Int Ophthalmol (2019) 39:2621–2628
https://doi.org/10.1007/s10792-019-01111-x

ORIGINAL PAPER

Association of *KIF26B* and *COL4A4* gene polymorphisms with the risk of keratoconus in a sample of Iranian population

Saman Sargazi · Mahdiyeh Moudi · Milad Heidari Nia · Ramin Saravani · Hamid Malek Raisi

Received: 23 October 2018 / Accepted: 30 April 2019 / Published online: 10 May 2019

Abstract

Purpose Keratoconus (KTCN) is a congenital corneal eye disorder which correlates with abnormal distribution of the collagen fiber and causes loss of visual acuity. *COLA4A* gene has a substantive role in collagen synthesis, whereas *KIF26B* as a new candidate gene belonging to kinesin superfamily (KIFs) has been suggested to be associated with this disease. So, in this preliminary study, we simultaneously evaluated the effects of two single nucleotide polymorphisms, 222855rs7C/T and rs12407427C/T, on KTCN susceptibility in a sample of Iranian population.

Methods The present case–control study consists of 144 patients confirmed with KTCN and 153 healthy controls. The variants are genotyped by using amplification refractory mutation system–polymerase chain reaction method.

Results The findings disclosed that rs2228557C/T and rs12407427C/T polymorphisms significantly increased the risk of KTCN in measured

S. Sargazi
Department of Clinical Biochemistry, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

S. Sargazi · M. Moudi · M. Heidari Nia · R. Saravani (✉)
Cellular and Molecular Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
e-mail: saravaniramin@yahoo.com

M. Moudi
Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

M. Heidari Nia
Department of Biology, Faculty of Science, Isfahan University, Isfahan, Iran

R. Saravani
Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

H. Malek Raisi
Infectious Diseases and Tropical Medicine Research Center, Resistant Tuberculosis Institute, Zahedan University of Medical Sciences, Zahedan, Iran

(codominant1; $p = 0.0001$, codominant2; $p = 0.0001$, codominant3; $p = 0.0006$, dominant; $p = 0.0001$, over-dominant; $p = 0.0005$) and (codominant1; $p = 0.0001$, codominant3; $p = 0.0005$, recessive; $p = 0.0001$) inheritance patterns, respectively.

Conclusion Our results did prove a statistical association of both rs2228557 and rs12407427 genotypes (TT and CT + CC) and allele (T) with KTCN susceptibility in Iranian population. Further studies in other ethnicities are required to verify our results.

Keywords *COL4A4* · *KIF26B* · Keratoconus · Gene polymorphism

Introduction

Keratoconus (KTCN) is known as a frequent asymmetric, congenital corneal ectasia which is indicated by myopic and irregular astigmatism, stroma hypoplasia [1], and abnormal distribution of the collagen fiber, causing the reduced mechanical resistance of the cornea. Using slit-lamp microscopy, Fleischer's ring is markedly observed in KTCN patients [2]. Studies have revealed that KTCN affects approximately between 1 in 500 and 1 in 2000 in the general population with no significant gender difference [3, 4], but early forms of KTCN may go undetected without performing the anterior corneal topography [2]. The onset of the disease is normally at puberty. Following 10–20 years, scars are formed in both eyes, and usually this condition results in severe visual impairment [5]. Despite the fact that this disease proved to have a strong genetic component, not many genes have been identified to be responsible for this non-inflammatory corneal thinning disease, while 6% to 23% of patients with KTCN report a positive family background, having a much higher concordance rate in twins from the same zygote [6, 7]. It has been proposed that ethnic origin influences the incidence of this genetic disorder since Asians have a higher incidence of KTCN compared with white patients [8]. Although KTCN is inherited in both recessive and dominant forms, it appears to be an isolated sporadic eye disease. Most family members of patients with KTCN are diagnosed with autosomal dominant [9] with an ill-defined underlying biochemical mechanism. Former investigations suggested a possible genetic association between KTCN and other rare inborn disorders such as Marfan syndrome, Ehlers–Danlos syndrome and Apert syndrome [4]. Also, linkage mapping analysis has revealed a number of candidate genes influencing KTCN including collagen *COL4A3* and *COL4A4* encoding the human basement membrane α3 (IV) and α4 (IV) collagen chains, respectively [10]. The *COL4A4* gene (mapped in the 2q35–q37 region) provides instructions for making one component of type IV collagen, a flexible and structural protein found exclusively in cell basement membranes of the various connective tissues [11]. Accordingly, type IV procollagen missense mutations are formerly linked to defects of the eye, kidney, and vascular stability [12]. Besides, variants found in the kinesin superfamily (KIFs) encoding genes have been recently found to be linked to the development of neurologic disorders, due to possessing several functions in axonal transport and neuronal migration [13]. Comparative evaluation of the aqueous humor proteome of patients with optical disorders indicated that *KIF26B* has a high protein level in individuals suffering from primary angle closure glaucomas (PACG) [14]. Meanwhile, genome-wide association studies identified *KIF26B* as a potential novel gene locus for KTCN [15, 16], but the underlying mechanisms are still ill-defined.

