GENOMIC RESPONSES TO CHROMOSOME-SCALE DOSAGE IMBALANCE

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Background

Diploid organisms have two copies of every non-sex chromosomal gene, but various events can change the copy number of a gene. These include:

- Whole genome duplication
- Aneuploidy, in which one chromosome is present in 1 or 3+ copies
- Sex chromosome evolution, which causes one of the chromosomes to degenerate and lose genes
- Small-scale duplication of one or multiple genes

Dosage-sensitive genes malfunction when present In the wrong number of copies. This can be because one copy is not enough to fulfil the gene's function, because the genes need to maintain stoichiometric balance with other members of protein complexes or enzymatic pathways, or to prevent protein aggregation. Hundreds of millions of years ago, the vertebrate lineage underwent two whole-genome duplications. The genes that have been retained in duplicate since then tend to be dosage-sensitive and are called ohnologs.

Here, the chicken sex chromosomes and human trisomies such as Down Syndrome are studied to investigate the genome-wide effects of chromosome-scale dosage imbalance.

Dosage Compensation on the Chicken Sex Chromosomes

Unlike mammals and flies, birds do not appear to have a chromosome-wide mechanism of dosage compensation to make up for the halved expression from the Z chromosome in females (Itoh et al., 2007).

In 2016, Zimmer et al argued that birds specifically compensate dosage-sensitive genes by showing that the male:female ratio was more similar for ohnologs.

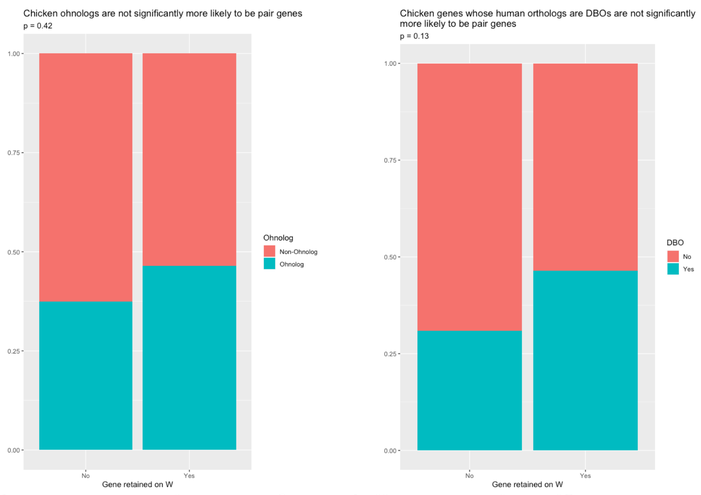
Here I look for evidence of selective dosage compensation of dosage-sensitive genes.

Possible strategies for restoring dosage balance:

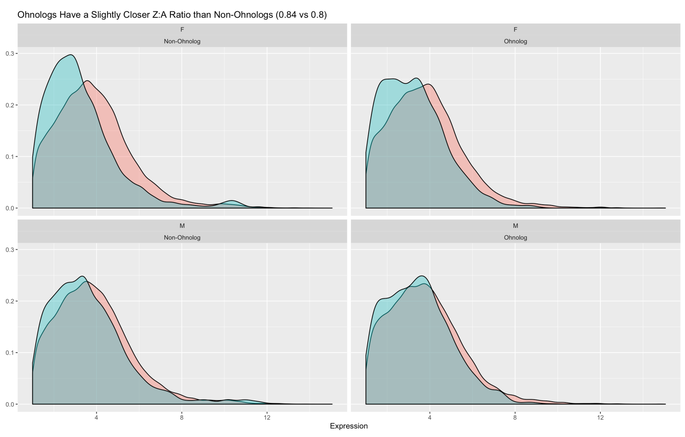
- Retain genes on the W
- Upregulate genes on the Z in females
- Move highly expressed or dosage-sensitive genes to the autosomes

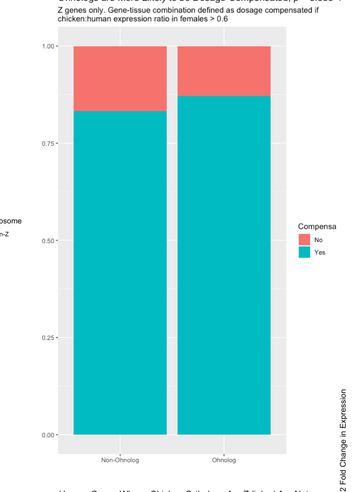
1. Do genes with a retained W homolog show evolutionary characteristics of dosage sensitivity?

Genes with a retained W homolog escape the dosage problem entirely. Bellott et al showed that these genes tend to be haploinsufficient and broadly expressed, but I find no evidence of enrichment in ohnologs or DBOs.

