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Genetic and biomechanical factors in keratoconus: a review of pathogenic mechanisms, diagnostic strategies, and risk stratification

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Abstract

Background. Keratoconus (KC) is a progressive, asymmetric corneal ectasia driven by inherited extracellular matrix variation that establishes a baseline biomechanical phenotype on which eye rubbing and atopy precipitate disease.

Aim. To synthesize current evidence on the genetic architecture, the biomechanical phenotype, and the diagnostic strategies that integrate them.

Materials and methods. A structured search of PubMed, Scopus, Web of Science, Google Scholar and bioRxiv covered primary research and meta-analyses on KC genetics, biomechanics, epidemiology, environmental risk, imaging and machine-learning diagnostics (1996–2026, plus selected earlier seminal papers).

Results. Tomography-era prevalence reaches 1:375 in Northern European registries and over 1% in Scheimpflug-screened cohorts. GWAS implicates matrix-organizing loci (*ZNF469*, *LOX*, *COL5A1*, *WNT10A*) and corneal-thickness genes shared with Mendelian connective-tissue disease; a corneal-hysteresis GWAS bridges the genetic and biomechanical strands. In vivo metrics (corneal hysteresis, stress-strain index, Brillouin shift) and combined tomographic-biomechanical indices achieve AUCs above 0.99 for manifest disease and for detecting subclinical KC below the tomographic floor.

Conclusions. Integrating genetic risk, biomechanical phenotyping and AI-based imaging enables earlier diagnosis, sharper risk stratification and better-timed cross-linking; multi-ancestry genetic studies and prospective biomechanical cohorts are research priorities.

Keywords: Keratoconus; Corneal biomechanics; Genetics; Corneal imaging; Corneal ectasia.

1. Introduction

Keratoconus (KC) is a progressive, bilateral but typically asymmetric ectatic disorder of the cornea. It is characterized by localized stromal thinning, conical protrusion, irregular astigmatism, and progressive loss of best-corrected visual acuity [1–3]. Onset is most often in the second decade, with the highest rate of progression during puberty and early adulthood, and a tendency toward stabilization after the fourth decade. However, the natural history is highly variable among affected individuals and even between fellow eyes of the same patient [1,3]. The earliest morphological changes are typically subclinical and detectable only on tomographic or biomechanical assessment, while the first symptoms reported by patients tend to be a steady drift of refraction, increasing astigmatism that resists optical correction, and reduced contrast sensitivity [2,3]. Because the disease threatens vision during the most productive years of life and is a common indication for keratoplasty worldwide, KC carries a disproportionate clinical and socioeconomic burden compared with its prevalence [3].

The contemporary view of KC is that it is a multifactorial disease. Mechanical weakening of the corneal stroma develops on a background of genetic susceptibility. Environmental triggers, most prominently chronic eye rubbing, can precipitate or accelerate the condition [3,4]. Inherited variation acts mainly through the structural collagen-matrix loci identified by genome-wide association studies and candidate-gene work. There is growing evidence that immunoregulatory and stromal remodelling pathways also have a role. Clinically, the same mechanistic complexity drives the case for early detection: identifying subclinical KC before refractive surgery and intervening at the first sign of progression with Corneal Cross-Linking (CXL) now depend on integrating tomographic imaging, in vivo biomechanical metrics, and emerging genetic risk markers rather than on any single test [3,4].

This review synthesizes current evidence on the epidemiology, etiology and pathophysiology, genetic architecture, environmental and behavioral risk factors, corneal biomechanics, and

modern imaging and artificial intelligence based diagnostics of KC. Particular emphasis is placed on the intersection of inherited susceptibility and biomechanical phenotype.

2. Materials and methods

A structured literature search was conducted to identify primary studies and quantitative syntheses that inform the genetics biomechanics axis of keratoconus (KC). PubMed, bioRxiv, Scopus, Web of Science, and Google Scholar were used. The primary date window was 1996-2026, but pre-1996 records were retained when judged seminal. This especially applied to the primary descriptions by Krachmer and colleagues and by Rabinowitz. Search strings combined the term “keratoconus” with “genetics”, “GWAS” (Genome-Wide Association Study), “candidate gene”, “polygenic risk score”, “corneal biomechanics”, “Ocular Response Analyzer”, “Corvis ST”, “Brillouin microscopy”, “optical coherence elastography”, “Pentacam”, “Scheimpflug”, “epithelial thickness mapping”, “tomographic biomechanical index”, “deep learning”, “convolutional neural network”, “eye rubbing”, “atopy”, and “epidemiology” or “prevalence”, joined with Boolean AND/OR operators. Medical Subject Headings (MeSH) were used in PubMed, where indexed terms were available.

Inclusion criteria were limited to peer-reviewed primary research and quantitative meta-analyses focused on KC or directly informative for the genetics by biomechanics question, available in English, and accessible in full text. Exclusion criteria comprised duplicate records across databases, conference abstracts lacking a full-text publication, single-case clinical reports unless of landmark mechanistic significance, non-English records without authoritative translation, and studies deemed off-topic upon full-text review.