Since the data on the literature are limited, in this preliminary study, we aimed to simultaneously evaluate rs12407427C/T (in *KIF26B*) and rs2228557C/T (in *COL4A4*) polymorphisms in a case–control sample panel of the Iranian population.

Methods

Subjects

The Ethics Committee of the Zahedan University of Medical Sciences approved the protocol of the study (ethical code: IR.ZAUMS.REC.1397.419). A total of 144 patients (63 men and 81 women) confirmed with KTCN recruited from Alzahra Eye Hospital, Zahedan University of Medical Sciences, Zahedan, Iran, with a wide age range (from 10 to 80 years), and also 153 healthy individuals (68 men and 85 women) were enrolled as the control group, aged 8 to 83 years. Diagnosis of KTCN was established based on both clinical examinations and medical history. Slit-lamp

biomicroscopy and retinoscopy examination was used to determine the presence or absence of KTCN symptoms (i.e., Fleischer ring, oil droplet sign, scissoring of the red reflex, photokeratoscopy, and videokeratography signs), while age, contact lens wearing, eye rubbing, and systemic and connective tissue diseases history were regarded as criteria for KTCN confirmation. All control participants also had a detailed ophthalmic examination to exclude severe KTCN. Keratometry was done using four quantitative video-keratographic indices such as Sim-K astigmatism 41.5 D, inferior–superior dioptric asymmetry over 1.2 D, central corneal power 447.2 D, and skewed radial axes $> 21°$. Table 3 summarizes the pathological and clinical features of patients with KTCN and their correlation with *COL4A4* polymorphisms. *p*-values < 0.05 are bolded in Tables 3 and 4.

Each participant was arranged to have a blood sample collected into a 0.5 M EDTA containing tube. By using the salting-out method, genomic DNAs were isolated from the peripheral white blood cells [17]. To verify the integrity of isolated DNA, all samples were run on a 1% agarose gel.

Genotyping

Information of the variants of *COL4A4* and *KIF26B* genes is shown in Table 1. The sequence of *COLA4A* and *KIF26B* gene was obtained from the gene database available at (http://www.ncbi.nlm.nih.gov). Specific reverse wild-type, reverse mutant and common forward primers designed using Gene Runner (version 3.00, Hasting Software, Inc.) were 5′-GCCAGAAGCTATACTTATTTGAG-3′, 5′-GCCAGAAGCTATACTTATTTGAA-3′ and 5′-TGTGTCTGAGCCCTAATTCT-3′ (for rs2228557) and 5′-GAGAACAGATGAGTGTCTCAAGCG-3′, 5′-GAGAACAGATGAGTGTCTCAAGCA-3′ and 5′-GATAATGTGTGTGCGATTGT-3′ (for rs12407427), respectively. Genotyping of rs12407427 and rs2228557 was performed via amplification refractory mutation system (ARMS)–PCR method [18]. For each PCR, 3 μL of genomic DNA ($\sim$ 100 ng/mL), 1 μL of each primer (10 ng/mL) (Pishgam Co., Tehran, Iran), 10 μL of master mix (Ampliqon Taq 2 × mastermix, Denmark), and 5 μL DNase-free distilled water (SinaClon Bio-Science Co., Tehran, Iran) were added to a final volume of 20 μL. Reactions were performed in a thermal cycler at 95 °C for 5 min followed by 35 cycles at 96 °C for 35 s, 55 °C or 61 °C (based on Table 3 for each SNP) for 35 s, and 72 °C for 35 s. These cycles were followed by a final extension step at 72 °C for 5 min. The PCR products were then electrophoresed on 2% agarose and observed by a standard ultraviolet transilluminator gel imaging system. In order to confirm the validity of our findings, at least 30% of the samples were re-genotyped.

