur secondary to an effect on the regression of the primary vitreous.

The mechanisms by which precise genetic mutations give rise to a specific lens phenotype are ill understood. We know that mutations in different genes may give rise to an identical lens phenotype, and we also know that different mutations within the same gene may give rise to very different patterns of lens opacification. Posterior polar cataract is itself genetically heterogeneous (Richards et al. 1984; Ionides et al. 1997; Yamada et al. 2000). Such genetic and allelic heterogeneity is common in other inherited eye disorders, particularly in retinal dystrophies (Briggs et al. 2001; Sohocki et al. 2001). It remains a challenge to identify the mechanism by which specific mutations give rise to regional opacification within the lens.

In our article, we suggested that the *CRYAB* mutation could give rise to posterior polar cataract by two possible mechanisms: either by impaired chaperone-like function or by increased tendency of the mutant polypeptides to aggregate as a direct effect of abnormal α-crystallin structure. Studies of the temporal and spatial distribution of the αA- and αB-crystallin in the human lens suggest that they are expressed ubiquitously, but their expression varies at different time points during human lens development. For instance, αB-crystallin is expressed in the lens placode at Carnegie stage 13, but by stage 15 the lens vesicle is intensely positive for both αA- and αB-crystallin (Oguni et al. 1994). The effects of the mutant protein could be manifested early in human lens development, but, of course, αB-crystallin is also widely expressed in many other cell types, including muscle, epithelial, and endothelial cells, although the lens is the tissue that expresses the highest physiological concentrations of these proteins. It is conceivable, therefore, that the reported mutation in *CRYAB* could have produced other clinical symptoms, and we were aware of this possibility. Indeed, cardiac muscle expresses high levels of αB-crystallin (Kato et al. 1991), but the family history and clinical analysis failed to identify any cardiac problems. We suggest, therefore, that the effects of the reported mutation are most likely restricted to the lens.

Impaired chaperone function and/or the increased tendency of the mutant αB-crystallin polypeptide to aggregate may affect the internal structure of lens fibers so that opacification occurs. The subcapsular posterior region of the lens is the one where α-crystallin polypeptides are most highly phosphorylated, at least in the bovine lens (Chiesa et al. 1989). It is also a lens region where there are functionally important cytoskeletal elements that utilize αB-crystallin to function properly (Quinlan and Prescott, in press). Phosphorylation modulates the oligomerization status and function of small heat-shock proteins and their interaction with the cytoskeleton, and so it is possible to rationalize a localized cataract at the lens posterior as the characteristic phenotypic manifestation of this *CRYAB* mutation.

Dr. Veromann suggests another mechanism to account for the position of the lens opacity. The hypothesis states that the mutation impairs regression of the primary vitreous and that this may result in posterior polar cataract. Lack of regression of the primary vitreous (or persistent hyperplastic primary vitreous [PHPV]) is associated with posterior polar cataract in humans, but the disorder is usually unilateral and associated with other developmental abnormalities of the eye. A family with autosomal recessive inherited nonsyndromic bilateral PHPV has shown linkage to a 13-cM region on chromosome 10 (Khaliq et al. 2001). However, in this family, posterior polar cataract was not a consistent feature. The association between PHPV and posterior polar cataract has been reported in mice (Colitz et al. 2000), but, again, there are other developmental abnormalities, including persistent tunica vasculosa lentis, detached retina, and anterior segment abnormalities. We have been unable to find any literature relating to a role for αB-crystallin in the regression of the primary vitreous, but, given the widespread expression αB-crystallin transcripts in the developing eye, it remains a possibility that it may influence regression of the primary vitreous. However, given the current state of knowledge of its function, it is difficult to identify a plausible biological mechanism by which a mutation in αB-crystallin would result in failure of re-

gression of the hyaloid system. Furthermore, in the family in our study, all affected members were examined carefully after pupil dilatation, and none showed any evidence of persistence of the hyaloid system.

Our knowledge of the relationship between genotype and phenotype in different forms of inherited cataract is at an early stage. In the family in our study, we can only speculate how mutations in αB-crystallin give such a localized opacity. Although Dr. Veromann has suggested another possible mechanism, the evidence for this is weak at present.

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