Citations identified through the search were exported to a reference manager and screened in two stages: an initial title and abstract screening based on eligibility criteria, followed by a full-text review of records that passed the first stage. For each included study, structured data were extracted regarding candidate genes and reported variants; GWAS-associated loci and effect sizes; in-vivo and ex-vivo biomechanical parameters with numerical values; diagnostic imaging indices with reported sensitivity and specificity; and odds ratios for environmental and behavioral exposures.

3. Epidemiology

The reported frequency of Keratoconus (KC) has shifted markedly since the introduction of corneal tomography. Slit lamp era prevalence estimates were on the order of 1:2,000, showing

a period when only clinically overt disease was counted; tomography based studies have since substantially revised this figure upward [3]. Drawing on a complete national health insurance dataset, Godefrooij et al. [5] reported a Dutch prevalence of 1:375, an incidence of 13.3 cases per 100,000 person-years, a mean age at diagnosis of 28.3 years, and a male preponderance of 60.6%. The Danish national registry documented a two to three fold rise in incidence over the past 10–15 years, reaching 3.60 per 100,000 person-years during 2011–2015 [6]. By contrast, a population-based analysis of the Korean Health Insurance Review and Assessment cohort, encompassing roughly 48 million individuals, returned a lower prevalence of 37.4 per 100,000 with no sex predisposition [7], while the meta-analysis of Hashemi et al. [8] produced a pooled global prevalence of 1.38 per 1,000 and confirmed eye rubbing (odds ratio [OR] 3.09), positive family history (OR 6.42), and allergy (OR 1.42) as the dominant risk factors. The Australian Raine Study, in which Scheimpflug imaging was prospectively applied to 20-year-olds, yielded a community prevalence of 1.2% (1 in 84) [9], underscoring how strongly the ascertainment method shapes the apparent burden of disease.

Substantial geographic and ethnic gradients are superimposed on this methodological variation, with the highest frequencies reported in Middle Eastern, South Asian, and Mediterranean populations, as well as in non-European minorities within Western registries. Millodot et al. [10] found a Jerusalem prevalence of 2.34% (4.91% among males) by clinical and videokeratographic screening, and Hashemi et al. [11] described a 4% prevalence (95% CI 3–4) in an Iranian rural population together with marked familial aggregation. In that cohort, sibling-pair odds ratios exceeded parent-offspring odds ratios, a pattern consistent with shared environmental exposure or a recessive contribution rather than purely additive autosomal-dominant transmission. Familial clustering is corroborated by Awwad et al. [12], who detected Scheimpflug-defined KC in 17.5% of pediatric first-degree relatives of Lebanese probands. Across registries, onset typically occurs around puberty or early adulthood, with progression slowing by the third decade. Although male predominance has been reported in several large series [5], this finding is not universal [7].

4. Etiology and pathophysiology

Keratoconus is now best conceptualized as a multifactorial disorder in which inherited susceptibility, environmental insults such as chronic mechanical trauma and atopy, and the resulting biomechanical failure of the corneal stroma converge on a common phenotype of progressive ectasia [3,4]. The sections that follow examine each of these axes in turn: Section

5 addresses the genetic substrate, Section 6 the environmental and behavioral amplifiers, and Section 7 the biomechanical consequences in the cornea. The present section establishes the cellular and molecular events that link them.

At the structural level, the keratoconic cornea is characterized by paracentral stromal thinning, disorganization and slippage of collagen lamellae, focal breaks in Bowman's layer, and a redistribution of elastic microfibrils away from their normal limbal anchorage. Meek et al. [13] demonstrated, using wide-angle X-ray scattering, that lamellae normally running orthogonally in the central cornea are reoriented around the cone, and second-harmonic generation microscopy has confirmed loss of lamellar interweaving and abnormal lamellar branching across Bowman's layer in keratoconic tissue [14]. These architectural abnormalities are the proximate cause of the focal loss of mechanical stiffness that ultimately defines the disease.

