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RESEARCH

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Relationship between expression levels of *TDRD7* and *CRYBB3* and development of age-related cortico-nuclear cataracts

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Abstract

Background The human lens develops age-related cataracts (ARCs) because of the complicated effects of aging and stressful conditions. Under conditions involving oxidative stress, cells form stress granules (SGs). *TDRD7* has been identified as an RNA granule component and an important component of SGs. *TDRD7* plays a role in the post-transcriptional expression of genes, such as the crystallin gene *CRYBB3*. Therefore, the present study investigated *TDRD7* and *CRYBB3* mRNA expressions in relation to age-related cortico-nuclear cataracts.

Methods Quantitative real-time PCR was used to determine the expression levels of *TDRD7* and *CRYBB3* in 52 patients with ARC and 52 healthy controls. Anterior lens capsules and peripheral blood samples from patients with ARC were included in the patient group, and peripheral blood samples from healthy subjects and human lens epithelial cells (HLE-B3) were included in the control group. Gene expression levels in the different age groups were compared. Correlation analysis was used to assess the gene expression levels and age.

Results The expression of *TDRD7* and *CRYBB3* was significantly up-regulated ($P < 0.0001$) in anterior lens capsules compared to that in HLE-B3 cells. Similarly, the expression of *TDRD7* ($P = 0.0004$) and *CRYBB3* ($P < 0.0001$) was higher in the peripheral blood samples of patients with ARC than in those of healthy subjects. Significant upregulation ($P < 0.05$) was observed in the 71–81-year age group of patients. No correlation was found between gene expression levels and age.

Conclusion Significantly higher expression levels of *TDRD7* and *CRYBB3* in patients with ARC than in controls suggest that *TDRD7* and *CRYBB3* are associated with the development of age-related cortico-nuclear cataracts and the aging process under chronic stress.

Keywords Age-related cataract, Cortico-nuclear cataracts, *TDRD7*, *CRYBB3*

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Background

Age-related cataract (ARC) is characterized by the opacification of the eye lens, which prevents external light transmission to the retina [1]. Depending on the location of the lens opacity, ARC is characterized into various subtypes, including cortical, nuclear, posterior subcapsular, and mixed types [2]. ARC is typically considered to be a multifactorial disease.

A variety of risk factors, including oxidative stress, senescent changes, systemic disease, genetic factors,

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smoking, and diet, have been associated with the development of cataracts [3].

In parallel with recent advances in molecular biology, genes that cause cataracts have been extensively investigated. Aging is a major factor in cataract development [4]. The combined effect of decreased detoxification capacity of the aging lens, post-translational modifications, and oxidative stress causes the degradation of lens proteins. This process is important for the onset and progression of opacity [5]. Opacities causing cortico-nuclear cataracts occur in nuclear and cortical fiber cells. Therefore, changes in gene expression profiles are most likely due to the response of lens epithelial cells to cataracts [6, 7]. Identifying the genes and proteins responsible for lens transparency will enable a greater understanding of the pathophysiology of cataracts.

Cytoplasmic RNA granules (RGs) play an important role in the posttranscriptional regulation of gene expression. RGs play a crucial role in determining mRNA stabilization or decay [8]. *TDRD7*, located on chromosome 9q22.33, consists of 17 exons and encodes the Tudor domain-containing 7 protein, identified as an RG component. The specific function of TDRD7, a scaffold protein, is unknown. However, mutations in *TDRD7* result in cataract formation. Misregulation of *TDRD7* alters the expression profiles of specific human cataract genes, including *CRYBB3*. *TDRD7* mediates a regulatory effect on βB3-crystallin mRNA [9].

Crystallins, a major class of soluble lens proteins, comprise α, β and γ crystallins that are found in all vertebrate lenses. In mature human lenses, α crystallins, β crystallins, and γ crystallins make up approximately 40%, 35%, and 25% of the total crystallin proteins [10]. β and γ crystallins form an extremely stable superfamily called the 'Greek key motifs' [11]. *CRYBB3*, located on chromosome 22q11.23, consists of six exons [12]. In humans, β-crystallin genes have been associated with cataracts [13, 14]. An increase in βB3 crystallin expression may be attributed to *CRYBB3* mutations [15].

