

Fig. S1. Both *Drosophila* wild type (dWT) and *sugarkill* (dM80T) enzymes follow traditional Michaelis-Menten kinetics. Michaelis-Menten nonlinear regression fits are shown, and all enzyme concentrations are indicated.

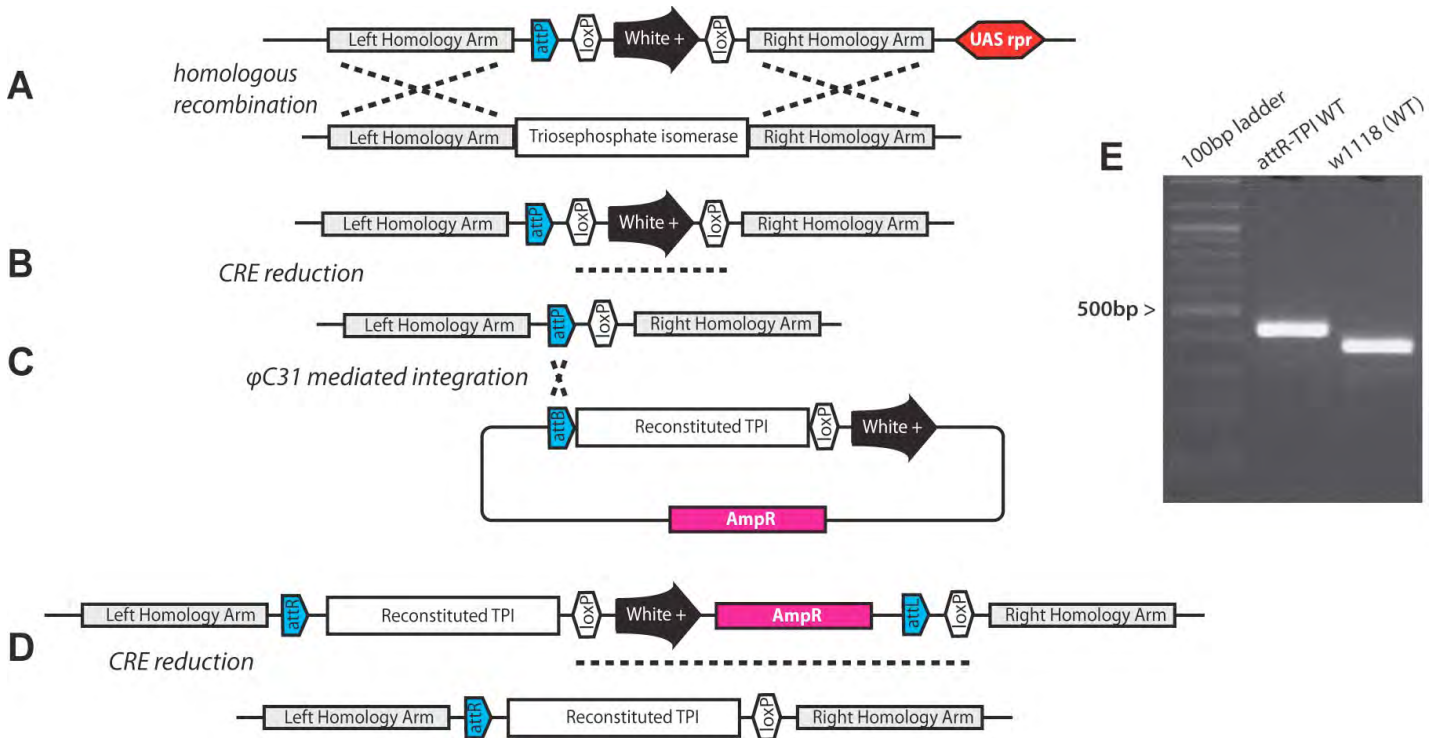


Fig. S2. Genomic engineering of the *TPI* locus. A) The target gene is replaced by the *attP* phiC31 integration site and a white minigene flanked by two *loxP* sites. B) The white minigene is removed by a CRE recombinase, leaving only the *attP* phiC31 integration site and a *loxP* site. C) *TPI* is cloned into the *pGE-attB* vector and modified, as desired. The construct is then injected into founder line embryos expressing the phiC31 integrase, which initiates specific and directional integration of the construct into the *TPI* locus. D) The *white* minigene and plasmid construct are removed through the expression of CRE recombinase, leaving only an *attR* and a *loxP* site. E) Molecular analysis reveals the addition of an *attR* site 5' of the reconstituted *TPI* gene.

