Physiological and pathological functions of βB2-crystallins in multiple organs: a systematic review

Meihui Li1,*, Shengnan Liu1,*, Wei Huang1, Junjie Zhang1,*

1Department of Obstetrics and Gynecology, Shanghai Hospital, Naval Military Medical University, Yangpu, Shanghai 200433, China
*Equal contribution

Correspondence to: Junjie Zhang; email: zhangjj910@163.com, https://orcid.org/0000-0002-2207-7741

Keywords: βB2-crystallin, physiological functions, pathological functions, tumor

Received: February 10, 2021   Accepted: May 18, 2021   Published: June 11, 2021

Copyright: © 2021 Li et al. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC BY 3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

Crystallins, the major constituent proteins of mammalian lenses, are significant not only for the maintenance of eye lens stability, transparency, and refraction, but also fulfill various physiopathological functions in extraocular tissues. βB2-crystallin, for example, is a multifunctional protein expressed in the human retina, brain, testis, ovary, and multiple tumors. Mutations in the βB2 crystallin gene or denaturation of βB2-crystallin protein are associated with cataracts, ocular pathologies, and psychiatric disorders. A prominent role for βB2-crystallins in axonal growth and regeneration, as well as in dendritic outgrowth, has been demonstrated after optic nerve injury. Studies in βB2-crystallin-null mice revealed morphological and functional abnormalities in testis and ovaries, indicating βB2-crystallin contributes to male and female fertility in mice. Interestingly, although pathogenic significance remains obscure, several studies identified a clear correlation between βB2 crystallin expression and the prognosis of patients with breast cancer, colorectal cancer, prostate cancer, renal cell carcinoma, and glioblastoma in the African American population. This review summarizes the physiological and pathological functions of βB2-crystallin in the eye and other organs and tissues and discusses findings related to the expression and potential role of βB2-crystallin in tumors.

INTRODUCTION

Crystallins are ubiquitous, abundant proteins mainly found in the ocular lens, which is the tissue with the highest protein content in the human body [1, 2]. Their discovery dates to about 200 years ago, when Berzelius first identified and named the crystallins as specific entities of the bovine lens [3, 4]. In 1894, Morner successfully isolated three primary types, the α-, β-, and γ-crystallins, which proved to have highly heterogeneous patterns of expression in most vertebrate lenses [4–7]. These three classes were classified mainly by the sizes of the oligomers they form. The largest multimers, formed by α-crystallin, are on the order of 500 kDa. The β-crystallins represent a dimer- to octamer-sized mixture with molecular masses ranging from 45 to 180 kDa, while γ-crystallin monomers are approximately 20 kDa. The α-crystallins belong to the family of small heat-shock proteins (HSPs) which act as molecular chaperones during embryonic development [8–9]. The α-crystallin family comprises two subunits, referred to as αA- and αB-crystallins, which are encoded by the Crya and Cryb genes, respectively [10]. The classical function of α-crystallin is to serve as a chaperone, protecting the lens against stress conditions. However, studies showed that α-crystallins participate also in the protection and remodeling of the cytoskeleton, and contribute to inhibition of apoptosis through binding to pro-apoptotic Bcl-2 and Bcl-2 like 1 proteins [11–13]. The β- and γ-crystallins are thought to play a common structural role in the eye lens of vertebrates. These proteins share a common polypeptide chain fold, have conserved sequences, and are thus grouped into the βγ-crystallin superfamily, which is encoded by at least 14 genes [14,
In mammals, these genes are not only organized as individual genes (Cryba1, Cryba2, Crygf, Crygs, CrygN), but also as duplets (Cryba4–Crybb1 and Crybb2–Crybb3) and into one major cluster (Cryga–Cryge) [11, 16]. The γ-crystallins are monomeric proteins with molecular masses of about 20 kDa, whereas the β-crystallins are a heterogeneous mixture of dimers and higher oligomers with native molecular masses ranging from about 50 kDa to 200 kDa [8]. Like all members of the βγ-crystallin superfamily, β-crystallins comprise two domains connected by an 8–10 amino acid inter-domain connecting peptide [17]. Each domain has two identical folded polypeptide chains, composed of a characteristic β-sandwich of two anti-parallel β-sheets conformations and N- and C-terminal extensions of varying lengths [17, 18]. Due to the similarity of these structures to paintings on ancient Greek pottery, they are known as ‘Greek key’ motifs [19, 20]. These motifs allow a dense packaging of the proteins to minimize light scattering, guaranteeing optimal transparency to the lens. For eye lens crystallins, the native folded state is required for lens transparency. In contrast, aggregated high molecular weight complexes are the source of light scattering leading to ocular pathologies. Seven β-crystallin genes, distributed on several chromosomes, code for homologous polypeptides termed βA1-, βA2-, βA3-, βA4-, βB1-, βB2-, and βB3-crystallin [7]. Four of the genes code for polypeptides with slightly lower isoelectric points, known as the βA (acidic) crystallins, while the other 3 encode the βB (basic) crystallins [4]. Unlike γ-crystallins, both acidic and basic β-crystallins have N-terminal extensions, whereas C-terminal extensions are found only in the basic polypeptides. Another difference between β- and γ-crystallins is that the two motifs comprising each β-crystallin domain are encoded by separate exons, whereas for γ-crystallins a single exon encodes both protein motifs [14].

**βB2-crystallin: more than a lens protein**

One of the most prominent members of the vertebrate eye lens is the βB2-crystallin (gene symbol CRYBB2 in humans and Crybb2 in mice) [21]. The mouse Crybb2 gene is located on chromosome 5, within a cluster that includes three other Cryb genes. The corresponding human gene (CRYBB2) is mapped to chromosome 22q11.2 [22]. Crybb2 consists of six exons; the first one is untranslated, the second codes for the N-terminal extension, and the subsequent four exons code for the Greek key motifs [14, 23]. Although βB2-crystallin is expressed at negligible amounts in the embryonic mouse lens, its expression increases sharply at birth [24] to become the most abundant β-crystallin in the mouse lens by postnatal week 6 [25, 26]. Endogenous βB2-crystallin gene activity is upregulated in cultured lens cells by overexpression of β-catenin, which suggests a link between canonical Wnt-signaling and crystallin gene regulation [27]. Like α-crystallin, βB2-crystallin is also involved in cAMP-dependent and cAMP-independent phosphorylation pathways [28]. Studies demonstrated that the Greek key motifs of β-crystallins represent potential Ca<sup>2+</sup>-binding sites, which suggests a role for these proteins in Ca<sup>2+</sup> buffering [29–31]. βB2 crystallin is the most energetically stable protein within the crystallin superfamily, capable of stabilizing and co-assembling other β-crystallins [32].

Until the 1990s, it was generally accepted that mammalian crystallins were evolutionarily highly conserved, lens-specific proteins. However, several discoveries changed this concept. Non-lenticular expression of α-crystallins is now well described, as the prominent expression of these proteins was demonstrated in rat spleen, thymus, rectum, cecum, liver, kidney, adrenal glands, cerebellum, and brainstem [13, 33]. In 1978, de Pomerai and Clayton provided one of the first reports on the presence of β-crystallin in non-lens tissue by demonstrating trace amounts of β-crystallin in a 60-day culture of 17-day embryonic chick neural retina [11]. In 1995, a more detailed study first reported clear evidence for the expression of βB2-crystallin in both murine and feline neural retina and retinal pigment epithelium (RPE), thus validating the presence in mammals of β-crystallin outside the lens [34]. These findings further contributed to challenging the original notion that crystallins are lens-specific proteins. Along with this evidence, it gradually took hold the concept that crystallins may originate in diverse cell types, pre-dating the evolution of the lens, and had a variety of functions before they were recruited to the lens to function as ‘crystallins’ [4].