In the present study, we elucidated the relationship between the mRNA expression of *TDRD7* and *CRYBB3* in patients with cortico-nuclear-type ARC.

Methods

Study participants

We enrolled 52 patients with ARC (aged 40–82 years) and 52 healthy controls (aged 42–81 years) admitted to the Department of Ophthalmology. Patients with ARC in this study had mixed types of cataracts. The inclusion criteria for patients with ARC were as follows: ARC diagnosis, age ≥ 40 years, and visual impairment due to cataracts. The exclusion criteria were as follows: complicated cataracts due to ocular trauma or uveitis, ocular inflammation, history of intraocular surgery, glaucoma, diabetes, use of systemic or topical steroids, congenital cataracts, and use of drugs with the potential to cause toxic cataracts (for instance, phenothiazines, cholinergics, photosensitive drugs, tranquilizers, diuretics, cancer drugs, and gut mediators).

Cell cultures

Human anterior lens capsule specimens, including lens epithelial cells (LECs) obtained during capsulorhexis, were washed with phosphate-buffered saline (PBS) for 15 s to remove fiber and blood cells. Specimens were immediately used for the experiment within four hours. Human anterior lens capsules, including cuboidal epithelial cells, were approximately 5 mm in diameter. As previously described, [16] after capsulorhexis, anterior lens capsules were placed in 1.5 mL centrifuge tubes with a culture medium RPMI-1640 supplemented with 10% fetal bovine serum (FBS) and 1% penicillin (1000 units/mL), and streptomycin (10 mg/mL). The collected human anterior lens capsules were then transferred to 24-well culture dishes for growth under in vitro conditions. To attach the anterior lens capsules to the bottom of the wells, the culture dishes were placed in a humidified incubator with 95% air and 5% CO_2 for one week. The cells that reached 70–80% confluence were selected for RNA extraction.

Human LECs (HLE-B3), purchased from ATCC (Manassas, VA, USA) were cultured in Eagle's minimum essential medium (EMEM; Sigma-Aldrich, USA) supplemented with 20% FBS (Sigma-Aldrich), 1% penicillin (1000 units/mL), and streptomycin (10 mg/mL) at 37 °C in a humidified atmosphere containing 5% CO_2.

Quantitative real-time PCR

Total RNA was extracted from human LECs, HLE-B3 cells, and white blood cells using the QIAzol reagent (Qiagen, Germany). For each sample, 1 µg of total RNA was used for cDNA synthesis using the RT^2 First Strand Kit (Qiagen), in accordance with the manufacturer's instructions. The expression of *TDRD7* and *CRYBB3* was analyzed by quantitative real-time PCR (qRT-PCR) performed on RotorGene Q using the RT^2 SYBR Green qPCR Mastermix (Qiagen). The RT^2 primer assays were conducted for both *TDRD7* (NM_014290, cat no. PPH19773B, Qiagen) and *CRYBB3* (NM_004076, cat no. PPH01744A, Qiagen). The data of samples were normalised with respect to the expression of *ACTB* (NM_001101, cat no. PPH00073G, Qiagen). The amplification curves for *TDRD7*, *CRYBB3* and *ACTB* mRNA are shown in Fig. 1.

