

The Genetics of Keratoconus: A Review

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Abstract

Keratoconus is the most common ectatic disorder of the cornea. Genetic and environmental factors may contribute to its pathogenesis. The focus of this article is to summarize current research into the complex genetics of keratoconus. We discuss the evidence of genetic etiology including family-based linkage studies, twin studies, genetic mutations, and genome-wide association studies. The genes implicated potentially include *VSX1*, *miR-184*, *DOCK9*, *SOD1*, *RAB3GAP1*, and *HGF*. Besides the coding mutations, we also highlight the potential contribution of DNA copy number variants in the pathogenesis of keratoconus. Finally, we present future directions for genetic research in the understanding of the complex genetics of keratoconus and its clinical significance. As new functional, candidate genes for keratoconus are being discovered at a rapid pace, the molecular genetic mechanisms underlying keratoconus pathogenesis will advance our understanding of keratoconus and promote the development of a novel therapy.

Keywords: Keratoconus, Genetics, *VSX1*, *miR-184*, *DOCK9*, GWAS, Linkage, Association, Cornea

Introduction

Keratoconus is the most common primary corneal ectatic disease [1,2]. Its name is derived from the Greek words *kerato* meaning cornea and *conus* meaning cone. Keratoconus is characterized by the non-inflammatory, localized paraxial stromal thinning of the cornea which often results in bilateral and asymmetrical corneal distortion and anterior corneal protrusion [3]. Patients with corneal protrusion often develop high myopia and irregular astigmatism resulting in significant impairment of visual acuity [1]. Keratoconus usually appears during puberty or the second decade of the life and normally progresses for the following two decades until it stabilizes [4]. In severe cases, corneal scarring from decomposition and corneal edema further contribute to vision loss. The clinical symptoms of keratoconus vary with disease severity. In moderate and advanced cases of keratoconus, a very common sign is Fleischer's ring around the cone base due to an accumulation of iron deposits [2]. Another characteristic is Vogt's striae (Figure 1), fine vertical lines due to compression of Descemet's membrane [2]. Eventually most of the patients develop Munson's sign [5] (Figure 2), bulging of the lower lid on downgaze caused by corneal protrusion. Patients with severe keratoconus were noticed to have corneal hydrops, acute stromal edema leading to stromal scarring due

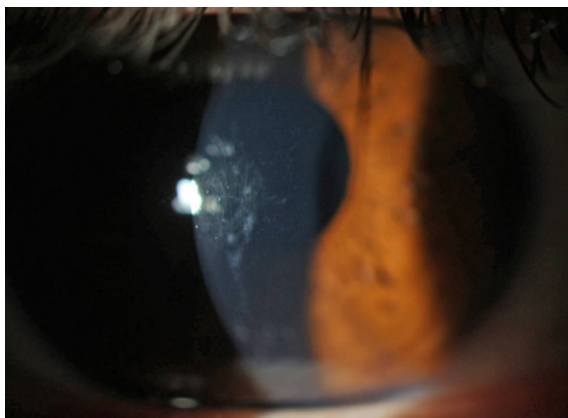


Figure 1: Vogt's Striae Sign. Vertical lines in Descemet's membrane are observed.

to breaks in Descemet's membrane [1] (Figure 3). Corneal topography is the most sensitive approach to detect early symptoms of keratoconus by identifying subtle corneal steepening (Figure 4). Keratoconus is a major indication for corneal transplantation in the Western world [6]. Despite extensive research, the exact cause of keratoconus remains unknown in the majority of patients. The aim of this article is to review the evidence for the complex genetics of keratoconus, to evaluate the currently identified genes/loci and candidate gene/loci, and to highlight current research methodologies which may be used to further elucidate the pathogenesis of keratoconus.

Epidemiology of Keratoconus

Keratoconus is the most common corneal ectatic disorder. It affects both genders and all ethnicities. The reported prevalence and incidence of keratoconus remains largely variable due to different

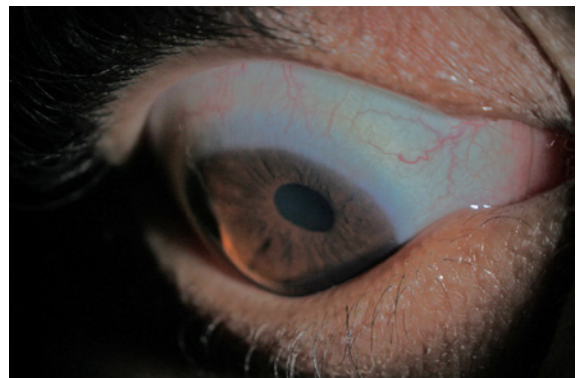


Figure 2: Munson's sign. Cone is noted on the lower eyelid on the downgaze.

