THE ROLE OF VISUAL SYSTEM HOMEBOX 1 IN KERATOCONUS

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Abstract
Keratoconus is a multifactorial corneal disorder, mainly characterised by the gradual thinning of the cornea. Visual system homebox 1 (VSX1) gene is one of the candidate genes which is implicated in keratoconus in various populations. Genotyping of VSX1 exons and flanking regions was performed in order to assess the allelic distributions of VSX1 variants in keratoconus patients and non-keratoconus controls. Univariate analysis showed that VSX1 variants, namely p.A182A, c.627+23G>A and c.627+84T>A were associated with keratoconus. Haplotypes of these variants further confirmed the association of the variants with keratoconus. Further continuation is required to understand the association of these variants.

Methods

Subject recruitment
- UMMC, KL and Ophir Clinic, Klang
- Consent forms

Selection criteria
- Exclude other ocular and systemic diseases
- Verified by consultant ophthalmologists

Laboratory assessment
- Blood sample collection and DNA extraction
- PCR and DNA sequencing

Bioinformatics
- Statistics: IBM SPSS statistical package
- Sequence alignment: Sequencher®; VSX1 reference sequence: NG_000831.1
- HWE and linkage association: Haploview

Objective
To assess allelic distribution of VSX1 SNPs in keratoconus patients

Results
In this study, p.A182A, c.627+23G>A and c.627+84T>A (known as p.R217H and p.P237P respectively) were segregated in patients and controls (Figure 2). A allele from p.A182A and A allele from c.627+84T>A variants were four times more likely to be found in patients (OR: 4.068 [95% CI: 2.098–7.885]; p=0.001). A allele from c.627+23G>A was two times more likely to be found in controls (OR: 0.534 [95% CI: 0.239–0.867]; p=0.011).

Discussion
It has been reported that the role of VSX1 in keratoconus could be either pathogenic or non-pathogenic (Burdon et al.). It has also been reported that two haplotype blocks involving c.425-11T>A (also known as VSX1-11T>A), p.N151S, p.G160V and p.L176L (denoted as Block A) and p.A182A, c.627+22C>T, c.627+23G>A and c.627+84T>A (Block B) were segregated in Korean keratoconus patients (Mok et al.). Block B was similar with our study, with the exception of c.627+22C>T. Class II transcripts encode proteins that lack either part or all of the homeodomain which is important in DNA-binding specificity (Hayashi et al.). However, actual function of Class II transcripts and their role in keratoconus remains unknown.

Materials and Methods

Keratoconus (OMIM: 148300)
- Corneal thinning disorder
- Has estimated prevalence of 50 to 230 per 100,000 in the general population, higher occurrence found among Asians
- A multifactorial disorder, involving genetic, biochemical and bio-mechanical factors

Visual system homebox 1 (VSX1) gene (OMIM: 605200)
- A part of paired-like homeodomain transcription factor known as visual system homebox (VSX)
- Location: at the short arm of chromosome 20 (20p11.2-13.1)
- Functions: Expresses VSX1 protein which binds to the core of the locus control region of the red/green visual pigment gene cluster; regulates expression of the cone opsin genes in early eye development
- The VSX1 gene is expressed in two classes of mRNAs transcripts, i.e. class I and class II transcripts (Figure 1)

Conclusion
In this study population, the SNP allelic distributions influenced the overall haplotype patterns that were found. VSX1 SNPs p.A182A, c.627+23G>A and c.627+84T>A were implicated in keratoconus.

Main References

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