REVIEW ARTICLE

Genetic Perspective and Clinical Characteristic of First-Degree Relatives of Keratoconus: A Review

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ABSTRACT

Keratoconus is a degenerative condition marked by corneal thinning and cone-shaped bulging, leading to impaired vision. Research highlights significant hereditary and environmental influences, with higher incidence among first-degree relatives. Familial clustering and high concordance in identical twins underscore a strong genetic component. Identifying corneal abnormalities in first-degree relatives is crucial for early diagnosis and intervention. This review covers twin, sibling, and parent studies, genetic inheritance patterns, clinical characteristics, and pathophysiology. Keratoconus is more common in monozygotic twins than dizygotic twins, with increased risk for those with affected parents or siblings. Recent genetic studies, including GWAS and SNPs, have identified several associated genetic loci, affirming the hereditary component. First-degree relatives display distinct corneal characteristics and overexpression of TLR2 and TLR4, linked to the innate immune system. Given the genetic risks, screening and awareness among first-degree relatives are essential for early detection.
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Keywords: Cornea abnormalities, First-degree relatives, Genes, Gene tics, Keratoconus

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INTRODUCTION

Keratoconus is a bilateral, non-inflammatory, and non-infectious disease characterised by progressive corneal thinning, protrusion, and scarring that leads to vision loss (1). Keratoconus affects both gender equally (2). But some studies reported there are significant difference where keratoconus is more common in male than female (3-6). Although some studies have reported greater rates of keratoconus in females (7-9), however recent study by (10) showed no predominance in gender, which most likely indicates that keratoconus does affects both sexes similarly. Keratoconus can occur in all ethnic groups and is influenced by geographical diversity and differences in genetic variation in a population (11). Epidemiological studies indicate substantial global variation, as the prevalence and incidence rates of keratoconus have been estimated to be between 0.2 and 4,790 per 100,000 persons and 1.5 and 25 per 100,000 persons/year, respectively (12). To date, the underlying cause of keratoconus remains elusive; however, it seems to stem from a complex interplay of factors, encompassing both genetic and environmental influences such as eye rubbing, atopy, and exposure to UV radiation (2). Genetic origins are substantiated by the presence of bilateral involvement, familial clustering, concordance in monozygotic twins, its connection to other genetic disorders, such as Down syndrome and Leber's congenital amaurosis, as well as the observed variations in prevalence and incidence rates among different ethnic groups (13). A high prevalence of a positive family history of keratoconus in patients with keratoconus is prominent. In Asian populations, family history reviews have exhibited a range of 4.4%–23.5% (14). Among 1496 cases of keratoconus, a family history of keratoconus was observed in 19.5% of cases in Iran (15). The term "first-degree relatives" encompasses a parent, full sibling, or child, as per its definition. This group of family members significantly aligns with the concept of a "nuclear family," excluding spouses. When individuals are linked by blood, their first-degree relatives typically share approximately 50% of their genetic makeup. Numerous studies support high first-degree family involvement in keratoconus incidence. In an early investigation, the projected prevalence of keratoconus among first-degree relatives was noted to be 3.34%, signifying a considerably elevated rate of 15 to 67 times higher than that in the general population (16). The prevalence of keratoconus in young first-degree relatives is also marked by a significant presence, with estimates of 11.5% to 15.5% among individuals aged less than 11 years, 18% among those aged 12–15 years, and 25.5% among those aged 16–18 years (17).

The highest reported involvement of a first-degree family was 20.50%, which was higher among Israeli Arabs (18). In another case series study of 109 family members, 52 (48%) were first-degree relatives (19). A recent study showed a correlation of 0.55 among parents, 0.29 among offspring, and 0.49 among siblings in terms of the likelihood of keratoconus occurrence in first-degree relatives (20). In contrast, a recent study reported that among 307 keratoconus patients in China, 3.52% had a history of first-degree relatives (21). Family history is one of the most pivotal risk factors for keratoconus. Delving deeper into the inheritance patterns of keratoconus among first-degree relatives through additional research could potentially provide valuable insights into early diagnosis and effective management strategies. This review attempts to demonstrate the correlation between first-degree relatives and keratoconus with respect to genetic and clinical characteristics. Gaining insight into keratoconus risk factors can be advantageous for early detection and for overseeing the advancement of the disease.