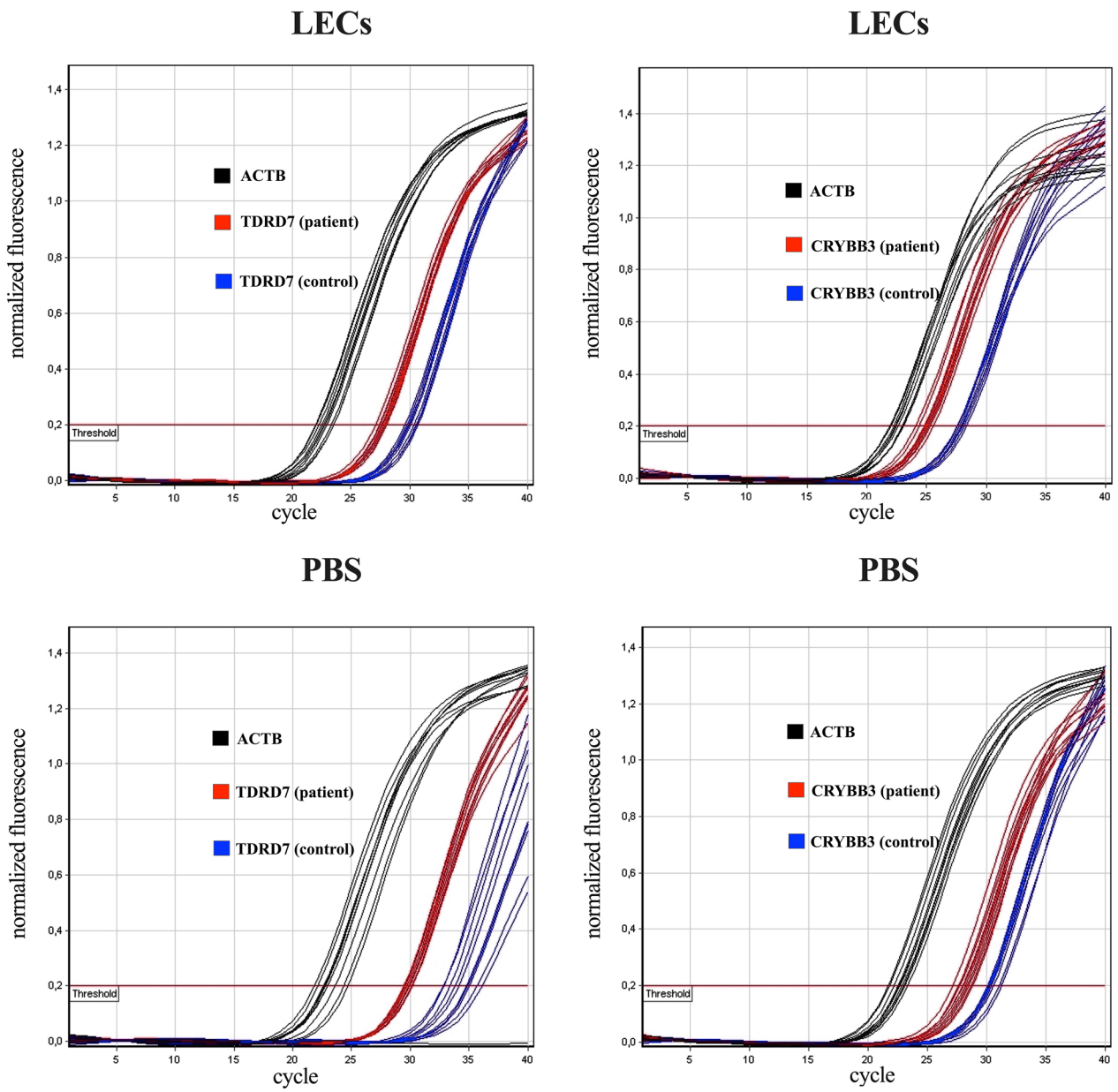


Fig. 1 Comparison of expression levels of *TDRD7* and *CRYBB3* in patient groups versus control groups by quantitative real-time PCR

Statistical analyses

qRT-PCR was performed twice for all the samples used in the experiments. The independent Student's *t*-test was used for between-group comparisons. Pearson's correlation coefficient was used to assess the correlation. Statistical calculations were performed using Graphpad Prism 8.4.2 software (San Diego, CA, USA). Statistical significance was set at $P < 0.05$.

Results

We performed primary cell cultures for in vitro growth of anterior lens capsules, as shown in Fig. 2A. After one week, the epithelial cells were trypsinized and passaged to release the cells from the capsule (Fig. 2B). RPMI-1640 medium supplemented with 10% FBS was the best medium for the propagation of LECs. We observed that