Thus, research efforts eventually demonstrated that in addition to the ubiquitous crystallins found in the eye lens, some crystallins are essentially tissue-specific, while others have a completely separate machinery of expression in non-ocular tissues [35]. Indeed, stemming largely from studies in mice harboring mutations in Crybb2, such as the Philly [36], Aey2 [37], and 0377 [22] strains, we now know that the role of βB2-crystallin, the most important member of the β-crystallin superfamily, goes beyond its classical refractive function as a lens protein. Therefore, the purpose of this review is to illuminate the function of βB2-crystallin within and outside the lens.

**Physiological functions of βb2-crystallins**

**Lens**

Crystallins are highly soluble structural proteins that comprise 90% of the mammalian lens. Among them, βB2 crystallins are the most abundant β-crystallins in
the human lens. The highly ordered, tightly packed crystallins make up the transparent structure of the lens and allow it to focus light onto the retina. To provide adequate lens structure and function, a protein must: (1) be highly soluble—high concentrations of soluble crystallins are responsible for the refractive index of the lens and maintain its transparency; (2) be extremely stable: the inherent stability of crystallins, arising from their native, compact structure, correlates tightly with their exceptional longevity; and (3) be able to have specific interactions with other crystallins: forming a stable protein matrix with a high degree of short-range order allows to increase resistance to oxidative stress and thermal denaturation, which is decisive to maintain lens transparency [8, 38, 39]. Therefore, the solubility and stability of βB2-crystallins are crucial determinants for the normal function of the lens: when these parameters are compromised, crystallin aggregation will affect lens transparency and reduce dioptric capacity [38–41]. Notable features of the molecular biology of the crystallin superfamily include the potential to be transported between cells via exosomes [42] and the ability of some of its members (e.g., αB- and βA3/A1-crystallins) to regulate lens differentiation and epithelial-mesenchymal transition (EMT) in RPE and tumor cells [43–45].

Retina

A 2000 study demonstrated the expression of βB2-crystallin mRNA and protein in the mammalian retina [28, 46]. Subsequently, in 2007 a nonrefractive function of βB2-crystallin was first suggested by a study that indicated that this protein prevents the degeneration of the RPE and moves from the retinal ganglion cells (RGCs) into the extracellular space and retrogradely into the RGCs, although the underlying mechanisms remain to be elucidated [47]. Colocalization of βB2-crystallin with calmodulin, the major Ca^{2+}-binding protein in the retinal ganglion cell (RGC) layer, provides further evidence that βB2-crystallins also operate via Ca^{2+} binding [48]. Immunohistochemical expression analyses in the retina, including filopodial protrusions and axons of adult RGCs, showed that βB2-crystallin is upregulated in the regenerating retina [49, 50] and promotes RGC survival after optic nerve axotomy through an autocrine mechanism [51]. In turn, cytoprotective functions of βB2-crystallin have been further demonstrated in cultured ARPE-19 (RPE) cells exposed to UV light, which showed increased viability and proliferation potential after addition of βB2-crystallin to the culture medium [47]. Indeed, evidence indicated that light-induced phosphorylation of β-crystallins mediates their anti-apoptotic chaperone activity in the RPE [52]. Of note, the latter function was further suggested in the uvea, as high expression of βB2-crystallins in retinal mitochondria was suggested to prevent cell death during the early stages of experimental autoimmune uveitis [53].

Brain

Considerable evidence has accumulated over the past 20 years for the expression of various crystallins in several cell types and tissues, including the nervous system [54]. Gene analysis of a dominant cataract mouse model unmasked a crybb2 mutation and revealed that βB2-crystallin is expressed within distinct regions of the brain [22]. The Crybb2 transcript was best detected in the brain during postnatal development and through adolescence and was expressed predominantly in neurons of the olfactory bulb (mitral cell layer and glomerular layer), hippocampus (pyramidal cells of the CA1, CA2, and CA3 regions and granule cells of the dentate gyrus), cerebral cortex (pyramidal cells throughout all layers), and cerebellum (Purkinje cells and stellate cells of the molecular layers) [22, 55, 56]. As illustrated in animal models of optic nerve injury and axonal regeneration, mounting evidence highlights βB2-crystallin as a momentous factor that operates through autocrine and paracrine mechanisms to support axonal growth and repair, at least in part by accelerating the production of ciliary neurotrophic factor (CNTF) [49, 51, 57]. Furthermore, an important role for βB2-crystallins in synaptic remodeling was suggested based on evidence that these proteins facilitate dendritic outgrowth through regulating thymosin β4 (Tmsb4X) expression [58]. Thymosins play a crucial role in numerous cellular processes by affecting morphology, migration, and vesicle trafficking [59, 60]. All these properties emphasize the therapeutic potential of βB2-crystallins in the treatment of neurodegenerative diseases.

Testis and ovary

Substantial evidence supports the expression of βB2-crystallin in both testis and ovary [61, 62]. Studies in the Philly mouse strain, which develops hereditary, progressive cataracts ~15 days after birth, led to identification of the crybb2philly mutation as the responsible factor. The Crybb2philly gene presents a 12-nucleotide in-frame deletion in the region encoding the fourth Greek key domain of the βB2-crystallin protein. Intriguingly, Philly mice were found to have poor fertility resulting from defective sperm and egg production [36, 62, 63]. Later on, the expression of βB2-crystallin was detected in spermatocytes from diverse mammals at the leptotene and zygotene stages [62, 64]. Indeed, βB2-crystallin transcripts are detected in the testis from birth throughout life and their expression is upregulated at postnatal day 17,
consisting with the beginning of meiosis II [65]. Interestingly, a plausible connection between βB2-crystallin and infertility was provided by studies that identified βB2-crystallin as a microtubule-associated protein. This interaction can prevent microtubules from denaturation and impact sperm motility [66, 67]. After the generation of a βB2-crystallin null mouse (Crybb2−/−mouse) [68], further experiments allowed exploration of the mechanisms underlying subfertility caused by deficits in βB2-crystallin [69]. Evidence showed that decreased levels of Ca2+/calmodulin-dependent protein kinase IV (CaMKIV) in Crybb2−/− mice may affect the expression of Bcl-2, a major anti-apoptotic protein, which would reduce fertility by leading to abnormal proliferation and apoptosis of germ cells in the testis [70-72].

In the ovary, βB2-crystallin is mainly expressed in granulosa cells, with lower levels detected in theca cells [72]. It was reported that the progression of granulosa cells was inhibited in Crybb2−/− mice, concomitant with decreased expression of two important cell cycle regulators, namely CDK4 and CCND2 [73]. In addition, in developing follicles the expression of Bcl-2 was distinctly lower after Crybb2 deletion, which demonstrated that βB2-crystallin influences female fertility by regulating granulosa cell apoptosis and follicular atresia [61, 74, 75]. Interestingly, further research indicated that downregulation of IncRNA A-30-P01019163 in ovary tissues from Crybb2−/− mice may impair ovarian cell cycle and proliferation by reducing the expression of the purinergic receptor P2RX7 [76-78].

