Clinical and Experimental Ophthalmology (2001) **29**, 345–351

Review Article

The genetics of keratoconus

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Abstract

Keratoconus is a relatively common, bilateral, non-inflammatory corneal ectasia. The aetiology of this condition is probably multifactorial, or it represents the final common pathway for a variety of different pathological processes. Although a familial history is present only in a minority of cases, one of the major aetiological factors is certainly genetic. This is evidenced by: the condition's familial inheritance; its discordance between monozygotic and dizygotic twins; and its association with other known genetic disorders such as Down's and Marfan's syndromes. In the keratoconic cornea, a possible genetic predisposition to increased sensitivity to apoptotic mediators by keratocytes has also been hypothesized. Differences in prevalence between ethnic groups have been identified. Recent advances in computerized topographic diagnostic techniques for keratoconus, including *forme fruste* keratoconus, enables higher accuracy in delineating abnormal from normal, and helps define study populations for genetic linkage studies. However, genetic heterogeneity and the phenotypic diversity of keratoconus means that genetic analysis continues to be a complex process. None the less, it is foreseeable that over the next decade, improved diagnostic techniques, in combination with molecular genetics, may reveal conclusive data on the precise nature of the genetic inheritance of keratoconus in specific populations. This review considers the evidence that suggests keratoconus is primarily an inherited condition, and examines research strategies aimed at unveiling the genetic predisposition, and the enigma of environmental influences on its phenotypic expression.

Key words: apoptosis, corneal topography, ectasia, genetics, keratoconus.

Introduction

Keratoconus is a bilateral non-inflammatory corneal ectasia, the exact cause of which remains unknown.[1] The condition's aetiology is probably multifactorial, or it represents the final common pathway for a variety of different pathological processes.[1] In an as yet unknown proportion of patients, one of the aetiological factors is certainly genetic.[2,3] Evidence for this is suggested by the condition's familial occurrence, its discordance between monozygotic and dizygotic twins,[4,5] and its association with other known genetic disorders.[1] However, exactly how the condition is inherited and then leads to ocular morbidity or interaction with other suggested co-pathologies, remains unknown.[1] The aim of this paper is to review the evidence that suggests keratoconus can be inherited, consider current research to elucidate the mechanism, and to highlight future research strategies.

Family History

The most common presentation of keratoconus is as a sporadic disorder,[6] but it has long been recognized that a significant minority of patients exhibit a family history.[7–9] Numerous studies have confirmed the inheritability of keratoconus,[4,10] noting variable proportions of subjects with familial disease. Most clinical studies support an autosomal dominant mode of inheritance with variable phenotypic expression.[11–13] However, the exact percentage of subjects who have inherited a predisposition to the disease remains unconfirmed.

The varying proportions of familial disease identified in different studies is influenced by the populations and gene pools studied, but will also be affected by other factors such as consanguinity.[14] The natural history of keratoconus is normally that of a slowly progressive condition with variable clinical expression.[2] Investigations into family history have largely been point prevalence studies, so variable disease expression means that detection rates in family members will depend on the sensitivity of diagnostic criteria used, and early or subclinical cases may often be missed.[1,15] For example, the advent of computerized videokeratoscopy enabled better classification of irregular astigmatism and keratoconus, including *forme fruste* keratoconus, allowing detection and appropriate classification of early disease.[16] Subsequently the apparent familial prevalence rate increased. Further evolution of corneal mapping with methods such

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as elevation topography[17] or automated quantitative evaluation[18] may mean that this rate is further modified.

Several large studies predating computerized videokeratoscopy highlighted an inherited element in between 6 and 8% of keratoconics.[6,14,19] Ihalainen (1986) found that in two different areas of Finland 9% and 19% of patients, respectively, had one or more first-degree relatives with the condition.[2] Rabinowitz's group have reported a similar percentage using videokeratoscopy,[10] but results of this technique have been used to postulate an even higher rate of inheritance. Corneal topographic findings of central corneal steepening, asymmetrical inferior steepening and asymmetry of central dioptric power between eyes have been shown to be early markers of keratoconus.[20] Interestingly, Gonzales and McDonnell showed in a small study (n = 12) that 58% of randomly selected keratoconics had one parent with at least one of these abnormal corneal indices,[13] and in another small study (n = 28) Rabinowitz found 50% of randomly selected family members of keratoconics had minor topographical abnormalities.[1] Further follow up of groups like these is necessary to establish if these abnormal corneae progress to keratoconus.