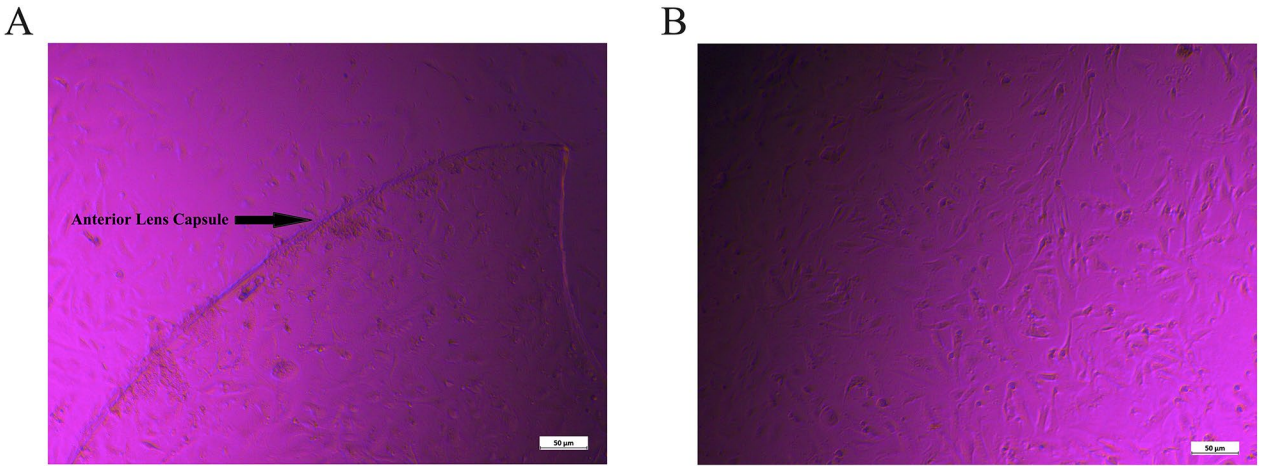


Fig. 2 **A** Section from anterior lens capsule specimen. **B** Passaged lens epithelial cells. Cultures were examined by inverted light microscopy (Leica, Germany). Scale bar = 50 µm

cell proliferation increased after the first passage but decreased remarkably after the second passage.

Human LECs and peripheral blood samples from patients with ARC were included in the patient group, while HLE-B3 and peripheral blood samples from healthy subjects were designated as the control group. Comparisons were made between human LECs and HLE-B3 and between peripheral blood samples from patients with ARC and healthy subjects. We found that the expression levels of *TDRD7* and *CRYBB3* were upregulated in 52 anterior lens capsules compared to those in HLE-B3 cells. qRT-PCR results indicated that *TDRD7* mRNA expression in anterior lens capsules was 11.15-fold ($P < 0.0001$) higher than that in HLE-B3 cells (Fig. 3A). Similarly, *CRYBB3* mRNA expression in the anterior lens capsules was 23.63-fold ($P < 0.0001$) higher than that in HLE-B3 cells (Fig. 3B).

Upon comparing the data of 52 peripheral blood samples to those of 52 healthy blood samples, we observed a 2.61-fold ($P = 0.0004$) increase in *TDRD7* mRNA levels (Fig. 4A) and a 4.98-fold ($P < 0.0001$) increase in *CRYBB3* mRNA levels in peripheral blood samples (Fig. 4B). The upregulation in the mRNA expression of *TDRD7* and *CRYBB3* in peripheral blood samples was correlated with the anterior lens capsules. The results showed that the expression of *TDRD7* and *CRYBB3* was significantly upregulated in both LECs from the anterior lens capsules and peripheral blood samples from the same sample group.

A comparison of gene expression levels in the different age groups showed statistical significance for both *TDRD7* and *CRYBB3* in the 71–81-year age group (Table 1). For a better understanding of the results, data visualization is presented as box-and-whisker plots in