In silico analysis

In silico analysis was performed to evaluate the possible structural effects of *COL4A4* rs2228557C/T and *KIF26B* rs12407427C/T polymorphisms in the intronic and exonic regions. The nucleotide sequences of the *KIF26B* and *COL4A4* genes (accession no. NG_053061.1 and NG_011592.1, respectively) were deduced from the National Center for Biotechnology Information (NCBI) data bank. Mode 2 of RNAsnp was applied to determine the effects of the SNPs on the *KIF26B* and *COL4A4*-mRNA secondary structures. RNAsnp server predicts the effects of these two genetic variants on the local RNA secondary structure with the RNA folding algorithms. The graphical summary of the RNAsnp results showed the local region which detected maximum structural changes and colored according to the *p* values. When the

Table 1 Information of the variants of *COL4A4* and *KIF26B* genes

dbSNP	Chromosome	Functional consequence	Amino acid exchange	Chromosome position	Allele (major/minor)	MAF	Heterozygosity
rs12407427	1	Intergenic variant	–	1:245133143	T/C	0.2408	0.33
rs2228557	2	Exon variant/ synonymous	Syn F1644 (TTC/TTT)	2:227007466	T/C	0.4856	0.50

MAF: minor allele frequency

p value was > 0.2, there is no significant structural change and the region was colored in black.

Statistical analysis

SPSS 23.0 statistical package (SPSS, Chicago, IL) was used to analyze our data. All p values in this study were two-sided, and $p < 0.05$ was considered statistically significant. We used independent sample t test and Chi-square tests based on types of our information. In order to calculate the relationship between gene polymorphisms and KTCN, the logistic regression was performed using odds ratios (ORs) and 95% confidence intervals (CIs).

Results

In the present study, significant differences were found between healthy individuals and the patients in terms of age (patients: 27.77 ± 1.03, $p = 0.31$; controls: $29.71 \pm 1.25.6$, $p = 0.49$). Also, no significant difference was observed between the two groups regarding gender ($p = 0.51$). As shown in Table 2, no significant correlation was found concerning rs12407427 and rs2228557 polymorphisms with the clinicopathological characteristics of KTCN patients and controls ($p > 0.05$). In Table 3, the distribution of allele frequencies and the genotype of rs2228557T/C are shown in the studied groups. Our findings revealed that *COL4A4* rs2228557T/C significantly increased the risk of KTCN in codominant (OR 6.31, 95% CI 33.17–12.62 for CT and OR 5.62, 95% CI 2.42–13.03 for CC), dominant (OR 0. 6.06, 95% CI 3.07–11.93), and over-dominant (OR 2.72, 95% CI 1.67–4.43) patterns ($p < 0.001$). The respective frequencies of the CT and CC genotypes of this SNP were 49.7 and 14.3% in the healthy controls and 72.9% and 18.8% in the patients with KTCN where the presence of C allele was associated with KTCN ($p < 0.001$).

According to genotype and allele frequencies of rs12407427 C/T (shown in Table 4), CC genotype increased the risk of KTCN in both codominant (OR 5.62, 95% CI 2.53–12.46, $p < 0.001$) and recessive (OR 5.31, 95% CI 2.53–11.12, $p < 0.001$) forms, whereas the CT genotype was not associated with KTCN risk/protection in a codominant pattern. The respective frequencies of the CT and CC were 53 and 6.5% in the healthy individuals, while 43% and 27% of the KTCN patients displayed these genotypes, respectively.

Predicting *KIF26B* rs12407427C/T and *COL4A4* rs2228557C/T effects on local RNA secondary structure, we found that rs12407427C/T polymorphism made fundamental changes on the secondary structure of *KIF26B*-mRNA ($p = 0.03$) (Fig. 1), but rs2228557C/T did not show significant structural change on the secondary structure of *COL4A4*-mRNA ($p = 0.6$) (data not shown).

