Padhy et al. (2017) Can J Biotech, Volume 1, Special Issue, Page 90
https://doi.org/10.24870/cjb.2017-a77

Canadian Journal of Biotechnology

ISSN 2560-8304

Poster Presentation OPEN ACCESS

Category: Clinical Genomics **Poster Prize Winner**

Pseudoexfoliation and Alzheimer's associated CLU risk variant, rs2279590 lies within an enhancer element and regulates CLU, EPHX2 and PTK2B gene expression

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Abstract

Pseudoexfoliation (PEX) is an age related ocular disorder characterized by deposition of protein aggregates on the surface of anterior eye tissues. Advanced stage of PEX is called as pseudoexfoliation glaucoma (PEXG) which leads to gradual degeneration of optic nerve and loss of vision compared to that of less severe stage called pseudoexfoliation syndrome (PEXS). PEXG is the leading contributor of secondary glaucoma worldwide. It shares similar pathological alterations with Alzheimer's disease (AD) with characteristic deposition of fibrilar protein aggregates and gradual deterioration of nerves with age. Studies done in the past suggest a prominent genetic factor underlying the pathogenesis of PEX. Here, we examined the role of two genetic variants (rs3087554 and rs2279590) within the gene clusterin (CLU) as risk factor in the pathogenesis of PEX by performing a case-control study in Indian population. Through, bidirectional sequencing and genetic analysis, both of the variants were found to be significantly associated with PEX. Further functional analysis was carried out for the 7th intronic SNP rs2279590 which previously has been picked as a risk factor for AD. In silico analysis suggests rs2279590 resides in an active regulatory region and is an eQTL for CLU gene expression from the data in ENCODE and GTEx project, respectively. Alleles at rs2279590 were shown to differentially regulate CLU expression in lens capsule tissues. Reporter assays show that rs2279590 is within an active enhancer element and 3C assays reveal a promoter-enhancer interaction mediated by CLU promoter and rs2279590 loci. Deletion of 115bp region flanking the rs2279590 variant through CRISPR-Cas9 demonstrated a decreased CLU expression. Molecular assays show that rs2279590 with allele "A" constitutes a transcription factor binding site for heat shock factor-1 (HSF1) but not with allele "G". After binding, HSF1 abrogates the enhancer effect of the locus as validated by reporter assays. Interestingly, rs2279590 locus also has a widespread enhancer effect on two nearby genes, PTK2B and EPHX2; both of which are risk factors for AD. Together, our study unveils a mechanistic role of the common variant rs2279590 that can affect both PEX and AD by regulating the expression of a specific set of genes.

Citation: Padhy, B., Hayat, B., Nanda, G.G., Mohanty, P.P. and Alone, D.P. Pseudoexfoliation and Alzheimer's associated CLU risk variant, rs2279590 lies within an enhancer element and regulates CLU, EPHX2 and PTK2B gene expression [Abstract]. In: Abstracts of the NGBT conference; Oct 02-04, 2017; Bhubaneswar, Odisha, India: Can J biotech, Volume 1, Special Issue, Page 90. https://doi.org/10.24870/cjb.2017-a77