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LETTER TO THE EDITOR

Analysis of the *SOD1* Gene in Keratoconus Patients from Saudi Arabia

Abdulrahman M. Al-Muammar¹, Hatem Kalantan¹, Taif Anwar Azad²,
Tahira Sultan², and Khaled K. Abu-Amro^{2,3}

¹Anterior Segment Unit, Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia, ²Ophthalmic Genetics Laboratory, Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia, and ³Department of Ophthalmology, College of Medicine, University of Florida, Jacksonville, FL, USA

ABSTRACT

We investigated Saudi patients with familial and sporadic Keratoconus for mutations in the Superoxide dismutase 1, soluble (*SOD1*) gene. We sequenced the entire coding region, exon-intron boundaries and intron 2 encompassing a 7-bp deletion in clinically confirmed Keratoconus patients (n = 55) and 100 ethnically matched healthy controls. All cases and controls were unrelated. Sequencing the *SOD1* gene revealed the presence of four nucleotide changes and all were non-coding. Those were g.12035 C>A; g.13978 T>A; g.12037 G>A and g.11931 A>C with similar frequencies in patients and controls. All four sequence changes were benign polymorphisms with no apparent clinical significance. Additionally, the 7-bp deletion in intron 2 reported previously, were not detected in any of our Keratoconus cohort. In our Keratoconus cohort, no pathogenic *SOD1* mutation(s) was identified.

Keywords: Keratoconus, mutation, Saudi Arabia, *SOD1* gene

Keratoconus (KTCN; OMIM 148300) is a non-inflammatory thinning and anterior protrusion of the cornea that results in steepening and distortion of the cornea, altered refractive powers and altered visual acuity. Symptoms are highly variable and depend on the stage of progression of the disorder. The incidence of KTCN ranges between 1/500 and 1/2000 individuals throughout the world. The disease occurs with no ethnic or gender preponderance and causes significant visual impairment. Most cases of KTCN are sporadic but some (5–10%) have a positive family history. There are several chromosomal loci and genes reported to be associated with KTCN.¹ Some of which were eventually excluded, while others showed no confirmed association with the disease. This is not the case for the visual system

homebox 1 (*VSX1*) gene where mutations associated with keratoconus cases have been found in different studies. Although other studies did not find *VSX1* mutations in cohorts of keratoconus patients from various populations.² This indicates that KTCN is a complex condition of multi-factorial etiology and that mutations in the *VSX1* gene are not responsible for all cases of keratoconus. We previously investigated whether Saudi patients with KTCN had mutations in the *VSX1* gene, but we found none.² Additionally, we could not detect any crucial abnormalities in a group of Saudi patients with isolated KTCN.³

The Superoxide Dismutase Isoenzymes (SODs) are differently distributed within human healthy cornea and cornea of patients with KTCN.⁴ Superoxide dismutase 1, soluble gene (*SOD1*; OMIM: 147450) is

located on chromosome 21 while Trisomy 21 is notably at high risk for Keratoconus; thus, a role in the increased oxidative damage found in keratoconic corneas could not be discarded. Udar and colleagues⁵ screened this gene in 15 unrelated patients and identified a 7-base genomic deletion within intron 2 in two of them. Moreover, mRNA analysis showed the presence of two additional transcript splice variants coding for proteins lacking the active site of the SOD1 enzyme. Thus we investigated whether mutations in the *SOD1* gene may play a role in keratoconus pathogenesis. Patients were selected from the anterior segment clinic at King Abdulaziz University Hospital after examination. Patients were diagnosed with keratoconus if the Schimpff-flow based elevation map showed posterior corneal elevation within the central 5 mm $\geq +20 \mu\text{m}$, inferior-superior dioptric asymmetry (I-S value) $>1.2\text{D}$ and the steepest keratometry $>47\text{D}$. Patients were considered as sporadic cases after examining the immediate family members and identifying the patient as isolated case of keratoconus. Exclusion criteria was based on the presence of post-LASIK ectasia and refusal to participate. Controls were recruited from the general ophthalmology clinic and had no ocular disease(s) or previous ophthalmic surgeries. Their slit lamp exam showed clear cornea and their Schimpff-flow based elevation map was within normal limit.

All KTCN cases, secondary to causes such as trauma, surgery, Ehlers Danlos syndrome, Osteogenesis Imperfecta and pellucid marginal degeneration were excluded from the study. DNA from patients and controls were extracted as detailed previously.⁶ Full *SOD1* gene-sequencing including the region having genomic 7-base deletion in intron 2 (IVS2+50 del7) (reported previously in three KTCN patients) was performed as previously described.⁵

A total of 55 unrelated KTCN patients and 100 unrelated controls were recruited into this study. Of the 55 KTCN patients there were 24 males and 31 females with a mean age of 28.9 (SD 7.7). Of the 100 controls there were 52 males and 48 females with a mean age of 61 (SD 18). Examining the family pedigrees in the KTCN patients indicated that the mode of inheritance was sporadic in 56.4% of cases, 34.6% were autosomal recessive; 5.4% were autosomal dominant and 3.6% of cases were indeterminable. We first screened all patients of the 7-base deletion in intron 2 of the *SOD1* gene and we did not detect this deletion in all our patients. This deletion was initially reported in three KTCN patients. Detecting this mutation in three KTCN patients only and lack of further studies confirming these findings (including our current study) raise doubts about the role of this deletion in KTCN pathogenesis.

When we screened the full coding region and exon-intron boundaries of the *SOD1* gene, we detected four sequence changes (g.12035 C>A; g.13978 T>A; g.12037 G>A and g.11931 A>C) which were all outside the coding area. These sequence changes were also present in the control group with similar frequency, thus eliminating their potential role as a risk factor for KTCN. This indicates that the *SOD1* gene may not play a role in KTCN pathogenesis at least at the sequence level. There might be other epigenetic factors contributing to KTCN pathogenesis in connection with the *SOD1* gene or even deep intronic sequences which we did not screen for in this study.

Previously we had shown that our KTCN patients (familial cases and sporadic) lack pathogenic sequence changes in the *VSX1* gene² and that sporadic cases also lack chromosomal copy number changes.³ These investigations by us and others still indicate that the gene or group of genes responsible for KTCN is still not identified. In the literature, most cases of KTCN are sporadic, but a proportion (5–10%) may be familial. In our population, as judged by the family pedigree, 56.4% of cases were sporadic, 34.6% had autosomal recessive mode of inheritance; 5.4% were autosomal dominant and 3.6% of cases were difficult to determine. So 40% (22 patients) of our KTCN cohort were familial and this percentage is higher than that reported previously in the literature. This high rate of familial cases, could be attributed to the soaring scale of consanguinity in this society which reaches up to 60% in some areas of the Kingdom. Other modes of inheritance have been described, including autosomal recessive mode in families with children of consanguineous parents. In conclusion, *SOD1* gene may not play a role in KTCN pathogenesis. Further studies in multiple ethnicities and larger cohorts may be required.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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