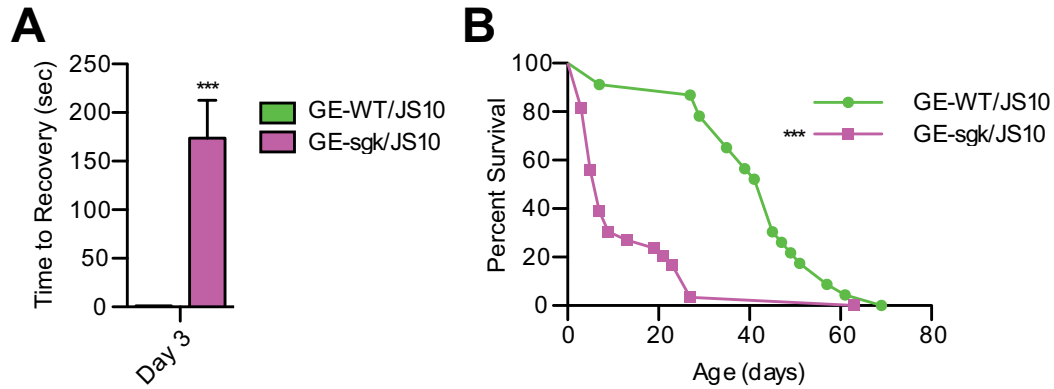


Fig. S3. Genomically engineered TPI^{sgk} displays aberrant behavior and reduced longevity. A) Genomically engineered TPI^+ ($GE-WT$) displays normal behavior, while the genomically engineered TPI^{sgk} ($GE-sgk$) displays marked mechanical stress sensitivity. B) $GE-sgk$ exhibits reduced longevity compared to $GE-WT$. $n > 20$ for all lifespans and behavior. A Student's t test was used to assess behavioral differences between genotypes, and a Log-rank (Mantel-Cox) Test was used to assess lifespans. *** indicates $p < 0.0001$ compared to $GE-WT$. Error bars indicate \pm s.e.m. Both genomically engineered alleles were assessed over TPI^{JS10} .

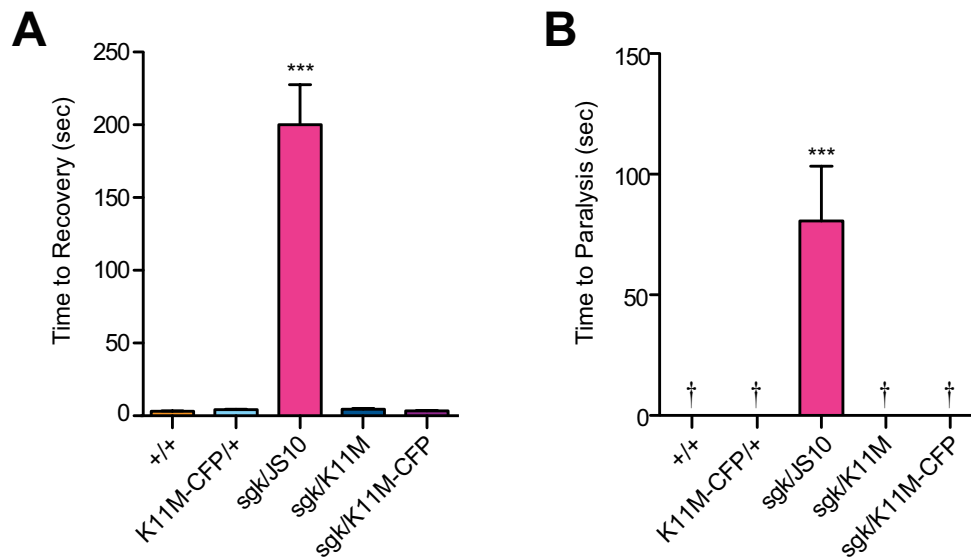


Fig. S4. The addition of the C-terminal CFP to TPI^{K11M} does not affect its capacity to genetically complement TPI^{sgk} A) mechanical stress sensitivity or B) thermal stress sensitivity. Mechanical stress sensitivity was assessed on Day 1 and thermal stress sensitivity was assessed on Day 5. $n > 15$. † indicates animals did not paralyze. A One-way ANOVA was performed to assess variance and data sets were compared using Tukey's post-hoc analysis. *** indicates that $p < 0.001$ and ns indicates no significant difference, both compared to WT. Error bars indicate \pm s.e.m.

Table S1. The catalytically inactive allele complements $TP1^{sgk}$ median lifespans. $n > 150$ animals per genotype for all lifespans.

	+/+	sgk/+	sgk/sgk	sgk/JS10	sgk/K11M
Median Lifespan (days)	65.5	67	29	6	73