MATERIAL AND METHODS

This review discusses the involvement of first-degree relatives in genetics, twin studies, and the presence and pathophysiology of corneal abnormalities. The literature search was performed using the PubMed, Medline, and Google Scholar databases and all English language articles published between 1985 and 2024. This involved utilizing keywords such as "keratoconus," "first-degree relatives," "genetics," "genes," and "cornea abnormalities." A total of 73 articles were obtained and subjected to analysis, with emphasis on more recent sources. Notably, non-English findings were excluded from the search process. (Figure 1) summarises the number of articles identified and reasons for exclusion at each stage.

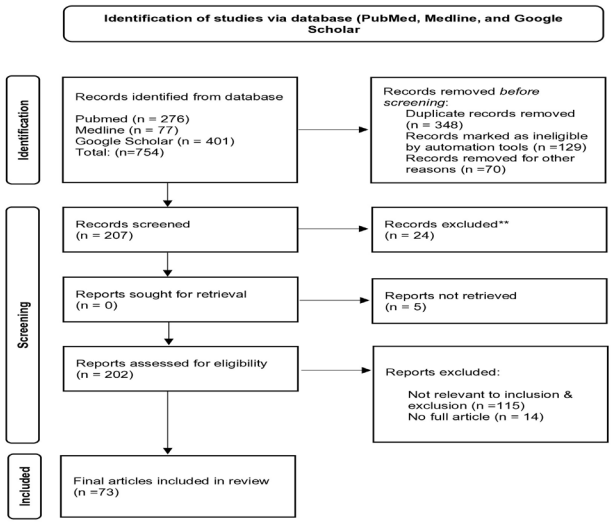

Figure 1: Flow Chart for Articles Selection Process

RESULTS

Twin Studies

Twin studies have emerged as a powerful tool for determining the effect of heredity on disease manifestations. The pathology of keratoconus, which combines environmental and genetic factors, makes the study of twins very meaningful. It has been previously established that there is a higher level of concordance between monozygotic twins (who share all genes owing to their identical nature) and dizygotic twins (who share only about half of their genetic makeup). This understanding can also be applied to keratoconus, as most twin studies have consistently reported elevated rates of trait similarity among monozygotic twins compared with dizygotic twins (22, 23). The concordance observed in keratoconus demonstrates a higher level of agreement among monozygotic twins than dizygotic twins, thereby confirming the presence of a robust genetic factor in the development of this disorder (24). Most studies showed that monozygotic twins were concordant with keratoconus, some of which were detected by video keratography (23, 25-27). This concordance supports evidence that heredity is a genetic factor in the aetiology of keratoconus (25). However, few studies showed that monozygotic twins are discordant with keratoconus (27-30), the unaffected twins had an asymmetric bow tie pattern and asymmetric steepening in one eye on computer assisted corneal video keratography was presented in the study by McMahon TT et al. (1990) (30).

A limited number of studies have reported dizygotic twins, and most of them showed results concordant with those of keratoconus. In a study of five sets of dizygotic twins by Tuft et al. (2012) (23), four were concordant, whereas another study by Liskova et al. (2005), demonstrated four sets of dizygotic twins, two of which were concordant, one was discordant, and one was not examined (31). However, a new discovery on the improvement of the discordance in keratometry indices after treating keratoconus among monozygotic twins (cross-linking and photorefractive keratectomy assessment) suggests that keratoconus occurs due to a combination of genetic and environmental factors (32). (Table I) provides a summary of the studies on keratoconus twins (22, 23, 25, 27, 29-31, 33-37).

Table I: Summary of Keratoconus in Twins

No.	Author	Study objective	Main finding
1.	Weed et al. 2007 (27)	Case report: monozygotic twin. Method: Computer video keratography.	evidence of subclinical keratoconus in the 'unaffected' twin (discordant)
2.	Parker et al. 1996 (22)	Case report: discordant of monozygotic twins Method: Video keratography.	normal twin brother showed subclinical keratoconus

CONTINUE

Table I: Summary of Keratoconus in Twins (CONT.)

