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Original Article

Expression Profiling of *ADAMTS* (L) Superfamily of Genes in Various Human Eye Tissues

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Abstract

Background: A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) is a superfamily of extracellular proteinases found in both mammals and invertebrates. Although there is some evidence about the role of ADAMTSs in ocular diseases such as glaucoma and ectopia lentis, but there is little information about the expression patterns of *ADAMTS-1-20* and ADAMTS-like (*ADAMTSL-1-6* and *PAPLN*) genes in human ocular tissues. This study aimed to evaluate the expression profiling of *ADAMTS*(L) superfamily of genes in different ocular tissues based on age.

Methods: In 2019, nine human donated eye globes were provided from the Central Eye Bank of Iran, and were divided into three different groups based on age (under 3 yr old, between 20 to 50 and upper 50 yr old). To assess expression patterns of *ADAMTS*(L) genes in different ocular tissues including trabecular meshwork, lens, retinal pigment epithelium, macula, and optic nerve in the three age groups, total RNA was extracted from the tissues and reverse transcription polymerase chain reaction followed by Real-time PCR was performed.

Results: We demonstrated not only each member of *ADAMTS*(L) superfamily shows different expression pattern between the five investigated ocular tissues, but also some members have differential expressions among the investigated age groups in same tissues.

Conclusion: Differential expression of *ADAMTS*(L) genes in ocular tissues from different age groups could explain some functional aspects of the tissues and also may be used as prognostic and diagnostic biomarkers for ocular diseases and pathologies. Further studies are required to explore their functional roles associated with ocular pathologies.

Keywords: ADAMTS Proteins; Gene expression; Eye

Introduction

Extracellular matrix (ECM) proteins are crucial for normal development and function of the tissues (1). Connective tissue disorders include various multisystem diseases that ordinarily have well-known ocular manifestations (2). Mutations in multiple ECM proteins or proteins involved in ECM homeostasis and function including some of the collagens, fibrillin-1 (*FBN1*), fibullin-5 (*FBLN5*), laminin and some of the A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS(L)) superfamily proteins have been reported in human diseases with ocular associations (1, 3). ADAMTS (L) as one of the ECM superfamilies contains 26 secreted molecules in humans dividing into 2 related families, 19 ADAMTS proteinases and at least seven ADAMTS-like (ADAMTSL) proteins without enzymatic activity (4-6). The ADAMTSs are zinc metalloproteinases consist of an N-terminal catalytic and disintegrin-like domain and C-terminal region containing thrombospondin repeats that can interact with the ECM components (5-7). In contrast, ADAMTSL proteins lack a metalloproteinase domain, reside in the ECM and have regulatory roles in ECM assembly and ADAMTS activity (3).

In the ADAMTS nomenclature, *ADAMTS-1* to *ADAMTS-20* was considered, but *ADAMTS-5* and *ADAMTS-11* are names of a same gene encoding a defined enzyme, and *ADAMTS-11* is no longer used (3). Human *ADAMTSL* subfamily also comprises seven genes including *ADAMTSL-1* to *-6* and *PAPLN*.

The ADAMTS (L) superfamily is participated in many biological functions associated with tissue development and homeostasis (3, 6). Although loss of function in some *ADAMTS* (L) members causes Mendelian inherited disorders, anomalous expression or function of the other members is associated with pathologies including arthritis, cardiovascular diseases and cancer (3, 4, 8).

There is some evidence about the role of *ADAMTS* (L) superfamily in ocular diseases such as glaucoma and ectopia lentis (9); however, expression patterns of *ADAMTS* (L) genes in ocular tissues were not well understood and there is no comprehensive study focusing on the expression patterns of *ADAMTS* (L) genes in ocular tissues and in different ages to determine the main subset of the *ADAMTS* (L) genes in different eye tissues and in different age stages. In this study, we investigated relative gene expression pattern of *ADAMTS*(L) superfamily in five ocular tissues including trabecular meshwork (TM), lens, retinal pigment epithelium (RPE), macula, and optic nerve in three different age groups.

Materials and Methods

Human eye samples and grouping

The study was approved by the Institutional Review Board of the Central Eye Bank of Iran and the ethics committee of Research Institute for Ophthalmology and Vision Science of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IRB no: IR.SBMU.ORC.REC.1391.008). Legal guardians of donors have given their written informed consent.

In 2019, nine normal human eye globes that were allocated for research purposes, were obtained from the Central Eye Bank of Iran (Tehran, Iran) and divided into three groups based on age: infants (<3 yr old), adults (20-50 yr old) and elderly (>50 yr old). None of the donors had past ocular or family history of inherited or familial ocular disorders. The RPE layer, optic nerve, lens, macula, and TM tissues were removed by an ophthalmic pathologist (MRK) and preserved in RNA later stabilization solution (#AM7020, Thermo Fisher Scientific, Waltham, MA, USA) for following experimental use.