Discussion

KTCN is slow-progressing corneal dystrophy with a disruptive and excrescent distribution of type IV collagen in the basement membrane of the corneal epithelium [19, 20]. Although genetic variants located in *FOXO1*, *TGFBI*, *COLA43*, *COLA4A,* and *SOD* genes are recently found to be correlated with the risk of this disorder, the complete etiology of this relatively complex disease is not clear and numerous genetic risk factors associated with KTCN still remain to be identified [21]. Genes coding seven corneal types of collagens were already proved to have decreased expression levels in KTCN corneas, as this widespread downregulation is regarded as a marker for KTCN. Compared to normal controls with the identical genotype, downregulation of the *COL5A1* gene in KTCN patients with rs1536482 polymorphism was reported by Bykhovskaya et al. [22].

Kinesin family member 26B (*KIF26B*) is basically among the most up-regulated genes in gastric, breast and other types of solid tumors as increased expression of this oncogene was linked to tumor size, distant metastases and poor prognosis [23–25]. Although *KIF26B* has been implicated in the progression of human tumors, the exact impact of nucleotide variations located in this type of KIF is limited to a small number of studies. As previously stated, there is an increasing interest in uncovering possible links between *KIF26B* genetic mutations and the susceptibility to both neurologic and eye disorders. To the best of our knowledge, this is the first report describing the simultaneous genetic screening of one type IV collagen and a KIF encoding gene in a sample of Iranian population, suggesting a significant association between rs2228557 (located in the coding region of

Table 2 Association between clinicopathological characteristics of KTCN patients and SNPs

Parameters evaluated	Patients, *n* (%)	rs12407427, *P* value	rs2228557, *P* value
ID subjective			
Red eye	7 (4.9%)	0.76	0.92
Itchy red eye	3 (2.1%)		
Decreased visual acuity	16 (11.2%)		
Decreased visual acuity (right eye)	35 (24.3%)		
Decreased visual acuity (left eye)	22 (15.2%)		
Decreased visual acuity (both eyes)	19 (13.2%)		
Visual acuity decreased many months ago	12 (8.3%)		
Visual acuity decreased many months ago	27 (18.7%)		
Red eye and visual acuity decreased	3 (2.1%)		
KTCN ocular			
Right eye	43 (29.9%)	0.24	0.61
Left eye	37 (25.6%)		
Both eyes	64 (44.5%)		
Level of KTCN			
Level 1	35 (24.3%)	0.13	0.71
Level 2	46 (32%)		
Level 3	63 (43.7%)		
Cross-linking surgery			
Right eye	40 (27.8%)	0.1	0.88
Left eye	41 (28.5%)		
Both eyes	43 (29.9%)		
Candidate	20 (13.8%)		
Visit to CXL			
1 months later	59 (41%)	0.37	0.71
6 months later	36 (25.1%)		
1 year later	19 (13.1%)		
2 years later	12 (8.4%)		
3 years later	10 (7%)		
5 years later	2 (1.3%)		
Many years later	6 (4.1%)		

KTCN: keratoconus

COL4A4) and rs12407427 (as an intergenic variant of *KIF26B* gene which is mapped to 1q44 region) polymorphisms and the risk of KTCN. Our findings indicated that *COLA4A* rs2228557 codominant CC, CT and TT genotypes, the T allele, dominant CT + CC, and over-dominant CC genotypes significantly increased the risk of KTCN. Regarding *KIF26B* rs12407427 C/T, T allele was correlated with an increased risk of KTCN in our population which is consistent with previous studies highlighting the association between single nucleotide variations in both *COLA4A* and *KIF26B* genes with KTCN (3, 26). There is no evidence concerning the correlation between rs12407427 and KTCN susceptibility, but a genome-wide association study revealed such correlation with a *p*-value less than 0.0001 (16). Genetic variations in collagen synthesis may alter the risk of KTCN in different populations. Gene variants, specifically SNPs, indicate a complex convergence of various disease-related mechanisms. Several studies

Table 3 Genotypic and allelic frequencies of *COL4A4* polymorphism (rs2228557 T > C) in KTCN patients and control subjects

