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GENETICS AND KERATOCONUS

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***Abstract*—Keratoconus is a relatively common bilateral, non-inflammatory corneal ectasia. Keratoconus has a multifactorial etiology with multiple genetic and environmental component contributing to the disease pathophysiology. In the keratoconic cornea, a possible genetic predisposition to increased sensitivity, to apoptotic mediators by keratocytes has also been hypothesized. Advances in Computerized Topographic Diagnostic Technique for KC including forme frust Keratoconus, enables higher accuracy in delineating abnormal to normal, and helps studying genetic linkages for populations.**

***Index Terms*— Apoptotic, Ectasia, Etiology, Genetic Linkages, Keratoconus.**

I. INTRODUCTION

Keratoconus comes the Greek word KERAS (Cornea) and KONOS (Cone). It was first described in literature in 1854 (Nottingham). Keratoconus is characterized as a (mostly) bilateral, progressive, non-inflammatory thinning of the cornea resulting in blurred vision due to irregular astigmatism. It has been shown that beside genetic factors- environmental effects such as inflammation, eye rubbing, allergic eye disease and wearing of contact lenses can play a role in development of Keratoconus. The etiology of Keratoconus is still poorly understood. Recent studies say that there is evidence of over expression of inflammatory mediators such as Cytokines and Interleukin 6 (IL-6) in tears of KC patients. One of the etiological factors for KC is certainly genetic. Evidence for this is suggested by the conditions familial occurrence, its discordance between monozygotic and dizygotic twins and its association with other known genetic disorders.

The aim of this paper is to review the evidence that Keratoconus can be inherited, and to review the current knowledge on genetic aspects of KC.

II. SIGNS AND SYMPTOMS

Keratoconus has variable clinical signs. In moderate stages a very common slit-lamp sign is Fleischer's Ring located in the basal epithelium around the cone which can be partial or complete. It consists of iron deposits. Vogt's Striae are fine vertical lines due to compression of the Descemet's membrane. In advance cases patients may develop an acute KC leading to "Hydrops" causing stromal edema, vision loss and associated pain. Corneal scarring occurs commonly in patients wearing contact lenses. KC is caused in both men and women. The most sensitive diagnostic tool to detect KC even in early stages is Corneal Tomography even if there are no further symptoms or signs.

III. TREATMENT

Spectacle corrections are done in early stages of KC. Contact Lenses (specially RGP's) are suggested in moderate stages presenting with irregular astigmatism. Intra Corneal Rings (ICR) are suggested if contact lenses are not tolerated by patients. Collagen Cross Linking (CXL) has been a successful means in stiffening of cornea and arresting progression and flattening of cornea by preventing enzymatic degradation of stromal collagen. If patients with severe KC don't improve their visions by the above method, they will eventually need Keratoplasty,Now being replaced by Deep Lamellar Keratoplasty (DLK).

IV. PREVALENCE OF KC

The burden of a disease in a community is evaluated by the knowledge of how much wide spread is that disease. This is demonstrated by its prevalence, which is a proportion (or percentage) of the total number of cases at a period divided by the size of the population from which the cases has been determined. Another measure of burden of disease is incidence, which is the number of new cases presenting during a defined period divided by the population size from which the cases has been determined.

If the disease is chronic, then

Prevalence = Incidence * Duration.

A. Hospital, Clinic based Reports

Prevalence studies has been conducted in hospital / clinic. The findings offer an estimate of prevalence, since the patients are usually symptomatic and early forms of conditions are missed as well as the patients are treated by independent Optometrists and Ophthalmologists. Although these studies are commonly cited they must be interpreted with caution.

Until a few years ago many publications on KC referred to one prevalence value obtained in Minnesota, USA in 1986 was 0.054% (54 persons out of 100000 people. The diagnosis was based on a combination of scissor movements in retinoscopy and keratometry similar to the prevalence studies published before 2011. The figures was similar to those reported in Finland or Denmark. It must be noted, précised video keratography is likely to yield higher prevalence than the older method. Recent studies using this method report higher prevalence, different factors may possibly correlate with the

method used since they come from the middle east and India with different climatic conditions than Europe or North America with if nearly diagnosed with a keratometer.

Table 1: shows the epidemiological study of KC

CLINIC BASED EPIDEMIOLOGICAL STUDIES OF KC.

