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IDENTIFYING GENETIC MODIFIERS OF APOPTOSIS IN RETINAL DEGENERATION

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In our research, we are studying how the inheritance of certain genetic variants will affect different physiological outcomes, specifically in endoplasmic reticulum (ER) stress pathways. ER stress triggers the unfolded protein response, which can lead to repair/refolding of proteins, or trigger apoptosis if the stress is too great. Apoptosis is a programmed cell death pathway that influences many diseases of degeneration, such as retinitis pigmentosa, but there is still much to learn. For example, these apoptotic driven diseases are known to be affected by genetic factors, including natural genetic variation in humans. We use the model organism *Drosophila melanogaster*, a fruit fly, to study how genetic variation influences apoptosis. Using a retinal degeneration disease model in *Drosophila*, we aim to find modifier genes that can affect this ER stress-driven disease. Understanding how genetic variation impacts retinal degeneration will identify novel genes in the ER stress pathway and potentially lay the groundwork for developing personalized treatments.

Our lab previously performed a study that examined the effect of genetic variation on our *Drosophila* model of the retinal degenerative disease retinitis pigmentosa. This study induced retinal degeneration by overexpressing a known apoptosis activator gene, *rpr*, in *Drosophila*. To see the effect of genetic variation on this model, these *rpr*-overexpression flies were crossed to the *Drosophila* Genetic Reference Panel (DGRP), a population of over 200 wild-derived *Drosophila* containing much genetic variation similar to human populations. We found striking strain differences in eye size, which is used as a quantitative measure of ER stress-driven degeneration - a decrease in eye size being a worse outcome, and vice versa. We were able to use these quantitative differences to perform a Genome-Wide Association Study (GWAS) and identify candidate modifier genes of degeneration. The study found that a majority of these candidate genes that influence variation in retinal degeneration also play a part in apoptosis or cell death, an important pathway in most forms of retinal degeneration. This suggested that variation in apoptosis pathways may also contribute to the variable outcome of patients with RP and other retinal degenerative disorders.

We followed up hits from this study by also crossing them to *p53*, a tumor suppressor gene known to activate apoptotic pathways that also induces eye degeneration, to test the specificity of our candidate genes. One of these specific genes, *bru1*, was a strong GWAS hit with a high correlation of eye degeneration to study more in depth. *Bru1* takes part in regulating stem cell differentiation and has a negative effect on translation. As we have found it has a suppressive effect on eye degeneration with the eye size increasing in all trials performed, we are performing experiments to understand how this gene impacts the ER stress response, such as through altering apoptosis or other means. These experiments involve knockdown of *bru1* gene expression and then examining the biochemical, physiological, and immunohistochemical outcomes in *Drosophila*. As *bru1* has not been previously implicated in ER stress, this work could help identify it as a novel player in degenerative diseases going forward.