The biochemical milieu of the keratoconic stroma favours net Extracellular Matrix (ECM) catabolism. Collier et al. [15] showed that membrane-type 1 matrix metalloproteinase (MT1-MMP) is over-expressed in keratoconic stroma relative to normal corneas and can activate latent Matrix Metalloproteinase 2 (MMP-2) in vitro, providing the cornerstone observation for the proteolytic hypothesis. Concurrently, Lysyl Oxidase (LOX)-mediated collagen and elastin cross-linking is hypothesized to be reduced, with transcriptomic and SNP-association evidence implicating *LOX* in keratoconic stroma [16,17], plausibly lowering the tensile strength of an already thinned matrix. Oxidative stress accompanies this proteolytic shift: Kenney et al. [18] reported elevated catalase and cathepsin V/L2 levels, along with reduced tissue inhibitor of metalloproteinases-1 (TIMP-1), in keratoconic corneas, and Chwa et al. [19] demonstrated that cultured KC fibroblasts generate excess Reactive Oxygen Species (ROS) and undergo apoptosis when challenged with oxidative or mechanical stressors. The systematic review and meta-analysis of Navel et al. [20] consolidated this evidence, confirming a quantitative imbalance between oxidants and antioxidants in keratoconic tissue and tear fluid. Transforming Growth Factor-β (TGF-β) signalling is also disturbed, with Engler et al. [21] documenting activation of TGF-β/Smad effectors in KC corneas, a pathway that couples mechanical stress to fibroblast phenotypic change. Whole-cornea RNA sequencing by Kabza et al. [16] integrated these observations at the pathway level, showing coordinated suppression of collagen-biosynthesis genes alongside downregulation of the core elements of the TGF-β, Hippo, and Wnt pathways, and subsequent methylome analysis localized differentially methylated regions to known KC linkage loci [22].

Cellular and inflammatory events complete the pathogenic loop. Keratocyte apoptosis depletes the population of cells responsible for ECM maintenance, while surviving stromal cells adopt a remodelling phenotype that further skews the protease/inhibitor balance. The classical view of KC as a strictly non-inflammatory thinning disorder has been progressively revised, as tear-film studies show elevated Interleukin-6 (IL-6), tumor necrosis factor- α(TNF-α), and MMP-9 in affected eyes [23], and Galvis et al. [24] have argued based on converging cytokine, proteolytic, and oxidative evidence that a low-grade inflammatory contribution is integral to disease progression. Together, these strands describe a self-sustaining cycle in which genetic predisposition, oxidative and inflammatory injury, ECM degradation, and biomechanical instability drive the cornea towards the ectatic phenotype detailed in the following sections.

5. Genetic background

5.1 Evidence for a genetic contribution

The familial clustering of keratoconus (KC) has been recognized since the earliest clinical descriptions and provides prima facie evidence of a heritable component. Formal segregation analysis of 95 multiplex KC families reported by Wang et al. [25] could not be reconciled with simple sporadic occurrence and instead favoured a major-gene model with reduced penetrance, an inference reinforced by tomographic screening of asymptomatic first-degree relatives, in whom subclinical corneal abnormalities are detected several-fold more often than in the general population [12]. Direct compatibility evidence in twins is sparser but congruent: in the largest series assembled to date, monozygotic twin pairs were strikingly more often concordant for KC than dizygotic pairs, supporting substantial additive genetic variance [26]. Population isolates with elevated consanguinity, such as the Iranian rural cohort studied by Hashemi et al. [11], show both higher prevalence and pronounced familial aggregation, providing further ecological support for genetic determination. A formal meta-analysis gathering 24 candidate-gene studies (53 polymorphisms across 28 genes or loci) has confirmed that several risk alleles replicate across ancestries despite considerable heterogeneity in effect size [27].

5.2 Candidate genes

Decades of candidate-gene work, summarised in Table 1, have converged on three biological aspects. The first is the integrity of the stromal extracellular matrix (ECM). Variants in *ZNF469*, a master regulator of corneal collagen organization, are enriched among non-

syndromic KC patients of European ancestry, with rare pathogenic alleles conferring substantial risk [28]. Intronic Single-Nucleotide Polymorphisms (SNPs) in *LOX*, which encodes the copper-dependent enzyme that cross-links stromal collagen and elastin, were associated with KC in family-based and case-control analyses in a North American cohort [17]. *COL5A1* and the basement-membrane *COL4A3*/*COL4A4* genes emerged from cross-trait Central Corneal Thickness (CCT) GWAS, including the meta-analysis of Lu et al. [29], which extended earlier CCT loci. The second theme concerns transcription-factor and microRNA regulators of corneal development: heterozygous mutations in *VSX1*, a homeobox transcription factor, were identified in early KC pedigrees [30]; post-transcriptionally, a seed-region substitution in *MIR184* co-segregates with the EDICT phenotype (corneal stromal thinning with anterior-segment anomalies) across a five-generation Galician family [31]. The third theme centers on oxidative-stress and growth-factor signalling: *SOD1*, encoding cytosolic superoxide dismutase, was proposed as a candidate after deletion alleles were detected in familial KC [32], and promoter polymorphisms in *HGF* (hepatocyte growth factor) increase KC risk in Australian and United States cohorts [33]. Pathway-level transcriptomic and methylation analyses additionally show coordinated collapse of TGF-β, Hippo and Wnt signalling in keratoconic stroma, providing convergent biological coherence to these otherwise heterogeneous candidate loci ([16]; see Section 4).

Selected genes associated with keratoconus, their function, the type of evidence, and primary references. Discovery context (population, study design) is provided in the prose of Section 5.