Many families with keratoconus occurring in two or three generations have been described in the literature,[1,2,6,8–11,21] most investigators suggesting an autosomal dominant mode of inheritance. In this context, the irregular astigmatism and corneal asymmetry previously described is seen by some authors as variable phenotypic expression, as most series suggest complete penetrance. Other forms of inheritance have been described, such as autosomal recessive, sex-linked and sporadic, but in none have three generations been adequately examined with modern techniques.[22–25]

It has been suggested that similarity of cone morphology between family members may represent an underlying common genetic basis. Rabinowitz *et al.* described a large family in which all individuals had nipple cones, as opposed to oval cones, which may be of different genetic or perhaps non-genetic cause.[12] However, a small study from Australia failed to confirm this observation.[26] More work is required in this field to ascertain whether related patients share topographic indices, and whether these indices can be related to suspected aetiology.

Twin Studies

Studies of twins are important when investigating a disease potentially of genetic origin. The higher the rate of concordance between monozygotic twins, the greater is the evidence for primary genetic causation rather then environmental aetiology. The same conclusion may be drawn if concordance is greater between monozygotic compared to dizygotic twins.[27]

In the published literature, there are studies of at least 18 sets of monozygotic twins, in which one or both of the pair shows some degree of keratoconus. Thirteen of these pairs were described before the advent of, or without use of, computerized video keratoscopy: seven being concordant,[2,7,21,28–30] and six discordant for keratoconus.[31–33] The lack of corneal topography, combined with other factors such as young age at the time of assessment, mean that all, but in particular the latter six cases, cannot be considered conclusive. Of greater interest are the monozygotic twins examined with modern computerized videokeratoscopy: Bechara *et al.* describe two sets concordant for keratoconus.[4] Owens and Watters[34] and Parker *et al.*[35] described two pairs in which both had the condition, but were topographically discordant. McMahon *et al.* report two sets of proven monozygotic twins in which one had clinical keratoconus, the other normal videokeratoscopy.[5]

Therefore, studies have generally reported monozygotic twins concordant rather than discordant for keratoconus. These strongly support a genetic aetiology. The cases of proven monozygotic discordance may lend additional credence to an environmental cofactor being necessary, in addition to a genetic susceptibility, for clinical manifestation of the disease, and this might also explain topographical variation between a pair of monozygotic twins. However, a primary genetic cause in discordant twins is still possible, in light of these data, as recent studies suggest that monozygotic twins may not be genetically identical in all tissues.[5]

There is little data on dizygotic twins with keratoconus, perhaps because of a much-reduced rate of concordance. A documented reduced concordance in comparison to the rate in monozygotic twins is supporting evidence for genetic causation. There is need for a more extensive, prospective longitudinal monozygotic and dizygotic twin study from databases of keratoconics to confirm these trends.

Associated Genetic Disorders

Keratoconus has been reported in association with a large number of other ophthalmic and systemic conditions such as Down syndrome, Leber's congenital amaurosis, eye rubbing, mitral valve prolapse, collagen vascular disease, pigmentary retinopathy, Marfan's syndrome, and a history of contact lens wear.[1,36] Many are probably chance associations, such as Turner's syndrome[37] or floppy eyelid syndrome,[38] no statistical link having been shown. Of particular interest are proven links with other conditions of known genetic origin, which may provide information on chromosomal associations. Such conditions include Down syndrome, Leber's congenital amaurosis, atopy and connective tissue disorders.

Down syndrome has a strong association with keratoconus, reported prevalence ranging from 0.5 to 15% (10–300 fold that of the normal population).[1,39,40] This suggests a link with chromosome 21, which has been the focus of early formal genetic analysis. However, the association has also been attributed to mechanical trauma from eye rubbing in these patients, but the evidence for this is mixed. Down syndrome patients are known to frequently suffer from blepharitis,[40] and severe eye rubbing has been described clinically, but whether, and how, eye rubbing contributes to keratoconus remains unclear.

Likewise, the association between keratoconus and autosomal recessive Leber's congenital amaurosis (up to 30% in adulthood[41]) has been attributed to eye rubbing, this time from an oculo-digital response. Whether these groups of patients rub their eyes,[41] whether this behaviour in keratoconus is cause or effect, and importantly whether mechanical trauma itself is a cause for keratoconus,[1] remain unclear. The genetic basis for Leber's amaurosis is now partly understood, and these known chromosomal loci are candidate genes for further work in keratoconus.[42–47]

Atopy is the congenitally determined predisposition to type one hypersensitivity reactions and allergic responses. Evidence of a link with keratoconus is mixed,[1,31,48,49] and as with Down syndrome and Leber's amaurosis, an association, if there is a genuine one, may be due to eye rubbing. As with other studies the clinical delineation of keratoconus leads to variable reporting, but in this setting is confounded, as definition of atopy is also partly subjective. In addition, the genetic basis for atopy is likely to be multifactorial.[50]

Keratoconus has been associated with a number of congenital connective tissue diseases and collagen abnormalities. The condition has been shown to occur with types of Ehlers–Danlos syndrome and osteogenesis imperfecta;[51,52] of particular note is a recent report of familial osteogenesis imperfecta with keratoconus in three generations of the same family.[53] Co-existence with joint hyper-mobility has been reported previously,[26] but two subsequent studies have failed to confirm this.[1,54] There is good evidence, however, for a link with mitral valve prolapse: Beardsley and Foulks finding 44% of keratoconics[55] and Sharif *et al.* 58% of those with severe disease[56] had coexisting mitral valve prolapse. Each of these associations, particularly the latter, which have similar biochemical and histopathological changes, might suggest a differing expression of an underlying collagen abnormality.

