A male-essential miRNA is key for avian sex chromosome dosage compensation

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A male-essential miRNA is key for avian sex chromosome dosage compensation

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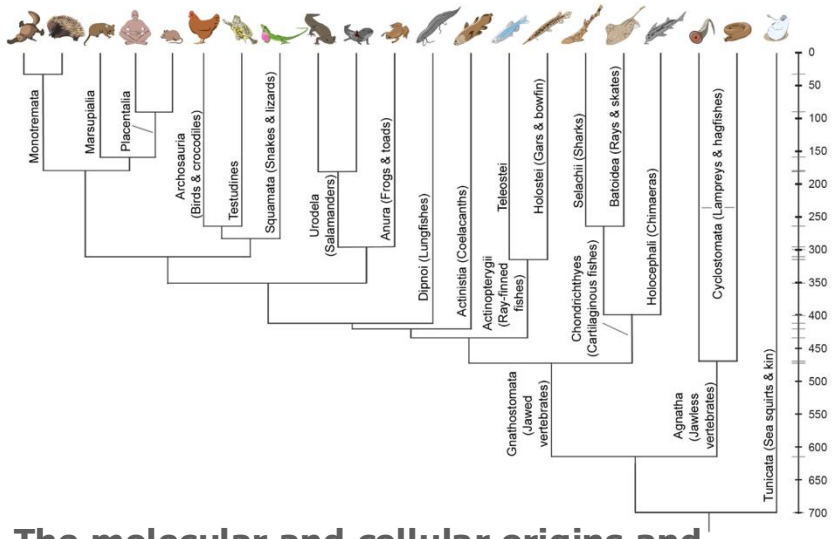
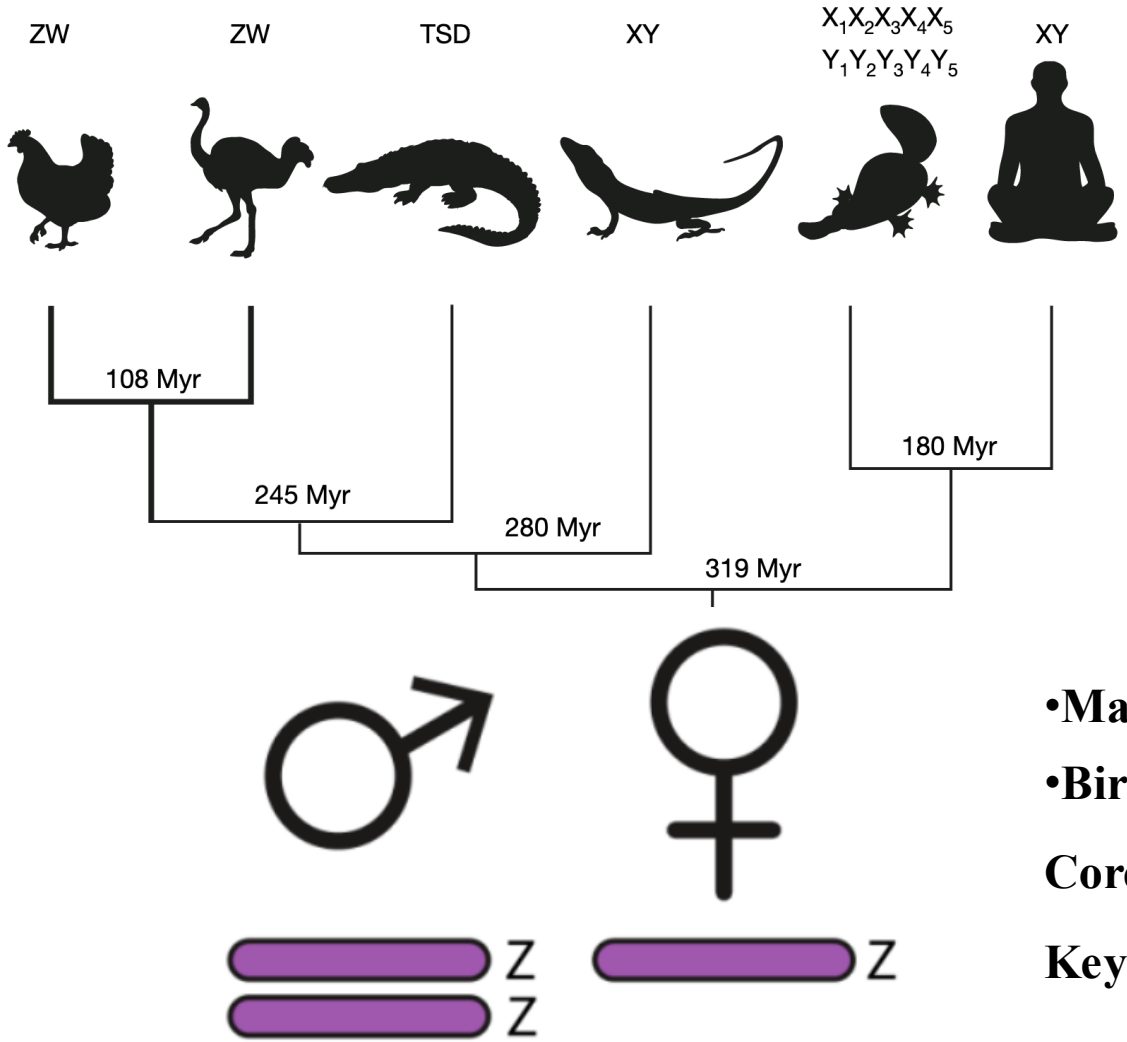
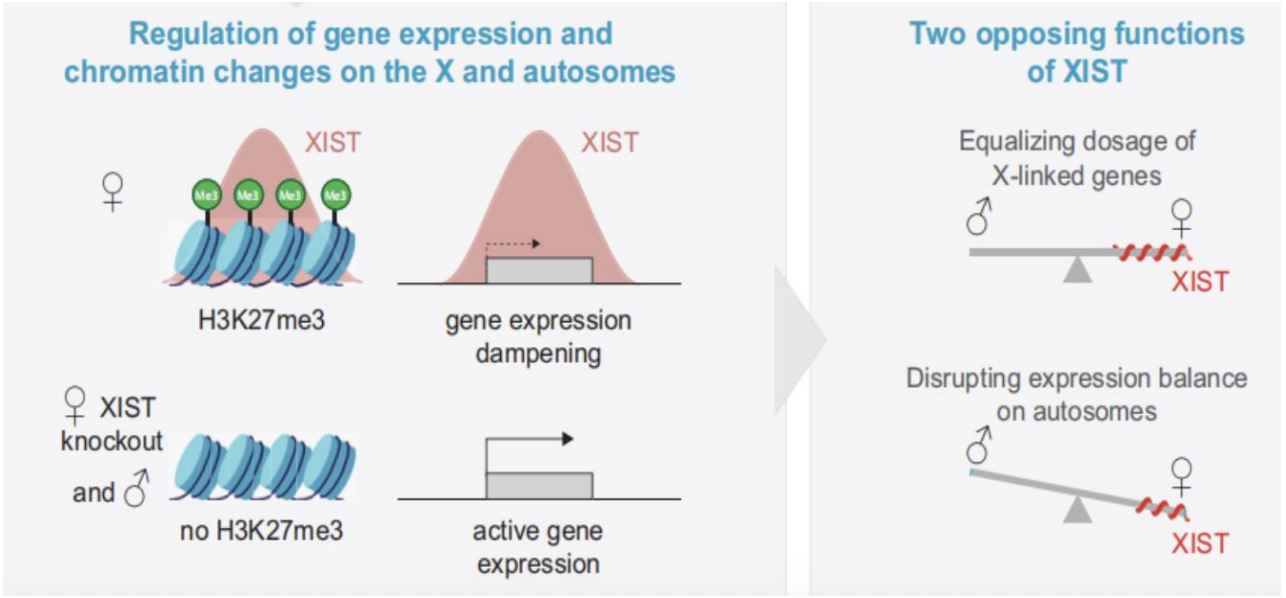


