Heterozygous Coding ZNF469 Variants Enriched in New Zealand Patients With Isolated Keratoconus

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Keratoconus (Online Mendelian Inheritance of Man [MIM] 148300) is a common bilateral ocular disease characterized by progressive corneal thinning and ectasia. The progressive corneal thinning (mean central corneal thickness [CCT]) results in myopia and corneal astigmatism. Genome-wide association studies (GWAS) in different populations have showed that common noncoding single nucleotide polymorphisms (SNPs) of zinc finger 469 (ZNF469 [MIM 612078]) are strongly associated with CCT.1,2 Moreover homozygous mutations in ZNF469 lead to brittle cornea syndrome type 1 (BCS1 [MIM 229200]), a rare autosomal recessive connective tissue disease associated with abnormal thin corneas.3 Since homozygous ZNF469 mutations result in a corneal thinning disorder, and since common SNPs 100-kb upstream of ZNF469 are strongly associated with CCT, Vincent et al.4 hypothesized that heterozygous variants in ZNF469 might predispose to the development of isolated keratoconus. Therefore, the coding regions of ZNF469 were investigated in 43 patients from New Zealand (one-half of which are Maori or Polynesian) with isolated keratoconus. Potentially pathogenic missense variants were found in 23% of this population. Interestingly, the current study converges well with a recent study by Lechner et al.5 revealing heterozygous coding variants in ZNF469 in 12.5% of three European cohorts with isolated keratoconus (two from the United Kingdom, and one from Switzerland, respectively), representing a significant enrichment of ZNF469 heterozygous alleles ($P = 0.00102$). In conclusion, the enrichment of rare mutations in ZNF469 in a New Zealand population with keratoconus uncovers, for the first time, coding ZNF469 alleles as potentially important genetic factors contributing to the pathogenesis of keratoconus.

References