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IDENTIFYING NATURAL GENETIC MODIFIERS OF APOPTOSIS AND RETINAL DEGENERATION

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Abstract

Retinitis pigmentosa (RP) is a retinal degenerative disease associated with mutations in a number of genes in different pathways. Like many diseases, RP is characterized by phenotypic heterogeneity. This heterogeneity is thought to be caused by genetic variation between patients, yet the identity of genetic modifiers remains unknown. A previous study conducted in our lab used the *Drosophila* Genetic Reference Panel (DGRP) to study the effects of natural genetic variation on a model of RP. In this model, a misfolded rhodopsin protein ($Rh1^{G69D}$) was overexpressed in the developing eye imaginal disc, inducing ER stress and cell death during development. Nearly half of the candidate genes identified through an association study were involved in apoptosis, suggesting that variation in apoptosis signaling may contribute to variation in retinal degeneration. Indeed, a number of RP therapies under development are aimed at inhibiting apoptosis. We hypothesized that genetic variation in apoptosis pathways might also contribute to variation in degeneration outcomes. Apoptosis is induced under a number of stress conditions that initiate *p53* signaling. In *Drosophila, p53* activates *reaper* (*rpr*), which inhibits Inhibitors of Apoptosis (IAPs), allowing apoptosis to proceed. *p53* and *rpr* are pro-apoptotic genes. To search for modifiers of apoptosis, we crossed transgenes overexpressing *p53* or *rpr* in the eye discs onto the DGRP strains. This results in degeneration in the adult eye, similar to the RP model described above. We quantified variation in eye size and found extensive phenotypic variation among the DGRP. This was apparent for both the *p53* and *rpr* models. We used an association analysis to identify candidate modifier genes from the completed *p53* model. A number of biologically interesting modifiers, including *sif, ftz*, *CycE*, and *bru1* function in transcription, translation, rhodopsin localization, cell migration, cell death, and cell cycle regulation. To test the functional effects of each modifier gene, we are using RNAi to identify interactions with the *p53* model. Identifying natural genetic modifiers of apoptosis may identify modifiers that may be applicable to a number of different retinal degeneration diseases.