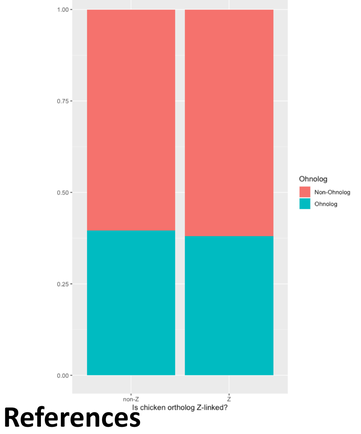


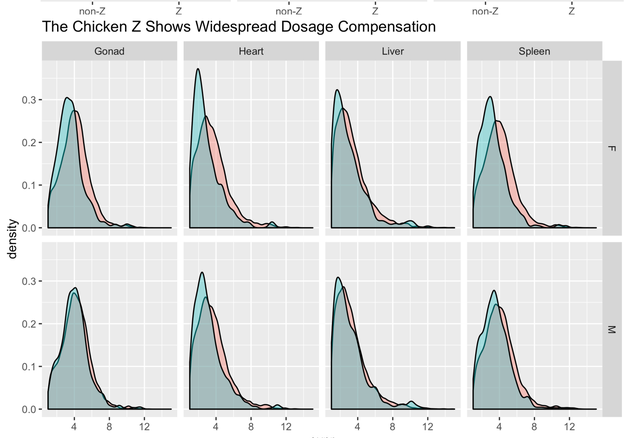
2. Are dosage-sensitive genes on the Z preferentially upregulated?





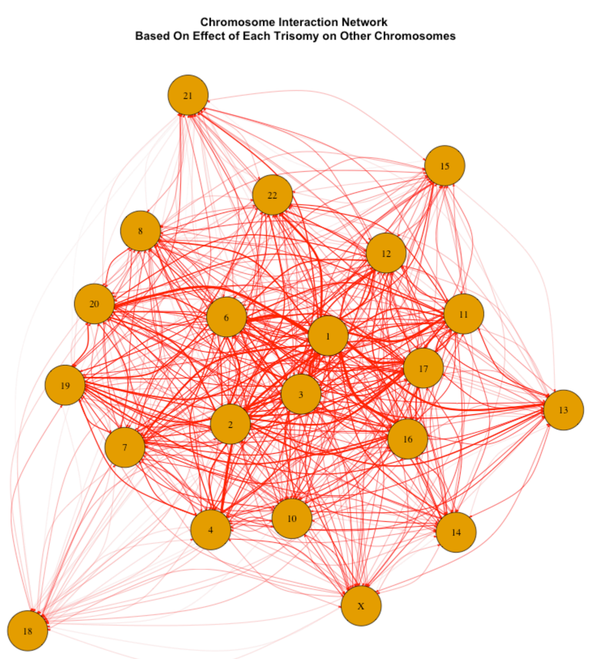
3. Are dosage-sensitive genes relocated off the Z?