VSX1	Visual system homeobox transcription factor; corneal development	Candidate gene (familial)	[30]
COL5A1 group	Fibrillar collagen type V,α 1; stromal collagen synthesis	Cross-trait CCT GWAS	[29]
COL4A3 / COL4A4	Basement-membrane collagens	Cross-ancestry CCT GWAS	[34]
ZNF469	Zinc-finger ECM regulator; corneal collagen organization	Rare-variant enrichment in non-syndromic KC; biallelic in BCS	[28]

PRDM5	PR/SET-domain transcription factor; ECM development	BCS Mendelian gene	[39]
LOX	Lysyl oxidase; collagen and elastin cross-linking	Family-based + case-control SNP association	[17]
MIR184	MicroRNA; corneal/lens development	Five-generation family co-segregation	[31]
SOD1	Cu/Zn superoxide dismutase; oxidative defence	Familial deletion alleles	[32]
HGF	Hepatocyte growth factor; cell motility/repair	Promoter SNPs in two cohorts	[33]
TGF- β / Hippo / Wnt pathways	Coordinated downregulation of stromal TGF-β, Hippo and Wnt signalling	Whole-cornea RNA-seq pathway analysis	[16]
FOXO1, *FNDC3B*, *MPDZ–NFIB*	Transcription/cell-adhesion regulators of CCT	GWAS lead loci shared with KC	[29]
WNT10A	Wnt-signalling ligand; ectodermal development	Exonic variant lowers CCT and raises KC risk	[35]
Multi-locus polygenic background	Aggregate ECM and corneal-development effect	36-locus multi-ethnic KC GWAS	[36]
Biomechanics-bridge variants	Loci affecting CH and CRF that also confer KC risk	GWAS of corneal biomechanics	[37]
Polygenic risk score	Genome-wide aggregate susceptibility	PRS development and external validation	[40]
Methylation (genome-wide)	Differentially methylated regions over KC linkage loci	Reduced-representation bisulfite sequencing	[22]

The last four rows represent genome-wide or epigenomic analytical units rather than individual genes or loci.

5.3 Genome-wide association studies

5.4 Syndromic associations

KC occurs at substantially elevated frequency in several Mendelian syndromes whose underlying genes encode ECM components. A systematic review of ophthalmic findings in trisomy 21 reports a markedly elevated prevalence of clinically manifest KC, more than 10-fold higher than in the general population, caused by a combination of generalized connective-tissue laxity and chronic eye-rubbing [38]. KC is a recognized feature of Marfan syndrome (*FBN1*) and of the kyphoscoliotic and classical forms of EDS. The most informative syndromic association is BCS, in which biallelic loss of function mutations in *ZNF469* or *PRDM5* produce extreme corneal thinning and spontaneous rupture; the *discovery of PRDM5 mutations defined a regulatory pathway controlling fibrillar collagen* expression that converges on the same ECM network implicated by KC GWAS [39]. These genetically encoded vulnerabilities of the stromal extracellular matrix converge on a common pathogenic axis of weakened collagen cross-linking, dysregulated proteolysis and oxidative stress.

5.5 Genetic heterogeneity, epigenetics and polygenic risk

The mode of inheritance in non-syndromic KC is heterogeneous. Most multiplex pedigrees are consistent with autosomal-dominant transmission with reduced, age-dependent penetrance, whereas the syndromic forms (BCS, certain EDS subtypes) follow autosomal-recessive patterns. This heterogeneity, together with the modest individual effect sizes of common variants, has shifted attention toward epigenetic and polygenic frameworks. Reduced representation bisulphite sequencing of KC corneas has produced the first methylation atlas of the disease, identifying multiple differentially methylated regions that overlap with previously reported KC linkage intervals and so plausibly mediate genotype-phenotype coupling [22]. Building on the GWAS catalogue, He et al. [40] developed and externally validated a comprehensive Polygenic Risk Score (PRS) for KC, demonstrating discriminative gain over pachymetry-based prediction alone in independent biobank cohorts. The convergence of segregation, candidate-gene, GWAS, methylation, and PRS evidence indicates that KC is best modelled as a polygenic stromal-matrix disease in which a heritable predisposition to a thinner, less cross-linked cornea is unmasked by environmental triggers reviewed in Section 6 and translated into the biomechanical phenotype examined in Section 7 [4].