COL4A4 polymorphism	Kerato *n* (%)	Control *n* (%)	OR (95% CI)	*p* value
Codominant				
TT	12 (8.3%)	55 (36%)		**< 0.0001**
CT	105 (72.9%)	76 (49.7%)	6.31 (3.17–12.62)	**< 0.0001**
CC	27 (18.8%)	22 (14.3%)	5.62 (2.42–13.03)	**0.0006**
Allele				
T	129 (44.7%)	186 (60.7%)		
C	159 (55.3%)	120 (39.3%)	0.52 (0.37–0.72)	**< 0.0001**
Dominant				
TT	12 (8.3%)	55 (35.9%)		
CT + CC	132 (91.7%)	98 (64.1%)	6.06 (3.07–11.93)	**< 0.0001**
Recessive				
TT + CT	117 (81.2%)	131 (85.6%)		
CC	27 (18.8%)	22 (14.4%)	1.37 (0.74–2.54)	0.31
Over-dominant				
TT + CC	39 (27.1%)	77 (50.3%)		
CT	105 (72.9%)	76(49.7%)	2.72 (1.67–4.43)	**0.0005**

$p < 0.05$ was considered statistically significant

CI confidence interval, *OR* odds ratio

Table 4 Genotypic and allelic frequencies of *KIF26B* polymorphism (rs12407427 T > C) in KTCN patients and healthy subjects

KIF26B polymorphism	Kerato *n* (%)	Control *n* (%)	OR (95% CI)	*p* value
Codominant				
TT	43 (30%)	62 (40.5%)		**< 0.0001**
CT	62 (43%)	81 (53%)	1.10 (0.66–1.83)	0.705
CC	39 (27%)	10 (6.5%)	5.62 (2.53–12.46)	**< 0.0001**
Allele				
T	148 (51.3%)	205 (66.9%)		
C	140 (48.7%)	101 (33.1%)	1.92 (1.37–2.67)	**< 0.0001**
Dominant				
TT	43 (29.8%)	44 (44%)		
CT + CC	101 (70.2%)	56 (56%)	1.6 (0.98–2.58)	0.55
Recessive				
TT + CT	105 (72.9%)	143 (93.5%)		
CC	39 (27.1%)	10 (6.5%)	5.31 (2.53–11.12)	**< 0.0001**
Over-dominant				
TT + CC	82 (56%)	72 (47.1%)		
CT	62 (43%)	81 (52.9%)	0.67 (0.42–1.66)	0.08

$p < 0.05$ was considered statistically significant

CI confidence interval, *OR* odds ratio

reported that the RNA secondary structure is essential for the proper function of many noncoding RNAs and cis-regulatory elements of messenger RNAs (mRNAs) [26, 27]. For example, the secondary structure of transfer RNA (tRNA) has the effects on its function in the translation process [28]. The single nucleotide polymorphisms in the RNA sequences could interfere with their proper folding and hence cause a phenotypic effect. The mode 2 of RNAsnp software determined that rs12407427C/T polymorphism made fundamental effects on local RNA secondary structure of *KIF26B*-mRNA [29]. So, this variant may be one of the SNPs that may disrupt the local secondary structure of *KIF26B*-mRNA, may interfere with their molecular function, and thus is associated with KTCN susceptibility.