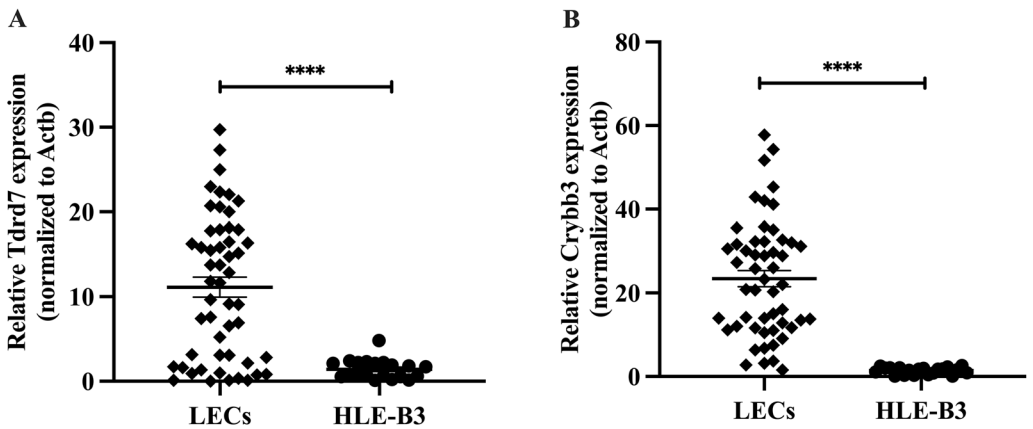


Fig. 3 Expression levels of *TDRD7* and *CRYBB3* in lens capsule samples in comparison to those in HLE-B3 cells. ****$P < 0.001$. *LECs* Lens Epithelial Cells, *HLE-B3* Human Lens Epithelial Cell Line

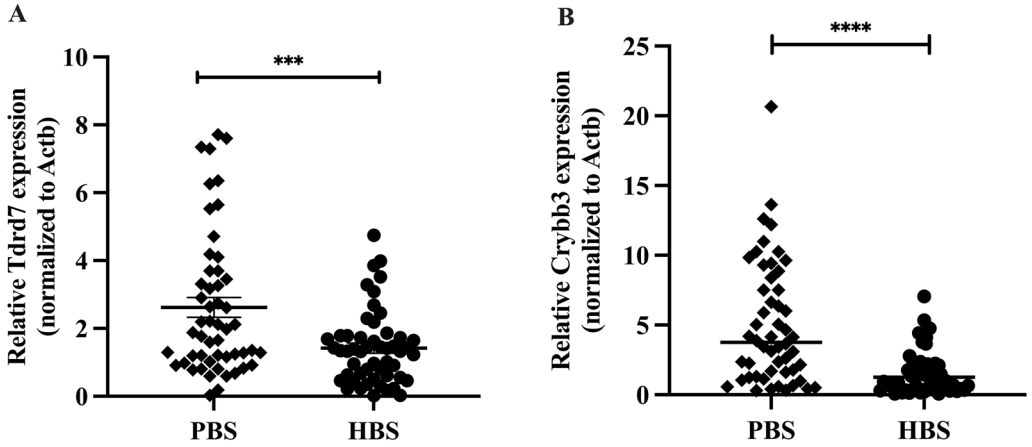


Fig. 4 Expression levels of *TDRD7* and *CRYBB3* in peripheral blood samples in comparison to those in healthy blood samples. ***$P < 0.001$, ****$P < 0.0001$. *PBS* Peripheral Blood Samples, *HBS* Healthy Blood Samples

Table 1 The expression levels of *TDRD7* and *CRYBB3* by age groups

Age	40–50 years		51–60 years		61–70 years		71–81 years	
	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value
Relative TDRD7 expression in LECs	11.94	< 0.0001	5.96 ± 9.25	0.1450	13.9 ± 12.58	0.0033	8.98 ± 10.01	0.0234
Relative CRYBB3 expression in LECs	NA	NA	12.53 ± 16.42	0.0390	41.96 ± 33.23	0.0004	39.42 ± 32.78	0.0006
Relative TDRD7 expression in PBS	2.22 ± 1.75	0.4915	4.69 ± 3.16	< 0.0001	3.17 ± 4.01	0.0590	6.16 ± 6.47	0.0034
Relative CRYBB3 expression in PBS	11.73 ± 11.70	0.0140	5.82 ± 6.36	0.0074	6.11 ± 7.83	0.0109	8.84 ± 8.81	0.0011

Fig. 5. We also performed a correlation analysis between gene expression levels and age. No statistically significant correlation between the expression levels of *TDRD7* and *CRYBB3* and age was observed (Fig. 6).

Discussion

Oxidative stress can cause apoptosis of HLE cells, leading to cataract formation [17]. The cortico-nuclear type of cataract is characterized by the most extensive oxidative stress levels [18]. During cellular oxidative stress, somatic cells form stress granules (SGs), which are cytoplasmic RGs that play crucial roles in posttranscriptional gene regulation [19].