6. Environmental and behavioral risk factors

Although genetic predisposition establishes individual vulnerability, clinical keratoconus rarely manifests without an external biomechanical or biochemical insult, and a two-hit framework in which inherited risk variants interact with modifiable exposures has emerged as the most parsimonious explanation for the heterogeneous clinical course [41]. Among these exposures, chronic eye rubbing is the dominant modifiable factor and the one most consistently linked to disease initiation and progression. Repetitive mechanical insult induces transient Intraocular Pressure (IOP) spikes, focal stromal warming, and concentrated shear stress on the central cornea, mechanisms that are compatible with the focal thinning observed in established disease. Epidemiological support is strong: an early case series demonstrated that the side, severity, and topographic asymmetry of keratoconus align with patient handedness and the dominant rubbing eye, providing one of the few naturalistic experiments that argue for a causal direction rather than reverse causation [42]. A pooled meta-analysis estimated an odds ratio of 3.09 for eye rubbing across heterogeneous populations [8], while a more recent allergy-focused synthesis raised the pooled estimate to 5.22 alongside an odds ratio of 6.67 for a positive family history [43]; the larger effect size in the latter reflects combining across studies enriched for atopic populations, in whom rubbing is more frequent and intense than in unselected community samples. Critically, a medium- to long-term follow-up cohort showed that structured cessation of rubbing was sufficient to halt tomographic progression in patients who had been progressing on serial Scheimpflug imaging, the strongest available evidence that the behavior is causal rather than merely associated [44]. Corneal epithelium RNA sequencing in a Polish case-control series further demonstrated that even non-allergic rubbers exhibit molecular stress signatures distinguishable from non-rubbing controls, anchoring the clinical observation in transcriptomic data [45].

Atopic disease is the second pillar of the environmental risk profile, both as an independent association and as a behavioral mediator that drives ocular itch and habitual rubbing. Vernal Keratoconjunctivitis (VKC), atopic dermatitis, and asthma have each been linked to keratoconus, with a pooled odds ratio of 2.21 for any allergic disease [43]. The contribution is not purely behavioral: patients with VKC or chronic allergic conjunctivitis present with thinner, steeper, and more advanced keratoconus at diagnosis than non-atopic counterparts, suggesting that ocular surface inflammation modifies disease severity beyond the rubbing it provokes [46]. Ultraviolet exposure and oxidative stress occupy a more equivocal position. Mechanistically, the cascade hypothesis states that ultraviolet photons, mechanical microtrauma, and contact-

lens wear converge on the generation of Reactive Oxygen Species (ROS), mitochondrial dysfunction, and aberrant matrix metalloproteinase activation [47], but a quantitative epidemiological link between solar exposure and keratoconus risk has not been firmly established at the population level. Contact-lens wear is mentioned here only for completeness: although historical case series reported an association with keratoconus, the relationship in modern literature is largely confounded by reverse causation, since contact lenses are prescribed precisely because subclinical irregular astigmatism degrades spectacle vision [8]. Table 2 summarises the magnitude and quality of the evidence for each modifiable factor. Environmental aspects do not act in isolation-risk variants identified in Section 5 likely set the threshold above which rubbing-induced or oxidative insults precipitate clinical keratoconus.

Environmental and behavioral risk factors for keratoconus. Pooled odds ratios are taken from cited meta-analyses and synthetic reviews; individual-study effect sizes are reported in the prose of Section 6.

Eye rubbing	Repetitive mechanical insult; transient IOP spikes; focal stromal warming; the dominant modifiable factor. Pooled OR 3.09 [8]; 5.22 in atopy-focused meta-analysis [43]. Cessation halts tomographic progression [44].	[8,42–45]
Atopy / allergic eye disease	Direct association plus behavioral mediation through itch-induced rubbing; pooled OR 2.21. Atopic patients present with thinner, steeper, more advanced KC.	[43,46]
Family history	Pooled OR 6.42 [8]; 6.67 in atopy-focused synthesis [43]; 17.5% Scheimpflug-detected KC in pediatric first-degree relatives.	[8,12,43]
UV / oxidative stress	Cascade hypothesis: photons + microtrauma + lens wear → ROS→ ECM proteolysis; epidemiological signal inconsistent across latitudes.	[47]
Contact lens wear	Historical association largely confounded by reverse causation (lenses prescribed because subclinical irregular astigmatism degrades spectacle vision).	[8]
Two-hit interaction	Genetic predisposition (Section 5) sets the threshold above which environmental insults precipitate clinical disease.	[41]

7. Corneal biomechanics

7.1 Stromal architecture and the basis of corneal stiffness

The mechanical competence of the cornea derives almost entirely from the stromal collagen lattice. Wide-angle X-ray scattering shows that fibrils in the central cornea are preferentially aligned along the superior–inferior and nasal–temporal meridians, while a circumferential limbal annulus resists the radial pull of intraocular pressure [13]. Anterior lamellae also interweave and insert obliquely into Bowman's layer, conferring disproportionate stiffness on the anterior third of the stroma. Both features are disrupted in keratoconus: X-ray scattering reveals redistribution of preferred orientation around the cone apex [13], and second harmonic generation imaging demonstrates loss of anterior interweaving with a paucity of lamellae inserting into Bowman's layer [14].

7.2 Theoretical framing

The contemporary mechanistic account is the focal biomechanical decompensation hypothesis, in which localized loss of stromal modulus initiates a self-sustaining cycle of strain redistribution, further thinning, and loss of apical modulus [48]. Finite-element simulations support this view: introducing a focal posterior-stromal softening in a healthy model reproduces the conical deformation of established keratoconus, and the same models show that vigorous eye rubbing concentrates stress in the deep posterior stroma-precisely the region where the primary lesion is hypothesized to originate [49]. This observation connects biomechanical failure directly to the behavioural risk discussed in Section 6.

