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Investigation of a CBP-Driven Mechanism of *Anopheles* Mosquito Dosage Compensation

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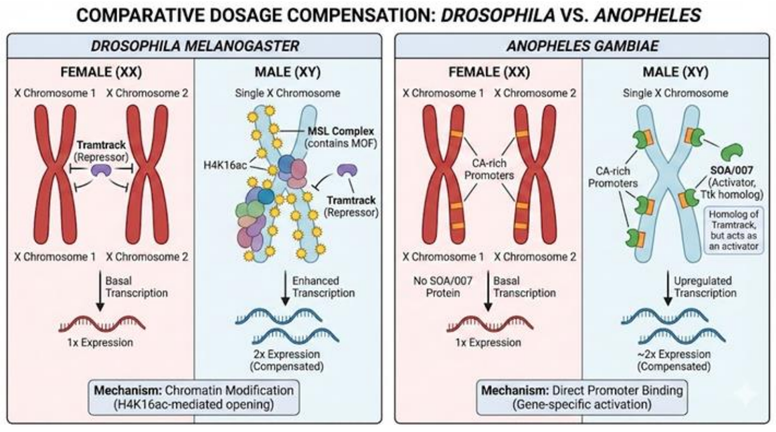
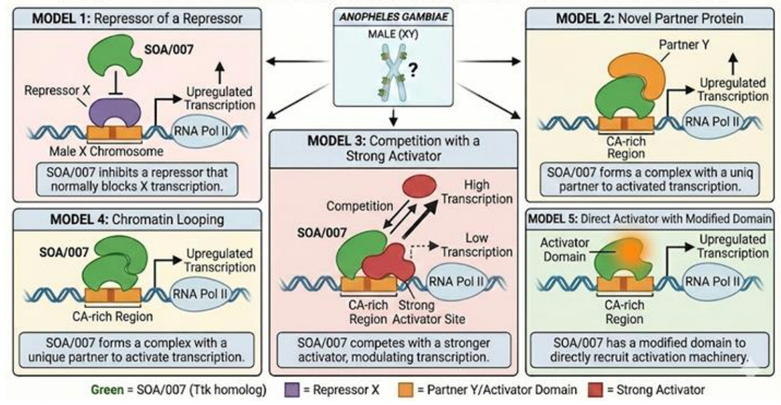
INTRODUCTION & RESEARCH AIM

INTRODUCTION: Dosage compensation is the essential mechanism by which X-linked gene expression is regulated between the sexes. Recent studies on *Anopheles* mosquitoes suggest that SOA/007, a homolog of the *Drosophila* Tramtrack protein, drives this process. However, further questions about the role of SOA/007 in mosquito dosage compensation remain unanswered. Another protein may be more central to this mechanism.



It is not immediately clear how a homolog of a repressor would upregulate mosquito X chromosome gene expression.



We propose, and began evaluation, of these five models for 007/SOA involvement in *Anopheles* dosage compensation.

METHODS

We employed a multi-pronged approach to uncover evidence for a role of another protein in *Anopheles* dosage compensation. Protein database searches, homology comparisons, literature searches, and analyses of existing histone modification datasets were used to infer a potential role for CBP in this process.

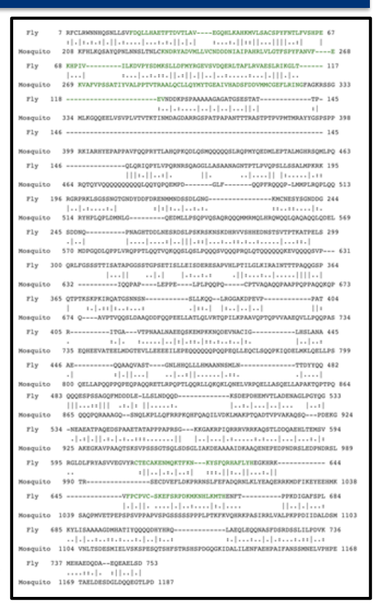
Raw sequencing data was obtained using SRR accession numbers and downloaded into Galaxy using the Faster Download and Extract Reads in FASTQ tool. Paired-end FASTQ files were aligned to the appropriate reference genome using the Galaxy tool Map with BWA-MEM. To generate normalized coverage tracks for visualization, BAM files were processed with deepTools bamCoverage, using CPM normalization and a bin size of 10–25 bp. Exported BigWig (.bw) files were loaded into Integrative Genomics Viewer (IGV) for visualization and analysis.