Author	Location	Age in years	Sample size	Incidence/100,000	Prevalence/100,000	Method
Kennedy et al. (1986)	Minnesota, USA	12–77	64-P	2	54.5	Keratometry + retinoscopy
Ihalainen (1986)	Finland	15–70	294-P	1.5	30	Keratometry + retinoscopy
Gorskova and Sevost'ianov (1998)	Urals, Russia				0.2–0.4	Keratometry
Pearson et al. (2000)	Midlands, UK	10–44	382-P	4.5-W 19.6-A	57 229	Keratometry + retinoscopy
Ota et al. (2002)	Tokyo, Japan		325-P	9		Keratometry?
Georgiou et al. (2004)	Yorkshire, UK		74-P	3.3-W 25-A		Clinical examination

A, Asian (Indian, Pakistani, and Bangladeshi); W, white; P, patient; NA, not available.

B. Population- Based Studies

Cross-sectional studies typically enroll people who volunteer to participate in the investigation, even though the population selected may have a selection bias. Individuals having disease may not participate at the same time some volunteers may keenly participate certain population of the volunteers, who were totally unaware, were discovered to have the disease during the survey. Therefore, population based screening studies are the best methodology to assess the true prevalence of the disease. Modern videography is the best tool to screen subjects in a population based study.

V. RISK FACTORS FOR KC

Environmental Factors

It is commonly accepted that etiology of KC is multifactorial combining environmental and genetics factors. Moreover it seems that an environmental factors may be essential to act as a trigger of the condition in genetically predisposed individuals.

Environmental factors which has been recognized are:

Eye-rubbing, Atopy and UV exposure, although the relative contribution of all these factors are currently unknown [6].An excess of any of these environmental factors cause oxidative damage to KC corneas because of the inability of KC corneas to process Reactive Oxygen Species (ROS) which leads to a degeneration process leading ultimately to corneal thinning and loss of vision due to lack of corneal enzymes such as Aldehyde Dehydrogenase Class3 (ALDH3), catalase, or superoxide dismustase to remove or neutralize the ROS.

1) Eye-Rubbing

An association between KC and Eye-Rubbing had been described and accepted by many of the authors. Usually the length of rubbing in KC patients is much longer (from 10- 180 sec.). Bawazeer et al, conducted a logistic regression analysis that included atopy and family history of KC and sound that only eye-rubbing was significantly associated with the disease, with an odd ratio (OR) of 3.98. This strong association was confirmed in other logistic analysis but at the same time not reported by all authors.

The micro trauma caused to the epithelium by rubbing KC corneas generate increased levels of Matrix-Metalloproteinases MMP-1 and MMP13, secreted by epithelial and stromal cells, and inflammatory mediators including IL-6 and TNF α. The release of these factors leads to KC and its progression.

2) Atopy

Atopy is a hypersensitivity reaction, which includes allergy, asthma and eczema. A positive association between KC and atopy has been reported by many authors , and many others did not find a statistically significant association when compared to a control group. Bawazeer et al. concluded that atopy was not significantly associated with KC but eye-rubbing.

3) UV Exposure

UV is a source of reactive oxygen species (ROS) and excessive exposures to sunlight leads to oxidative damage to KC cornea, in which there is a reduced amount of aldehyde dehydrogenase class3 and superoxide dismustase necessary to remove the ROS.

VI. Genetics In Keratoconus

A. Role Of Heredity In Keratoconus

Majority of Keratoconus cases are sporadic; autosomal dominant with reduced penetrance and autosomal recessive mode of inheritance have also been documented.First degree relatives are at much higher risk of disease than the general population.

Monozygotic twins shows a high concordance of KC with a greater similarity of phenotypes indicating a strong role of genetic components in the disease phenotype. These data provide strong evidence to support the role of heredity in KC.

B. Genetic Studies In KC

Corneal topographical assessment in vivo confocal microscopy, Placido disk analysis, and slit lamp biomicroscopy have greatly aided the diagnosis of KC, but are often highly variable and difficult to interpret in young individuals with mild symptoms. Identification of specific genetic markers may thus be a valuable tool in clinical diagnosis.

Multiple genomic approaches have been used to identify chromosomal loci and genes involved in KC.

C. Linkage Analysis

Susceptible genetic loci is mapped using a very powerful tool i.e, Linkage analysisand also been utilized at genome-wide level KC.

To date, 17 distinct genomic loci have been mapped for KC indicating that there exists high degree of genetic heterogenecity in this disease [28] (Table 1).

Unfortunately, only three of these loci namely 5q21, 5q32, and 14q11 have been replicated independently [24]. At the same time, MIR 184 and DOCK 9 the two potential genes associated with KC has been determined using this approach, as described below (Table 2).