No.	Author	Study objective	Main finding
3.	Tuft et al. 2012 (23)	To describe the concordance of keratoconus in 18 sets of twins. Method: Computer-assisted video keratography.	Keratoconus appears to have a stronger genetic basis in monozygotic twins compared to dizygotic twins.
4.	Bechara et al. 1996 (25)	Case report: Present two pairs of monozygotic twins. Method: Video keratography.	Keratoconus is concordant with Monozygotic.
5.	Etzine 1954 (33)	Case report: monozygotic twins	Keratoconus is concordant with Monozygotic.
6.	Owens and Walters 2021 (29)	Case report: monozygotic twins Method: Video keratography	Both monozygotic are detected keratoconus with different in severity and non-equivalent cone types.
7.	McMahon et al. 1999 (30)	Case report: two cases of monozygotic twins Method: Computer-based video keratography.	Monozygotic twins discordant for keratoconus does not preclude possibility of genetic component.
8.	Liskova et al. 2005 (31)	Case report: 5 pair of twins	one set of monozygotic twins was concordant for keratoconus and four sets of dizygotic twins, two of which were concordant, one discordant
9.	Incorvaia et al. 2003 (34)	Case Report: Congenital Adrenal Hyperplasia and Keratoconus in two dizygotic female twins	Both dizygotic twins are concordant with keratoconus
10.	Zadnik et al. 1984 (35)	Case report: monozygotic twin Method: Slit-lamp microscopy, photo keratography.	Both monozygotic twins are concordant with keratoconus
11.	Harrison et al. 1989 (36)	Case report: monozygotic twin Method: Slit-lamp microscopy, keratometry.	Keratoconus is discordant in Monozygotic twin
12.	Bourne and Michaels 1982 (37)	Case report: monozygotic twin Method: Slit-lamp microscopy, retinoscopy, keratometry, photo keratography.	Keratoconus is concordant in Monozygotic twins

Siblings and Parents Studies

Identical twins (monozygotic) shared 100% of their DNA, whereas siblings and parents shared 50% and 47.5%, respectively. A study reported a family with three children from a single father, and three unrelated mothers demonstrated classical inferior corneal steepening corresponding to the diagnostic criteria for keratoconus (38). Another study reported a case of two brothers diagnosed with retinitis pigmentosa and associated keratoconus (39). In another study, 12.3% of keratoconus cases and 6.6% of keratoconus suspects were diagnosed among 150 siblings of keratoconus patients (40). In a recent study, clinical keratoconus was diagnosed in one of 48 parents (2.08%) of patients with keratoconus (41). Furthermore, a study on the parental corneal tomographic and biomechanical properties of patients with keratoconus suggested that there is a potential predisposition to keratoconus (42). Research has also indicated that approximately 13.3% of immediate family members may display indications of keratoconus, often with mild symptoms that could go undetected without comprehensive evaluation (43). Therefore, studies of first-degree families, such as twin studies, should also be considered when investigating a disease with a high potential for genetic origination.

Genetic Inheritance Patterns of Keratoconus

Advances in genetic technology within the context of keratoconus have the potential to offer a valuable understanding of the underlying mechanisms of the disease. It also holds the promise of identifying biomarkers that could enhance early detection, enable more precise targeted therapies, facilitate monitoring of disease progression, and potentially offer insights into the prognosis of treatment outcomes (2). Most keratoconus patients have indicated a sporadic form of the disease; however, there is an increasing body of evidence pointing towards the presence of familial cases of keratoconus, bolstering the notion of genetic involvement (44). In most cases of familial keratoconus, inheritance occurs through an autosomal dominant pattern, with a smaller proportion attributed to autosomal recessive inheritance (16, 24, 44-47).

Linkage analysis and association studies are the primary methodologies used to identify the genes responsible for a condition. Linkage analysis, a conventional genetic technique, examines the concurrent inheritance of a chromosomal region labelled by polymorphic genetic markers alongside a trait locus. In 12 different studies, at least 17 genomic loci have been identified using linkage analyses with keratoconus (46). Thus, there is supporting evidence of genetic heterogeneity in which keratoconus could be caused by mutations in several genes in different families (38). Linkage analysis identified six chromosomal loci associated with isolated keratoconus: 2p24.15, 3p14-q13.16, 5q14.3-q21.12, 13q32.18, 16q22.3-q23.119, and 20q12.20. However, no definitive disease-causing mutations have been isolated from these loci (48). Linkage analysis has pinpointed six chromosomal loci associated with isolated keratoconus: 2p24.15, 3p14-q13.16, 5q14.3-q21.12, 13q32.18, 16q22.3-q23.119, and 20q12.20. Nevertheless, no definitive disease-causing mutation has been isolated from these loci (49). Numerous studies have shown robust linkage analysis results pointing to specific chromosomal regions associated with keratoconus. These include a locus on chromosome 3p14–q13 (50), and regions 5q32-q33, 5q21.2, 14q11.2, and 15q2.32 (51), 14q24.3 (31), and 5q14.1-q21 (52). Notably, a substantial keratoconus genome-wide association study encompassing cohorts from the United States, Australia, and Northern Ireland identified a significant locus on