RNA purification and quantitative Real-time PCR

Total RNA was extracted from the tissues by using QIAzol Lysis Reagent according to the manufacturer's instructions (#79306, Qiagen, Germany). NanoDrop (Thermo Fisher Scientific, Waltham, MA, USA) and agarose gel electrophoresis

were used to determine the concentration/purity and the integrity of the isolated RNAs, respectively. Reverse transcription was performed using Random hexamers and avian myeloblastosis virus reverse transcriptase (Cinnagen, Tehran, Iran) according to the instructions. Primers were designed for all 26 human ADAMTS(L) genes superfamily and quantitative real-time PCR was then performed using the QuantiFast SYBR Green PCR Kit (#204054, Qiagen, Germany) and Corbett 65H0 instrument (Corbett Research, Sidney, Australia). The real-time PCR parameters were an initial denaturation (one cycle at 95 °C for 15 min); denaturation, annealing and extension at 95 °C for 15 sec, 55 °C for 25 sec and 72 °C for 25 sec, respectively, for 40 cycles; and a melting curve, 72 °C, with the temperature gradually increasing (0.5 °C) to 95 °C. All defined real-time PCR reactions were repeated four times. *GAPDH* was used as a normalizer gene. Analyses of expression levels for gene transcripts were performed by evaluating threshold cycle (Ct) values using RotorGene 6000 software of the instrument (Corbett Industries, Sydney, Australia). All the expression curves were confirmed by comparing the melting temperatures of the amplicons to omit any misinterpretation of the data, especially in the low level expressed genes (Ct more than 35).

Statistical analysis

Ct values were exported from the RotorGene 6000 software into Excel and analyzed. Normalized data against the control gene were used for comparisons between groups by using SAS6.12 software (SAS institute Inc., Cary, NC, USA). Comparisons of the means of normalized Ct values for each gene between age groups and between ocular tissues were done using Duncan's new multiple range test (MRT). The values were presented as mean ± standard error of the mean (SEM). $P< 0.01$ was considered statistically significant.

Results

We had the results of more than 4000 real-time PCR reactions for analysis (26 genes × 5 tissues × 9 samples × 4 repeats= 4680 reactions). Two kinds of comparisons were done: a) assessment of expression level for each gene in each age group with comparison between all the five different ocular tissues (Table 1) and b) assessment of expression level for all *ADAMTS*(L) genes superfamily in each investigated tissue with comparison between all the age groups (Table 2, Figs. 1-5). All the significant *P*-values are shown in the Table 1 and 2. Generally, in each age group, and each investigated ocular tissue, some of the *ADAMTS*(L) genes showed relative high expression levels compared with the other family members.

Table 1: Significant difference in the expression of each *ADAMTS* (L) member between different ocular tissues in each age group

Gene	*Age groups*	*TM vs. LENS*	*TM vs. RPE*	*TM vs. MAC*	*TM vs. ON*	*LENS vs. RPE*	*LENS vs. MAC*	*LENS vs. ON*	*RPE vs. MAC*	*RPE vs. ON*	*MAC vs. ON*
ADAMTS-1	Infant										
	Adult		*	*		*					
	Elderly		*	*			*				*
ADAMTS-2	Infant									*	
	Adult		*	*		*					
	Elderly		*	*		*	*			*	*
ADAMTS-3	Infant		*	*	*	*	*	*			
	Adult										
	Elderly	*		*	*	*		*	*	*	*
ADAMTS-4	Infant										
	Adult		*		*	*		*		*	*
	Elderly	*	*		*	*		*	*	*	*
ADAMTS-5	Infant	*									
	Adult										
	Elderly			*			*	*	*		*
ADAMTS-6	Infant		*	*	*					*	
	Adult		*	*	*	*	*	*			

Table 1: Continued: Significant difference in the expression...

	Elderly		*	*	*	*	*	*				*
ADAMT	Infant		*	*	*							
S-7	Adult											
	Elderly											
ADAMT	Infant			*								
S-8	Adult											
	Elderly				*							*
ADAMT	Infant											
S-9	Adult	*			*							
	Elderly	*	*	*	*	*		*	*	*	*	
ADAMT	Infant											
S-10	Adult											*
	Elderly	*	*	*	*			*	*	*	*	
ADAMT	Infant		*	*	*	*	*	*				
S-12	Adult								*			
	Elderly	*	*				*	*	*	*		
ADAMT	Infant		*	*	*		*		*		*	
S-13	Adult	*		*	*							
	Elderly	*	*						*			
ADAMT	Infant		*	*	*	*	*	*				
S-14	Adult						*		*		*	
	Elderly	*			*	*	*	*		*	*	
ADAMT	Infant		*		*				*	*		
S-15	Adult							*				
	Elderly		*		*	*		*	*	*	*	
ADAMT	Infant								*		*	
S-16	Adult	*	*		*		*				*	
	Elderly	*	*			*		*			*	
ADAMT	Infant		*	*	*						*	
S-17	Adult	*				*		*				
	Elderly	*	*	*	*	*	*	*				
ADAMT	Infant				*			*	*	*		
S-18	Adult											
	Elderly											
ADAMT	Infant		*	*	*				*		*	
S-19	Adult					*			*			
	Elderly	*	*		*							
ADAMT	Infant		*							*	*	
S-20	Adult		*	*		*	*					
	Elderly	*				*	*	*				
ADAMT	Infant		*	*					*	*	*	
SL-1	Adult										*	
	Elderly	*	*		*							
ADAMT	Infant		*	*		*	*					*
SL-2	Adult											
	Elderly											
ADAMT	Infant		*	*								
SL-3	Adult	*		*	*	*		*	*		*	
	Elderly	*	*		*	*	*	*	*		*	
ADAMT	Infant									*		
SL-4	Adult		*			*						
	Elderly											
ADAMT	Infant						*	*	*	*		
SL-5	Adult											
	Elderly											
ADAMT	Infant											
SL-6	Adult											
	Elderly											
PAPLN	Infant											
	Adult											
	Elderly											