TDRD7 plays a crucial role when the cells are exposed to stressful conditions. Knockdown of *TDRD7* mediates a reduction in SGs and downregulation of important lens genes, such as *CRYBB3*. *CRYBB3* might be targeted by *TDRD7* in lens regulatory networks [9].

The present study is the first to investigate the mRNA transcripts of *TDRD7* and *CRYBB3* using qRT-PCR in human LECs of anterior lens capsules obtained from patients and compare the results with those of HLE-B3 cells. Moreover, the mRNA transcription of *CRYBB3* was compared for the first time between the plasma levels of patients with cataracts and those of healthy individuals. In this study, we identified higher mRNA levels of *TDRD7* and *CRYBB3* in the anterior lens capsules and peripheral blood samples than those in HLE-B3 cells and healthy individuals. Although the downregulation of the expression of *TDRD7* and *CRYBB3* in patients with ARC has been reported in several studies, their expression profiles in cortico-nuclear cataracts remain unclear.

Lachke et al. showed that mutations in the *TDRD7* gene can result in the development of cataracts. They found that knocking down *TDRD7* resulted in the downregulation of the crystallin gene *CRYBB3*. They suggested that *TDRD7* mediated cataracts owing to insufficient crystallin [9]. The plasma levels of *TDRD7* in patients with cataracts are lower than those in healthy individuals [20]. The inclusion criteria of this study did not match those of our experiment, as this experiment included diabetes mellitus samples. Diabetes is a known risk factor for development of cataracts [21]. In contrast to these previous studies, we found that *TDRD7* was highly expressed in human LECs and blood samples.

CRYBB3 mRNA expression has been observed in postnatal rat LECs. In addition, the β-crystallin expression has been observed adult mammals, including humans, in the same study [22]. Hawse et al. conducted microarray analysis in LECs from patients with cataracts and clear