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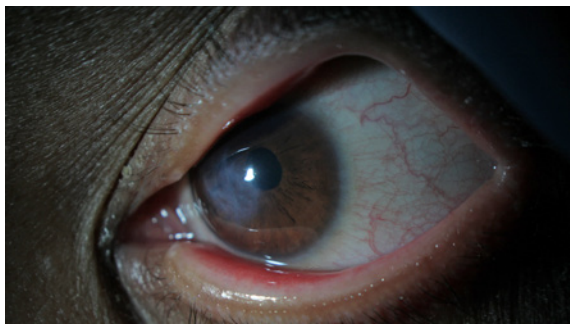


Figure 3: Corneal Hydrops. Breaks in Descemet's membrane in severe keratoconus cause acute stromal edema and scarring.

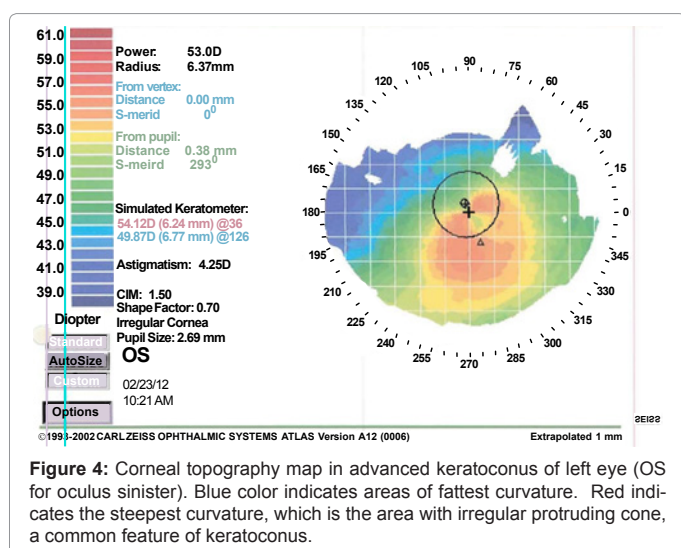


Figure 4: Corneal topography map in advanced keratoconus of left eye (OS for oculus sinister). Blue color indicates areas of flattest curvature. Red indicates the steepest curvature, which is the area with irregular protruding cone, a common feature of keratoconus.

clinical definitions and diagnostic criteria utilized between studies and populations. By best estimates, the incidence of keratoconus in the European Caucasian population is reported to be between 5 and 23 with a mean prevalence of 54 per 100,000 [2,7]. Based on a 48-year epidemiological study conducted in the United States, keratoconus reportedly affects approximately one person in 2,000 with a total mean incidence of two new cases per 100,000 per year [8].

Although the source of case reports may be biased and affected by disproportional cornea transplants in keratoconus patients, increased incidence of keratoconus has been described in a number of populations. It was reported to exhibit a higher incidence in Asians compared to Caucasians, a ratio of 7.5:1 respectively [9]. In comparison to incidence rates in Caucasians, similar rates of keratoconus incidence (1.3 patients per 100,000 residents per year) and prevalence (86 patients per 100,000) were reported in a Danish population [10]. In an Israeli epidemiological study, keratoconus prevalence was reported to be as high as 2.34% [11]. Moreover, increased incidence of keratoconus was reported in an Indian rural population and a Saudi Arabian population with 2.3 and 20 cases per 100,000 respectively [12,13]. In these three populations, the influence of consanguinity and a positive family history of keratoconus were suggested to have contributed to the increased incidence. Although the majority of patients present to the clinic as a sporadic form of the disease, a large number of familial cases of keratoconus have been reported. Many studies have shown that 11-14% of unaffected relatives of keratoconus patients who initially present to

the clinic as sporadic cases are often reclassified as familial keratoconus if complete slit-lamp examination, refraction, and corneal topography were performed [14]. It is becoming increasingly clear in most familial cases of keratoconus that the disease is inherited as a Mendelian trait, where specific genetic mutations cause keratoconus.