TM; Trabecular Meshwork, RPE; Retinal Pigment Epithelium, MAC; Macula, ON; Optic Nerve.
*; $P < 0.01$ and it was considered statistically significant.

Table 2: Significant difference in the expression of each *ADAMTS* (L) member between different age groups in each ocular tissue

Gene	*Ocular Tissue*	*Infants vs. Adults*	*Infants vs. Elderly*	*Adults vs. Elderly*
ADAMTS-1	TM			
	LENS			
	RPE			
	MAC			
	ON	*	*	
ADAMTS-2	TM			
	LENS			
	RPE			
	MAC			
	ON		*	
ADAMTS-3	TM		*	
	LENS			
	RPE	*	*	
	MAC	*	*	
	ON			
ADAMTS-4	TM	*		*
	LENS	*	*	
	RPE	*	*	
	MAC	*	*	
	ON	*	*	
ADAMTS-5	TM			
	LENS	*	*	
	RPE			
	MAC			
	ON			
ADAMTS-6	TM	*	*	
	LENS			
	RPE		*	*
	MAC		*	*
	ON		*	
ADAMTS-7	TM	*	*	
	LENS	*	*	
	RPE			
	MAC			
	ON			
ADAMTS-8	TM	*	*	
	LENS			
	RPE			
	MAC			
	ON		*	
ADAMTS-9	TM			
	LENS			
	RPE			
	MAC			
	ON			
ADAMTS-10	TM		*	
	LENS			
	RPE			
	MAC			
	ON			
ADAMTS-12	TM		*	*
	LENS			
	RPE			
	MAC			
	ON	*	*	
ADAMTS-13	TM			
	LENS			
	RPE			
	MAC			
	ON			*
ADAMTS-14	TM		*	*
	LENS			
	RPE	*	*	
	MAC			
	ON	*	*	*

Table 2: Continued: Significant difference in the expression…

ADAMTS-15	TM			
	LENS			
	RPE	*	*	
	MAC			
	ON	*	*	*
ADAMTS-16	TM	*		*
	LENS	*	*	*
	RPE	*	*	*
	MAC	*		*
	ON	*		*
ADAMTS-17	TM		*	*
	LENS		*	*
	RPE	*	*	
	MAC	*	*	
	ON		*	
ADAMTS-18	TM	*		
	LENS			
	RPE	*	*	
	MAC			
	ON			
ADAMTS-19	TM			
	LENS			*
	RPE	*		*
	MAC			
	ON		*	*
ADAMTS-20	TM			
	LENS			
	RPE	*	*	*
	MAC			*
	ON			
ADAMTSL-1	TM	*	*	
	LENS			*
	RPE	*	*	*
	MAC			
	ON			
ADAMTSL-2	TM			
	LENS			
	RPE	*		*
	MAC	*		
	ON			
ADAMTSL-3	TM			
	LENS	*	*	
	RPE	*	*	*
	MAC	*	*	
	ON		*	*
ADAMTSL-4	TM		*	*
	LENS		*	*
	RPE			
	MAC			
	ON		*	*
ADAMTSL-5	TM	*		*
	LENS	*		
	RPE	*		*
	MAC	*		*
	ON			
ADAMTSL-6	TM			
	LENS			
	RPE			
	MAC			
	ON			
PAPLN	TM			
	LENS			
	RPE			
	MAC	*		*
	ON	*	*	*

TM; Trabecular Meshwork, RPE; Retinal Pigment Epithelium, MAC; Macula, ON; Optic Nerve.
*; $P<0.01$ and it was considered statistically significant.