Other Evidence

The prevalence of keratoconus has been reported to vary in different studies, from 8.8 to 54.4 per 100 000,[2,6,57] the variation in part due to the different diagnostic criteria used in each study. Other factors influencing prevalence could be differing exposure to environmental cofactors, and in particular, different genetic predisposition in study populations. A recent comparative study from Britain has described a fourfold greater incidence of keratoconus in Asians from the Indian subcontinent, compared to white Caucasians living in the same geographical area.[58] This and other reports also demonstrate racial differences in disease severity and rate of progression.[59,60] If other racial differences are demonstrated, such populations, especially if small, may prove invaluable in future molecular genetic studies.[61]

Computerized videokeratography of keratoconus shows different cone morphology between patients. However, between the two eyes of the same patient topography may show characteristic non-superimposable mirror image symmetry, suggesting genetic control of phenotypic expression in early to moderate disease.[62] It seems less probable that any intrinsic biology or extrinsic aetiology could result in such symmetrical 'enantiomorphism', unless it is the expression of an underlying natural symmetry beneath the pathological process.[63]

Molecular Genetics

From the available evidence, there is little doubt about the existence of genetically determined keratoconus. However, identifying the causative genetic abnormality, or abnormalities, and correlating them to the morphological features of the disease continues to be elusive.

Molecular genetics is rapidly identifying genes associated with ophthalmic conditions, for example corneal dystrophies have been mapped to chromosome 5 in the last decade[64] and the gene *Keratoepithelin* identified as the causative gene. The major techniques of disease-causing gene identification are by (i) candidate genes; or (ii) linkage methods. Candidate genes identify likely proteins that could cause disease (based on biochemical studies of the disease process) and look for mutations in that gene. Linkage analysis identifies chromosomal regions shared by affected members in a family with a disease and identifies novel genes mapped to that region. Now that the Human Genome project has identified all the genes, a hybrid of these two approaches is used, known as the positional candidate approach. These techniques have shortcomings in keratoconus: the former because the exact molecular or tissue abnormalities are not yet known, the latter because of genetic heterogeneity and phenotypic diversity.

Most work to date has been in rare family groups that have a significant number of known keratoconics. In these families genetic heterogeneity is minimized, so results from linkage analysis is valid. Expensive linkage analysis studies between different families are not valid because of presumed heterogeneity. These issues mean that presently molecular genetic studies are only possible with restricted numbers, so progress is slow. As our ability to accurately diagnose and differentiate early keratoconus from normal improves, study populations should increase in size and aid further work. Such information may be gained in the future from quantitative analysis of corneal topography and complex segregation analysis of results to show true inheritance patterns and markers for early disease.[65]

Interestingly, Wang *et al.* recently reported the first testing of genetic models with segregation analyses demonstrating a strong familial association, best fitting a major gene model, with recessive transmission. In contrast, sporadic or environmental models were rejected. In this study, the estimated keratoconus prevalence in first-degree relatives was 15–67 fold higher than in the general population.[66]

Although a unifying molecular cause for keratoconus has yet to be elucidated, a variety of enzymatic and biochemical abnormalities are known in affected corneae.[1] The

chromosomal determinates of these products are potential candidate genes for genetic studies into the aetiology of the condition. Examples include the genes for the collagens, the interleukin-1 system,[67] proteases[68] and protease inhibitors.[69,70] Rabinowitz's group has used the different types of collagen as the targets for study. Their reasons for choosing the collagen genes included the association of keratoconus with mitral valve disease[54–56] and osteogenesis imperfecta.[53] Collagen types I, III, IV, V, VI, VII and VIII are all found in different layers of the cornea.[71] The group's initial work, in a single family, excluded a role for collagen type COL6A1 by failing to show genetic linkage.[12] Subsequent work has similarly excluded, in a single family, numerous other collagen genes.[1] These results are valuable, but again because of the genetic heterogeneity of keratoconus, mean that these genes can only be definitely excluded as a cause in these single families.

