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A GENETIC STUDY OF HETEROCHROMATIN FORMATION MEDIATED BY A GAA₃₁₀ TRIPLET REPEAT IN *DROSOPHILA MELANOGASTER*

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Genome integrity depends on effective silencing of repetitive DNA and transposable elements (TEs), as their mobilization can lead to gene disruptions, deletions, and translocations. Packaging DNA into heterochromatin is a mechanism used by higher eukaryotes to silence repetitive DNA. Heterochromatic regions are generally inaccessible to elements of the transcriptional machinery and are thus transcriptionally silenced. The human disease Friedreich's ataxia (FRDA), which has no cure, is caused by expansion of the DNA nucleotide triplet repeat GAA in the first intron of the gene *FXN* from 10 to 66+ copies, resulting in aberrant silencing of *FXN* via heterochromatin formation. To characterize DNA triplet repeat-mediated heterochromatin formation in *Drosophila melanogaster*, the Elgin Lab generated a transgenic fly line with a P-element construct carrying 310 copies of the triplet GAA (originating from an FRDA patient) upstream of an *hsp70-white* reporter. (The *white* gene is required for red pigmentation in the fly eye.) When this P-element is inserted near a heterochromatic mass (base of chromosome arm 2L), a variegating phenotype (PEV) is observed, indicating local heterochromatin formation. The PEV phenotype is dependent on the presence of the GAA₃₁₀ repeat. We launched a genetic investigation to characterize this repeat-dependent silencing. We tested the sensitivity of GAA₃₁₀-*hsp70-white* silencing to mutations in histone deacetylation, H3K9 methylation, HP1a binding, Polycomb binding, and RNA interference pathways. Eye pigment assays were used to quantitatively evaluate the dominant impact of these mutations on GAA₃₁₀-*hsp70-white* silencing. Genetic analyses indicate a role for histone deacetylation, H3K9 methylation, and HP1a binding in maintenance of silencing, in common with transposable element silencing. Investigating the genetic makeup of the silencing triggered by the repetitious GAA sequence could inform potential therapeutic strategies for FRDA aimed at reversing silencing at the *FXN* locus.