**Pathological functions of βb2-crystallin**

**Ocular pathologies**

In line with the main findings in the Crybb2 knockout mouse, several human studies attested to the association between mutations in the βB2-crystallin locus and cataracts [68, 79]. Besides a functional βB2-crystallin locus, in humans there is a second βB2-crystallin-derived pseudogene, termed CRYBB2P1. Conversion of the βB2 locus to the pseudogene results in lens opacification and cataract formation [80]. As shown in the Philly mouse model, misfolding of the mutated βB2-crystallin protein alters its aggregation properties, favoring the development of cataracts [81]. Subsequently, studies revealed additional amino acid-altering mutations in the CRYBB2 gene, in association with multiple types of congenital cataract, that result not only in structural changes in βB2-crystallin [82] but reduce also the solubility of these proteins to increase lens opacity [83-88]. Significant upregulation of βB2-crystallin occurs in several ocular pathologies, including age-related macular degeneration [89, 90], glaucomatous neuropathy [91], and cataract-induced hypertension in rat model [91], and ocular hypertension in the rat [21, 90, 92].

**Neuropsychiatric disorders**

Mutations in the mouse Crybb2 gene give rise to alterations in prepulse inhibition (PPI; an operational measurement of sensorimotor gating) and reduce hippocampal size, i.e., features typical of patients with schizophrenia [55, 93, 94]. Studies in mutant Crybb2Philly, Crybb2Δex52, and Crybb2377 mice revealed C-terminal mutations of the βB2-crystallin protein, likely associated with abnormal Ca2+ binding, which correlated with consistent alterations in adult behavior and evolution of neuropsychiatric disorders [56, 93, 95]. Notably, a meta-analysis of gene expression in the human cortex illustrated that the CRYBB2 gene shows the most significant association with five psychiatric disorders, namely attention-deficit hyperactivity disorder, autism, major depressive disorder, bipolar disorder, and schizophrenia [96, 97]. The distribution and function of βB2-crystallin in several organs are listed in Table 1.

**Cancer**

**Breast tumors**

In recent years, a potential role for CRYBB2 in carcinogenesis has been widely investigated. Research shows that African-American breast cancer patients have a higher risk of mortality than non-African-American patients [98, 99]. It has been proposed that the survival health disparity associated with breast cancer may be attributed to differences in tumor biology [100, 101]. As part of the Clinical Breast Care Project, Field et al. performed differential gene expression analysis in breast cancer samples and found that CRYBB2 had >2.5-fold higher expression in African American compared to Caucasian women [102]. Of note, this finding was consistent with a previous study that combined CRYBB2 and PSPHL expression data to reliable distinguish African American from Caucasian breast cancer samples [103, 104]. Interestingly, a more recent study provided additional evidence that upregulation of the pseudogene CRYBB2P1, and not CRYBB2, is associated with race and poor outcome in breast cancer and possibly other tumors [102, 105]. Although molecular evidence is still inconclusive, these findings suggested that differential expression of CRYBB2/CRYBB2P1 contribute to poor outcomes in African American women by impacting tumor cell proliferation, invasion, metastasis, and tumor immunity [102].
Table 1. Distribution and function of βB2-crystallin.

| Organs       | Expression                     | Regulation | Biological consequence                  | References                          |
|--------------|--------------------------------|------------|-----------------------------------------|-------------------------------------|
|              |                                |            | Physiological                           | Pathological                        |
| lens         | lens fiber cells               | normal     | maintain lenticular transparency and    | [8, 41, 42]                         |
|              |                                |            | diopter anti-apoptosis                  |                                     |
|              | mitochondria                   | up-regulated|                                          | [44]                                |
| lens fiber cells | mutant                    |            | multiple types of cataract              | [68, 79] [87–89]                    |
| Retina       | retinal pigment epithelium cells | normal     | prevent degeneration                    | [47, 48]                            |
|              | retinal ganglion cells         | up-regulated| retina regeneration                     |                                     |
|              | retinal pigment epithelium cells | up-regulated| cytoprotective function                | [47, 52]                            |
|              | retinal ganglion cells         | up-regulated|                                          |                                     |
| Retina       | outer plexiform layer of retinal ganglion cells | up-regulated| age-related macular degeneration        | [90, 91]                            |
| Brain        | retinal ganglion cells         | up-regulated| catarization-induced hypertension       | [92]                                |
|              | hippocampal neurons            | up-regulated| ocular hypertension in rat              | [21, 93]                            |
|              | hippocampal                    | mutant     | Hippocampal abnormalities               | [54, 94, 95]                        |
|              | hippocampal                    |            | attention-deficit hyperactivity disorder| [97, 98]                            |
|              | hippocampal                    |            | autism                                  |                                     |
|              | cortex                         | normal     | major depressive disorder               | [97, 98]                            |
|              | cortex                         | normal     | bipolar disorder                        | [97, 98]                            |
| Testis       | sperm                          | normal     | maintain sperm motility                 | [61, 66]                            |
|              | seminiferous tubule            | normal     | prevent microtubules from denaturation   | [64, 67]                            |
| Ovary        | granulosa cells and theca cells | gene knockout| subfertility                            | [69, 72]                            |

**Colorectal cancer, prostate cancer, glioblastoma, and renal cell carcinoma**

Similar to the breast cancer findings mentioned in the previous section, a 2008 study comparing gene expression profiles of prostate tumors from African American and Caucasian men pointed out a two-gene signature comprising CRYBB2 and PSPHL that accurately differentiated between these two groups [106]. Another report, dating back to 2012, described significant upregulation of CRYBB2 in colorectal cancer samples from African-American patients compared to European Americans [107]. In turn, a case-control association study reported that a genetic variant in the CRYBB2 gene (rs9608380) is associated with the risk of prostate cancer in African Americans [108]. Interestingly, a recent analysis identified CRYBB2 as one of 13 genes significantly associated with increased survival in African-American glioma patients in comparison to Caucasian ones [109]. Moreover, a study analyzing the significant disparities in survival between black and white patients with renal cell carcinoma showed that CRYBB2 was overexpressed in black patients associated in association with the WNT signaling pathway [110]. Altogether, these findings reaffirmed the notion that CRYBB2 expression in cancer is impacted by ethnicity [111]. Differences in βB2-crystallin expression between African American
Table 2. βB2-crystallin in African-American and non-African-American cancer patients.

| Types                  | Number | Regulated in African-American | Comparison items between African-American and Non-African-American | Outcome in African-American | References |
|------------------------|--------|--------------------------------|---------------------------------------------------------------|-----------------------------|------------|
| Breast cancer          | 52     | up-regulated                   | age, size, grade, stage, ER status, subtype                   | poor                        | [108]      |
| Breast cancer          | 161    | up-regulated                   | age and stage                                                 | poor                        | [110]      |
| Breast cancer          | 108    | up-regulated                   | age, size, grade, ER status, subtype                          | poor                        | [109]      |
| Colorectal Cancer      | 126    | up-regulated                   | age, gender, location, stage                                  | no mention                  | [112]      |
| Prostate cancer        | 69     | up-regulated                   | source, stage, gleason sum score, seminal vesicle invasion, surgical margin status | no mention                  | [103]      |
| Prostate cancer        | 527    | up-regulated                   | age, PSA, family history                                     | poor                        | [113]      |
| Renal cell carcinoma   | 116    | up-regulated                   | patients, performance score, smoking status, tumor laterality, clinical, pathologic | no mention                  | [115]      |
| Glioblastoma           | 995    | up-regulated                   | age, gender, PS, histological type, G-CIMP status, person neoplasm cancer status, history of neoadjuvant treatment, targeted molecular therapy, radiation therapy, ethnicity | well (under the condition of KPS ≥ 80) | [114]      |

and non-African American cancer patients are summarized in Table 2.