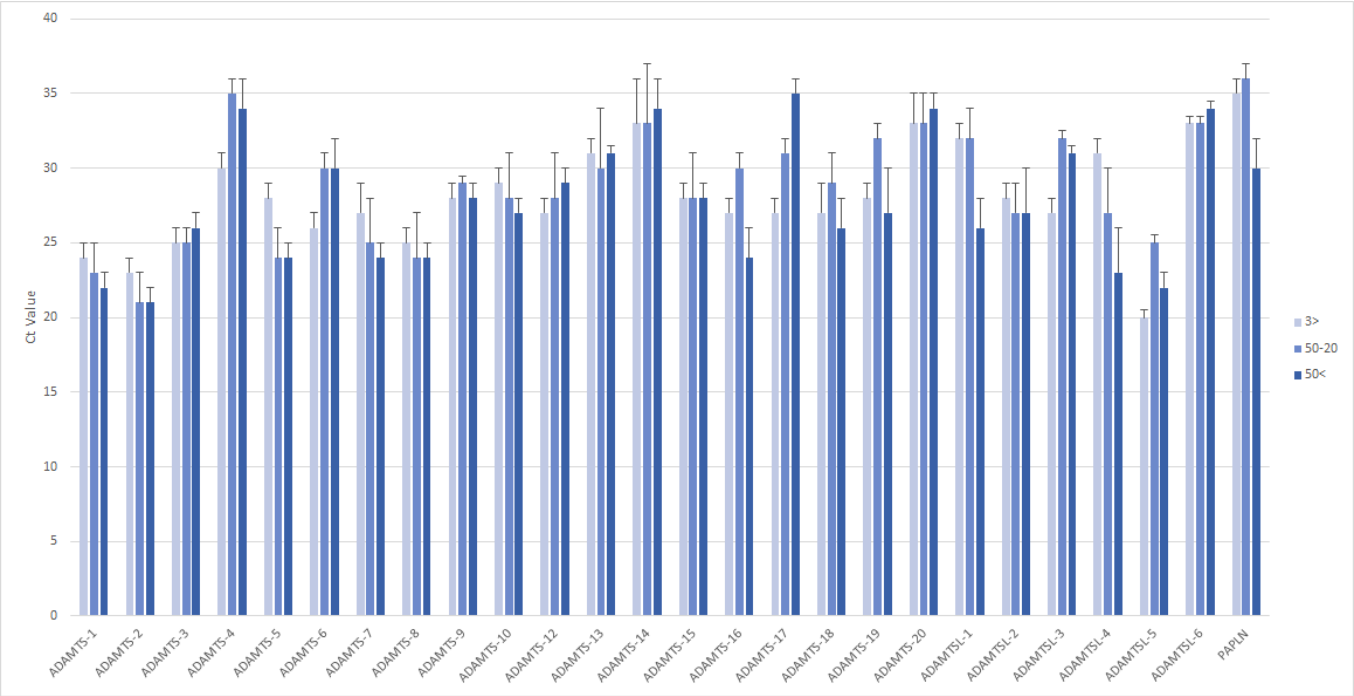

Fig. 1: Differential expression of each *ADAMTS*(L) member among three different age groups in lens tissue