Chromosomal Loci for Keratoconus

A genetic predisposition to keratoconus is well documented with increased incidence in some familial groups and numerous reports of concordance between monozygotic twins [14-19]. Familial keratoconus cases are common with reports of incomplete penetrance in first and second degree family members of affected individuals. Approximately 6 - 23.5% of patients with keratoconus have a positive family history [14,20,21]. Similar to other ocular genetic disorders, studies have indicated that relatives of keratoconus patients have an elevated risk (15-67 times higher risk of developing keratoconus) compared to those with unaffected relatives [1,21]. The majority of familial keratoconus is inherited through an autosomal dominant pattern [2,22]. Other models of inheritance such as autosomal recessive pattern have been suggested especially in populations of high consanguinity [22-24].

Family-based linkage studies have provided invaluable insight into identifying candidate genetic loci that may harbor pathogenic mutations [2,21,25]. Linkage analyses with keratoconus have identified at least 17 genomic loci from 12 different studies (Table 1), suggesting genetic heterogeneity in keratoconus epidemiology [2,26]. This means that keratoconus could be caused by mutations in a number of different genes in different families [2,21]. While most of these loci have not been independently replicated, the 5q21.2 locus has been independently replicated in two different studies [27,28]. A third study by Li et al. [29] in 2006 identified a region on 5q23.2, overlapping with the replicated region 5q21.2. The overlap between these three independent linkage analyses indicates the possibility of the same locus for keratoconus. In addition, the linkage locus in 5q32-33 overlaps between two studies, one from Li et al. [29] in 2006 and Bisceglia et al. [27] in 2009 although both studies provided suggestive linkage. An additional linkage locus in 14q11.2 was also suggested by these two studies [27, 29]. The suggestive linkage region 16q23 reported by Bisceglia et al. [27] is very close to the region 16q22.3-q23.1 identified by Tyynismaa et al. [30]. In summary, these three linkage regions independently identified in at least two

Location	Mode of Inheritance	Population	Reference
1p36.23-36.21	Autosomal-dominant	Australian	[120]
2p24		European, Arabic, Caribbean African	[121]
3p14-q13	Autosomal-dominant	Italian	[122]
5q14.3-q21.1	Autosomal-dominant	Caucasian, Southern Italian	[27,28]
5q23.2		Caucasian, Hispanic	[29]
5q32-q33		Southern Italian	[27]
8q13.1-q21.11	Autosomal-dominant	Australian	[120]
9q34		Caucasian, Hispanic	[29]
13q32	Autosomal-dominant	Ecuadorian	[57]
14q11.2		Southern Italian	[27]
14q11.2		Caucasian, Hispanic	[29]
14q24.3		Multi-ethnic	[123]
15q2.32		Southern Italian	[27]
15q22.33-24.2	Autosomal-dominant	Northern Irish	[20]
16q22.3-q23.1	Autosomal-dominant	Finnish	[30]
17p13	Autosomal-recessive	Pakistani	[124]
20q12	Autosomal-dominant	Australian, Tasmania	[125]

Table 1: List of the identified genomic loci through linkage studies.

different familial datasets provide further evidence of association with keratoconus development. Despite the extensive genetic research in keratoconus over the past decades, only few genes have been reported: *VSX1* (visual system homeobox 1), *miR-184*, and *DOCK9* (dedicator of cytokines 9).

Reported Keratoconus Genes

VSX1 (Visual System Homeobox 1)

VSX1 (OMIM 605020) is located on chromosome 20p11–q11 [31,32], a linkage locus known for a corneal dystrophy called posterior polymorphous dystrophy (PPCD) [33]. PPCD has been associated with keratoconus in several reports [34–39]. It was first reported in 2002 that *VSX1* mutations cause keratoconus and posterior polymorphous dystrophy [40]. Two mutations in *VSX1* (R166W and L159M) were reported to be associated with keratoconus. *VSX1* is a member of the paired-like homeodomain transcription factors. This gene encodes a pair-like homeodomain protein which binds to the core of the locus control region of the red and green visual pigment gene cluster and may regulate expression of the cone opsin genes during embryonic development [41, 42]. It is expressed in several ocular tissues including the nuclear layer of the retina, and embryonic craniofacial tissue [31,32,40]. The expression of *VSX1* in human or mouse cornea is still up to debate since many studies did not confirm the expression in cornea [40,41,43]. Mouse models with the loss of *VSX1* function did not reveal cornea-related phenotypes [42].