The molecular and cellular origins and evolution of vertebrate organs:
transcriptional regulation and other genomic changes

Background





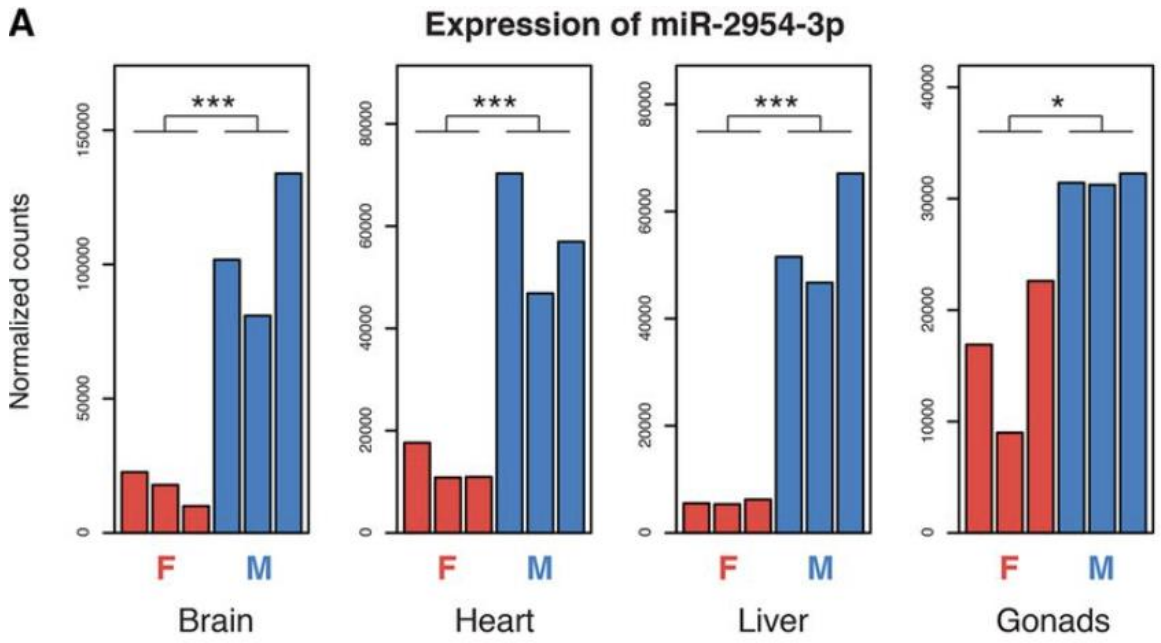
(Cell, 2023)

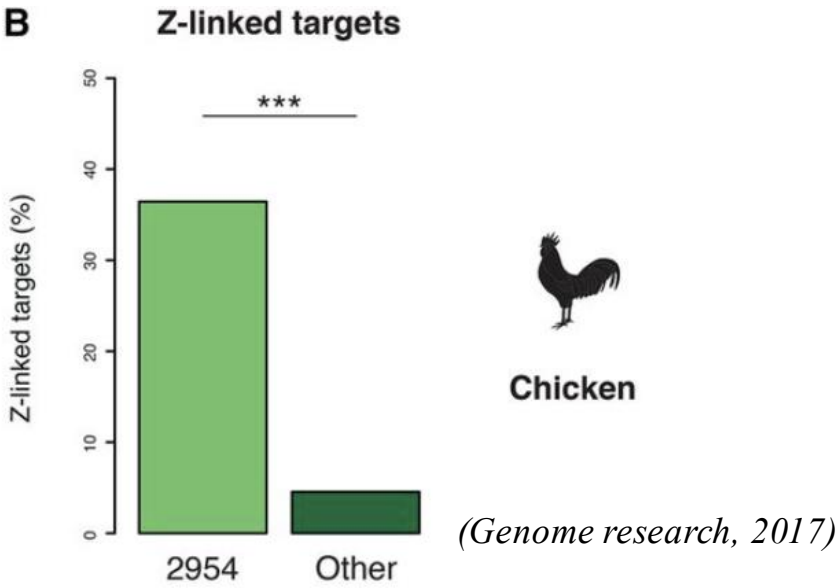
- **Mammals:** XY system, X inactivation in females (XIST)
- **Birds:** ZW system, unknown