**Summary and prospect for CRYBB2 expression in tumors**

High expression of CRYBB2/CRYBB2P1 is associated with higher breast cancer-related mortality in African-American women, likely in relation to enhanced tumor cell proliferation. Similarly, compared to Caucasians, upregulation of CRYBB2 is observed also in African-American patients with colorectal cancer, prostate cancer, renal cell carcinoma, and glioblastoma. Interestingly, dysregulated CRYBB2 expression is associated with poor outcomes in prostate cancer patients but correlates with better prognosis in African-American glioblastoma patients with Karnofsky performance score (KPS) ≥ 80. Still, for other tumor types and other populations, e.g., Asians, the correlation between CRYBB2/CRYBB2P1 expression and cancer progression and prognosis remains less certain. Although it remains unclear if and how a major lens protein would contribute to tumorigenesis, a likely connection may reside in the known regulation of less differentiation and crystallin expression exerted by the WNT signaling pathway [27, 112, 113], which is also a ubiquitous mediator of tumor growth and progression [114, 115]. Considering that no documented or hypothesized role for CRYBB2 in carcinogenesis has been explicitly put forward, it is conceivable that no causal relationship exists, at least for some malignancies, between high tumor CRYBB2 levels and tumor development. Clearly, mechanistic studies addressing potentially direct effects of β-crystallins on tumor cells are needed. Nevertheless, the documented association between CRYBB2 expression and multiple tumor types suggests that CRYBB2/CRYBB2P1 may serve as promising diagnostic or prognostic biomarkers in specific populations.

**CONCLUSIONS**

βB2-crystallin, a main member of the βγ-crystallin superfamily, fulfills a key role in lens refraction and is also expressed in several extraocular tissues where it has distinct, non-lens functions. Besides functioning as a Ca\(^{2+}\)-binding protein, βB2-crystallin is also involved in cAMP-dependent and cAMP-independent phosphorylation pathways. Notably, overexpression of either CRYBB2, the gene encoding for βB2-crystallin in humans, or its highly homologous pseudogene, CRYBB2P1, correlates with differential survival outcomes in African American patients with different malignant tumors. We hypothesize that βB2-crystallin contributes to poor diagnosis in malignancies such as breast and prostate cancer through regulating the TGF-β pathway or WNT signaling pathway and promoting epithelial to mesenchymal transition (EMT) [27, 116].
Considering the paucity of basic experimental research on the relationship between βB2-crystallin and tumorigenesis, a detailed exploration of the above mechanisms is needed to ascertain the role of βB2-crystallins in tumor development and metastasis.

**Abbreviations**

CRYBB2/Crybb2: βB2-crystallin; WNT: Wingless-related integration site; Tmsb4X: thymosin β4; RPE: retinal pigment epithelium; RGCs: retinal ganglion cells; CNTF: ciliary neurotrophic factor; CaMKIV: Ca\(^{2+}\)/calmodulin-dependent protein kinase IV; Bcl-2: B-cell lymphoma 2; CDK4: Cyclin-dependent kinase 4; CCND2: G1/S-specific cyclin-D2; P2rx7: purinergic receptor P2X7; PSPHL: phospho serine phosphatase-like protein; EMT: epithelial-mesenchymal transition.

**AUTHOR CONTRIBUTIONS**

ML contributed to the search and draft of the manuscript. SL and WH performed the literature collation. JZ performed the literature review and revised the manuscript. All authors read and approved the final manuscript.

**ACKNOWLEDGMENTS**

This work was supported by a project of the National Natural Science Foundation of China (Grant NO: 8157060587); Youth initiation Foundation of Changhai Hospital, Naval Military Medical University, China (Grant NO: 2020QNB07).

**CONFLICTS OF INTEREST**

The authors declare that they have no competing interests.

**FUNDING**

This work was supported by a project of the National Natural Science Foundation of China (Grant NO: 8157060587).

**Editorial note**

*This corresponding author has a verified history of publications using a personal email address for correspondence.*

**REFERENCES**

1. Hoehenwarter W, Klose J, Jungblut PR. Eye lens proteomics. Amino Acids. 2006; 30:369–89. https://doi.org/10.1007/s00726-005-0283-9 PMID:16583312

2. Sprague-Piercy MA, Rocha MA, Kwok AO, Martin RW. α-Crystallins in the Vertebrate Eye Lens: Complex Oligomers and Molecular Chaperones. Annu Rev Phys Chem. 2021; 72:143–63. https://doi.org/10.1146/annurev-physchem-090419-121428 PMID:33321054

3. Izumi K. Studies on the Soluble Proteins of Bovine Lens. On Immunochemical Analyses of Protein Fractions. Kyushu J Med Sci. 1964; 15:41–48. PMID:14187458

4. Zigler JS Jr, Sinha D. βA3/A1-crystallin: more than a lens protein. Prog Retin Eye Res. 2015; 44:62–85. https://doi.org/10.1016/j.preteyeres.2014.11.002 PMID:25461968

5. Lulli M, Nencioni D, Papucci L, Schiavone N. Zeta-crystallin: a moonlighting player in cancer. Cell Mol Life Sci. 2020; 77:965–76. https://doi.org/10.1007/s00018-019-03301-3 PMID:31563996

6. Bloemendal H, de Jong WW. Lens proteins and their genes. Prog Nucleic Acid Res Mol Biol. 1991; 41:259–81. https://doi.org/10.1016/s0079-6603(08)60012-4 PMID:1882078

7. Bari KJ, Sharma S. A Perspective on Biophysical Studies of Crystallin Aggregation and Implications for Cataract Formation. J Phys Chem B. 2020; 124:11041–54. https://doi.org/10.1021/acs.jpcb.0c07449 PMID:33297682

8. Bloemendal H, de Jong W, Jaenicke R, Lubsen NH, Slingsby C, Tardieu A. Ageing and vision: structure, stability and function of lens crystallins. Prog Biophys Mol Biol. 2004; 86:407–85. https://doi.org/10.1016/j.pbiomolbio.2003.11.012 PMID:15302206

9. Fu C, Xu J, Yang X, Chen X, Yao K. Cataract-causing mutations L45P and Y46D impair the thermal stability of γC-crystallin. Biochem Biophys Res Commun. 2021; 539:70–76. https://doi.org/10.1016/j.bbrc.2020.12.096 PMID:33422942

10. Berry V, Ioniades A, Pontikos N, Georgiou M, Yu J, Oaca LA, Moore AT, Quinlan RA, Michaelides M. The genetic landscape of crystallins in congenital cataract. Orphanet J Rare Dis. 2020; 15:333. https://doi.org/10.1186/s13023-020-01613-3 PMID:33243271

11. Graw J. Genetics of crystallins: cataract and beyond. Exp Eye Res. 2009; 88:173–89.
12. Mao YW, Liu JP, Xiang H, Li DW. Human alphaA- and alphaB-crystallins bind to Bax and Bcl-X(S) to sequester their translocation during staurosporine-induced apoptosis. Cell Death Differ. 2004; 11:512–26. https://doi.org/10.1038/sj.cdd.4401384 PMID:14752512

13. Kannan R, Sreekumar PG, Hinton DR. Novel roles for α-crystallins in retinal function and disease. Prog Retin Eye Res. 2012; 31:576–604. https://doi.org/10.1016/j.preteyeres.2012.06.001 PMID:22721717

14. Lubsen NH, Aarts HJ, Schoenmakers JG. The evolution of lenticular proteins: the beta- and gamma-crystallin super gene family. Prog Biophys Mol Biol. 1988; 51:47–76. https://doi.org/10.1016/0079-6107(88)90010-7 PMID:3064189

15. Bhat SP. Transparency and non-refractive functions of crystallins—a proposal. Exp Eye Res. 2004; 79:809–16. https://doi.org/10.1016/j.exer.2004.08.020 PMID:15642317