Since the initial report in 2002, mutations in *VSX1* have been demonstrated to be associated with keratoconus and other corneal dystrophies (Table 2) [44–52]. However, many studies did not identify any potential *VSX1* mutations in keratoconus patients [22,24,53–60]. It remains unclear whether and how mutations in *VSX1* contribute to the pathogenesis of keratoconus [2,9,61]. It is suggested that mutations within *VSX1* only affect a small number of keratoconus patients. This is consistent with the concept of genetic heterogeneity in keratoconus.

miR-184

miR-184 is a microRNA. microRNAs (miRNAs) are small regulatory strands of RNA with 19–25 nucleotides in length. miRNAs bind to complementary sequences mostly in the 3' untranslated region (UTR) of mRNA of target genes and lead to mRNA degradation or translational suppression. Recently, a mutation altering the *miR-184* seed region was reported in a family with keratoconus and early-onset anterior polar cataract [62]. This genomic region chr15q22–q25 was

previously mapped as a keratoconus linkage locus [20,63]. This 5 Mb linkage region was enriched in affected and unaffected family members using a custom sequence capture array from NimbleGen. The enriched DNA was sequenced using second generation DNA sequencing (Genome Analyzer II from Illumina), identifying a mutation (r.57c>u) within *miR-184* [62]. *miR-184* has been reported to be abundantly expressed in the cornea and lens [64,65]. The authors hypothesized that *miR-184* with the r.57c>u mutation fails to compete with another miRNA – *miR-205* for overlapping target sites on the 3' UTR of two target genes, *INPPL1* (inositol polyphosphate phosphatase-like 1) and *ITGB4* (integrin beta 4) while these two target genes are involved in corneal healing after injury as the principal component of corneal basal epithelial hemidesmosomes [62]. The finding of mutations in the seed region of *miR-184* suggests that regulatory variants may directly impact transcriptional activity of key genes in corneal development and maintenance. It will be necessary to replicate this original finding in other studies of keratoconus.

DOCK9 (Dedicator of Cytokines 9)

DOCK9 (Dedicator of cytokines 9) (OMIM 607325) encodes a member of the DOCK protein family that possesses GTP/GDP exchange factor activity and specifically activates G-protein CDC42 [66]. *DOCK9* is a strong candidate gene for keratoconus. Mutations in *DOCK9* were recently reported through sequencing candidate genes in a previously identified linkage locus, 13q32 [57]. This locus was first identified by Gajecka M et al. [57] in a large Ecuadorian family, and was reported to segregate under an autosomal dominant model [67]. A mutation screening of eight candidate genes within the 13q32 locus identified 100% segregation of one non-synonymous mutation and three different sequence variants in the *DOCK9* gene and two additional genes, *IPO5* (importin 5, OMIM 602008) and *STK24* (serine/threonine kinase 24, OMIM 604984) [67]. All these three genes are expressed in the human cornea [67]. Based on the bioinformatics analyses with two available programs PolyPhen (polymorphism phenotyping) and SIFT (sorting intolerant from tolerant) [68,69], the authors suggested that the most functionally significant of these three candidate genes is *DOCK9*. However, functional work of the identified non-synonymous mutation (Gln754His) and additional keratoconus families with mutations in the *DOCK9* gene will be necessary to demonstrate the true pathogenic potential of this gene in relation to keratoconus [67].

cDNA change	Protein	dbSNP135	Accession#	Pathogenic	References
c.50 T>C	L17P	rs74315436	NM_014588	Polymorphic	[46,49,50]
c.315 C>A	D105E	rs6115023	NM_014588	Polymorphic	[54]
c.391 C>A	R131S	rs6050307	NM_014588	Polymorphic	[53,54]
c.432 C>G	D144E	rs140122268	NM_014588	Polymorphic	[40,46,47,49,50,53,54]
c.452 A>G	N151S	-	NM_014588	Pathogenic	[44]
c.475 T>A	L159M	rs74315434	NM_014588	Polymorphic	[40,56]
c.479G>A	G160D	rs74315433	NM_014588	Polymorphic	[40,46,49,50]
c.479 G>T	G160V	rs74315433	NM_014588	Polymorphic	[44]
c.496 C>T	R166W	-	NM_014588	Pathogenic	[40,52]
c.525 G>C	Q175H	-	NM_014588	Pathogenic	[48,51]
c.650 G>A	R217H	rs6138482	NM_199425	Polymorphic	[49,54,59]
c.715 G>C	G239R	-	NM_014588	Pathogenic	[50]
c.731 A>G	H244R	rs148957473	NM_014588	Polymorphic	[40,52,56]
c.740 C>G	P247R	-	NM_014588	Pathogenic	[40,46,50]
c.766 G>T	A256S	rs74315435	NM_014588	Polymorphic	[45]

Table 2: List of sequence variants identified in the *VSX1* gene.