Core problem: Dosage imbalance

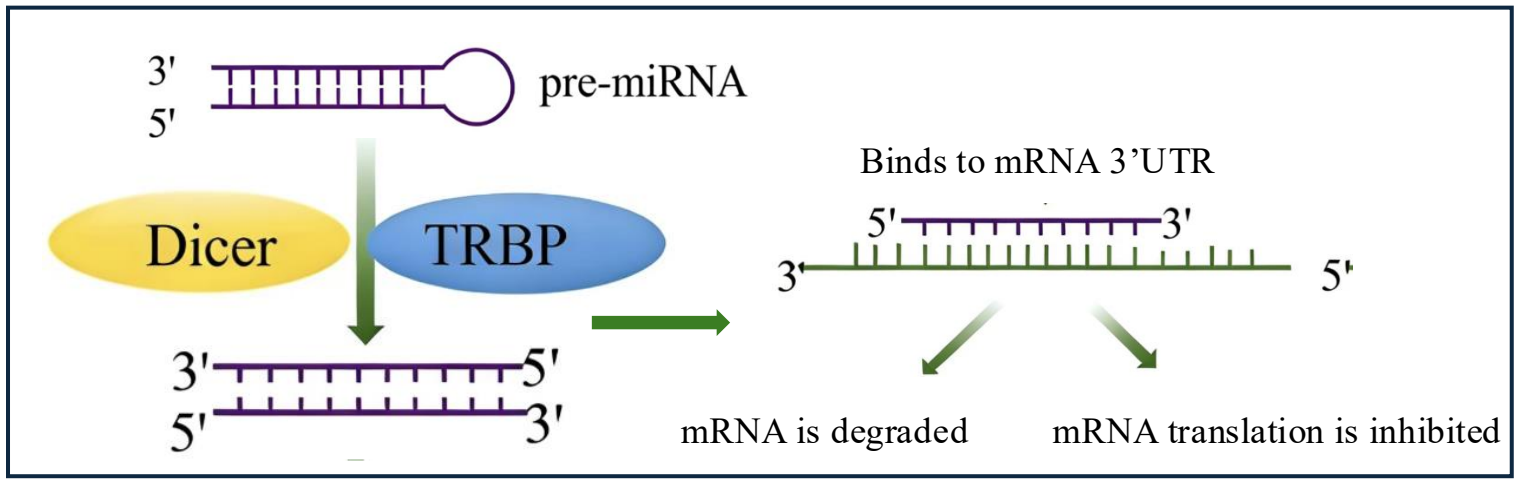
Key question: How do birds compensate?

Background





(Genome research, 2017)



- **Previous study**:

Z-linked miRNA with 5-10× male-biased expression;

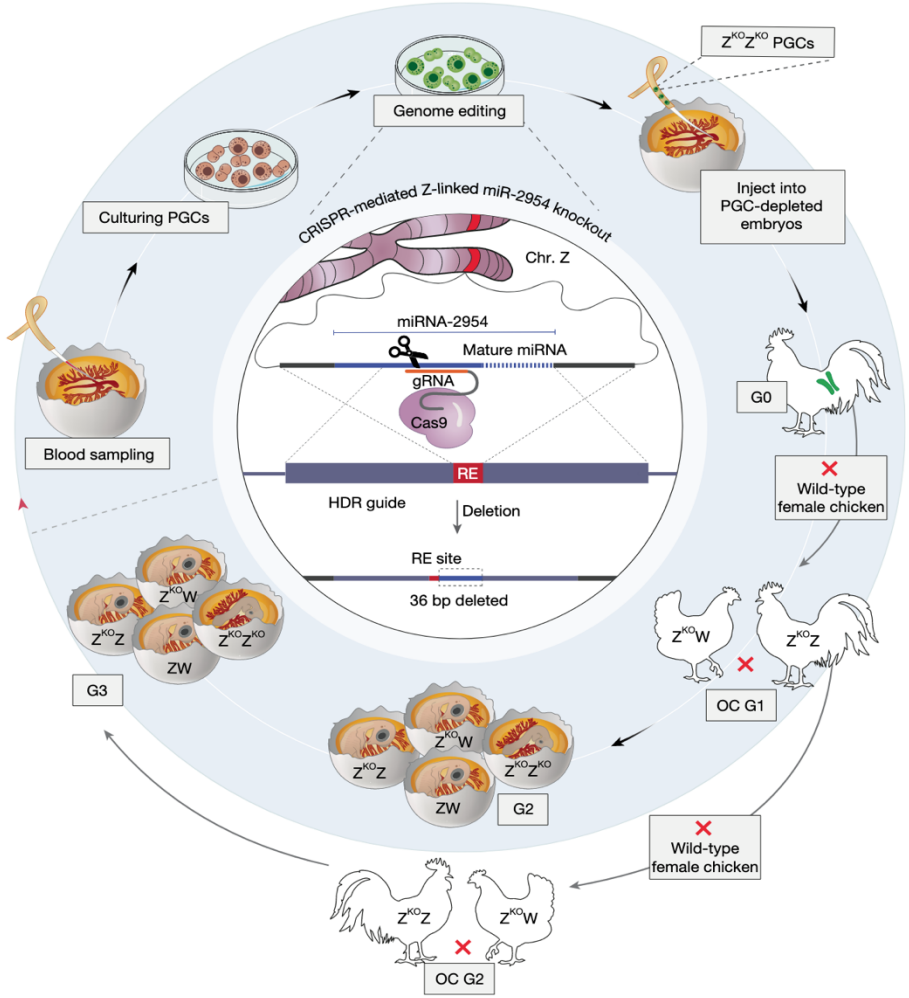
Targets enriched for dosage-sensitive Z genes

