Autosomal dominant high myopia is a complex common eye disorder, with implications for blindness due to increased risk of retinal detachment, choroidal degeneration, premature cataracts, and glaucoma. An interval of 2.2 cM was defined on chromosome 18p11.31 using 7 families with AD high myopia and was designated the MYP2 locus. We sought to characterize the causative genes by direct sequencing of 9 known positional candidate genes in the region. The BLAST algorithm was used to query BAC clones against the genomic sequence for evidence of expression of candidate genes from the MYP2 interval. Exon/intron boundaries were also determined from known gene structures described in the NCBI Map Viewer. Reverse transcription polymerase chain reactions (RT-PCR) and queries of the UniGene database were performed to substantiate gene expression in ocular tissues. Coding regions, intron/exon boundaries and untranslated exons of all known genes were sequenced using genomic DNA samples from 12 affected and 8 unaffected MYP2 pedigree members, and from 4 unaffected and 1 highly myopic external controls. Polymorphic sites were compared to known variants from the dbsNP database. In total, 116 polymorphisms were found by direct sequencing; 12 were missense, 17 were silent, 34 were not translated, 51 were intronic, and 2 were homopolymeric deletions. Forty-six polymorphisms were novel. Novel SNPs were submitted to dbsNP; observed frequencies were submitted for known SNPs. No identified sequence alterations were associated with this interval is in progress.

We sequenced the full coding regions of nine positional candidate genes in our patient samples of individuals from pedigrees with MYP2 autosomal dominant high myopia. No DNA sequence variants were noted that implicated any as the causative gene. We were especially interested in the TGIF candidate gene because of its published association with MYP2 by SNP association studies[13]. TGIF exon 10 (exon 3 in the initial build of this gene) did not show the same level of polymorphic variants in our cohort[14]. This may be peculiar to our specific sample set, although family-1 of the MYP2 pedigrees studied was of Chinese descent. All other families were of Northern European descent. All other families of Northern European descent. Given that TGIF mutations cause holoprosencephaly also reduces the likelihood that it is directly associated with simplex myopia.

We interpreted our negative findings with caution; it is quite possible that one of these genes is responsible for MYP2 high myopia but that the common variant is located distally in a promoter region, within an intron, or within an isoform that was not represented in our study.

In-silico prediction of novel genes, refinement of known genes and further studies of MYP2 candidate genes are currently underway.

CONCLUSION

Mutation analysis of 9 positional candidate genes shown to be expressed in ocular tissues for MYP2 autosomal dominant high myopia did not identify sequence alterations associated with the disease phenotype. Further studies of MYP2 candidate genes are needed to determine the gene(s) causative for this potentially blinding disorder. Mutation screening of other genes that also map to this interval is in progress.

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References