7.3 In-vivo measurement

Two air-puff devices dominate clinical biomechanical assessment. The Ocular Response Analyzer (ORA) was the first instrument to quantify corneal viscoelasticity in vivo, deriving Corneal Hysteresis (CH) - the pressure difference between inward and outward applanation events - and the Corneal Resistance Factor (CRF) from a bidirectional applanation trace, both in mm Hg [50]. The Corvis ST couples an air puff with high-speed Scheimpflug imaging, from which Deformation Amplitude (DA) and the DA-ratio (central to paracentral deformation), the Stiffness Parameter at first applanation (SP-A1, in mm Hg/mm), and the dimensionless Stress-Strain Index (SSI) are extracted [51]. CH and CRF capture predominantly viscoelastic, time-dependent behavior, whereas SP-A1 and SSI estimate stiffness - the slope of the stress-strain

curve - both of which differ from ocular rigidity, the integrated pressure-volume relationship of the whole globe, which is probed indirectly by tonometry. Two research grade modalities complement them: Brillouin microscopy probes the longitudinal modulus via GHz-range frequency shifts of inelastically scattered light [52], and Optical Coherence Elastography (OCE) derives the shear modulus from the velocity of micrometer-scale displacement waves.

7.4 Biomechanical alterations in keratoconus

Keratoconic corneas manifest reduced viscoelastic damping and reduced stiffness across all available platforms. In the original version of Reichert ORA validation, both CH and CRF were significantly reduced in keratoconus compared with age-matched controls [53]. SP-A1 is reduced and the DA-ratio elevated, and the SSI declines progressively across a 1,221-eye cohort, falling from approximately 1.04 in healthy eyes to 0.85 in bilateral keratoconus and 0.74 in severe disease, supporting its use as an Intraocular Pressure and central corneal thickness independent stiffness biomarker [54]. Composite indices now dominate screening: the Corvis Biomechanical Index (CBI) achieved an AUC of 0.983 with 94% sensitivity and 100% specificity in its derivation cohort [55], although external-cohort performance has been somewhat lower, particularly for specificity in the very asymmetric normal tomography subgroup. Fusing Corvis data with Pentacam tomography in a random forest classifier yielded the Tomographic Biomechanical Index (TBI), with AUCs of 0.996 for clinical ectasia and 0.985 for the very asymmetric, topographically normal fellow eye [56]; a deep-learning successor extends this approach [57]. Brillouin microscopy localizes the lesion: ex vivo, the apical Brillouin shift falls from 8.17 ± 0.06 GHz in controls to 7.99 ± 0.10 GHz in keratoconus, with the deficit confined to the cone [52]. The biomechanical rationale for Corneal Cross-Linking (CXL) is grounded in the same parameter space: ex vivo riboflavin–UVA treatment increased Young's modulus 4.5-fold in human and 1.8-fold in porcine corneas [58].

7.5 Subclinical keratoconus and clinical relevance

Perhaps the most striking clinical observation is that biomechanical abnormalities precede topographic and tomographic ones. In the unaffected fellow eyes of patients with unilateral keratoconus-eyes normal by Placido and Scheimpflug criteria - the DA-ratio and SP-A1 already separate the cohort from age-matched controls, identifying subclinical disease that would otherwise pass refractive-surgery screening [59]. In-vivo motion tracking Brillouin microscopy likewise separates subclinical keratoconus from controls with an AUC of 1.0 in a

single-centre cohort of 30 eyes (15 with subclinical KC and 15 controls), a near perfect estimate that requires multicentre replication before clinical translation [60]. Biomechanical phenotyping therefore shifts the diagnostic threshold earlier than tomography alone, carrying clear implications for pre-refractive screening and for the timing of cross-linking. The amalgamation of these descriptors with Scheimpflug, anterior-segment optical coherence tomography, and epithelial thickness mapping including the full diagnostic-imaging context for the TBI - is the subject of Section 8.

8. Diagnostic imaging and artificial intelligence

Modern diagnosis of KC is built on a stepwise stack of imaging modalities, each layered onto the previous to extract progressively earlier signs of ectasia, with machine learning classifiers now sitting atop the imaging output and increasingly fusing tomographic and biomechanical inputs. The principal modalities discussed below are Placido-disc axial topography, rotating Scheimpflug tomography summarised in the Belin-Ambrósio Display Deviation, and anterior-segment optical coherence tomography with epithelial thickness mapping.

