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A Genetic Study of Heterochromatin Formation Mediated by a Triplet Repeat in *Drosophila melanogaster*

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Packaging DNA into heterochromatin is a mechanism used in higher eukaryotes to silence repetitive DNA, remnants of transposons, etc. Genome integrity depends on effective silencing of transposable elements, as their mobilization can lead to gene disruptions, deletions, and translocations. Heterochromatic regions are generally inaccessible to elements of the transcriptional machinery and are thus transcriptionally silenced. The human disease Friedreich's ataxia is caused by expansion of the DNA nucleotide triplet repeat GAA from 10-66 copies in the first intron of the gene *FXN* to 66+ copies, resulting in silencing of *FXN* via heterochromatin formation. To characterize DNA triplet repeat-mediated heterochromatin formation in *Drosophila melanogaster*, we built a transgenic construct with a DNA fragment of 310 copies of the triplet GAA (originating from a Friedreich's ataxia patient) inserted upstream of an *hsp70-white* reporter. (The *white* gene is required for red pigmentation in the fly eye.) The transgene was incorporated at the base of chr. 2L at a site within the actively transcribed gene *nesd* but in close proximity to a heterochromatic block. At this location, *hsp70-white* yields a red-eye phenotype. When GAA_{310} is upstream of the reporter at this site, we observe *hsp70-white* silencing (variegating phenotype). Eye pigment assays were used to quantitatively evaluate the dominant impact of gene mutations on GAA_{310}-*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 (TE) silencing. In contrast to TEs, the RNAi system does not appear to play a role in targeting GAA_{310}-induced silencing. When GAA_{310} was inserted into another site in the euchromatic arm of chr. 2L, transformants did not show a silencing phenotype. We are continuing to investigate the importance of genomic context in heterochromatin formation triggered by insertion of the repetitious GAA sequence.