chromosome 11 in the PNPLA2 region (47). In general, linkage analyses have revealed multiple genomic loci, with chr5q21.2 being the sole independently replicated locus (51).

A genome-wide association study (GWAS) has been used in genetic research to establish connections between specific genetic variations and the identification of potential novel gene loci associated with keratoconus. The initial genome-wide linkage study determined that the responsible gene for keratoconus is situated within the chromosomal region 16q22.3-q23.1 (53). In a further exploration, a genome-wide linkage scan conducted on a multi-generational Caucasian pedigree pinpointed a new locus related to keratoconus on chromosome 5q14.3-q21.1 (54). In another study among white and Hispanic family's sib-pair origin study, locus5q23.2 was found, the same locus was reported overlapping with the replicated region 5q21.2 (55). Lysyl oxidase (LOX) gene polymorphism is associated with keratoconus, in which LOX encodes collagen cross-linking enzymes in the cornea and other tissues (56). Genome-wide association studies (GWAS) conducted on cohorts of cases and controls have revealed common genetic variations near HGF, RAB3GAP1, and LOX as potential candidate risk factors for keratoconus. Recently, a significant breakthrough emerged in identifying 36 genetic loci that were strongly associated with keratoconus. Notably, the most profound association ($p = 1.34 \times 10{-}13$ for rs76747345) was detected within a region devoid of genes on chromosome 21q2 (57).

Studies using single nucleotide polymorphism (SNP) linkage analysis identified the following genes: LOX, CAST, DOCK9, IL1RN, SLC4A11, HGF, RAB3GAP1, TGFBI, ZNF469, ZEB1, VSX1, COL5A1, COL4A3, COL4A4, FNDC3B, FOXO1, MPDZ-NF1B, WNT10A, SOD1, IL1B, and IL1A, in addition to the microRNA MIR184 as a possible pathogenesis of keratoconus (58). VSX1 remains the most commonly studied gene and is frequently identified which may cause keratoconus through an autosomal dominant inheritance pattern with different variable expressivity (59). Initially designated as RINX, the gene was named VSX1 (Visual System Homeobox 1) by the Human Gene Nomenclature Committee. Notably, VSX1 displays exclusive expression within a particular subset of cells, likely bipolar cells, within the retinal inner nuclear layer (INL) (60). Furthermore, VSX1, along with ZNF469, SOD1, and miR184, have been the focus of many studies. However, it is worth noting that only miR184 mutations have been definitively linked to corneal abnormalities (59). The discovery of a mutation in MIR184 associated with keratoconus has opened a new avenue of research for exploring miRNA regulation in the context of eye diseases (44). With more definitive research on the role of miRNAs in keratoconus, miRNAs might play a role as dynamic biomarkers for the early diagnosis of keratoconus.

Ocular Clinical Characteristic in First Degree Relatives

At an earlier time, there was no significant association between "severity index" and family history of keratoconus (61). However, recent studies have reported that keratoconus patients with more family members showed higher disease severity according to the Amsler-Krumeich classification (15). Further research has been conducted to identify corneal abnormalities in first-degree family members. Abnormalities in connective tissues have been observed in first-degree relatives (26). Additionally, these relatives exhibit distinct corneal characteristics along with certain specific features such as central corneal thickness, thinnest pachymetry readings, posterior elevation values, and the distance between the most prominent anterior and posterior elevation points (62, 63). The topographic pattern of oval from inferior steepening in the keratoconus-suspect group was reported at 51.4% and 70% in the keratoconus group, where both groups were categorised from first-degree relatives (40). Corneal biomechanical values in first-degree relatives were also lower than those in normal subjects (64).