8.1 Placido topography and the KISA index

Reflection-based Placido-disc videokeratography remains the historical anchor of quantitative KC diagnosis, encoding curvature pattern as color-coded axial and tangential maps and condensing classical Rabinowitz indices into a single number. The KISA% index combines central K-reading, inferior-superior asymmetry, skewed-radial-axis and astigmatism components on a multiplicative scale and was originally validated against expert clinical classification: a value correctly classified 280 of 281 cases (99.6%) as manifest KC, while values between 60% and 100% flagged topographic suspects requiring further work-up [61]. Although Placido alone misses posterior-surface changes, the KISA threshold is a useful first-pass screen and a reference standard against which newer indices are benchmarked.

8.2 Scheimpflug tomography and ABCD grading

Rotating Scheimpflug imaging extends curvature analysis to a true three-dimensional reconstruction of anterior and posterior corneal surfaces and full pachymetric mapping, with the Belin-Ambrósio Display Deviation (BAD-D) summarising elevation, thickness progression, and curvature deviations on a unified normative scale [56]. The ABCD grading

system formalizes staging through four anatomically anchored variables - anterior radius of curvature in the 3-mm zone (A), posterior radius (B), thinnest pachymetry (C), and corrected distance visual acuity (D), with an optional scarring suffix-each scaled to stages 0-4 [62]. Validation in 1,000 patients (1,917 corneas) at the Homburg Keratoconus Center confirmed that parameter B, derived from the posterior surface, increases faster than A across decades of life, reframing the posterior elevation map as the earliest morphological signature of progression and explaining why anterior-curvature-only criteria underdiagnose subclinical disease [63].

8.3 Anterior-segment OCT and epithelial mapping

Spectral-domain Optical Coherence Tomography (OCT) and Very-High-Frequency (VHF) ultrasound resolve the corneal epithelium as a separate layer, revealing the pathognomonic "doughnut" pattern of central thinning surrounded by an annulus of compensatory thickening over the apex of an evolving cone. In topographically and algorithmically normal fellow eyes of unilateral KC patients, epithelial-thickness analysis reclassified roughly half as abnormal and unmasked occult disease that would have been missed by curvature criteria alone [64]. Combining Pentacam tomography with VHF - derived epithelial thickness in a multiparametric classifier yielded 97.3% sensitivity and 100% specificity for clinical keratoconus versus normal corneas [65].

8.4 Combined biomechanical-tomographic indices

Pure tomography reaches its detection floor in the very-asymmetric-normal-tomography eye, where shape is preserved, but biomechanical reserves are already eroded. As outlined in Section 7, the Corvis Biomechanical Index complements shape with deformation features; such fusion with BAD-D into the Tomographic and Biomechanical Index (TBI) achieves an Area Under the Curve (AUC) of 0.996 for manifest KC and, critically, 0.985 for the very asymmetric NT subgroup at an optimized cut-off of 0.29 [56]. A more recent random forest reformulation, TBI version 2, raises subclinical ectasia detection to AUC 0.945 in multicentre cross-validation [57]; independent prospective external validation in non-overlapping cohorts is still a research priority, and the Corvis Biomechanical Index detects bilateral abnormality in topographically and tomographically normal fellow eyes of patients with very asymmetric keratoconus [55,59].

8.5 Machine learning and deep learning

Algorithmic classifiers progressed from interpretable decision trees on dual-Scheimpflug input, with 93.6% sensitivity and 97.2% specificity for forme-fruste keratoconus versus normal corneas [66], to Convolutional Neural Networks (CNNs) operating directly on topography images: KeratoDetect reached 99.3% test-set accuracy on Placido maps [67], and a ResNet152 backbone with Grad-CAM saliency reached AUC 0.995 with interpretable heat-maps localizing the cone [68]. CNNs trained on Corvis ST dynamic deformation videos extend the same architecture to the biomechanical domain, achieving an internal AUC of 0.94 and 0.93 on an independent external cohort [69]. A 36-study meta-analysis of artificial intelligence for KC pipelines reports a pooled accuracy of 99.2% for manifest KC and 96.4% for forme-fruste KC, with the caveat that most contributing studies relied on internal cross-validation rather than independent external testing [70].

9. Discussion

Taken together, the evidence reviewed here points toward a single coherent model of keratoconus pathogenesis. Inherited variation in extracellular matrix genes sets a biomechanical baseline - a cornea that is thinner, less stiff, and more vulnerable to deformation - upon which environmental insults such as chronic eye rubbing act to push individual eyes past the threshold of irreversible focal decompensation. The keystone of this synthesis is the genome-wide association study of corneal hysteresis and the corneal resistance factor by Khawaja et al. [37], which directly maps biomechanics-defining variants to KC susceptibility, providing the first molecular evidence that the genetic and biomechanical strands of this review converge on the same loci. Susceptibility variants reviewed in Section 5 act through the extracellular-matrix substrate - exemplified by the *WNT10A* exonic allele that increases KC risk by reducing central corneal thickness [35] - while finite-element modelling shows that knuckle-driven rubbing concentrates posterior-stromal stress at exactly the inferotemporal location where the cone first emerges [49], delivering a quantitative bridge from behavioral exposure to the focal-decompensation framework articulated by Roberts et al. [48]. Together, these threads dissolve the historical separation between structural and mechanical hypotheses of pathogenesis.