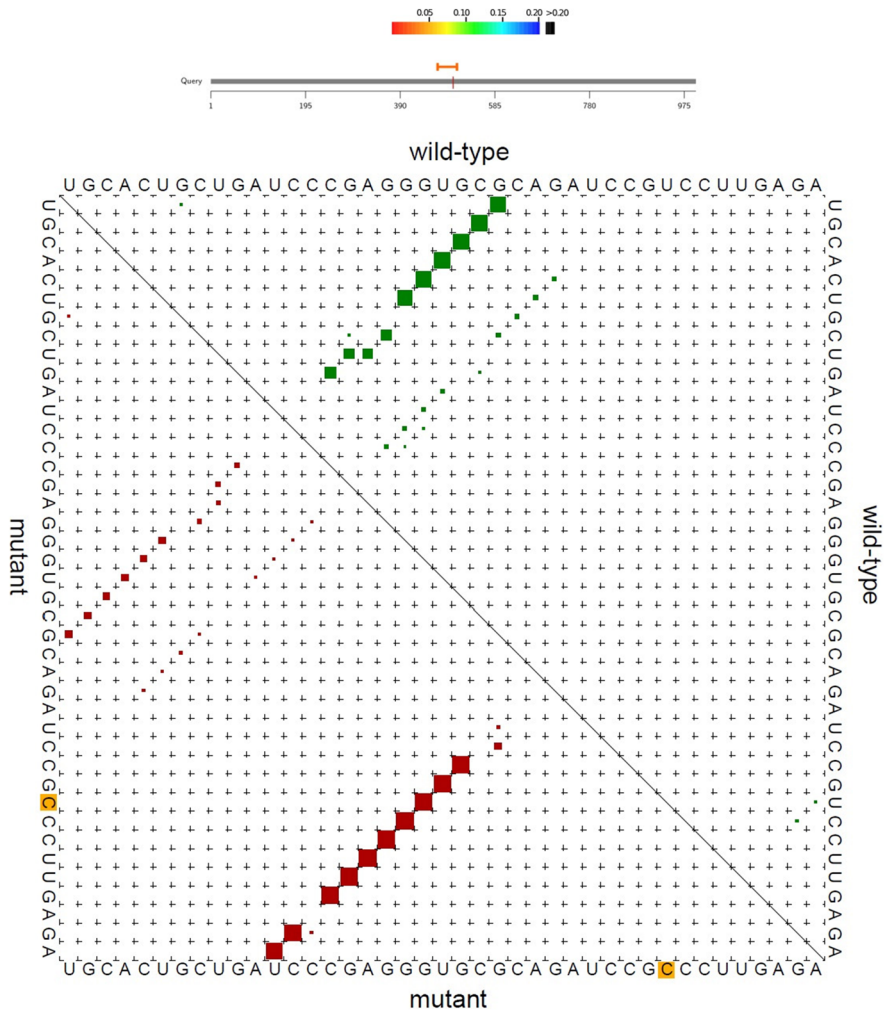

Fig. 1 Prediction of *KIF26B* rs12407427C/T on local RNA formation. In silico analysis revealed that the rs12407427C/T polymorphism affected the fundamental changes on the secondary structure of *KIF26B*-mRNA (p = 0.03)

Conclusion

We conducted a case–control study regarding the polymorphism screening of two genes in Iranian KTCN patients. Our results did confirm a possible involvement of both *COLA4A* and *KIF26B* in KTCN pathogenesis. Further mutation analysis of other fibrillar collagen genes on different populations is required to validate our results.

References

1. Guan T, Liu C, Ma Z, Ding S (2012) The point mutation and polymorphism in keratoconus candidate gene TGFBI in Chinese population. Gene 503(1):137–139
2. Rabinowitz YS (1998) Keratoconus. Surv Ophthalmol 42(4):297–319
3. Štabuc-Šilih M, Ravnik-Glavač M, Glavač D, Hawlina M, Stražišar M (2009) Polymorphisms in COL4A3 and COL4A4 genes associated with keratoconus. Mol Vis 15:2848
4. Kennedy RH, Bourne WM, Dyer JA (1986) A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol 101(3):267–273
5. Kumar NL, Rootman DS (2010) Newer surgical techniques in the management of keratoconus. Int Ophthalmol Clin 50(3):77–88
6. Tang YG, Rabinowitz YS, Taylor KD, Li X, Hu M, Picornell Y et al (2005) Genomewide linkage scan in a multigeneration Caucasian pedigree identifies a novel locus for keratoconus on chromosome 5q14.3-q21.1. Genet Med 7(6):397
7. McMahon TT, Shin JA, Newlin A, Edrington TB, Sugar J, Zadnik K (1999) Discordance for keratoconus in two pairs of monozygotic twins. Cornea 18(4):444–451