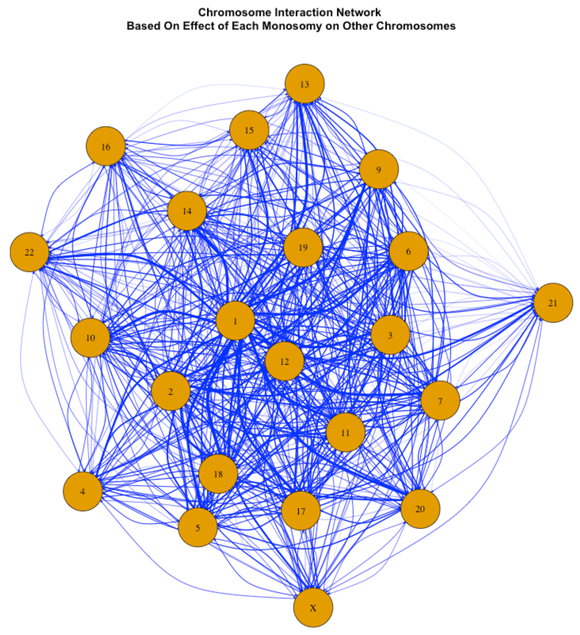




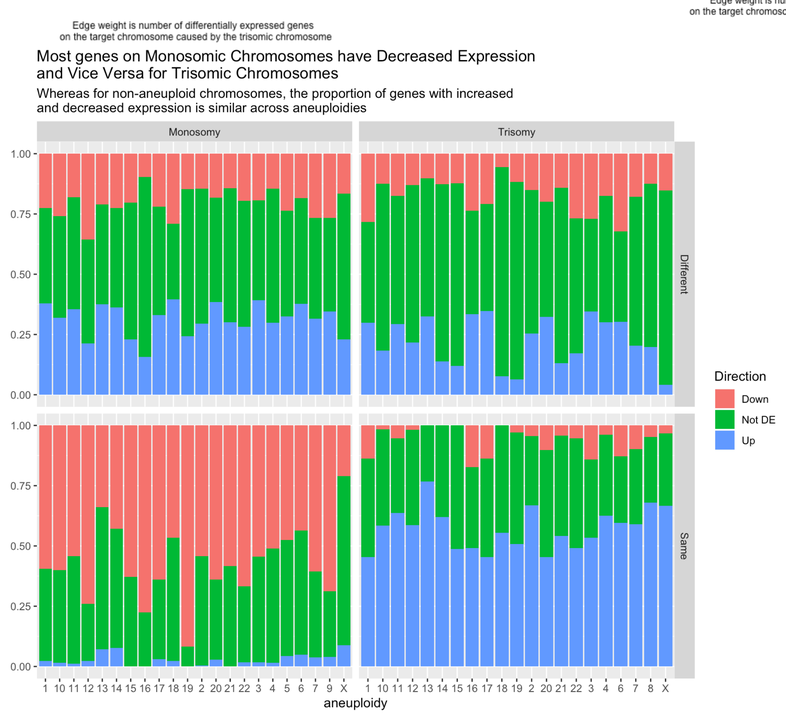
It seems that gene expression from the Z is quite similar to non-Z chromosomes overall.

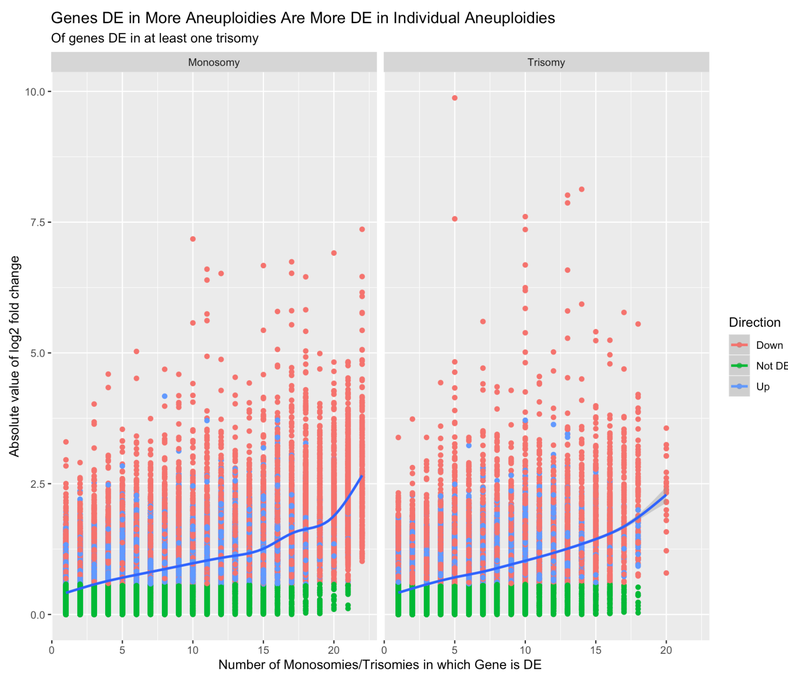
Genome-Wide Consequences of Trisomies and Monosomies

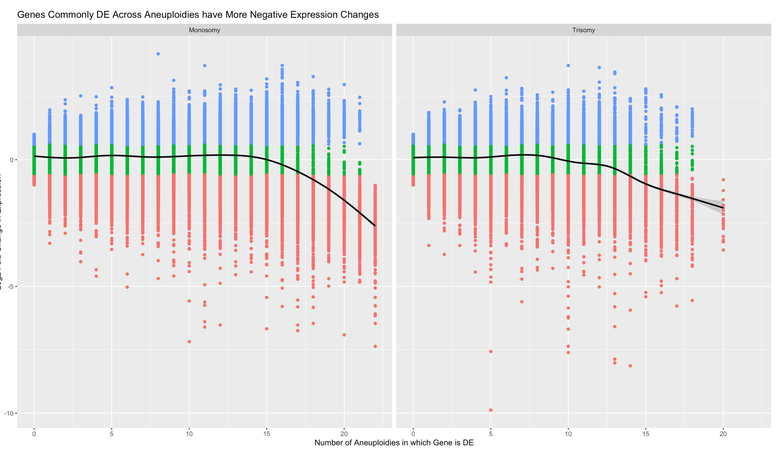




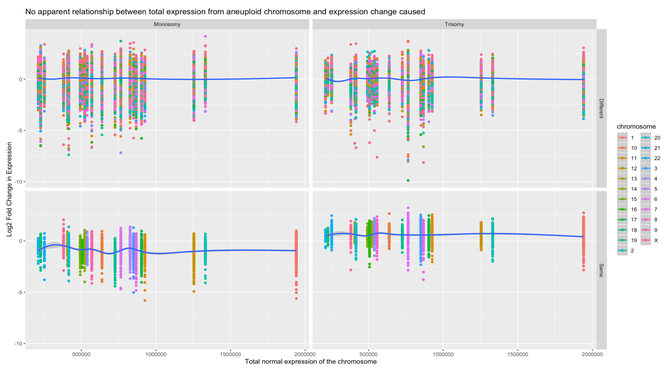
Creating a network from the number of differentially-expressed (DE) caused on each chromosome by each trisomy and monosomy shows that the viable trisomies (13, 18, 21 and X) are on the network periphery, suggesting they have less of an impact on other chromosomes so the embryo can survive.







