REPORT

Homozygous Mutations in *PXDN* Cause Congenital Cataract, Corneal Opacity, and Developmental Glaucoma

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Anterior segment dysgenesis describes a group of heterogeneous developmental disorders that affect the anterior chamber of the eye and are associated with an increased risk of glaucoma. Here, we report homozygous mutations in *peroxidasin* (*PXDN)* in two consanguineous Pakistani families with congenital cataract-microcornea with mild to moderate corneal opacity and in a consanguineous Cambodian family with developmental glaucoma and severe corneal opacification. These results highlight the diverse ocular phenotypes caused by *PXDN* mutations, which are likely due to differences in genetic background and environmental factors. Peroxidasin is an extracellular matrix-associated protein with peroxidase catalytic activity, and we confirmed localization of the protein to the cornea and lens epithelial layers. Our findings imply that peroxidasin is essential for normal development of the anterior chamber of the eye, where it may have a structural role in supporting cornea and lens architecture as well as an enzymatic role as an antioxidant enzyme in protecting the lens, trabecular meshwork, and cornea against oxidative damage.

Anterior segment dysgenesis (ASD) describes a group of ocular developmental disorders affecting the anterior chamber structures behind the cornea and in front of the lens, including the iris, trabecular meshwork, and ciliary body.[1,2] These abnormalities can give rise to elevated intraocular pressure through obstruction of the trabecular meshwork drainage channels, increasing the risk of developing glaucoma.[3] Examples of this phenotype include Axenfeld-Rieger syndrome due to dominant mutations in *FOXC1* (MIM 601090)[4,5] or *PITX2* (MIM 601542),[6,7] isolated aniridia caused by dominant mutations in *PAX6* (MIM 607108),[8,9] isolated trabeculodysgenesis resulting from recessive mutations in *CYP1B1* (MIM 601771),[10] and megalocornea associated with microspherophakia caused by recessive mutations in *LTBP2* (MIM 602091).[11,12] Some anterior segment anomalies are also associated with cataracts, because during development the anterior lens secretes factors that induce the differentiation of the cornea and trabecular meshwork.[13,14] Examples of corneal opacity or microcornea with cataract include dominant mutations in *CRYAA* (MIM 123580),[15] *CRYBA4* (MIM 123631),[16] *CRYBB1* (MIM 600929),[17] *CRYBB2* (MIM 123620),[18] *CRYGC* (MIM 123680),[19] *CRYGD* (MIM 123690),[15] *GJA8* (MIM 600897),[15,20–22] *MAF* (MIM 177075),[15,23–25] or *FOXE3* (MIM 601094)[26–28] and a recessive mutation in *CRYAA*.[29] These phenotypes may be expressed asymmetrically and can be highly variable, even between affected family members, because of genetic background and environmental factors.

We recently described genetic heterogeneity for recessively inherited congenital cataract-microcornea with corneal opacity (CCMCO) in three unrelated consanguineous families, MEP57, MEP60 and MEP68, from the Punjab province of Pakistan.[30] We have since ascertained one additional Pakistani family, MEP59, with a history of poor vision that fits the description for CCMCO (Figure 1 and Table 1). Microcornea and corneal opacification, due to the sclera encroaching on the cornea, were the defining features for these families, with variable degrees of expression between affected members of the same family. Concurrently, through an epidemiological survey of blind schools in Cambodia,[31] we also identified a consanguineous family, CA2, in which four affected individuals had severe developmental glaucoma associated with extensive corneal opacification and buphthalmos (Figure 2 and Table 1). In all the families described in this study, the patients did not have any systemic problems, or any neurological abnormalities, and the unaffected family members did not show any eye defects. The purpose of the current study was to identify the pathogenic

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