In a separate study focusing on paediatric first-degree relatives, analysis of tomography data revealed that 17.5% of the participants displayed keratoconus characteristics. Additionally, a separate assessment labelled 19.1% of participants as exhibiting keratoconus traits through automated decision tree classifier (17). Among the Pentacam results, parameters such as the index of surface variance (ISV), central keratoconus index, and index of vertical asymmetry (IVA) demonstrated the highest heritability levels (81.2 %) among family members (65). A recent prospective case-control study showed that first-degree relatives with keratoconus had significantly more abnormal anterior corneal topography patterns than healthy controls (17%) (66). A recent study of parents with keratoconus showed significant differences in thickness and posterior surface elevation values (41). In a subsequent study, parental results of the Corvis biomechanical index (CBI) from Oculus Corvis ST and thinnest pachymetry (TP) from Oculus Pentacam were identified as the major influential factors for keratoconus in their offspring, with an accuracy of 73.3% (42). Corneal topography, tomography, and aberrometry assessments among first-degree relatives of keratoconus showed differences compared to normal individuals (43). Careful consideration should be given to performing kerato-refractive surgery on first-degree relatives of patients with keratoconus, and a comprehensive preoperative examination should be conducted to identify any subtle corneal topographic, biomechanics, and higher-order aberrations in these individuals. (Table II) summarises studies of corneal abnormalities in first-degree relatives of keratoconus (17, 26, 38, 40, 41, 62, 63, 65-67).

Table II: Summary of corneal abnormalities studies of keratoconus.

No.	Author/Citation	Finding
1.	Awwad et al. 2019 (17)	Out of a total of 183 first-degree relatives in the paediatric age range of 6 to 18, tomography data revealed that 17.5% of the participants exhibited characteristics consistent with keratoconus. However, a more objective analysis labelled 19.1% of these participants as having keratoconus. Among keratoconus patients aged between 16 and 18, 25.5% had corneal curvature measurements of 49.7±6.1 dioptres and a corneal thickness of 486.0±66.5 micrometres.
2.	Ihalainen 1986 (26)	Out of 122 first-degree relatives from the town of Oulu and its surrounding area, connective tissue abnormalities were observed in 60 individuals, accounting for 49% of the group.
3.	Besharati et al. 2010 (40)	Topographic pattern of oval from inferior steepening in keratoconus suspect group 51.4% and 70% respectively (P=0.017). Topographic indices containing central keratometry (CK) and inferior-superior value (I-S) were significantly high in keratoconus suspect group.
4.	Li et al. 2020 (41)	There were significant differences in the thickness and posterior surface elevation value in parents with keratoconus
5.	Kaya et al. 2008 (62)	Significant disparities were observed in various corneal parameters between the group of first-degree relatives and normal subjects. These differences encompassed central corneal thickness, thinnest pachymetry reading, posterior elevation value, the distance between the greatest anterior/posterior elevation points, corneal centre, posterior best fit sphere (BFS) values, posterior BFS, anterior BFS ratio, and irregularity values. For first-degree relatives of individuals with keratoconus, who did not exhibit a topographic keratoconus pattern, abnormal corneal topographic values were identified.
6.	Gonzalez and McDonnell 1992 (63)	Of the 12 sets of parents, at least one parent in each of seven sets had abnormal corneal characteristics.
7.	Ionescu et al. 2018 (64)	In the group of relatives, the mean values of corneal hysteresis (CH), corneal resistance factor (CRF), and keratoconus match index (KMI) were found to be lower than those in the control group, yet higher compared to keratoconus patients. This underscores the significance of evaluating corneal biomechanics in individuals who are at risk of developing primary ectasia
8.	Heydarian et al. 2019 (65)	Sex is the strongest factor to affect keratoconus indices.
9.	Shneor et al. 2020 (66)	Through qualitative analysis, it was determined that first-degree relatives of individuals with keratoconus exhibited a notably higher prevalence of abnormal anterior corneal topography patterns compared to the control group. Specifically, the percentage of abnormal patterns in the keratoconus relatives' group was 34%, while it was 17% in the control group. This difference was statistically significant, as indicated by the $\chi 2$ test ($\chi 2$ (1, N = 152) = 5.9, p = 0.02).
10.	Oleynikov and Rabinowitz 2009 (38)	3 male siblings children demonstrated classical inferior corneal steepening meeting the diagnostic criteria for keratoconus.