Candidate Genes Associated with Keratoconus

SOD1 (superoxide dismutase 1)

Several reports have suggested the potential contribution of *SOD1* (superoxide dismutase 1) in keratoconus [70]. *SOD1* (OMIM 147450) maps to the 20p11.2 and encodes a major cytoplasmic antioxidant enzyme that metabolizes superoxide radicals and provides a defense against oxygen toxicity [71]. Mutations in the *SOD1* gene have been implicated in familial amyotrophic lateral sclerosis (ALS) [71,72]. No keratoconus phenotype was reported in ALS patients. To date, it is widely accepted that oxidative stress plays a critical role in the progression of keratoconus [2,22]. Numerous reports have shown an accumulation of cytotoxic byproducts, mitochondrial DNA damage, and high levels of oxidative stress in keratoconus corneas [73-76]. *SOD1* was selected as a candidate gene and was examined in many studies. However, no mutations were found in keratoconus patients [50,52,57,59,70,77]. It remains unclear whether *SOD1* plays a role in the pathogenesis of keratoconus.

Genome-Wide Association Studies

Genome-wide association studies (GWAS) assay several hundred thousand to over a million single nucleotide polymorphisms (SNPs) in thousands of individuals using high throughput DNA genotyping technology [78]. GWAS has been shown to be a powerful tool to investigate the genetic etiology of many complex traits and diseases, including Fuchs' corneal dystrophies (FECD) and central corneal thickness [79-84]. Li and colleagues recently performed a GWAS with keratoconus in the Caucasian population of 222 patients and 3324 controls using Illumina 370k beadchips and no variants reached genome-wide significance (p -value 5×10^{-8}) [85]. The authors then selected a set of 4905 SNPs with p -value $< 10^{-4}$ in the discovery dataset for replication in two datasets, one with 304 cases and 518 controls and another with 70 multiplex families of 307 individuals. The meta-analysis of these selected SNPs did not identify any SNP with genome-wide significant association. However, the most significant association (p -value 1.6×10^{-7}) was with SNP rs4954218, located near the *RAB3GAP1* (RAB3 GTPase activating protein subunit 1 (catalytic)) gene on chromosome 2q21.3 [85]. Interestingly, mutations in the *RAB3GAP1* gene are reportedly associated with Warburg Micro Syndrome, a rare, autosomal recessive syndrome characterized by ocular and neurodevelopmental abnormalities, especially microphthalmos, microcornea, congenital cataracts and optic atrophy [86,87].

A second GWAS in keratoconus was reported by Burdon and colleagues in Australia using pooled DNA in 97 keratoconus patients and 216 controls [88]. Although no variants reached genome-wide significance, the most significant association was with SNP rs1014091, located upstream of the *HGF* (hepatocyte growth factor) gene. Further genotyping additional tagging SNPs for the *HGF* gene identified another SNP rs3735520 with significant association (p -value 9.9×10^{-7}). This SNP was also found to be associated with serum HGF level in normal individuals (p -value 0.036). Interestingly, the *HGF* gene has been associated with refractive error in several populations including Han Chinese and Caucasians [89-91]. The association of *HGF* with keratoconus suggests the potential involvement of inflammatory pathway [88].

DNA Copy Number Variation

In addition to sequence variants, DNA structural variants, or copy number variants (CNV) have been shown to play important roles in human diseases, including many ocular disorders [25, 92,93]. The

role of CNV in keratoconus has been explored in two studies. First, Abu-Amero and colleagues investigated DNA copy number alteration in 20 sporadic keratoconus patients and 10 ethnically-matched health controls from Saudi Arabia using a genome-wide CGH array (comparative genomic hybridization) containing over 244,000 probes from Agilent [94]. This study did not identify genomic deletions or duplications specific for keratoconus. However, this finding should be interpreted with caution due to the relatively small sample size and low density of the probes. Second, Rosenfeld and colleagues identified DNA duplications and deletions of chromosome 5q31.1-q35.3 in a family with autosomal dominant keratoconus [95]. This genomic region on chr5 has been shown to be linked with keratoconus. The 5q31 region has also been implicated in granular, lattice and Reis Bucklers corneal dystrophies due to mutations in the TGF beta 1 gene (*TGFBI*) [96]. However, the copy number alterations in this region need to be replicated in additional datasets with keratoconus patients. We expect more CNV studies will be reported with keratoconus.