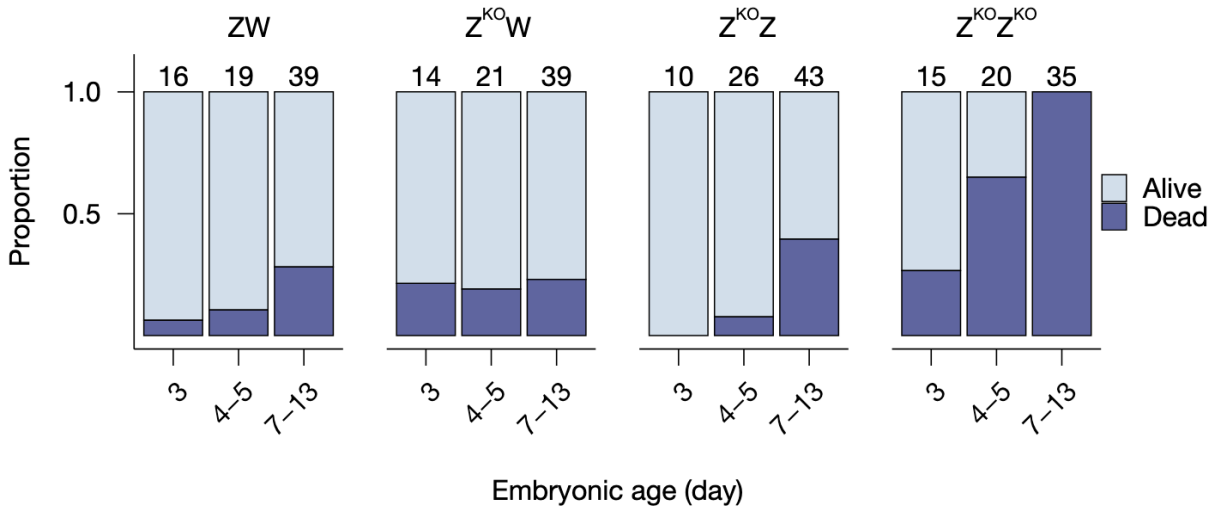
- **Questions:**

miR-2954 functionally essential?

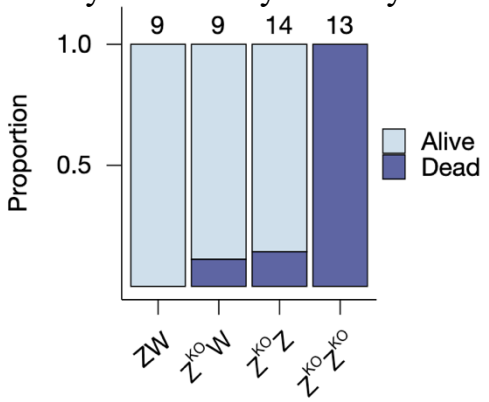
dosage compensation? Mechanisms?

Generation of miR-2954 chicken KO





Embryos at embryonic day 14



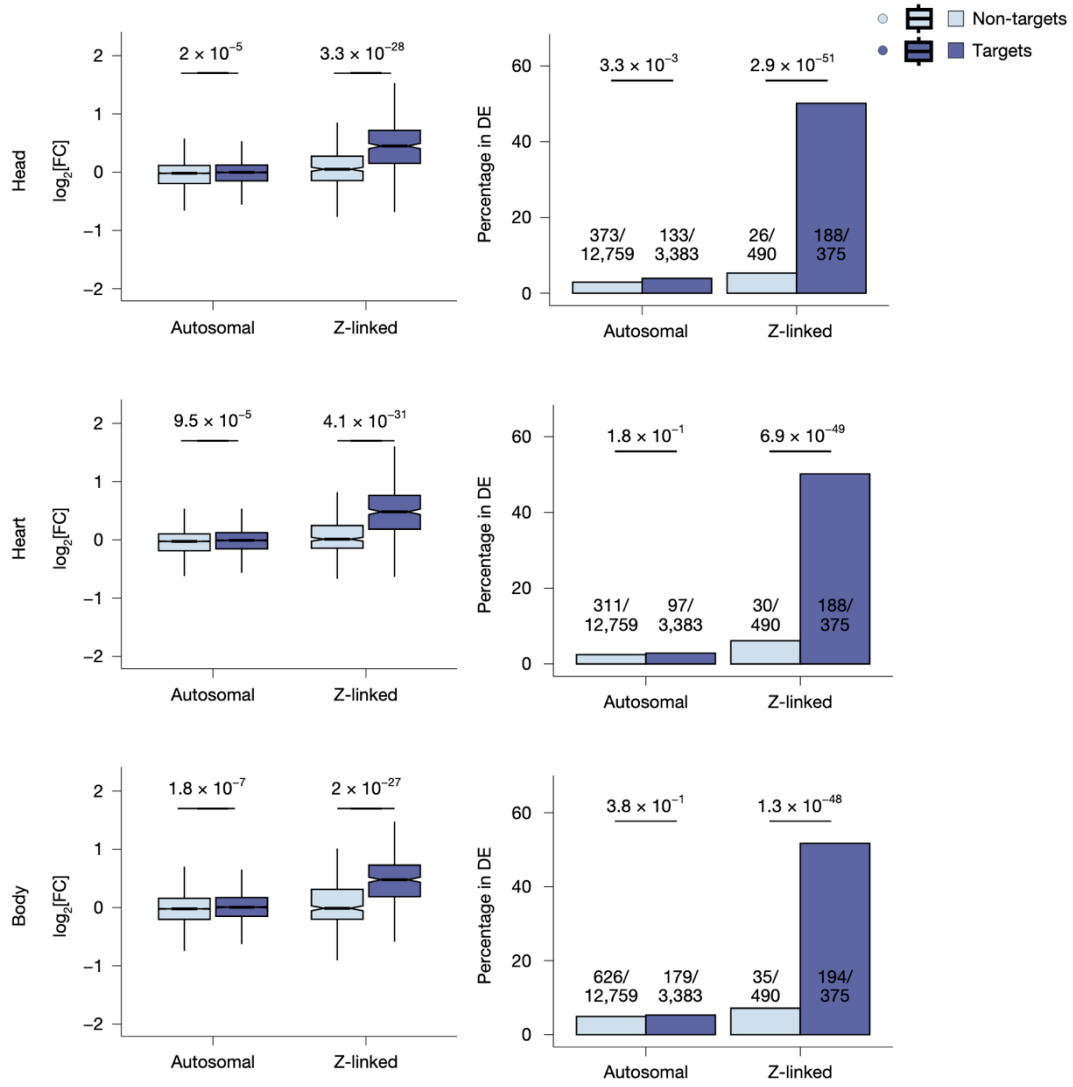
$Z^{ko}Z^{ko}$: Dead rate reaches 100%!