16. Frankfater C, Bozeman SL, Hsu FF, Andley UP. Alpha-crystallin mutations alter lens metabolites in mouse models of human cataracts. PLoS One. 2020; 15:e0238081. https://doi.org/10.1371/journal.pone.0238081 PMID:32833997

17. Hejtmancik JF, Wingfield PT, Sergeev YV. Beta-crystallin association. Exp Eye Res. 2004; 79:377–83. https://doi.org/10.1016/j.exer.2004.06.011 PMID:15336500

18. Bax B, Lapatto R, Nalini V, Driessen H, Lindley PF, Mahadevan D, Blundell TL, Slingsby C. X-ray analysis of beta B2-crystallin and evolution of oligomeric lens proteins. Nature. 1990; 347:776–80. https://doi.org/10.1038/347776a0 PMID:2234050

19. Lapatto R, Nalini V, Bax B, Driessen H, Lindley PF, Blundell TL, Slingsby C. High resolution structure of an oligomeric eye lens beta-crystallin. Loops, arches, linkers and interfaces in beta B2 dimer compared to a monomeric gamma-crystallin. J Mol Biol. 1991; 222:1067–83. https://doi.org/10.1016/0022-2836(91)90594-v PMID:1762146

20. Velasco-Bolom JL, Dominguez L. Exploring the folding process of human betaB2-crystallin using multiscale molecular dynamics and the Markov state model. Phys Chem Chem Phys. 2020; 22:26753–63. https://doi.org/10.1039/d0cp04136j PMID:33205789

21. Thanos S, Bohm MR, Meyer zu Horste M, Prokosch-Willing V, Henning M, Bauer D, Heiligenhaus A. Role of crystallins in ocular neuroprotection and axonal regeneration. Prog Retin Eye Res. 2014; 42:145–61. https://doi.org/10.1016/j.preteyeres.2014.06.004 PMID:24998680

22. Ganguly K, Favor J, Neuhäuser-Klaus A, Sandulache R, Puk O, Beckers J, Horsch M, Schädler S, Vogt Weisenhorn D, Wurst W, Graw J. Novel allele of crybb2 in the mouse and its expression in the brain. Invest Ophthalmol Vis Sci. 2008; 49:1533–41. https://doi.org/10.1167/iovs.07-0788 PMID:18385073

23. Richardson JS. beta-Sheet topology and the relatedness of proteins. Nature. 1977; 268:495–500. https://doi.org/10.1038/268495a0 PMID:329147

24. Ueda Y, Duncan MK, David LL. Lens proteomics: the accumulation of crystallin modifications in the mouse lens with age. Invest Ophthalmol Vis Sci. 2002; 43:205–15. PMID:11773033

25. Van Leen RW, Breuer ML, Lubsen NH, Schoenmakers JG. Developmental expression of crystallin genes: in situ hybridization reveals a differential localization of specific mRNAs. Dev Biol. 1987; 123:338–45. https://doi.org/10.1016/0012-4600(87)90280-8 PMID:3653512

26. Cvekl A, Duncan MK. Genetic and epigenetic mechanisms of gene regulation during lens development. Prog Retin Eye Res. 2007; 26:555–97. https://doi.org/10.1016/j.preteyeres.2007.07.002 PMID:17905638

27. Lyu J, Joo CK. Wnt signaling enhances FGF2-triggered lens fiber cell differentiation. Development. 2004; 131:1813–24. https://doi.org/10.1242/dev.01060 PMID:15084465

28. Magabo KS, Horwitz J, Piatigorsky J, Kantorow M. Expression of betaB(2)-crystallin mRNA and protein in retina, brain, and testis. Invest Ophthalmol Vis Sci. 2000; 41:3056–60. PMID:10967064

29. Sharma Y, Balasubramanian D. Calcium binding properties of beta-crystallins. Ophthalmic Res. 1996 (Suppl 1); 28:44–47. https://doi.org/10.1159/000267942 PMID:8727963
30. Jobby MK, Sharma Y. Calcium-binding to lens betaB2- and betaA3-crystallins suggests that all beta-crystallins are calcium-binding proteins. FEBS J. 2007; 274:4135–47. 
https://doi.org/10.1111/j.1742-4658.2007.05941.x
PMID: 17651443

31. Srivastava SS, Mishra A, Krishnan B, Sharma Y. Ca2+-binding motif of βγ-crystallins. J Biol Chem. 2014; 289:10958–66. 
https://doi.org/10.1074/jbc.o113.539569
PMID: 24567326

32. Marin-Vinader L, Onnekink C, van Genesen ST, Slingsby C, Lubsen NH. In vivo heteromer formation. Expression of soluble betaA4-crystallin requires coexpression of a heteromeric partner. FEBS J. 2006; 273:3172–82. 
https://doi.org/10.1111/j.1742-4658.2006.05326.x
PMID: 16774643

33. Kato K, Shinohara H, Kurobe N, Goto S, Inaguma Y, Ohshima K. Immunoreactive alpha A crystallin in rat non-lenticular tissues detected with a sensitive immunoassay method. Biochim Biophys Acta. 1991; 1080:173–80. 
https://doi.org/10.1016/0167-4838(91)90146-q
PMID: 1932094

34. Xi J, Farjo R, Yoshida S, Kern TS, Swaroop A, Andley UP. A comprehensive analysis of the expression of crystallins in mouse retina. Mol Vis. 2003; 9:410–19. 
PMID: 12949468

35. Wistow G. The human crystallin gene families. Hum Genomics. 2012; 6:26. 
https://doi.org/10.1186/1479-7364-6-26
PMID: 23199295

36. Chambers C, Russell P. Deletion mutation in an eye lens beta-crystallin. An animal model for inherited cataracts. J Biol Chem. 1991; 266:6742–46. 
PMID: 1707874

37. Graw J, Löster J, Soewarto D, Fuchs H, Reis A, Wolf E, Balling R, Hrabé de Angelis M. Aey2, a new mutation in the betaB2-crystallin-encoding gene of the mouse. Invest Ophthalmol Vis Sci. 2001; 42:1574–80. 
PMID: 11381063

38. Delaye M, Tardieu A. Short-range order of crystallin proteins accounts for eye lens transparency. Nature. 1983; 302:415–17. 
https://doi.org/10.1038/302415a0
PMID: 6835373

39. Takemoto L, Sorensen CM. Protein-protein interactions and lens transparency. Exp Eye Res. 2008; 87:496–501. 
https://doi.org/10.1016/j.exer.2008.08.018
PMID: 18835387

40. Graw J. Congenital hereditary cataracts. Int J Dev Biol. 2004; 48:1031–44. 
https://doi.org/10.1038/302415a0
PMID: 15558493

41. Li L, Fan DB, Zhao YT, Li Y, Kong DQ, Cai FF, Zheng GY. Two novel mutations identified in ADCC families impair crystallin protein distribution and induce apoptosis in human lens epithelial cells. Sci Rep. 2017; 7:17848. 
https://doi.org/10.1038/s41598-017-18222-z
PMID: 29259299

42. Slingsby C, Wistow GJ. Functions of crystallins in and out of lens: roles in elongated and post-mitotic cells. Prog Biophys Mol Biol. 2014; 115:52–67. 
https://doi.org/10.1016/j.pbiomolbio.2014.02.006
PMID: 24582830

43. Medvedovic M, Tomlinson CR, Call MK, Grogg M, Tsonis PA. Gene expression and discovery during lens regeneration in mouse: regulation of epithelial to mesenchymal transition and lens differentiation. Mol Vis. 2006; 12:422–40. 
PMID: 16710166