Pathophysiology of keratoconus and First-Degree Relatives

Keratoconus is a multifaceted condition influenced by both genetic and environmental factors. The pathophysiology of keratoconus can be categorised into several components, including alterations in the composition of the stroma, an imbalance between pro-inflammatory and anti-inflammatory molecules, disruption in the equilibrium of enzymes responsible for degrading the extracellular matrix and their inhibitors, oxidative stress, and heightened sensitivity of cells (13). Tear samples from patients with KC have elevated levels of proinflammatory cytokines (IL-6) (68). Several studies have examined the pathophysiology of keratoconus in first-degree families. The mean values of the cytokines in first-degree relatives were significantly higher than those in controls. Notably, important differences were observed in the levels of IL-4 between keratoconus patients and their relatives and between relatives and controls (67). Toll-like receptors of the innate immune system, TLR2 and TLR4, are overexpressed in corneal epithelial cells and conjunctiva of keratoconus relatives compared to the control (normal). TLR2 and TLR4 are both type I immune proteins which detect agents associated with cell damage. These findings may support its involvement in the pathophysiology of keratoconus (67, 69). A comprehensive review that focused on structural genetic studies pertaining to keratoconus revealed notable associations with two distinct pathways: the interleukin 1 (IL-1) processing pathway and the assembly of collagen fibril pathways. Specifically, IL-1 plays a role in inducing the degradation of corneal collagen, and has been implicated in the process of collagen degradation in corneal fibroblasts. Hence, inflammation and degradation of the corneal extracellular matrix leads to keratoconus (70). In contrast, highly ordered collagen fibrils are altered in keratoconus and hence induce abnormalities in the corneal shape and curvature.

Summary of original articles on genetic and clinical characteristics of first-degree relative are presented in (Table III).

Table III: Summary of genetic, clinical characteristics and pathophysiology of first-degree relative articles

Author/Citation	Type of article	Findings
Naderan et al. 2016 (15)	Original article	Positive family history of KC had more severe disease, according to the Amsler-Krumeich classification ($p < 0.05$)
Wang et al. 2000 (16)	Original article	The estimated KC prevalence in first-degree relatives was 3.34% which is 15 to 67 times higher than that in the general population.
Awwad et al. 2019 (17)	Original article	Tomographic evaluation in paediatric first-degree relatives revealed 32 were diagnosed keratoconus (17.5%), while 35 (19.1%) were diagnosed by objective analysis.
Antunes-Foschini et al. 2020 (19)	Original article	There were 109 self-related affected family members, 52 (48%) were first degree, 18 (16%) were second degree, and 39 (36%) were third-degree relatives.
Lapeyre et al. 2020 (20)	Original article	The prevalence of KC was estimated equal to 0.14, 0.07-0.22] among parents, 0.03 among offspring, and 0.10 among siblings
Ihalainen A. 1986 (26)	Original article	The inheritance was found to be attributable to a dominant autosomal mode in 24 out of 28 multiple-case families (85%)
Bitton et al. 2022 (28)	Original article	A case of discordant keratoconus in a set of monozygotic twins with contrasting environmental risk factors.
Zemba et al. 2020 (39)	Original article	A case of retinitis pigmentosa and bilateral keratoconus in two brothers, one of whom developed corneal hydrops bilaterally
Li et al. 2023 (42)	Original article	Parental corneal tomographic and biomechanical index were identified as the influential factors for KC in their offspring
Khaled et al. 2019 (45)	Original article	Keratoconus inheritance occurs through an autosomal dominant pattern, with a smaller proportion attributed to autosomal recessive inheritance
McComish et al. 2020 (47)	Original article	This study identified a genome-wide significant locus for keratoconus in the region of PNPLA2 on chromosome 11
Brancati et al. 2004 (50)	Original article	This study could not detect any pathogenic mutations in the coding sequences and exon–intron boundaries of COL8A1.
Bisceglia et al. 2009 (51)	Original article	This study represents the first KC linkage replication study on the chromosomal region 5q21.2
Tyynismaa et al. 2002 (53)	Original article	This study suggests that the causative gene in keratoconus is located within the 16q22.3-q23.1 chromosomal region.
Tang et al. 2005 (54)	Original article	Evidence of suggestive linkage from the initial scan was observed at the 82 to 112 cm region of chromosome 5q14.1-q21.3 with a maximum lod score (LOD)
Li et al. 2006 (55)	Original article	Locus5q23.2 was found, the same locus was reported overlapping with the replicated region 5q21.2
Bykhovskaya et al. 2012 (56)	Original article	Strong genetic evidence showed that LOX variants lead to increased susceptibility to developing of keratoconus.
Hardcastle et al. 2021 (57)	Original article	This study report 36 genetic loci strongly associated with keratoconus, 31 of which we identify for the first time.
Hayashi et al. 2000 (60)	Original article	RINX gene is a candidate for this phenotype in another subset of patients. it has been named VSX1 by the Human Gene Nomenclature Committee.
Namdari et al. 2023 (43)	Original article	Tomographic indices and irregularity indices in 3- and 5-mm zone in Orbscan were significantly higher in the first-degree relative group.
Ionescu et al. 2018 (67)	Original article	Important differences were found in IL-4 levels between keratoconus patients and relatives and between relatives and controls
Regueiro et al. 2021 (69)	Original article	Mean expression of TLR2 in corneal epithelial cells and both TLR2/TLR4 in conjunctival epithelial cells were significantly higher in relatives than in controls