Related Ocular and Systemic Disorders

Although the majority of keratoconus patients occur as an isolated disorder, keratoconus has been reported to be related with at least a dozen other ocular, syndromic, and systemic disorders [1-3], which include Marfan's syndrome, mitral valve prolapse, collagen vascular disease, pigmentary retinopathy, Leber congenital amaurosis, and Down Syndrome [2, 3]. Studies have reported that approximately 0.5 to 15% of patients with Down Syndrome manifest signs of keratoconus [2]. This increased incidence has been suggested to result in a 10 to 300 fold higher prevalence of keratoconus amongst patients with Down syndrome [2,97]. It has also been reported that approximately 35% of patients with Leber congenital amaurosis, a clinically heterogeneous group of childhood retinal degenerations inherited in an autosomal recessive manner, also suffer from keratoconus [98]. Of note, gene mutations in Aryl-hydrocarbon-interacting protein-like 1 (*AIPL1*) and Crumbs homolog 1 (*CRB1*) in patients with Leber congenital amaurosis have been suggested to contribute keratoconus susceptibility [99-103]. Keratoconus and Leber congenital amaurosis concordance could likely be explained by the possibility for polygenic or multifactorial inheritance resulting in direct genetic alterations that affect both the retina and cornea. Since mutations in genes that affect retinal development have been well established for Leber congenital amaurosis, it may suggest that a common ocular developmental genetic modifier could contribute to disease susceptibility for patients with keratoconus. Moreover, since keratoconus onset and severity is reported to be more advanced in patients with Leber congenital amaurosis, a common genetic modifier could contribute to the rapid disease pathogenesis due to adverse corneal development. Associations between keratoconus and connective tissue disorders have also been reported including: osteogenesis imperfecta, GAPO syndrome, type IV Ehlers-Danlos syndrome, and mitral valve prolapse [104-107]. Interestingly, an association study between mitral valve prolapse, hypermobility, and keratoconus failed to detect a statistically significant difference in the prevalence of these disorders in keratoconus patients and controls [108]. In summary, the potential contribution of the associated disorders with keratoconus provides a further illustration of the genetic heterogeneity in keratoconus pathogenesis.

In addition, environmental factors have also been reported to potentially contribute to keratoconus. These factors include contact lens wear, chronic eye rubbing, magnesium deficiency, and atopy of the eye [1-3]. Notably, a growing body of evidence supports a potential association between atopy and keratoconus [109-114]. Pathologically, keratoconus patients with atopy have been shown to present with

corneal topographic and pachymetric characteristics different than those keratoconus patients without atopy [115]. It was speculated that atopy-induced itching might result in increased eye rubbing and contribute to keratoconus [111]. Supporting this hypothesis, in a multivariate analysis, Bawazeer and colleagues demonstrated a significant association in a case-control study between atopy, keratoconus, and eye rubbing [116]. More studies will be necessary to examine the interaction between the genetic and environmental factors and its contribution to keratoconus pathogenesis.

Future Direction in Genetic Studies of Keratoconus

Recent genome technology development has enabled novel and high throughput genetic approaches to study both Mendelian and complex disorders. Among these approaches, whole exome or genome sequencing will be very powerful to identify the causal mutations in multiplex families with keratoconus [117-119]. The existing linkage data on these families will be tremendously useful in the interpretation of exome sequencing data. We expect to see more publications using this approach to study keratoconus in the near future.

Another approach is to perform genome-wide association studies in a large number of keratoconus cases and controls using high density SNP arrays. This approach has been shown to be very promising in keratoconus [85,88]. Since GWAS studies need thousands of cases and controls, different laboratories will need to collaborate and combine each available dataset in order to identify genome-wide significant associations, which will help identify new genes involved in keratoconus pathogenesis. The available genome-wide genotype data will make it possible to study any potential gene-environment interactions.

Conclusion

Keratoconus is the most common ectatic disorder of cornea. It usually develops in the second decade of the life around puberty time and progress in the next two decades. It affects both genders and all ethnic groups. Genetics has been shown to play an important role in its pathogenesis through twin studies, family-based linkage studies, and genetic association studies. However, despite the extensive research in the past decades, the genetic etiology of keratoconus still remains unclear. Keratoconus is associated with many ocular or systematic disorders. Newly developed genetic technologies including whole-exome or genome sequencing and GWAS will significantly advance the genetic research of keratoconus, which will improve our understanding of the genetic etiology of keratoconus, thus leading to future development of improved diagnostics and targeted therapeutics.

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