Table 1: Loci identified in keratoconus patients by linkage analysis and identity-by-descent approach

Locus	LOD score	Candidate genes excluded‡	Population
1p36, 8q13-q21	3.4	ENO1, CTNNBIP1, PLOD1, UBIAD1, SPSB1, and TCEB1	Australian
2p24	5.13	—	Caucasian and Arab
3p14-q13	3.09	COL8A1	Italian
4q, 5q, 12p, and 14q (suggestive)	—	—	Caucasian and Hispanic
5q14.1-q21.3	3.53	—	Americans
5q21, 5q32-q33, and 14q11 (suggestive)	—	—	Italian
9p34	4.5	—	Caucasian and Hispanic
14q24.3	3.58	VSX2	Mixed

16q22-q23	4.1	—	Finnish
20q12†	—	MMP9	Australian (UK descent)

Table 2: Some of the genes reported in keratoconus using different genomic approaches.

Genes	Method	Population
MIR184	Linkage	Northern Irish
DOCK9	Linkage	Ecuadorian
VSX1	Candidate gene	European
ZEB1	Candidate gene	European
TGFB1	Candidate gene	Chinese
COL4A3/COL4A4	Candidate gene	European
FLG	Candidate gene	European
IL1A	Candidate gene	Korean, Chinese
IL1B	Candidate gene	Korean, Japanese
CAST	Linkage/candidate gene	Americans
SOD1	Candidate gene	Americans
HGF	GWAS	Australian, Americans
RAB3GAP1	GWAS	Americans, Australian
LOX	Linkage/GWAS	Americans
MPDZ-NFIB, BANP-ZNF469	GWAS/candidate gene	European/Asian and Australian
COL5A1	Linkage/GWAS	Americans
KRT72	Gene expression	European
TIMP1, TIMP3, BMP4,and CFL1	Gene expression	Korean

MIR- 184 is abundantly expressed in cornea and lens epithelia and mutations in the seed region of MIR 184 is likely to affect its function.

DOCK 9 is expressed in the cornea and specifically activates CDC 42, a G- Protein. It is known that the mutation is located in DHR1 domain which binds to phospholipids and recruits a protein to the membrane which is predicted to be possibly damaging.

Despite efforts to screen numerous candidate gene in these loci, identification of causative genes (and mutations), however remains elusive to a large extent. This may be due to the several limitations posed by linkage studies of complex diseases. The size of the genetic effect, power of analysis to identify genes with small effects, presence of phenocopies with reduced penetrance and various subclinical forms of KC may be the reasons in many instances.

D. Candidate Gene Analysis

The complex etiology of the disease makes the identification of genetic risk factors difficult. Based on the underlying biological traits of the disease, candidate genes are predicted depending on their known biological functions and expression patterns relevant to the disease. Candidate gene approaches are particularly useful in studying complex multi-factorial diseases and enables us to identify even small gene effects using large case control cohorts.

Mutations in visual system homeobox 1 (VSX1; OMIM 605020) and zinc- finger E-box binding homeobox 1 (ZEB1; OMIM 189909) genes have been previously implicated in PPCD and hence, their role on KC has been investigated.

Since oxidative stress has been hypothesized to play a role in the etiology of KC and given the association of trisomy α 1(Down Syndrome) with Keratoconus, association of variants in SoD1 gene localized on chromosome 21 has also been investigated.

E. Genome- Wide Association Studies

Genome- Wide Association Studies (GWAS) in case-control cohorts provide a powerful platform to identify common risk variants in complex genetic diseases. These studies identify SNP (s) that are in linkage disequilibrium with causative variants and require large population- based samples to achieve a genome- wide significance.

A stage 2 genome wide linkage scan in keratoconus families and identified a locus at chromosome 5q 23.2, overlapping the gene encoding lysyl oxidase (LOX; OMIM 1534550.

LOX is involved in corneal collagen and elastin cross-linking. Artificial collagen fibre cross-linking following riboflavin and UV light exposure is a procedure for the treatment of KC and therefore this gene may have therapeutic implications.

VII. CONCLUSION

KC is the most common ecstatic disorder of the cornea. It usually affects people of both genders and all ethnicities in the second decade of life with a descending progression after thirties. Genetic and environmental factors plays a major role in the pathogenesis of KC. However, the etiology of KC is far from being understood with environmental behavior and genetic factors all – in a variety of ways contributing to the disease.

Newly developed genetic technologies including whole-exome or genome sequencing and GWAS will significantly propel the genetic research of KC, which in turn will improve our understanding of the genetic factors in the etiology of the KC. Hopefully this will ameliorate our diagnostics and allow for targeted treatments.

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