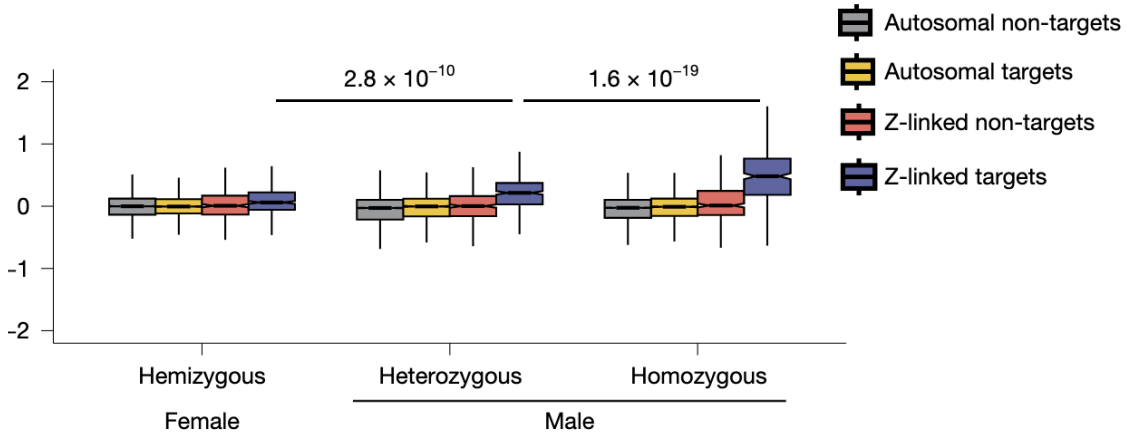
The survival rates of other genotypes are >79%

36 bp deletion of mature miR-2954 in PGCs (primordial germ cells):
Multi-generational crossing to get homozygous ($Z^{KO}Z^{KO}$) males

Results

$Z^{KO}Z^{KO}$ vs wild-type males—Is this dead specific to Z-linked genes?



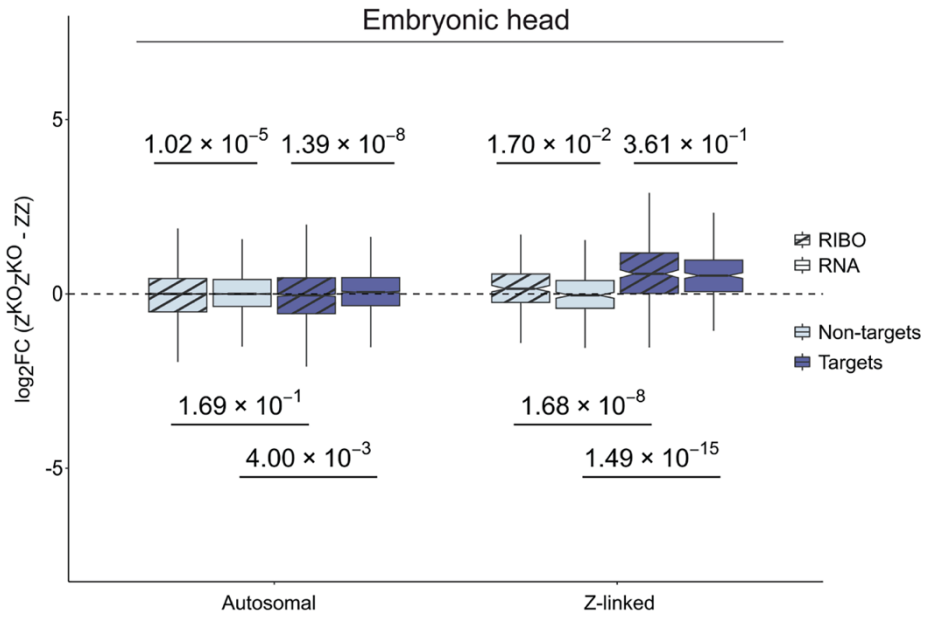


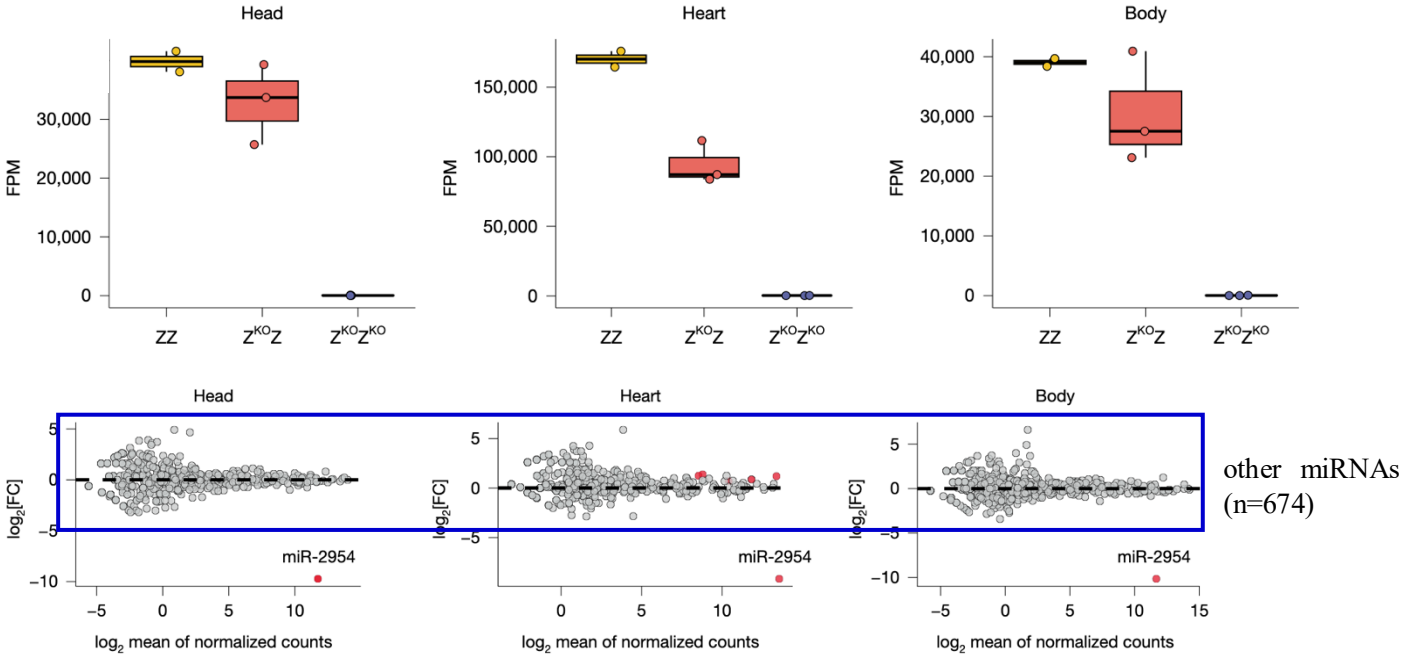
Z-linked targets were upregulated by 40% on average
Autosomal targets remained largely unchanged

