Abstract: 72

Natural Selection constraints in Inherited retinal diseases

Jose Pulido, M.D.
Rochester, MN

Alexander Tanner, B.S., Hwei Wuen Chan, MBBS (UCL), MMed (Ophth), FAMS, FRCOphth (UK), Elena Schiff, PhD, Gavin Arno, PhD, Andrew Webster

Purpose:
To determine if there are natural selection constraints on genes associated with inherited retinal diseases (IRD). The frequency of haploinsufficiency by the loss of one functional allele in a large human genome database can inform the constraint of a protein.

Methods:
Genes associated with IRD were obtained from the online RetNet resource. All genes were evaluated in gnomAD and DECIPHER databases. Genes that met the criteria of either a pLI>0.9 and CI upper limit <0.4 and/or a DECIPHER pli>0.9 and HI<10 (these indices indicate intolerance to loss of function) were then evaluated using the GO PANTHER gene ontology resource to characterise functional clusters in affected molecular pathways.

Results:
Of 311 IRD genes listed in RetNet, 12 were mitochondrally inherited and another 24 genes had insufficient genomic variation data to evaluate constraint variables. Thus 275 genes were evaluated for intolerance to loss of function. 37 genes (13.5%) met the criteria for selection in gnomAD. DECIPHER identified 2 additional genes, LRP5 and PGK1. Thus a total of 39 (14.2%) IRD genes met criteria for further evaluation. Eight (20.5%) were X-linked. 25/39 (64%) coded for proteins greater than 600 amino acids in length. Ten genes (26%) were neither X-linked nor coded for proteins greater than 600 amino acids. Overall, genes clustered into the Norrin signaling pathway and the spliceosome when evaluated in the GO PANTHER database (p=3.4x10^-5 and FDR (false discovery rate) of 0.014, and p=2.6x10^-6 and FDR of 0.002, respectively).

Conclusions:
Approximately 14% of IRD genes are extremely intolerant to loss of function. Of these, the majority (74%) coded for proteins longer than 600 amino acids and/or were X-linked. Functionally, many appeared to be involved in the spliceosome or the Norrin signalling pathway.