8. Pearson A, Soneji B, Sarvananthan N, Sandford-Smith J (2000) Does ethnic origin influence the incidence or severity of keratoconus? Eye 14(4):625
9. Wang Y, Rabinowitz Y, Rotter J, Yang H (2000) Genetic epidemiological study of keratoconus: evidence for major gene determination. Am J Med Genet 93(5):403–409
10. Momota R, Sugimoto M, Oohashi T, Kigasawa K, Yoshioka H, Ninomiya Y (1998) Two genes, COL4A3 and COL4A4 coding for the human α3 (IV) and α4 (IV) collagen chains are arranged head-to-head on chromosome 2q36 1. FEBS Lett 424(1–2):11–16
11. Kokolakis NS, Gazouli M, Chatziralli IP, Koutsandrea C, Gatzioufas Z, Peponis VG et al (2014) Polymorphism analysis of COL4A3 and COL4A4 genes in Greek patients with keratoconus. Ophthalmic Genet 35(4):226–228
12. Favor J, Gloeckner CJ, Janik D, Klempt M, Neuhäuser-Klaus A, Pretsch W et al (2006) Type IV procollagen missense mutations associated with defects of the eye, vascular stability, brain, kidney function and embryonic or postnatal viability in the mouse, Mus musculus: An extension of the Col4a1 allelic series and the identification of the first 2 Col4a2 mutant alleles. Genetics 175:725
13. Niwa S (2015) Kinesin superfamily proteins and the regulation of microtubule dynamics in morphogenesis. Anat Sci Int 90(1):1–6
14. Kaur I, Kaur J, Sooraj K, Goswami S, Saxena R, Chauhan VS et al (2018) Comparative evaluation of the aqueous humor proteome of primary angle closure and primary open angle glaucomas and age-related cataract eyes. Int Ophthalmol 39(1):69–104.
15. Rong SS, Ma STU, Yu XT, Ma L, Chu WK, Chan TCY et al (2017) Genetic associations for keratoconus: a systematic review and meta-analysis. Sci Rep 7(1):4620
16. Li X, Bykhovskaya Y, Haritunians T, Siscovick D, Aldave A, Szczotka-Flynn L et al (2011) A genome-wide association study identifies a potential novel gene locus for keratoconus, one of the commonest causes for corneal transplantation in developed countries. Hum Mol Genet 21(2):421–429
17. Hashemi M, Amininia S, Ebrahimi M, Hashemi SM, Taheri M, Ghavami S (2014) Association between hTERT polymorphisms and the risk of breast cancer in a sample of Southeast Iranian population. BMC Res Notes 7(1):895
18. Tonks S, Marsh S, Bunce MM, Bodmer J (1999) Molecular typing for HLA class I using ARMS-PCR: further developments following the 12th international histocompatibility workshop. Tissue Antigens 53(2):175–183
19. Nakayasu K, Tanaka M, Konomi H, Hayashi T (1986) Distribution of types I, II, III, IV and V collagen in normal and keratoconus corneas. Ophthalmic Res 18(1):1–10
20. Ghosh A, Jeyabalan N, Shetty R, Mohan RR (2017) Keratoconus in Asia. Adv Vis Res 1:363–374
21. Burdon KP, Vincent AL (2013) Insights into keratoconus from a genetic perspective. Cli Exp Optom 96(2):146–154
22. Bykhovskaya Y, Gromova A, Makarenkova HP, Rabinowitz YS (2016) Abnormal regulation of extracellular matrix and adhesion molecules in corneas of patients with keratoconus. Int J Keratoconus Ectatic Corneal Dis 5(2):63
23. Zhang H, Ma R, Wang X, Su Z, Chen X, Shi D et al (2017) KIF26B, a novel oncogene, promotes proliferation and metastasis by activating the VEGF pathway in gastric cancer. Oncogene 36(40):5609
24. Liu X, Gong H, Huang K (2013) Oncogenic role of kinesin proteins and targeting kinesin therapy. Cancer Sci 104(6):651–656
25. Wang Q, Zhao Z-B, Wang G, Hui Z, Wang M-H, Pan J-F et al (2013) High expression of KIF26B in breast cancer associates with poor prognosis. PLoS ONE 8(4):e61640
26. Bartoszewski RA, Jablonsky M, Bartoszewska S, Stevenson L, Dai Q, Kappes J et al (2010) A synonymous single nucleotide polymorphism in ΔF508 CFTR alters the secondary structure of the mRNA and the expression of the mutant protein. J Biol Chem M110:154575
27. Chen J-M, Férec C, Cooper DN (2006) A systematic analysis of disease-associated variants in the 3′ regulatory regions of human protein-coding genes I: general principles and overview. Hum Genet 120(1):1–21
28. Wittenhagen LM, Kelley SO (2003) Impact of disease-related mitochondrial mutations on tRNA structure and function. Trends Biochem Sci 28(11):605–611
29. Sabarinathan R, Tafer H, Seemann SE, Hofacker IL, Stadler PF, Gorodkin J (2013) RNA snp: efficient detection of local RNA secondary structure changes induced by SNP s. Hum Mutat 34(4):546–556