This change most obvious in $Z^{KO}Z^{KO}$:
miR-2954 specifically represses Z-linked genes

Results

Translational Upregulation Confirmed—will this upregulation affect protein synthesis?





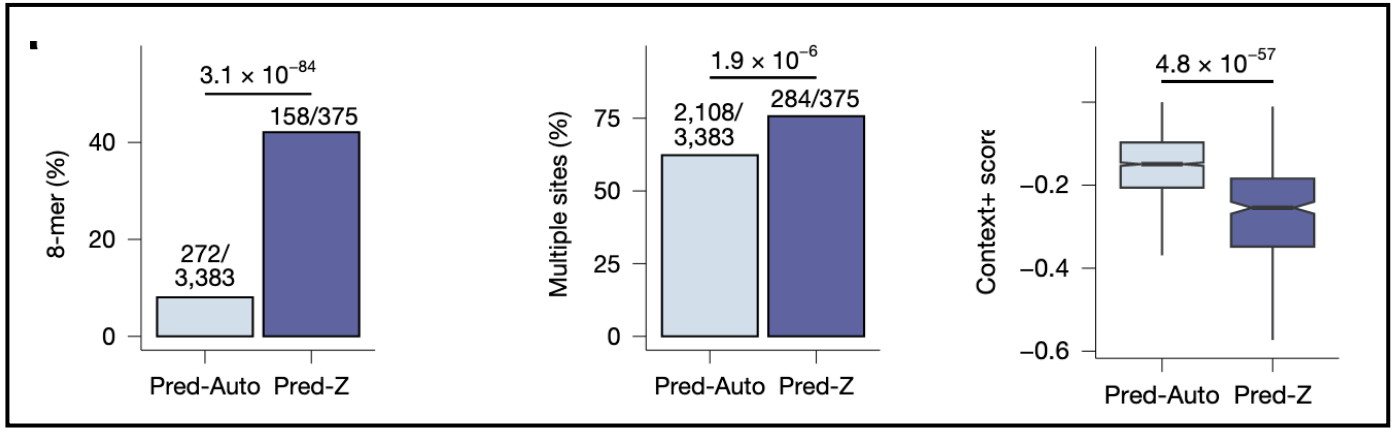
Ribosome profiling (measures protein synthesis rates at high resolution) showed that the upregulation extends to the translational level

Other miRNAs did not change after miR-2954 KO

miR-2954 directly represses Z-linked transcripts

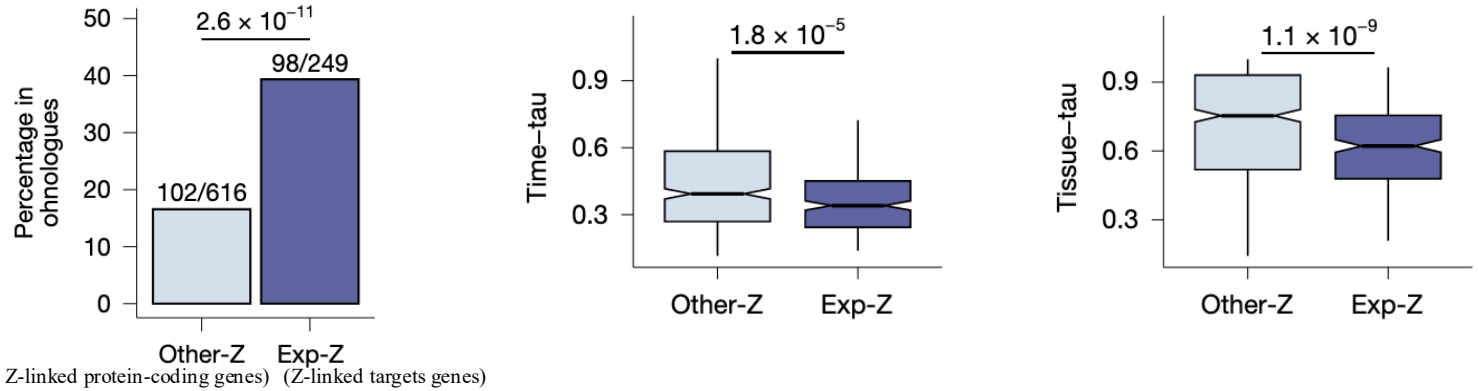
Results

Targeting of Dosage-Sensitive Genes—why does miR-2954 preferentially target Z-linked genes?