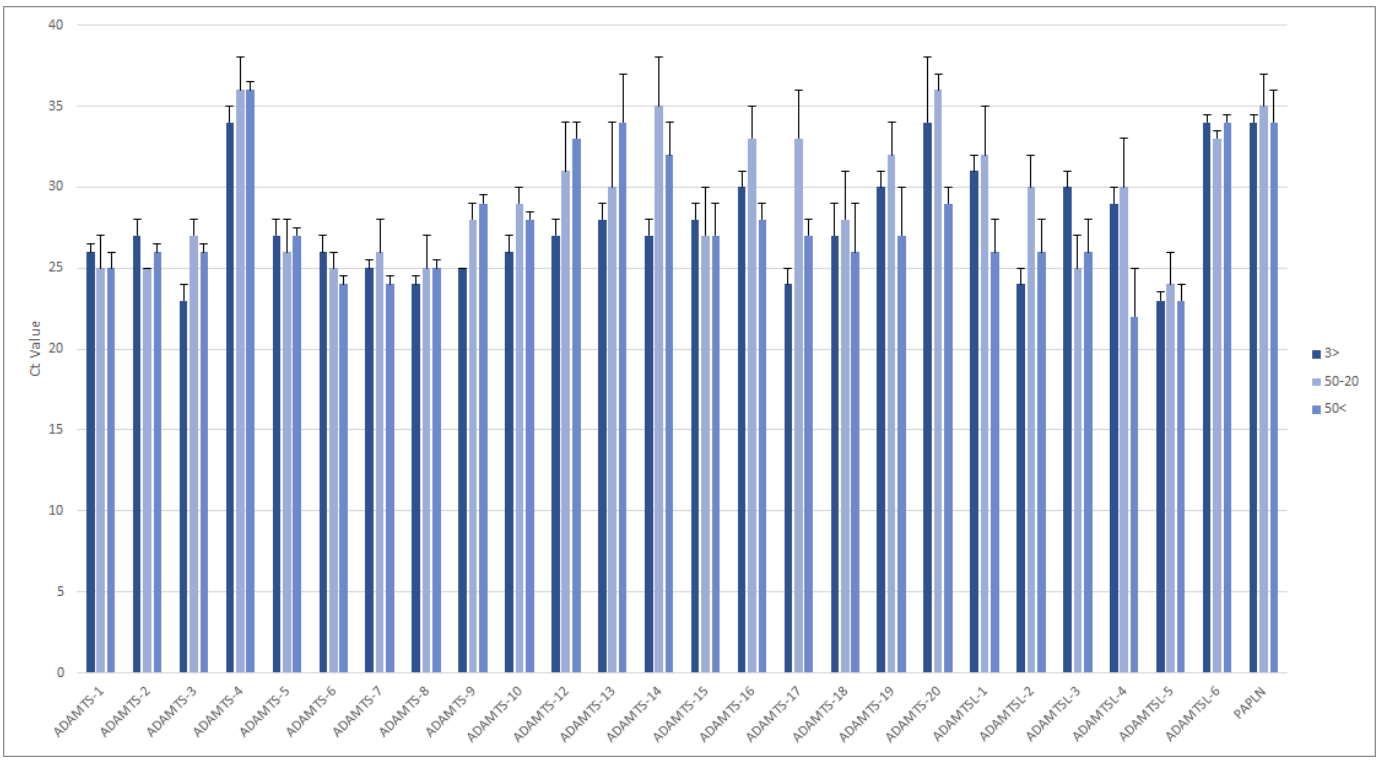

Fig. 2: Differential expression of each *ADAMTS*(L) member among three different age groups in macular tissue

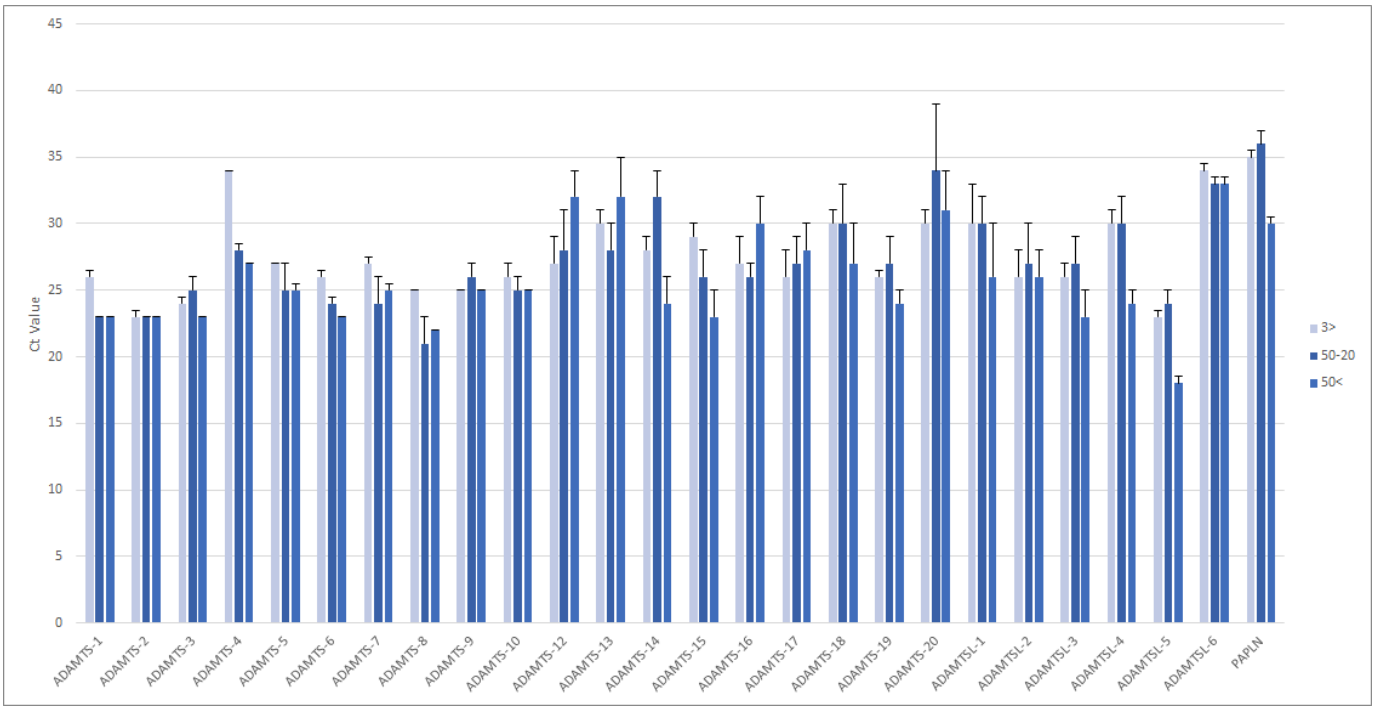

Fig. 3: Differential expression of each *ADAMTS*(L) member among three different age groups in optic nerve tissue