Zero Sum Game

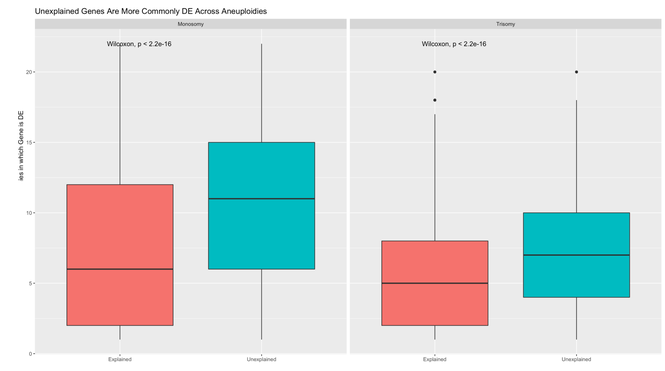


There is no correlation between the (logged) mean normal expression of a gene and its log2 fold change in aneuploidy (r = 0.037), nor is there a correlation between the total expression from a chromosome and the change in expression caused when it's aneuploid. This provides no evidence in support of the idea that gene expression is a 'zero sum game', i.e increasing expression of some genes requires decreasing expression of others.

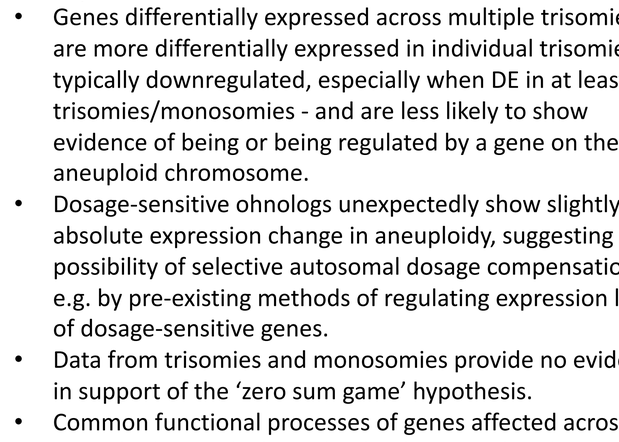
Coping with Transcriptional Dysregulation

Some transcriptional changes are caused by the gene being on the aneuploid chromosome or by being regulated by a transcription factor on the aneuploid chromosome. Others, however, may be responses that occur in an attempt to rescue cellular dysfunction, vicious cycles, or just random noise and individual variation.

I defined 'Explained' genes as those on the aneuploid chromosome or in the TRRUST database as being regulated by a transcription factor on that chromosome, regardless of direction of regulation. 'Unexplained' are everything else.



Genes differentially expressed across many trisomies or monosomies are enriched for processes involved in neural development and function (regulation of gliogenesis, myelination, cell communication and chloride homeostasis) and mitochondrial energy generation (GOrilla).



Conclusions

- Despite the fact that no chromosome-wide mechanism of dosage compensation has been found in birds, the chicken Z chromosome shows widespread dosage compensation.
- This seems to have been done on a gene-by-gene basis by various methods including upregulating Z genes in females and moving highly-expressed genes off the Z. This happened for most of the genes, with a slight preference for known dosage-sensitive genes.
- Viable trisomies are peripheral in the chromosome interaction network.
- Trisomies and monosomies show reciprocal patterns on the aneuploid chromosome but have similar effects on euploid chromosomes.
- Genes differentially expressed across multiple trisomies are more differentially expressed in individual trisomies – typically downregulated, especially when DE in at least 15 trisomies/monosomies - and are less likely to show evidence of being or being regulated by a gene on the aneuploid chromosome.
- Dosage-sensitive ohnologs unexpectedly show slightly less absolute expression change in aneuploidy, suggesting the possibility of selective autosomal dosage compensation, e.g. by pre-existing methods of regulating expression level of dosage-sensitive genes.
- Data from trisomies and monosomies provide no evidence in support of the 'zero sum game' hypothesis.
- Common functional processes of genes affected across aneuploidies – which tend to be downregulated – are neural function and energy generation.

References

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R Core Team (2017)
Wickham (2009) ggplot2

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