RESULTS

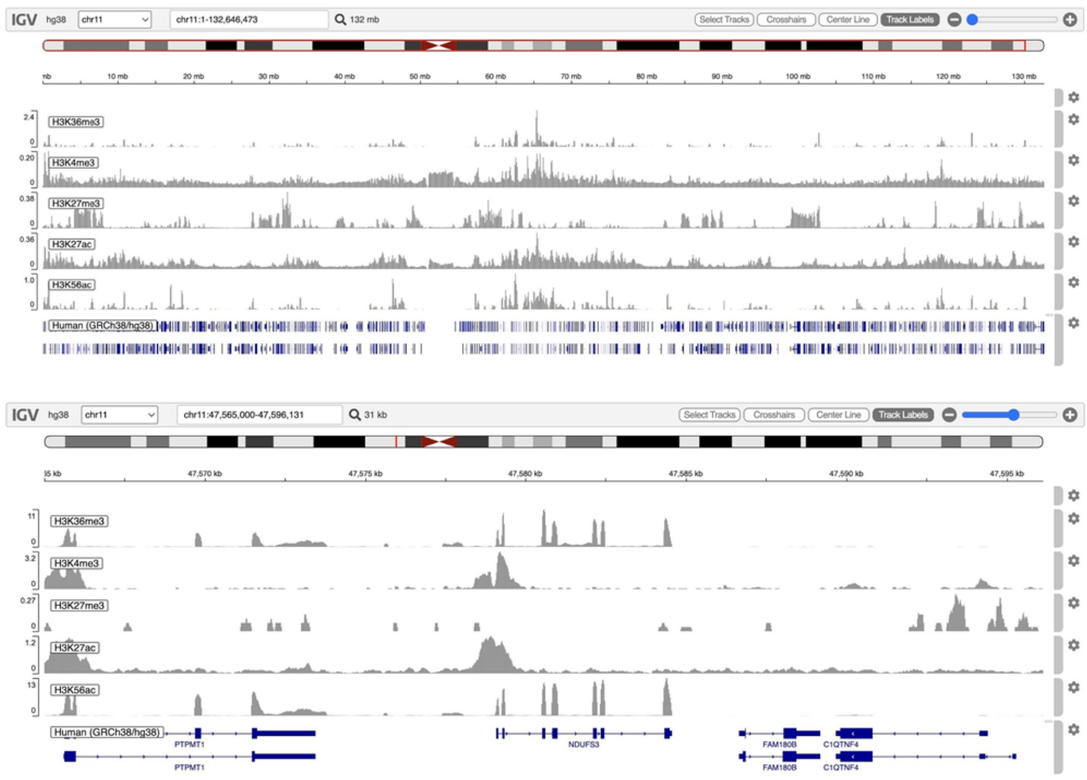
Literature Review: Ttk Mechanistic Insights

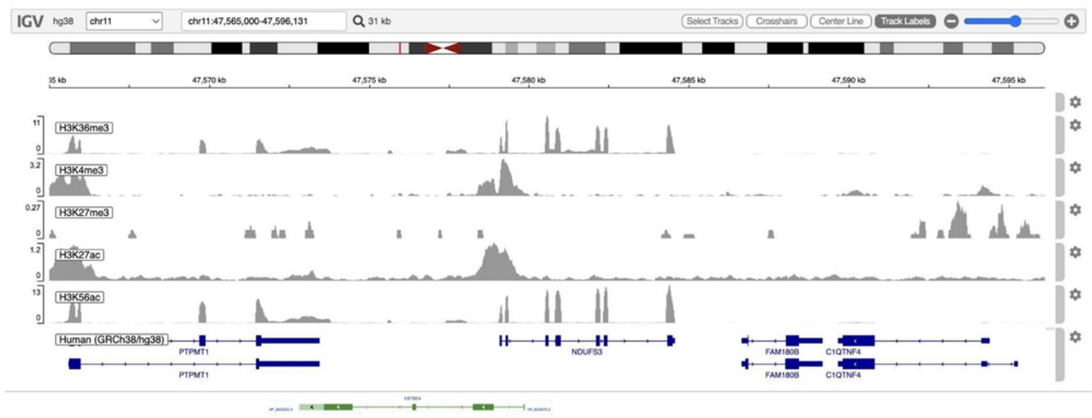
- Ttk Directly Represses GAGA Function (PMID: 12384587)
- Ttk Modifies H3 acetylation via Rpd3 (PMID: 27622813)
- Ttk is a physical block to RNAPII loading, and Ttk anti-looping prevents distal enhancer function (PMID: 22645339)
- Ttk Recruits NuRD for Txn Repression (PMID: 2073304)
- NuRD Lowers RNAPII & H3K27ac (PMID: 30008319)
- NuRD **Activates** Txn via GATA-1 TF (PMID: 19927129)
- Ttk May Limit Cell Plasticity Potential (PMID: 38531872)
- Ttk Suppresses Precocious Development (PMID: 32764744)

Arose from a gene duplication. Closest Dm Ttk ortholog in Ag: AGAP003537, ~75% similar



RESULTS, CONTINUED





Visualizing human histone modification data at the orthologous locus can provide insights into these relationships in the mosquito.

CONCLUSIONS & DISCUSSION

Further studies are needed to better understand the mechanisms of dosage compensation in mosquitoes. Enhanced application of molecular biology techniques will be the key to gathering the necessary data. Dosage compensation provides further opportunities to identify targets useful for mosquito-borne disease prevention strategies.

Insights from histone modification data in humans (*above*) and mosquito species (*ongoing*) is one preliminary way to gauge the role of Ttk, CBP, Rpd3, and other partner proteins. Further studies will involve development of reagents to mark candidate loci fluorescently on chromosomes (FISH), H3K56ac immunofluorescence analysis in male-derived cultured *Anopheles* cells, and MuD-PiT analysis using 007/SOA IP to identify protein co-factors.

FUTURE WORK / ACKNOWLEGEMENTS / REFERENCES

- **We will next measure the histone modification in mosquitoes, IP CBP protein partners, and find the mechanism of DC in mosquitoes.**
- **We wish to thank Tiana Mamaghani, Brenden Bjorklund, Arshdeep Kaur, Gabriel Hergenroeder, and Joanna Owen for helpful project discussions.**
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