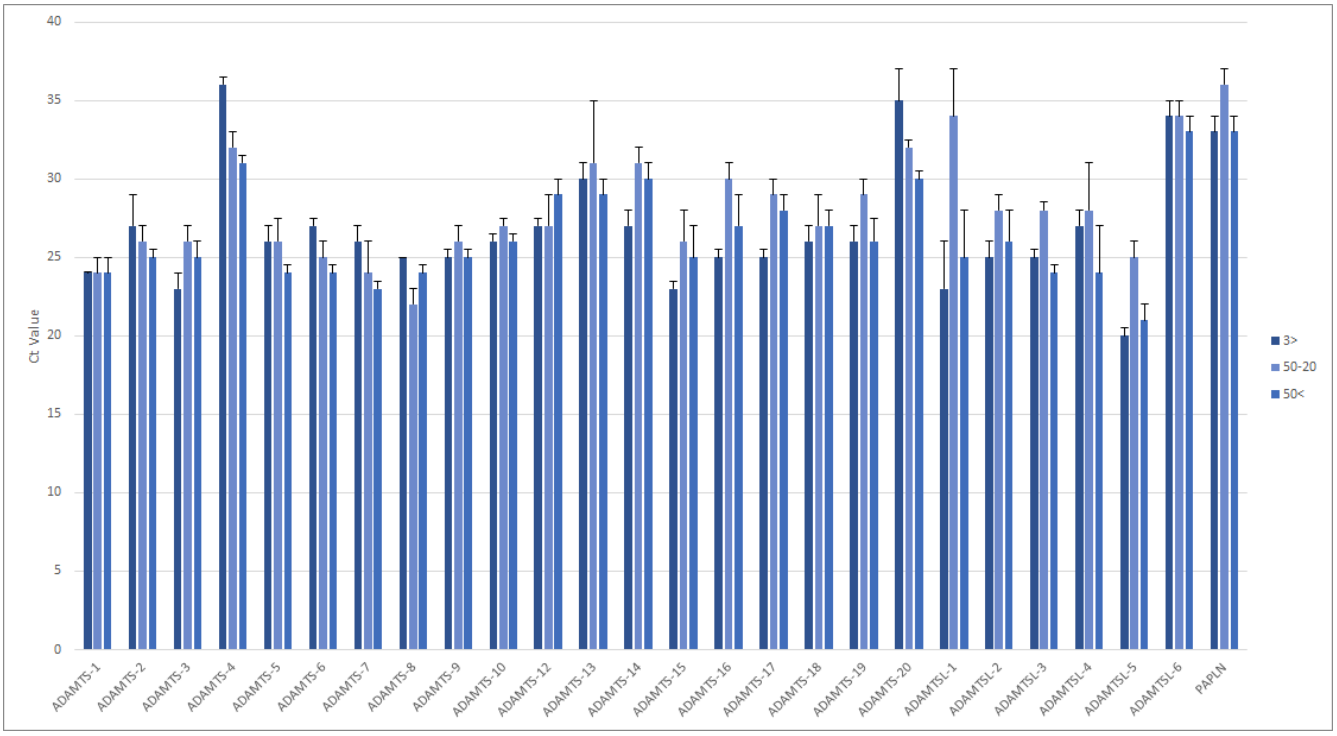

Fig. 4: Differential expression of each *ADAMTS*(L) member among three different age groups in retinal pigment epithelium tissue