Z-linked targets significantly enriched for 8-mer sites/muti-matches VS. autosomal targets

Lower context+ score meaning the more easily it is to be inhibited by miR-2954



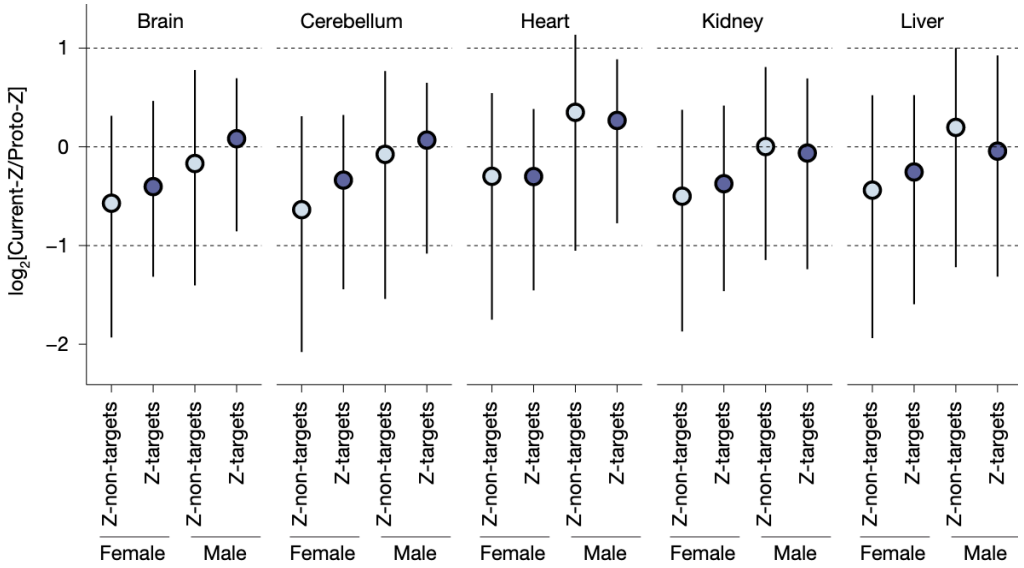
Broad expression across tissues and developmental time, indicating essential developmental functions

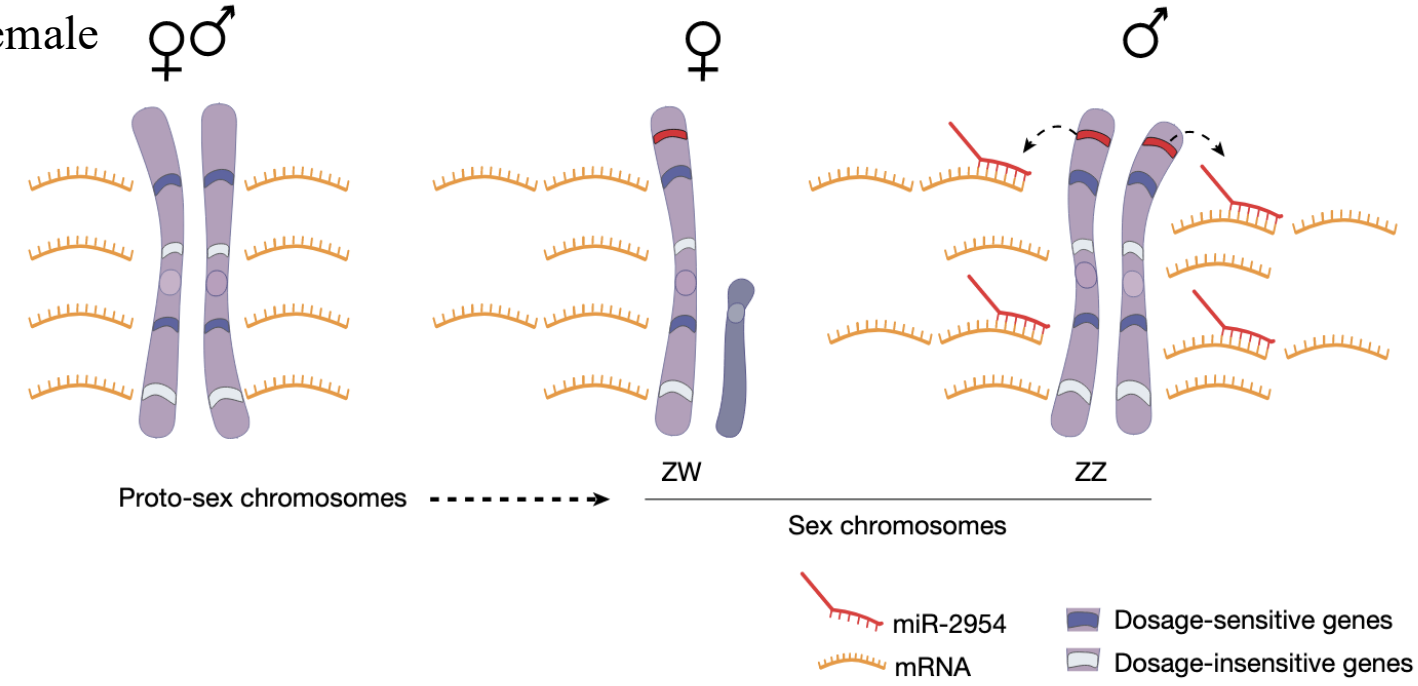
Tissue and developmental tau scores (0, broad; 1, specific)

Ohnologue: Dose-sensitive genes preserved by whole-genome replication of vertebrates

Evolutionary Model of Avian Dosage Compensation—Why did birds evolve miRNA?

$$\frac{\text{Current}-Z}{\text{Inferred ancestral levels (proto}-Z)}$$ should be 0.5 in female