44. Huang XY, Ke AW, Shi GM, Zhang X, Zhang C, Shi YH, Wang XY, Ding ZB, Xiao YS, Yan J, Qiu SJ, Fan J, Zhou J. αB-crystallin complexes with 14-3-3ζ to induce epithelial-mesenchymal transition and resistance to sorafenib in hepatocellular carcinoma. Hepatology. 2013; 57:2235–47. 
https://doi.org/10.1002/hep.26255
PMID: 23316005

45. Ghosh S, Shang P, Terasaki H, Stepicheva N, Hose S, Yazdankhah M, Weiss J, Sakamoto T, Bhutto IA, Xia Y, Zigler JS Jr, Kannan R, Qian J, et al. A Role for βA3/A1-Crystallin in Type 2 EMT of RPE Cells Occurring in Dry Related Macular Degeneration. Invest Ophthalmol Vis Sci. 2018; 59:AMD104–AMD113. 
https://doi.org/10.1167/iovs.18-24132
PMID: 30098172

46. Head MW, Sedowofia K, Clayton RM. Beta B2-crystallin in the mammalian retina. Exp Eye Res. 1995; 61:423–48. 
https://doi.org/10.1016/s0014-4835(05)80137-x
PMID: 8549683

47. Bohm MR, Melkonyan H, Oellers P, Thanos S. Effects of crystallin-β-b-2 on stressed RPE in vitro and in vivo. Graefes Arch Clin Exp Ophthalmol. 2013; 251:63–79. 
https://doi.org/10.1007/s00417-012-2157-7
PMID: 23073841

48. Kovacs B, Gulya K. Calmodulin gene expression in the neural retina of the adult rat. Life Sci. 2003; 73:3213–24. 
https://doi.org/10.1016/j.lfs.2003.05.005
49. Thanos S, Bohm MR, Schallenberg M, Oellers P. Traumatology of the optic nerve and contribution of crystallins to axonal regeneration. Cell Tissue Res. 2012; 349:49–69. https://doi.org/10.1007/s00441-012-1442-4 PMID:22638995

50. Piri N, Song M, Kwong JM, Caprioli J. Modulation of alpha and beta crystallin expression in rat retinas with ocular hypertension-induced ganglion cell degeneration. Brain Res. 2007; 1141:1–9. https://doi.org/10.1016/j.brainres.2006.11.095 PMID:17316577

51. Liedtke T, Schwamborn JC, Schröer U, Thanos S. Elongation of axons during regeneration involves retinal crystallin beta b2 (crybb2). Mol Cell Proteomics. 2007; 6:895–907. https://doi.org/10.1074/mcp.m600245-mcp200 PMID:17264069

52. Lee H, Chung H, Lee SH, Jahng WJ. Light-induced phosphorylation of crystallins in the retinal pigment epithelium. Int J Biol Macromol. 2011; 48:194–201. https://doi.org/10.1016/j.ijbiomac.2010.11.006 PMID:21094180

53. Saraswathy S, Rao NA. Mitochondrial proteomics in experimental autoimmune uveitis oxidative stress. Invest Ophthalmol Vis Sci. 2009; 50:5559–66. https://doi.org/10.1167/iovs.08-2842 PMID:19578012

54. Bhat SP, Rayner SA, Chau SC, Ariyasu RG. Pax-6 expression in posthatch chick retina during and recovery from form-deprivation myopia. Dev Neurosci. 2004; 26:328–35. https://doi.org/10.1159/000082274 PMID:15855761

55. Giegling I, Hartmann AM, Genius J, Konte B, Maul S, Straube A, Eggert T, Mulert C, Leicht G, Karch S, Hegerl U, Pogarell O, Hölter SM, et al. Polymorphisms in CRYBB2 encoding BB2-crystallin are associated with antisaccade performance and memory function. Transl Psychiatry. 2020; 10:113. https://doi.org/10.1038/s41398-020-0791-0 PMID:32317624

56. Sun M, Hölter SM, Stepan J, Garrett L, Genius J, Kremmer E, Hrabé de Angelis M, Wurst W, Lie DC, Bally-Cuif L, Eder M, Rujescu D, Graw J. Crybb2 coding for betaB2-crystallin affects sensorimotor gating and hippocampal function. Mamm Genome. 2013; 24:333–48. https://doi.org/10.1007/s00335-013-9478-7 PMID:24096375

57. Böhm MR, Pfrommer S, Chiwitt C, Brückner M, Melkonyan H, Thanos S. Crystallin-β-b2-overexpressing NPCs support the survival of injured retinal ganglion cells and photoreceptors in rats. Invest Ophthalmol Vis Sci. 2012; 53:8265–79. https://doi.org/10.1167/iovs.12-10334 PMID:23132806

58. Sun M, Ahmad N, Zhang R, Graw J. Crybb2 associates with Tmsb4X and is crucial for dendrite morphogenesis. Biochem Biophys Res Commun. 2018; 503:123–130. https://doi.org/10.1016/j.bbrc.2018.05.195 PMID:29864422

59. Marks ED, Kumar A. Thymosin β4: Roles in Development, Repair, and Engineering of the Cardiovascular System. Vitam Horm. 2016; 102:227–49. https://doi.org/10.1016/bs.vh.2016.04.010 PMID:27450737

60. Mollinari C, Ricci-Vitiani L, Pieri M, Lucantoni C, Rinaldi AM, Racianni M, De Maria R, Zona C, Pallini R, Merlo D, Garaci E. Downregulation of thymosin beta4 in neural progenitor grafts promotes spinal cord regeneration. J Cell Sci. 2009; 122:4195–207. https://doi.org/10.1242/jcs.056895 PMID:19861493

61. Gao Q, Sun LL, Xiang FF, Gao L, Jia Y, Zhang JR, Tao HB, Zhang JJ, Li WJ. Crybb2 deficiency impairs fertility in female mice. Biochem Biophys Res Commun. 2014; 453:37–42. https://doi.org/10.1016/j.bbrc.2014.09.049 PMID:25245288

62. Duprey KM, Robinson KM, Wang Y, Taube JR, Duncan MK. Subfertility in mice harboring a mutation in betaB2-crystallin. Mol Vis. 2007; 13:366–73. PMID:17392687

63. Kador PF, Fukui HN, Fukushi S, Jernigan HM Jr, Kinoshita JH. Philly mouse: a new model of hereditary cataract. Exp Eye Res. 1980; 30:59–68. https://doi.org/10.1016/0014-4835(80)90124-4 PMID:7363969

64. Kessaris DN, Wasserman P, Mellinger BC. Histopathological and cytopathological correlations of percutaneous testis biopsy and open testis biopsy in infertile men. J Urol. 1995; 153:1151–55. PMID:7869485

65. Nebel BR, Amarose AP, Hacket EM. Calendar of gametogenic development in the prepuberal male mouse. Science. 1961; 134:832–33. https://doi.org/10.1126/science.134.3482.832 PMID:13728067

66. Xi JH, Bai F, McGaha R, Andley UP. Alpha-crystallin expression affects microtubule assembly and prevents their aggregation. FASEB J. 2006; 20:846–57.
67. Inaba K. Molecular architecture of the sperm flagella: molecules for motility and signaling. Zoolog Sci. 2003; 20:1043–56. https://doi.org/10.2188/zsj.20.1043
PMID: 14578564

68. Zhang J, Li J, Huang C, Xue L, Peng Y, Fu Q, Gao L, Zhang J, Li W. Targeted knockout of the mouse betaB2-crystallin gene (Crybb2) induces age-related cataract. Invest Ophthalmol Vis Sci. 2008; 49:5476–83. https://doi.org/10.1177/0144801408324614
PMID: 18719080