As previously outlined, the association between keratoconus and known genetic disorders can be used as a source for candidate genes. Rabinowitz's group has used linkage analysis on chromosome 21 in a single family with autosomal dominant keratoconus; chromosome 21 being chosen because of the strong link between keratoconus and Down syndrome.[39,40] They have shown linkage with a small 6.8 centiMorgan (cM) section of the chromosome, adjacent to its centromere, between markers D21S1905 and D21S1409.[3,72] However, at present no major genes are known to be located at this site. Hameed *et al.* have recently described a restricted area of genetic linkage on chromosome 17, in a family with autosomal recessive Leber's congenital amaurosis and keratoconus.[47] Genes involved in the former have been mapped to, or very close to, this 10.77 cM area, but did not exhibit a mutation in this family. In addition, no products potentially involved in the pathogenesis of keratoconus have been mapped to this area, but it is known to be very gene rich and further work is on going. A chromosome 13 ring abnormality (46,XX,r(13)) on the long (q) arm, has recently been associated with keratoconus.[73] This is interesting as the genes coding for the α1 and α2 chains of collagen IV are located nearby on the q arm of chromosome 13.[74]

As already stated, larger studies may become practical as assessment of computerized topography gets better at clearly delineating abnormals from normals. Pure segregation analysis of keratoconus is difficult at present for the reasons already described, but one potential way round this is study of certain limited populations. The principle of founder populations has been recognized for some years by geneticists as a way to identify novel candidate genes for single gene disorders. When a relatively small population whose ancestry is limited has a high rate of a genetic disease, it may be safe to presume that all affected individuals share the same genetic defect. A group from Melbourne has used this technique in studying keratoconics in north-west Tasmania, and have reported a founder haplotype, located on 18p, that warrants further work.[61] Another group in Finland have performed initial genome scans of 22 unrelated keratoconics who all originated from the same restricted geographical area.[75] Perhaps further work in similar small populations in other areas around the world will reveal other potential target genes.

Eye Rubbing

A positive relationship between eye rubbing and keratoconus has been suspected for decades.[76,77] The link with vernal keratoconjunctivitis and atopy fuels speculation as to whether rubbing the eye could exacerbate or even cause keratoconus, or whether the rubbing is simply a symptom of underlying pathology. Certainly, rubbing behaviour is strongly associated with the disease.[36,78] This raises the question as to whether keratoconic patients have a genetic predisposition to eye rubbing, or possibly a genetic keratocyte hypersensitivity to the trauma of eye rubbing. A genetic basis for atopy is well known,[79] and atopic individuals do rub their eyes more; however, prospective case reports exist showing that keratoconus can arise in those whose only recognized risk factor is eye rubbing, without clinical evidence of atopy.[80,81]

The association between rubbing and the pathogenesis of keratoconus is unknown. It has been suggested that chronic epithelial damage can induce chronic keratocyte apoptosis, which has been shown to be much higher in the keratoconic cornea. Kim *et al.* (1999) detected apoptotic keratocytes in 60% of corneae with keratoconus, compared to 35% of corneae with stromal dystrophies ($P = 0.03$), and 0% in normals.[82] However, rabbit models have shown eye rubbing to predominantly affect cells of the tarsal conjunctiva, and spare all but a few sparse superficial epithelial cells of the cornea.[83,84]

It is possible that the release of inflammatory cytokines from damaged corneal epithelium, or from the considerably more delicate columnar upper tarsal conjunctival epithelial cells, could act as local mediators of keratocyte apoptosis. Fas ligand binding to a Fas site provides stimulation for a cell to undergo apoptosis. Fas ligand has been demonstrated to be released by damaged corneal epithelium,[67] and interleukin-1 (IL-1) has been shown to induce Fas ligand production in corneal keratocytes.[85] Interestingly, keratoconic fibroblasts express, on average, fourfold the number of IL-1 receptors compared to normal corneae,[86] potentially making them more susceptible to chronic local inflammatory challenge. The genetic basis for this is unknown. Rubbing the eye is a behaviour that feasibly could chronically activate apoptosis, through inflammatory mediators such as these, and lead to onset and progression of keratoconus.

Despite the strong historical association, and some speculative causative factors, there remains insufficient evidence to make a firm aetiological link between eye rubbing and keratoconus. Research into the possible genetic cause of the keratoconic keratocyte IL-1 receptor over-endowment,[86] could help bridge the gap to link the potential histopathological and genetic bases for keratoconus.

Conclusion

Keratoconus is a complex disorder that can have a genetic aetiology. There is probable genetic heterogeneity, where several gene abnormalities may manifest a similar phenotype. This genetic heterogeneity and the condition's phenotypic diversity, in that even genetically affected family members may not exhibit clinical keratoconus, means that formal genetic analysis continues to be a complicated process. However, it is foreseeable that over the next decade molecular genetics may reveal firm evidence on the nature of genetic inheritance of keratoconus in specific populations.

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