Letters to the Editor

Am. J. Hum. Genet. 71:684–685, 2002

Theoretical Considerations Regarding the Study "Alpha-B Crystallin Gene (*CRYAB*) Mutation Causes Dominant Congenital Posterior Polar Cataract in Humans"

To the Editor:

In a recently published article (Berry et al. 2001), it was shown that a novel eye lens crystallin mutation of the αB gene (*CRYAB*) caused dominant well-demarcated congenital posterior polar cataract in a four-generation family of English descent. The described perinatal nonprogressive opacity was confined to the posterior pole of the lens and was 0.5–3 mm in diameter. Sequence analysis of the *CRYAB* gene revealed a deletion mutation (450delA) that cosegregated with the disease in the family. It was speculated that cataract in this family may have resulted from an increasing tendency of the mutant polypeptide to aggregate and/or from loss of the chaperone-like activity of αB-crystallin, since its protective role in suppressing aggregation of denatured proteins was diminished or lost (Berry et al. 2001).

It is known, however, that during normal lens development, α-crystallins are the first crystallins synthesized in the lens during embryogenesis (Zwaan 1983) and that the lens tissue grows throughout the life span of an individual: new lens fibers develop, and crystallins, including αA- and αB-crystallins, are synthesized continuously. The latter are the most abundant soluble crystallins in the lens and play an important role in maintaining the transparency of the lens (Delaye and Tardieu 1983). If the defective gene *CRYAB* is responsible for the perinatal posterior nonspreading opacity of the lens, then synthesis of defective proteins should have ceased before and after the perinatal life period, which presumes a temporary self-recovery of the mutation. If, however, the described autosomal dominant perinatal posterior lens opacity is caused solely by the synthesized defective protein, then lens opacity should have also been detectable in the lens embryonic nucleus and should have expanded all over the lens during the later life of the individual, which did not occur. Therefore, it can be supposed that the described defective gene, situated in the *CRYAB* locus (Berry et al. 2001), may not be the cause for posterior polar nonspreading opacity, since the lens embryonic nucleus and the developing postnatal lens tissue were transparent. Therefore, it is suggested that the described opacities might depend on the temporary persistent primary vitreous, located in Cloquet's canal after the regression of the hyaloid artery during the last trimester of fetal development. Cloquet's canal extends from the optic cup, through the vitreous, to the lens posterior pole. Evidently, compared with the surrounding secondary gel vitreous, the watery content of the temporary persistent primary vitreous facilitates abnormal metabolism of the posterior lens, enabling osmotic and oxidative stresses (Ohta et al. 1999) to reach the lens posterior pole, where they can affect it and cause posterior lens opacity. The localization and size of the described opacity fits well with that of the distal orifice of Cloquet's canal. The fact that the opaque plaque on the lens posterior pole did not expand, irrespective of the persistence of *CRYAB* gene mutation, serves as strong evidence suggesting that the described novel mutation might be related to the facilitated perinatal metabolism of some substances or to oxidative stress through Cloquet's canal to the lens posterior pole, resulting in the posterior polar opacity. Thus, the deletion mutation might be wholly responsible for the retarded regression of the primary vitreous. The absence of the other ocular or systemic abnormalities in this family history supports this hypothesis.

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0002-9297/2002/7103-0026$15.00

Am. J. Hum. Genet. 71:685–686, 2002

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-