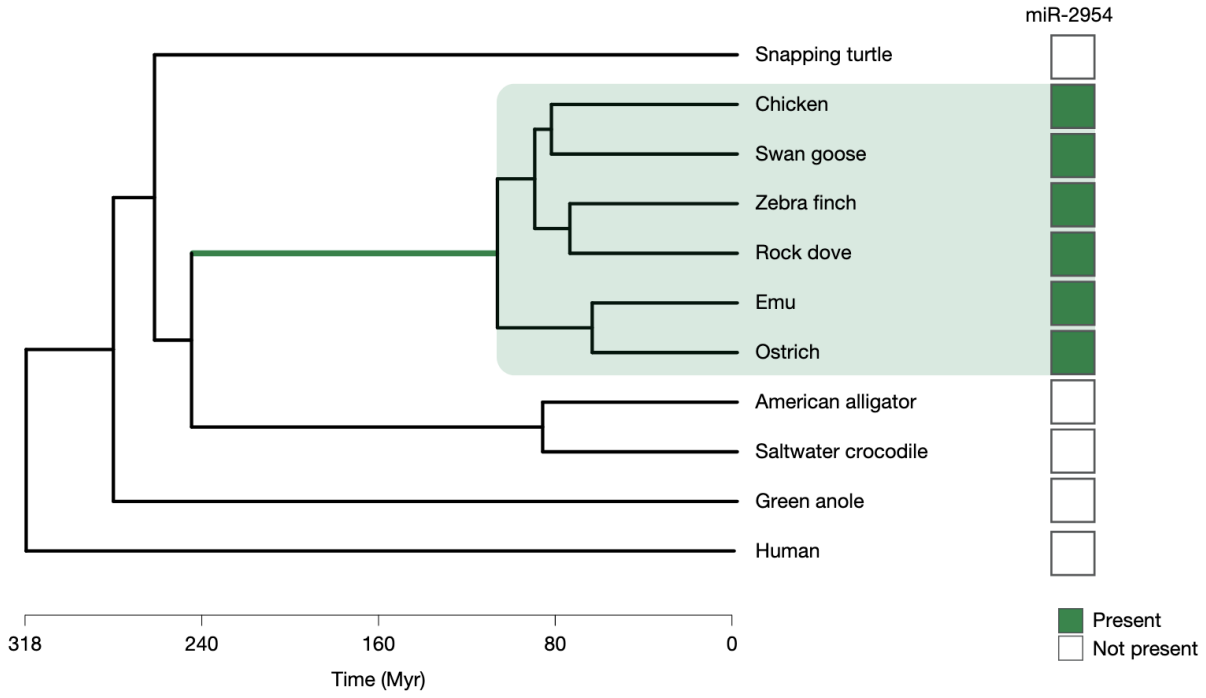
Female: current-to-ancestral expression ratios exceeding 0.5 ($\log_2$ ratio greater than −1)

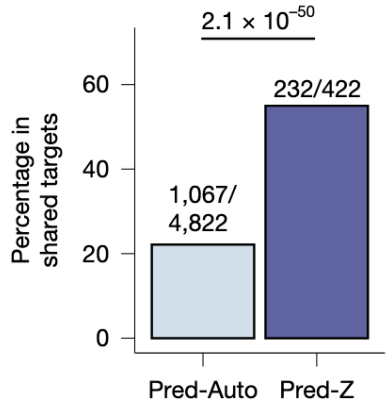
Male: Expression of both targets and non-targets remained close to the ancestral levels ($\log_2$ ratio ≈ 0)

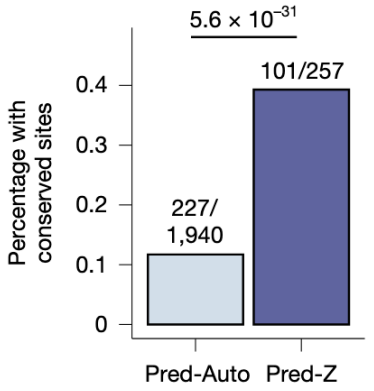
W loss → upregulation of dose-sensitive Z-linked genes in both sexes → male ZZ double dose causes overexpression
→ evolution of transcriptional degradation mechanism mediated by miR-2954

Results

Conservation Across Birds—is this mechanism is conserved?



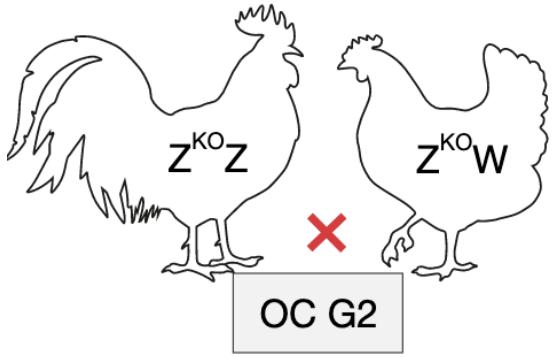


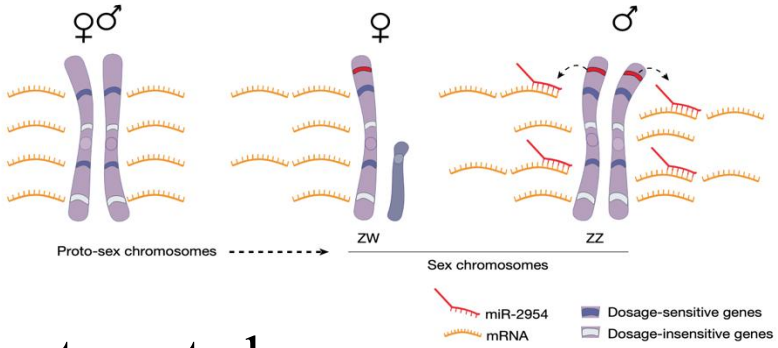


Conservation in Zebra Finch:
78% Z-linked targets conserved
Z-specific: More conserved than autosomal targets/binding sites

MiR-2954:
exists in all avian genomes
absent in all non-bird species

Summary





miR-2954 is essential for male viability by targeted repression of dosage-sensitive Z-linked genes

🔄 **Evolutionary Model:** Female upregulation → Male overexpression → miR-2954 compensation

🦅 **Avian-Specific Mechanism:** miR-2954 emerged with ZW sex chromosomes, conserved across all birds

🧬 **RNA-Guided Precision:** MicroRNA-mediated post-transcriptional regulation solves dosage imbalance

Innovation and limit

- **Innovations:**
  - **Functional evidence** that a miRNA can be sex-essential
  - **A evolutionary strategy in birds:** Targeted degradation vs. mammalian silencing
  - **Solves** the avian dosage compensation mystery

- **Limitations:**
  - Phenotype limited to **early embryonic lethality**
  - Single **chicken breed**
  - Potential **indirect effects** on host gene

Thanks for your attention!