69. Xiang F, Cui B, Gao Q, Zhang J, Zhang J, Li W. Decreased levels of Ca²⁺-calmodulin-dependent protein kinase IV in the testis as a contributing factor to reduced fertility in male Crybb2−/− mice. Int J Mol Med. 2012; 30:1145–51. https://doi.org/10.3892/ijmm.2012.1116
PMID: 22948125

70. Wu JY, Ribar TJ, Cummings DE, Burton KA, McKnight GS, Means AR. Spermiogenesis and exchange of basic nuclear proteins are impaired in male germ cells lacking Camk4. Nat Genet. 2000; 25:448–52. https://doi.org/10.1038/78153
PMID: 10932193

71. Illario M, Giardino-Torchia ML, Sankar U, Ribar TJ, Galgani M, Vitiello L, Masci AM, Bertani FR, Ciaglia E, Astone D, Maulucci G, Cavallo A, Vitale M, et al. Calmodulin-dependent kinase IV links Toll-like receptor 4 signaling with survival pathway of activated dendritic cells. Blood. 2008; 111:723–31. https://doi.org/10.1182/blood-2007-05-091173
PMID: 17909078

72. Kitsos CM, Sankar U, Illario M, Colomer-Font JM, Duncan AW, Ribar TJ, Reya T, Means AR. Calmodulin-dependent protein kinase IV regulates hematopoietic stem cell maintenance. J Biol Chem. 2005; 280:33101–8. https://doi.org/10.1074/jbc.m505208200
PMID: 16020540

73. Rane SG, Dubus P, Mettus RV, Galbreath EJ, Boden G, Reddy EP, Barbacid M. Loss of Cdk4 expression causes insulin-deficient diabetes and Cdk4 activation results in beta-islet cell hyperplasia. Nat Genet. 1999; 22:44–52. https://doi.org/10.1038/7851
PMID: 10319860

74. Janumyan YM, Sansam CG, Chattopadhyay A, Cheng N, Soucie EL, Penn LZ, Andrews D, Knudson CM, Yang E. Bcl-xL/Bcl-2 coordinately regulates apoptosis, cell cycle arrest and cell cycle entry. EMBO J. 2003; 22:5459–70. https://doi.org/10.1093/emboj/cdg533
PMID: 14532118

75. Greider C, Chattopadhyay A, Parkhurst C, Yang E. BCL-x(L) and BCL2 delay Myc-induced cell cycle entry through elevation of p27 and inhibition of G1 cyclin-dependent kinases. Oncogene. 2002; 21:7765–75. https://doi.org/10.1038/sj.onc.1205928
PMID: 12420213

76. Gao Q, Ren H, Chen M, Niu Z, Tao H, Jia Y, Zhang J, Li W. Long non-coding RNAs regulate effects of β-crystallin B2 on mouse ovary development. Mol Med Rep. 2016; 14:4223–31. https://doi.org/10.3892/mmr.2016.5761
PMID: 27666820

77. Hangauer MJ, Vaughn IW, McManus MT. Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs. PLoS Genet. 2013; 9:e1003569. https://doi.org/10.1371/journal.pgen.1003569
PMID: 23818866

78. Huang MD, Chen WM, Qi FZ, Xia R, Sun M, Xu TP, Yin L, Zhang EB, De W, Shu YQ. Long non-coding RNA ANRIL is upregulated in hepatocellular carcinoma and regulates cell apoptosis by epigenetic silencing of KLF2. J Hematol Oncol. 2015; 8:50. https://doi.org/10.1186/s13045-015-0146-0
PMID: 25966845

79. Xu J, Wang H, Wang A, Xu J, Fu C, Jia Z, Yao K, Chen X. βB2 W151R mutant is prone to degradation, aggregation and exposes the hydrophobic side chains in the fourth Greek Key motif. Biochim Biophys Acta Mol Basis Dis. 2021; 216018. https://doi.org/10.1016/j.bbadis.2020.166018
PMID: 33246011

80. Vanita, Sarhadi V, Reis A, Jung M, Singh D, Sperling K, Singh JR, Bürger J, Bürger J. A unique form of autosomal dominant cataract explained by gene conversion between beta-crystallin B2 and its pseudogene. J Med Genet. 2001; 38:392–401. https://doi.org/10.1136/jmg.38.6.392
PMID: 11424921

81. Russell P, Chambers C. Interaction of an altered beta-crystallin with other proteins in the Phillie mouse lens. Exp Eye Res. 1990; 50:683–87. https://doi.org/10.1016/0014-4835(90)90114-a
PMID: 2373162

82. Javadiyan S, Craig JE, Souzeau E, Sharma S, Lower KM, Mackey DA, Staffieri SE, Elder JE, Taranath D, Straga T, Black J, Pater J, Casey T, et al. High-Throughput Genetic Screening of 51 Pediatric Cataract Genes...
83. Zhuang J, Cao Z, Zhu Y, Liu L, Tong Y, Chen X, Wang Y, Lu C, Ma X, Yang J. Mutation screening of crystallin genes in Chinese families with congenital cataracts. Mol Vis. 2019; 25:427–37. PMID:31523120

84. Banerjee PR, Puttamadappa SS, Pande A, Shekhtman A, Pande J. Increased hydrophobicity and decreased backbone flexibility explain the lower solubility of a cataract-linked mutant of yD-crystallin. J Mol Biol. 2011; 412:647–59. https://doi.org/10.1016/j.jmb.2011.07.058 PMID:21827768

85. Ching YH, Yeh JJ, Fan WL, Chen KC, Yeh MC, Woon PY, Lee YC. A CRYBB2 mutation in a Taiwanese family with autosomal dominant cataract. J Formos Med Assoc. 2019; 118:57–63. https://doi.org/10.1016/j.jfma.2018.01.005 PMID:29395391

86. Yao K, Li J, Jin C, Wang W, Zhu Y, Shentu X, Wang Q. Characterization of a novel mutation in the CRYBB2 gene associated with autosomal dominant congenital posterior subcapsular cataract in a Chinese family. Mol Vis. 2011; 17:144–52. PMID:21245961

87. Li FF, Zhu SQ, Wang SZ, Gao C, Huang SZ, Zhang M, Ma X. Nonsense mutation in the CRYBB2 gene causing autosomal dominant progressive polymorphic congenital corneal cataracts. Mol Vis. 2008; 14:750–55. PMID:18449377

88. Xu LJ, Lv ZG, Liu Y, Zhang XX, Cui YX, Li XC, Zhu YJ, He J. A novel CRYBB2 mutation causes autosomal dominant cataract: A report from a Chinese family. Eur J Ophthalmol. 2020. [Epub ahead of print]. https://doi.org/10.1177/1120672120926450 PMID:32498547

89. Umeda S, Suzuki MT, Okamoto H, Ono F, Mizota A, Terao K, Yoshikawa Y, Tanaka Y, Iwata T. Molecular composition of drusen and possible involvement of anti-retinal autoimmunity in two different forms of macular degeneration in cynomolgus monkey (Macaca fascicularis). FASEB J. 2005; 19:1683–85. https://doi.org/10.1096/fj.04-3525fje PMID:16099945

90. Johnson PT, Brown MN, Pulliam BC, Anderson DH, Johnson LV. Synaptic pathology, altered gene expression, and degeneration in photoreceptors impacted by drusen. Invest Ophthalmol Vis Sci. 2005; 46:4788–95. https://doi.org/10.1167/iovs.05-0767 PMID:16303980

91. Prokosch V, Schallenberg M, Thanos S. Crystallins are regulated biomarkers for monitoring topical therapy of glaucomatous optic neuropathy. PLoS One. 2013; 8:e49730. https://doi.org/10.1371/journal.pone.0049730 PMID:23468831