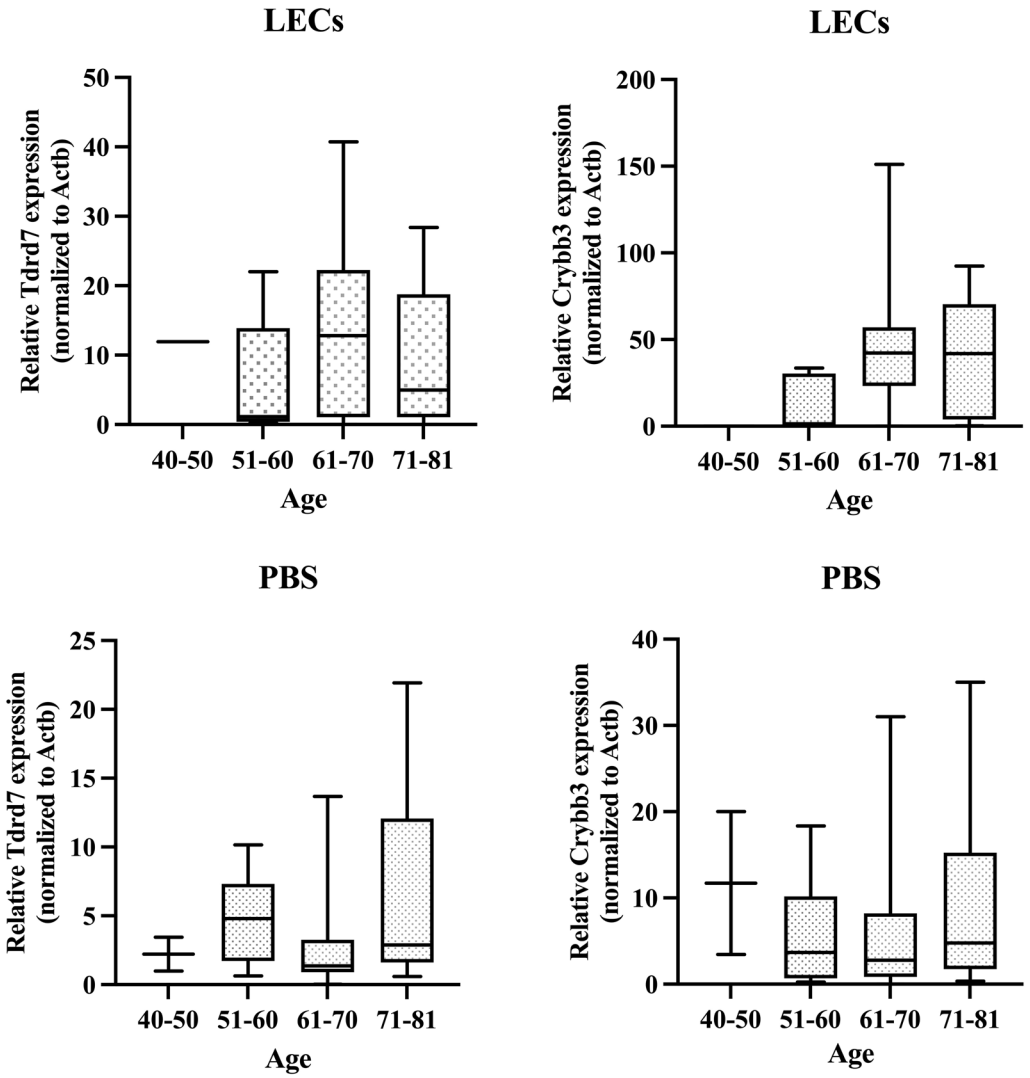


Fig. 5 Comparison of expression levels of *TDRD7* and *CRYBB3* according to age groups. *LECs* Lens Epithelial Cells, *PBS* Peripheral Blood Samples

lens epithelia and found considerable downregulation of the expression of *TDRD7* and *CRYBB3* [23]. However, the accuracy of these data was not confirmed using qRT-PCR. In contrast, *CRYBB3* was significantly expressed in human LECs and blood samples.

The eye lens has a protective antioxidant system that resists oxidative stress. These antioxidant mechanisms gradually diminish as a result of an increase in the active forms of oxygen (e.g., hydrogen peroxide) with age [24]. The normal concentration of hydrogen peroxide (H_2O_2) is approximately 25–30 µM in aqueous humour. Patients with cataracts exhibit H_2O_2 concentrations 10- to 30-fold higher than those of healthy individuals [25, 26]. Constant exposure to oxidative stress leads to the formation of SGs in proliferative and presenescent cells [27]. Cells trigger the formation of SGs, which are crucial cell protection mechanisms under extracellular stresses (e.g., oxidative stress). This regulates gene expression during cellular damage [28]. LECs from patients with ARC are known to be less proliferative and exhibit fewer lens stem cells than clear lenses. With increasing age, LECs become more prone to senescence [29]. Based on these findings, we speculate that LECs can generate SGs. The generation of SGs in LECs may induce the significant overexpression of the important RG components *TDRD7* and *CRYBB3* under the transcriptional regulatory effect of *TDRD7*. ZBP1 has been defined as a component of SG, similar to *TDRD7*. During cellular stress, it regulates the expression of various mRNAs. The overexpression of ZBP1 leads to the elevation of corresponding mRNAs targeted by ZBP1