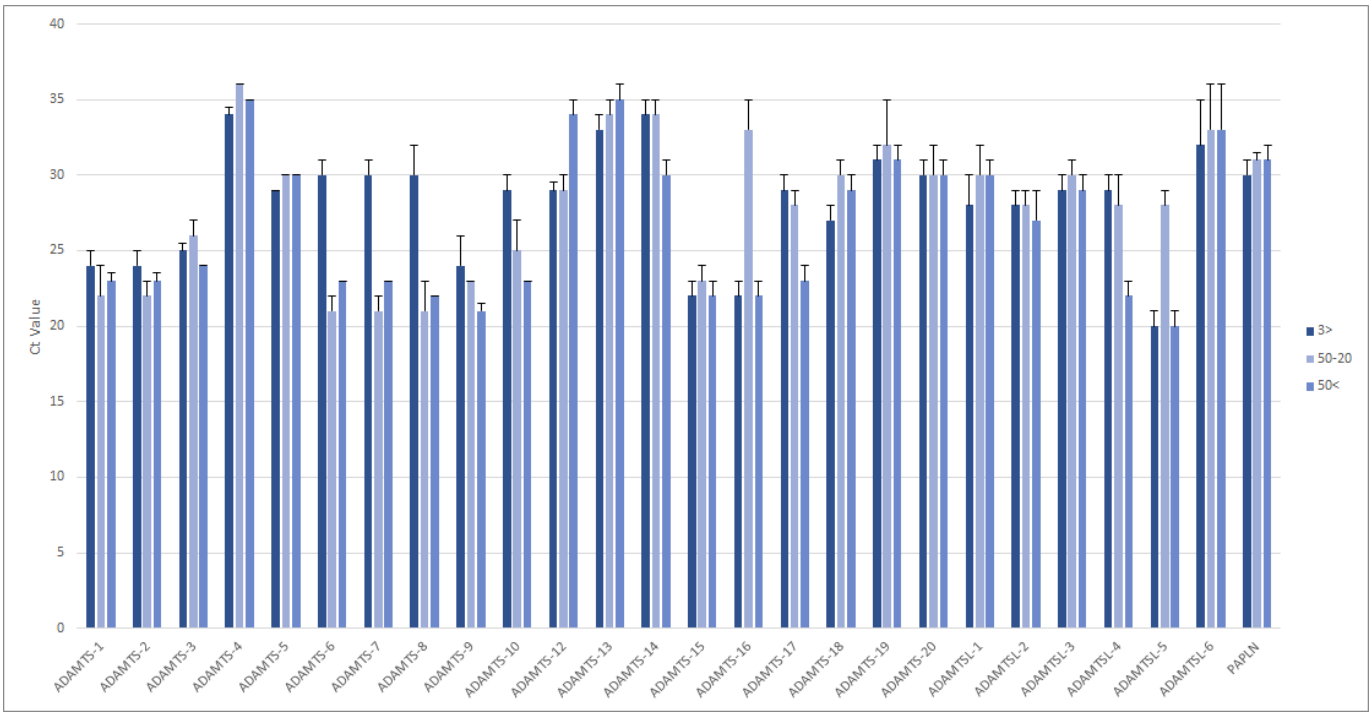

Fig. 5: Differential expression of each *ADAMTS*(L) member among three different age groups in trabecular meshwork tissue

Relative expression of ADAMTS(L) members in the ocular tissues of infants

Regarding relative expression analysis between age groups, *ADAMTSL-1* in TM tissue, *ADAMTS-4* and *ADAMTSL-3* in lens tissue, *ADAMTS-3*, *-14*, *-15*, *-16*, *-17*, *-18* and *ADAMTSL-1* in RPE tissue, *ADAMTS-3*, *-4*, *-17* and *ADAMTSL-3* in macular tissue and *ADAMTS-12* in optic nerve tissue received from infant subjects had significantly high expression level in comparison with other age groups. Moreover, *ADAMTS-4* in TM tissue, *ADAMTS-17* in optic nerve and lens tissue from infant donors had significantly higher expression than elderlies. Moreover, *ADAMTS-18* in TM tissue, *ADAMTSL-2* in RPE and macular tissue, *ADAMTSL-5* in lens, RPE and macular tissue, *ADAMTS-16* and *PAPLN* in macula and optic nerve tissue and *ADAMTS-14* in optic nerve donated from infant subjects had significantly higher expression than adults (Table 2).

Relative expression of ADAMTS(L) members in the ocular tissues of adults

Only *ADAMTS-8* had high expression level in RPE tissue received from adult group in comparison with the RPE tissue extracted from other age groups. *ADAMTS-6*, *-7*, *-8* in TM tissue, *ADAMTS-5*, *-7* in lens tissue, *ADAMTS-4* in RPE and optic nerve tissues, *ADAMTS-1*, *-15* in optic nerve tissue from adult subjects had higher expression levels compared with the tissues of infants. Moreover, *ADAMTS-12* in TM tissue, *ADAMTS-17* in lens tissue, and *ADAMTS-13* in optic nerve tissue from adult subjects showed higher expression levels in comparison with elderlies (Table 2).

Relative expression of ADAMTS(L) members in the ocular tissues of elderlies

ADAMTS-14, *-17* in TM tissue, *ADAMTS-16* and *ADAMTSL-4* in lens tissue, *ADAMTS-6*, *-20* and *ADAMTSL-3* in RPE tissue, *ADAMTS-6* in macular tissue and *ADAMTS-14*, *-15*, *-19* and *ADAMTSL-3*, *-4*, and *PAPLN* in optic nerve

tissue from elderlies had higher expression levels in comparison with other age groups. Moreover, *ADAMTS-3*, *-6*, *-7*, *-8*, *-10* in TM tissue, *ADAMTS-5*, *-7* in lens tissue, *ADAMTS-4* in RPE tissue, and *ADAMTS-1*, *-2*, *-4*, *-6*, *-8* in optic nerve tissue of elderlies had higher expression levels compared with infants. Moreover, *ADAMTS-4*, *-16* and *ADAMTSL-5* in TM tissue, *ADAMTS-19* and *ADAMTSL-1* in lens tissue, *ADAMTS-16*, *-19* and *ADAMTSL-1*, *-2*, *-5* in RPE tissue, *ADAMTS-16*, *-20* and *ADAMTSL-5*, and *PAPLN* in macular tissue, and *ADAMTS-16* in optic nerve tissue had higher expressions in elderly subjects in comparison with adults (Table 2).

Discussion

Expression profiling of *ADAMTS*(L) genes in human ocular tissues of three different age groups have been shown in this study. Differential expression of these genes may be associated with some ocular phenotypic features and functional roles reported for the *ADAMTS*(L) genes. Among ADAMTS(L) proteins, ADAMTS-2, -3 and -14 have procollagen N-propeptidases activity (10-12). Mutations in the *ADAMTS-2* gene is associated with Ehlers-Danlos syndrome type 7C, a connective tissue disorder (13). Our results showed that *ADAMTS-2*, *-3*, and *-14*, has more expression levels in ocular tissues obtained from elderlies. The pathogenesis process of some of the late onset ocular diseases may be associated with disruption in expression or function of these ADAMTSs, as some ocular diseases like age-related macular degeneration (AMD) and retinopathies are emerged in elderly ages (14).

