



Category: Functional Genomics

Poster Prize Winner

Genetic and functional involvement of ZEB1 and FEN1 genes in FECD pathogenesis

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Abstract

Fuchs' endothelial corneal dystrophy (FECD) is a dominantly inherited complex disorder, clinically manifested as thickened collagenous deposition on corneal Descemet's membrane with excrescences called guttae [1, 2]. The current study intends to understand the genetic and functional role of FECD candidate genes, ZEB1 (Zinc finger E-Box binding homeodomain) and FEN1 (Flap endonuclease 1). For this, genetic co-segregation of polymorphic variants in these genes with FECD was assessed in a sample Indian population comprising of 76 FECD patients and 180 unrelated age-matched controls. Gene scan through bi-directional sequencing identified novel polymorphic association at rs220057 (OR= 1.92, 95% CI= 1.246-2.96, P= 0.016) in ZEB1. Gel-shift assays confirmed the binding of transcription factor, ZEB1 at the promoter proximal region of a collagen gene, COL8A2 that contains DNaseI hypersensitivity signatures as per ENCODE data.

Genotyping of the polymorphisms in FEN1 (rs174538 and rs4246215) gene indicate a higher risk of developing FECD (OR= 6.50, 95% CI= 1.84-23.01, P= 0.004) for rs4246215/TT carriers. Comet assay analysis from blood leucocytes of study participants also revealed heightened endogenous DNA damage in FECD carriers of rs4246215/TT genotype. These results confirm genetic involvement of ZEB1 and FEN1 genes in Indian FECD cohort and provide insights on their functional roles. ZEB1 binding on COL8A2 promoter proximal region provides initial reports suggesting probable regulatory role of this transcription factor over collagen expression. Our report also suggests a predisposition of FECD patients to increased endogenous DNA damage, which can be reasoned with increased FEN1 expression reported previously in rs4246215/TT lung tissues [3]. Further analysis on downstream effects of ZEB1 regulation and FEN1-coupled DNA denaturation will advance the current knowledge on FECD pathogenesis.

References

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