The clinical translation of this integrated model rests on three complementary uses, each tied to a metric already defined in earlier sections. First, the screening of refractive surgery

candidates benefits from biomechanical and combined indices - the Tomographic and Biomechanical Index discussed in Section 8 and the Corvis Biomechanical Index, with case-series evidence that biomechanical metrics flag bilateral abnormality in topographically and tomographically normal fellow eyes of asymmetric KC patients [59] - because these instruments retain discriminative power in the very asymmetric normal tomography eye that single modality tomography misclassifies as healthy [55,56]. Second, risk stratification can now combine family history with the validated polygenic risk score of He et al. [40] and a baseline biomechanical profile, yielding a quantitative pre-test probability that informs surveillance frequency and the timing of stabilising intervention; CXL remains the prototypical biomechanical disease modifier, having been shown to increase stromal stiffness in human and porcine corneas after riboflavin-ultraviolet-A treatment [58], and the integrated risk profile helps identify the high-progression patients most likely to benefit from early treatment. Third, subclinical detection in the era of OCT epithelial mapping and deep learning extends diagnosis below the tomographic floor - through the doughnut epithelial pattern [64], multiparametric classifiers [65], interpretable convolutional models [68], and motion-tracking Brillouin microscopy resolving subclinical longitudinal modulus reduction [60].

Several limitations temper the strength of this summary. Cohorts assembled for KC genome-wide association remain modest in absolute case numbers, with the largest multi-ethnic effort to date including approximately 4,700 cases [36], bottlenecking variant discovery and statistical power for trans-ancestry fine-mapping. Ethnic representation skews to European, Han Chinese, and select Middle Eastern populations, leaving sub-Saharan African, South Asian, and Indigenous American risk architectures essentially uncharacterized. Prospective biomechanical progression cohorts are scarce, so the trajectory of the stress-strain index and dynamic deformation variables during conversion from subclinical to manifest disease is inferred largely from cross-sectional comparisons [51,54]. Diagnostic definition heterogeneity worsens these gaps: Flockerzi et al. [63] demonstrated that ABCD-stage prevalence depends on whether posterior or anterior criteria define the threshold, and Chan et al. [9] showed that Scheimpflug screening of an unselected community cohort yields a prevalence an order of magnitude higher than slit lamp era estimates. Pediatric biomechanics remains the most undersampled compartment despite carrying the highest risk of progression.

Future progress should accordingly target four specific designs. Multi-ancestry KC genome-wide association meta-analyses with imputation against ancestry matched reference panels are required to validate the polygenic risk score from He et al. [40] in non-European populations

and to fine-map the biomechanics loci identified by Khawaja et al. [37]. Prospective cohorts with annual stress-strain index, integrated inverse radius and Brillouin longitudinal modulus measurement would convert today's cross-sectional biomechanical signatures into individualized progression trajectories. Multimodal artificial-intelligence pipelines that ingest tomography, dynamic deformation videos, epithelial-thickness maps and a polygenic risk score within a single classifier - following the architecture of Ambrósio et al. [57] - should be benchmarked against external test sets distinct from the training population to address the internal-validation bias documented in current meta-analyses. Finally, the customization of cross-linking protocols in relation to spatial stiffness maps, and the longer-horizon prospect of gene-targeted modulation of extracellular-matrix loci in syndromic ectasias, follow directly from a model that treats KC as the convergent end point of genetic, biomechanical, and behavioral axes rather than a single mechanism disease.

10. Conclusion

Keratoconus is most accurately described as a multifactorial ectatic disease in which inherited variation in extracellular matrix and corneal developmental loci specifies a baseline biomechanical phenotype that environmental triggers, principally chronic eye rubbing and atopy, push past the threshold of focal stromal decompensation. The most consequential conceptual advance of the last decade is the demonstration that genome-wide association studies of corneal hysteresis recover loci that simultaneously confer keratoconus susceptibility, fusing the genetic and biomechanical narratives into a single pathogenic axis. This integrated view yields three concrete clinical gains: earlier diagnosis through the combination of dynamic biomechanical metrics, epithelial mapping and artificial-intelligence classifiers that operate below the tomographic detection floor; sharper risk stratification through the joint use of family history, polygenic risk scores and baseline biomechanical profiling; and better-timed stabilizing intervention informed by individual progression risk. Continued progress depends on multi-ancestry genetic studies, prospective biomechanical progression cohorts, and externally validated multimodal artificial intelligence pipelines. Translating this evidence into routine clinical practice requires prospective validation studies and broader genetic representation, but the components of an integrated diagnostic and prognostic framework are now in place.

After conclusions:

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Declaration on the Use of Artificial Intelligence

During the preparation of this work, the authors used generative AI to assist with grammar and stylistic editing to ensure appropriate academic language and for translation into English. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final content of the manuscript.

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