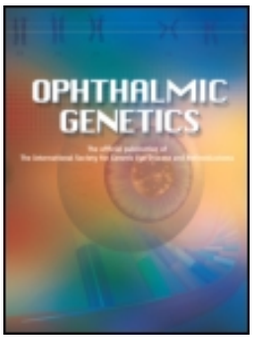

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LETTER TO THE JOURNAL

Linkage Analysis of High-density SNPs Confirms Keratoconus Locus at 5q Chromosomal Region

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Previously we reported on a two-stage genome-wide linkage scan using microsatellite markers in a four-generation Caucasian family with autosomal-dominant keratoconus[1] which identified a peak of 8.2 MB with Lod score of 3.53 located at the 5q14.1-q21.1 chromosomal region.[2] To confirm this linkage region we performed a second scan using high density single nucleotide polymorphisms (SNPs) and tested them for genetic linkage and association with keratoconus in 27 family members including those diagnosed with keratoconus denoted by black symbols (Figure 1A). The study was approved by the Institutional Review Board (IRB) and conducted in accordance with the provisions of the Declaration of Helsinki. A total of 525K SNPs (HumanOmniExpress BeadChip, Illumina, Inc.) were tested for linkage under an autosomal dominant model with the same parameters (phenocopy rate of 0.01 and penetrance of 0.5) and pedigree-splitting method as was described in our original paper[2] using Merlin 1.1.2.[3] A maximum Lod score of 2.49 was calculated at approximately 99 MB region of chromosome 5 overlapping the original linkage peak (Figure 1B). In addition, based on Lod scores greater than 2 we narrowed down the linkage region to 5MB between 95 MB and 100 MB located at 5q15-5q21.1.

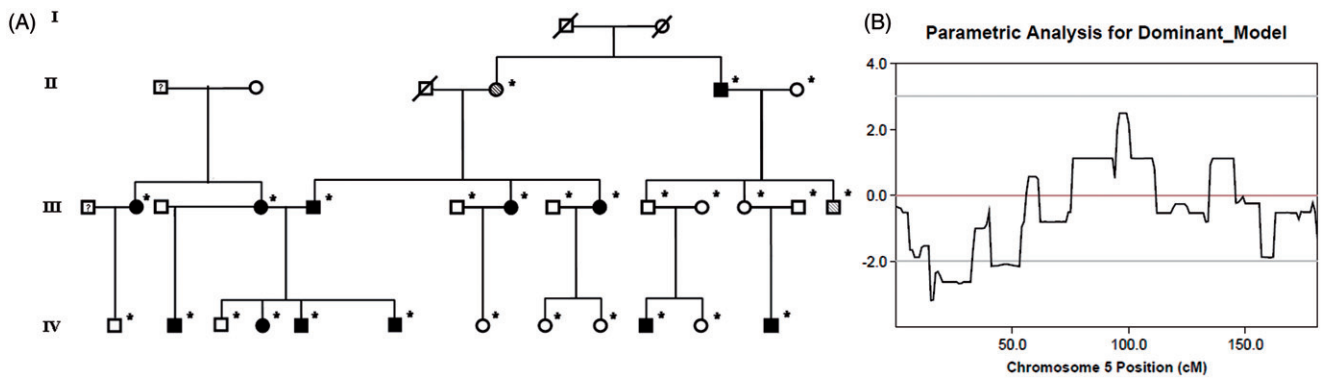

FIGURE 1. (A) Family structure of the four generation Caucasian family with keratoconus. *Denotes genotyped individuals. (B) Results of parametric linkage analysis.

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We also tested for genetic association 445 SNPs located in this region using generalized estimation equation models accounting for familial correlations (GWAF).[4] Association tests under the dominant model identified 32 SNPs with p values ranging from 0.05–0.004; three associated SNPs were located within 50 KB of known genes. These SNPs were rs3853203 ($p = 0.01$), rs39597 ($p = 0.03$), and rs11738579 ($p = 0.05$) located in or adjacent to genes *CAST*, *RIOK2*, and *RHOBTB3*, respectively. All three genes were present in the human keratoconus cornea cDNA library constructed by our group;[5] however, variants in CAST gene were implicated in genetic susceptibility to keratoconus in family and case-control panels by our group[6] making it a top candidate gene in the region.

In short, confirmation of this linkage locus makes 5q chromosomal region the strongest candidate for potential identification of a genetic defect associated with familiar nonsyndromic keratoconus in this family as well as possibly in other families with familiar keratoconus.[7,8]

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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