92. Chiu K, Zhou Y, Yeung SC, Lok CK, Chan OO, Chang RC, So KF, Chiu JF. Up-regulation of crystallins is involved in the neuroprotective effect of wolfberry on survival of retinal ganglion cells in rat ocular hypertension model. J Cell Biochem. 2010; 110:311–20. https://doi.org/10.1002/jcb.22539 PMID:20336662

93. Heermann T, Garrett L, Wurst W, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Graw J, Hölter SM. Crybb2 Mutations Consistently Affect Schizophrenia Endophenotypes in Mice. Mol Neurobiol. 2019; 56:4215–4230. https://doi.org/10.1007/s12035-018-1365-5 PMID:30291584

94. Ludewig K, Geyer MA, Vollenweider FX. Deficits in prepulse inhibition and habituation in unmedicated, first-episode schizophrenia. Biol Psychiatry. 2003; 54:121–28. https://doi.org/10.1016/s0006-3223(02)01925-x PMID:12873801

95. Powell CM, Miyakawa T. Schizophrenia-relevant behavioral testing in rodent models: a uniquely human disorder? Biol Psychiatry. 2006; 59:1198–207. https://doi.org/10.1016/j.biopsych.2006.05.008 PMID:16797265

96. Kim Y, Xia K, Tao R, Giusti-Rodriguez P, Vladimirov V, van den Oord E, Sullivan PF. A meta-analysis of gene expression quantitative trait loci in brain. Transl Psychiatry. 2014; 4:e459. https://doi.org/10.1038/tp.2014.96 PMID:25290266

97. Graw J. From eyeless to neurological diseases. Exp Eye Res. 2017; 156:5–9. https://doi.org/10.1016/j.exer.2015.11.006 PMID:26593886

98. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006; 295:2492–502. https://doi.org/10.1001/jama.295.21.2492 PMID:16757721

www.aging-us.com 15685 AGING
99. Smigal C, Jemal A, Ward E, Kokkinides V, Smith R, Howe HL, Thun M. Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin. 2006; 56:168–83. https://doi.org/10.3322/canclin.56.3.168 PMID:16737949

100. Amend K, Hicks D, Ambrosone CB. Breast cancer in African-American women: differences in tumor biology from European-American women. Cancer Res. 2006; 66:8327–30. https://doi.org/10.1158/0008-5472.CAN-06-1927 PMID:16951137

101. Hayanga AJ, Newman LA. Investigating the phenotypes and genotypes of breast cancer in women with African ancestry: the need for more genetic epidemiology. Surg Clin North Am. 2007; 87:551–68. https://doi.org/10.1016/j.suc.2007.01.003 PMID:17498544

102. Field LA, Love B, Deyarmin B, Hooke JA, Shriver CD, Ellsworth RE. Identification of differentially expressed genes in breast tumors from African American compared with Caucasian women. Cancer. 2012; 118:1334–44. https://doi.org/10.1002/cncr.26405 PMID:21800289

103. Grunda JM, Steg AD, He Q, Steciuk MR, Byan RJ, Abud HE, Huelsken J, Robinson ML, de Iongh RU. A role for Wnt/beta-catenin in epithelial differentiation. Dev Biol. 2003; 259:48–61. https://doi.org/10.1016/s0012-4209(03)00179-8 PMID:12812787

104. Martin DN, Boersma BJ, Yi M, Reimers M, Howe TM, Yfantis HG, Tsai YC, Williams EH, Lee DH, Stephens RM, Weissman AM, Ambrosone CB. Differences in the tumor microenvironment between African-American and European-American breast cancer patients. PLoS One. 2009; 4:e4531. https://doi.org/10.1371/journal.pone.0004531 PMID:1925562

105. Barrow MA, Martin ME, Coffey A, Andrews PL, Jones GS, Reaves DK, Parker JS, Troester MA, Fleming JM. A functional role for the cancer disparity-linked genes, CRYBB2 and CRYBB2P1, in the promotion of breast cancer. Breast Cancer Res. 2019; 21:105. https://doi.org/10.1186/s13058-019-1191-3 PMID:31511085

106. Wallace TA, Prueitt RL, Yi M, Howe TM, Gillespie JW, Yfantis HG, Stephens RM, Caporaso NE, Loffredo CA, Ambrosone CB. Tumor immunobiological differences in prostate cancer between African-American and European-American men. Cancer Res. 2008; 68:927–36. https://doi.org/10.1158/0008-5472.CAN-07-2608 PMID:18245496

107. Jovov B, Araujo-Perez F, Sigel CS, Stratford JK, McCoy AN, Yeh JJ, Keku T. Differential gene expression between African American and European American colorectal cancer patients. PLoS One. 2012; 7:e30168. https://doi.org/10.1371/journal.pone.0030168 PMID:22276153

108. Faruque MU, Paul R, Ricks-Santi L, Jinwei Y, Ahaghotu CA, Dunston GM. Analyzing the Association of Polymorphisms in the CRYBB2 Gene with Prostate Cancer Risk in African Americans. Anticancer Res. 2015; 35:2565–70. PMID:25964531

109. Wu M, Miska J, Xiao T, Zhang P, Kane JR, Balyasnikova IV, Chandler JP, Horbinski CM, Lesniak MS. Race influences survival in glioblastoma patients with KPS ≥ 80 and associates with genetic markers of retinoic acid metabolism. J Neurooncol. 2019; 142:375–84. https://doi.org/10.1007/s11060-019-03110-5 PMID:30706176

110. Paulucci DJ, Sfakianos JP, Skanderup AJ, Kan K, Tsao CK, Galsky MD, Hakimi AA, Badani KK. Genomic differences between black and white patients implicate a distinct immune response to papillary renal cell carcinoma. Oncotarget. 2017; 8:5196–205. https://doi.org/10.18632/oncotarget.14122 PMID:28029648

111. Strickler HD, Bur R, Shah K, Viscidi R, Jackson A, Pizza G, Bertoni F, Schiller JT, Manns A, Metcalf R, Qu W, Goedert JJ. A multifaceted study of human papillomavirus and prostate carcinoma. Cancer. 1998; 82:1118–25. PMID:9506358

112. Stump RJ, Ang S, Chen Y, von Bahr T, Lovicu FJ, Pinson K, de Jongh RU, Yamaguchi TP, Sassoon DA, McAvoy JW. A role for Wnt/beta-catenin signaling in lens epithelial differentiation. Dev Biol. 2003; 259:48–61. https://doi.org/10.1016/s0012-4209(03)00179-9 PMID:12812787

113. Cain S, Martinez G, Kokkinis MI, Turner K, Richardson RJ, Abud HE, Huelsken J, Robinson ML, de Jongh RU. Differential requirement for beta-catenin in epithelial and fiber cells during lens development. Dev Biol. 2008; 321:420–33. https://doi.org/10.1016/j.ydbio.2008.07.002 PMID:18652817

114. Polakis P. Wnt signaling in cancer. Cold Spring Harb Perspect Biol. 2012; 4:a008052. https://doi.org/10.1101/cshperspect.a008052
115. Anastas JN, Moon RT. WNT signalling pathways as therapeutic targets in cancer. Nat Rev Cancer. 2013; 13:11–26. 
   https://doi.org/10.1038/nrc3419
   PMID: 23258168

116. Ishikawa K, Sreekumar PG, Spee C, Nazari H, Zhu D, Kannan R, Hinton DR. αB-Crystallin Regulates Subretinal Fibrosis by Modulation of Epithelial-Mesenchymal Transition. Am J Pathol. 2016; 186:859–73. 
   https://doi.org/10.1016/j.ajpath.2015.11.014
   PMID: 26878210