ADAMTS-4 and -5 have aggrecan degradation property (15, 16). ADAMTS-4 expression level is increased in response to elevation of intraocular pressure in normal and glaucomatous eyes. "Also, in human TM cells, ADAMTS-4 colocalized with cortactinin podosome- or invadopodia-like structures and therefore can increase outflow facility. ADAMTS-4 is expressed in the juxtacanalicular region of the TM in increased pressure situation of anterior segments. Moreover, cytokine treatment of TM cells increases mRNA expression of *ADAMTS-1*, *-4*, and *-5"* (17). In this study, observed high expression of *ADAMTS-4* in TMs of both infants and elderly subjects may be related to the supposed role of ADAMTS-4 for outflow facility which its disruption is the major glaucomatous feature.

ADAMTS-1 has anti-tumor and anti-angiogenesis activities based on VEGF inhibition (18, -19). We observed a high expression level of *ADAMTS-1* in optic nerve tissues from adult and elderly subjects, related to its inhibitory role for the angiogenesis process.

Similarly, ADAMTS-8 (20) and -9 (21) have anti-angiogenesis activity. Tumor necrosis factor-α (TNFα) plays a role in the development of retinal neovascularization (22) and RPE cell migration (23), which are features of AMD and other retinal disorders. The expression of ADAMTS-1, -6 and -9 was upregulated in the treatment of ARPE-19 cells, a human retinal pigment epithelial cell line, with TNFα (24), indicating that these ADAMTSs may have a role in inflammatory eye diseases (24). Our results showed that these ADAMTSs are expressed in ocular tissues with adult and elderly ages, specifically in RPE, TM and optic nerve tissues, associated with anti-angiogenesis activity in the tissues.

ADAMTS-18 is required for proper photoreceptor cell function and pathogenic role of mutated *ADAMTS-18* gene in inherited retinal dystrophies has been indicated (25, 26). In addition, *ADAMTS-18* gene is associated with Knobloch syndrome (27). In this study, high levels of *ADAMTS-18* were expressed in the TM and RPE tissues of infants, as previously revealed the expression of ADAMTS-18 in lens and retinal tissues in the developing murine eyes (27).

Similarly, ADAMTS-16 controls optic fissure closure through the basement membrane degradation at the closing optic fissure edges and promoting cell proliferation (28). We demonstrated high expression of *ADAMTS-16* in RPE, macula and optic nerve tissues received from infant subjects. In contrast, its high expression level was observed in TM and lens tissues of elderlies.

ADAMTS-10 is a regulator of fibrillin microfibril assembly (29), by binding to fbn1 (7). Moreover, this ADAMTS binds heparan sulphate (HS) and supports epithelial cell–cell junction and focal adhesion formation (30). Mutations in *ADAMTS-10* are associated with Weill–Marchesani Syndrome (WMS) (9, 31) and primary Norwegian Elkhound primary glaucoma (32). Our results identified high expression level of *ADAMTS-10* in TM tissue of elderly subjects.

Similarly, ADAMTS-6 as an active homologue of ADAMTS-10 (33), can bind to HS and cleave Fbn1 and syndecan-4 (30). ADAMTS-10 has essential role in ZO-1-rich tight junction integrity in epithelial cells. In contrast, ADAMTS-6 depletion enhances tight junctions and ADAMTS-10 negatively regulates ADAMTS-6 expression (30). We demonstrated that ADAMTS-6 has a high expression level in TM tissues from adults. Additionally, ADAMTS-6 showed high expression levels in TM, RPE, macula and optic nerve tissues from elderly group, in which the ZO-1-rich tight junction integrity in the corresponding ocular tissues may be weak.

ADAMTS-17 plays pivotal role in crystalline lens zonules and connective tissue formation, and mutations in *ADAMTS-17* cause WMS-like syndrome (9, 34, 35). In this study, this ADAMTS showed a high expression only in lens tissue of adults. Besides, high expressions of *ADAMTS-17* were observed in RPE, macula, optic nerve and lens tissues from infants. Moreover, a high expression level of *ADAMTS-17* was detected in TM tissue of elderly subjects.

Conclusion

To the best of our knowledge, this is a comprehensive study focusing on the expression pattern of *ADAMTS*(L) superfamily of genes in various ocular tissues at different age groups. We demonstrated that the members of *ADAMTS*(L) superfamily have often different expression in different ocular tissues. In addition, the expression of the most members was different between age groups in the same tissues. This knowledge gives the researches a better chance of selection of the *ADAMTS*(L) superfamily members to identify diagnostic and prognostic markers. Further studies are required to explore the other ocular tissues not included in this study and also determine their protein expression levels.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

All the authors declare that they have no competing interests.

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