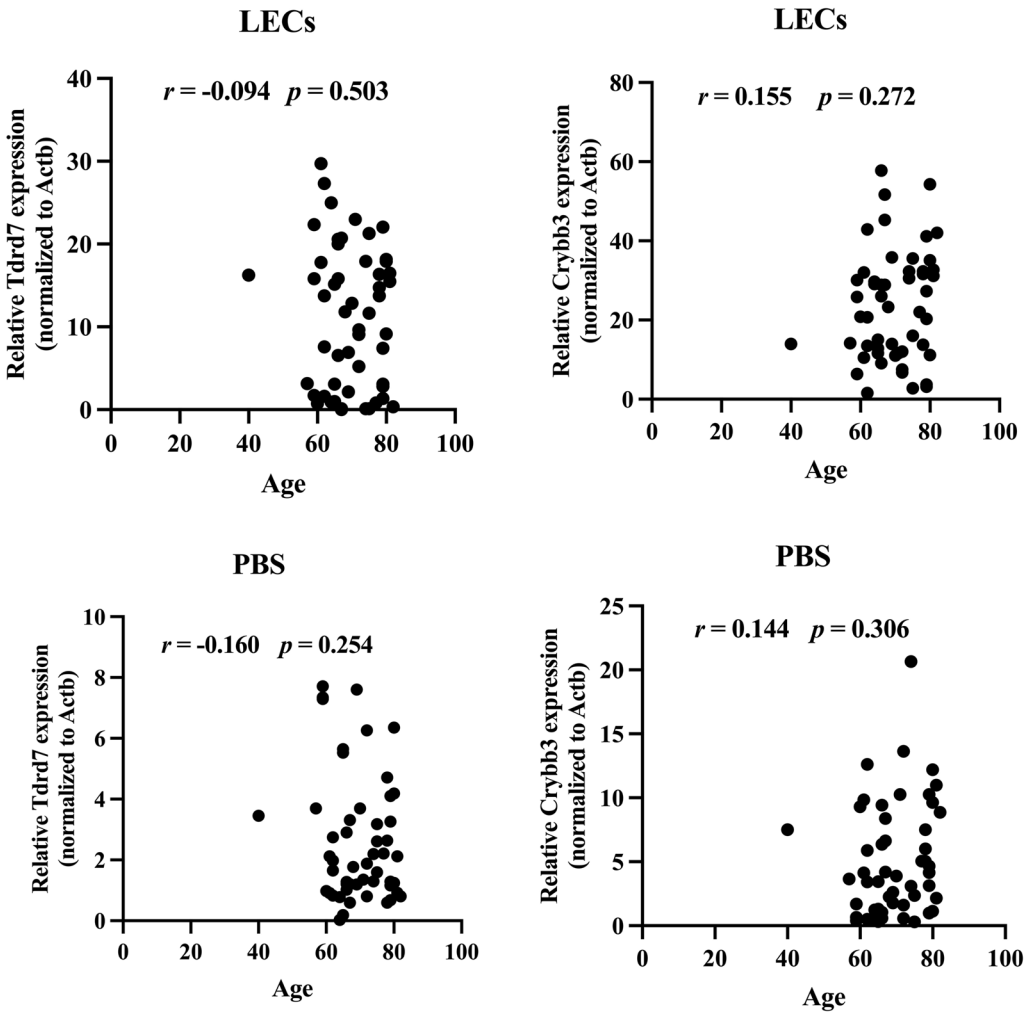


Fig. 6 Correlation analyses between age and genes, *TDRD7* and *CRYBB3*. *LECs* Lens Epithelial Cells, *PBS* Peripheral Blood Samples

[30]. Oxidative stress plays an important role in aging and telomere attrition [31]. An increase in reactive oxygen species (ROS) in circulating leukocytes is associated with cardiovascular diseases [32]. High levels of *TDRD7* and *CRYBB3* mRNAs in peripheral blood samples from patients with cataracts compared to those in matched healthy blood samples in the current study may be attributed to augmented ROS levels. It seems likely that cells will attempt to compensate for stress by increasing the levels of these mRNAs.

Conclusions

In summary, crystalline lenses are constantly exposed to oxidative stress, which leads to elevated ROS levels and LEC aging. The results of the current study suggest that overexpression of *TDRD7* and *CRYBB3* is associated with the development of ARC. Our work revealed the relationship between the mRNA expression levels of *TDRD7* and *CRYBB3* and age-related cortico-nuclear cataracts. Further studies are required to define the relationship between these genes and cataracts. These observations provide new insights into gene expression associated with ARCs.

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Author contributions

SHY and MS provided grants. CK performed experiments. RD and RD collected the samples. NV made statistical analyzes. MÖE and ME supervised and consulted for the study. All authors help writing the article section by section and contributed discussion.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of Afyonkarahisar Kocatepe University (Approval No. 2016/2-19 and 2016/2-20). Written informed consent was obtained from all participants.

Consent for publication
Cem Karaosmanoğlu hereby declare that I participated in the study and in the development of the manuscript titled '***The Relationship Between Expression Levels Of Tdrd7 And Crybb3 And Development Of Age-Related Cortico-Nuclear Cataracts***'. I have read the final version and give my consent for the article to be published in Egyptian Journal of Medical Human Genetics.

Competing interests
The authors declare that they have no competing interests.

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