DISCUSSION

Studies on monozygotic and dizygotic twins with keratoconus mostly showed concordance, with some discordant cases revealing that unaffected twins still exhibited corneal abnormalities (pre-clinical keratoconus or forme fruste), highlighting the hereditary nature of the disease. The differences between concordant and discordant monozygotic twins suggest that environmental factors, alongside genetic predisposition, are crucial in keratoconus manifestation. Environmental factors such as eye rubbing and allergen exposure can contribute to the development of keratoconus in genetically predisposed individuals (71). Clinical differences may enhance the reliability of identifying co-factors that explain topographic variations between twin pairs.

The exploration of candidate genes, family linkage analyses, and genome-wide association studies have played pivotal roles in identifying genetic loci and gene variants associated with keratoconus (59). The identification of causative genes in keratoconus is an ongoing and complex pursuit. Despite significant research efforts, no single gene variant has been definitively linked to a heightened prevalence of the disease. Instead, keratoconus appears to be a genetically heterogeneous condition that is influenced by multiple genetic and environmental factors (72). To date, numerous genes have been proposed as potential contributors to keratoconus, including the VSX1 gene, which is associated with posterior polymorphic corneal dystrophy; the SOD1 gene, which influences the impact of reactive oxygen species; the ZNF 469 gene, which is linked to brittle corneal syndrome; the TGFβ pathway,

which regulates the composition of the extracellular matrix; and the TGFI gene, which is involved in cell-to-collagen interactions, along with microRNAs (particularly miRNA 184), mitochondrial DNA, and reactive oxygen species in the context of keratoconus (24). Ongoing research, including high-density SNP arrays and whole genome/exome sequencing, is essential to unravel the genetic underpinnings of keratoconus and to develop targeted therapies (47, 58).

From the perspective of corneal topography, curvature, and biomechanics, first-degree relatives of keratoconus showed significant differences when compared to normal individuals (17, 41, 42, 64-66). Advancements in diagnosing and staging keratoconus have significantly improved with the emergence of multimodal imaging technologies such as the Pentacam and Oculus Corvis ST compared to older versions of video keratography. These technologies offer comprehensive assessments of the cornea, enhancing the accuracy and early detection of keratoconus, which is crucial for timely intervention and management (73). Genome data can be included in keratoconus prediction models based on clinical parameters, such as refractive error, corneal thickness, corneal shape, and corneal biomechanics, to estimate the risk of disease (57).

CONCLUSION

Being a first-degree relative is a significant factor in the development of keratoconus or corneal abnormalities, as supported by studies on prevalence, genetics, topography, biomechanics, and immune system receptors. The risk of corneal ectasia persists after refractive and cataract surgeries; hence, this group requires proper screening. This review emphasises the importance of screening first-degree relatives of patients with KC. Employing multiple imaging methods, such as Scheimpflug tomography, biomechanics analyzer and optical coherence tomography (OCT), enhances keratoconus diagnosis by providing a comprehensive understanding of the cornea. This multimodal approach identifies subtle corneal structures and biomechanical changes that a single technique may miss. Future studies should explore multimodal imaging for early keratoconus detection and screening in first-degree relatives.

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