



Sex Chromosome Evolution

Mammalian X and Y evolved from a pair of homologous autosomes (Fig. 1). In the absence of X-Y recombination, caused by a series of inversions on the Y chromosome, the Y lost much of its gene content. Are some types of genes more likely to be lost? Is it possible to predict the fate of Y-linked genes?

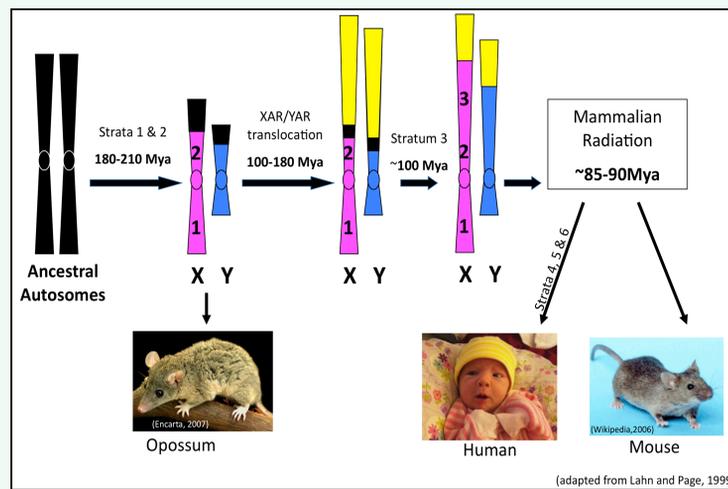


Figure 1. Some strata (labeled with numbers) are shared between mammals while some are species-specific. This means that Y-evolution is unique to each species and highlights the need for a general understanding of how Y chromosomes evolve.

Classifying X-linked genes

Genes present on the ancestral X chromosome (Figure 2) were categorized into three classes (Figure 3). We identified hundreds of previously undescribed Y-linked pseudogene sequences using lastZ.

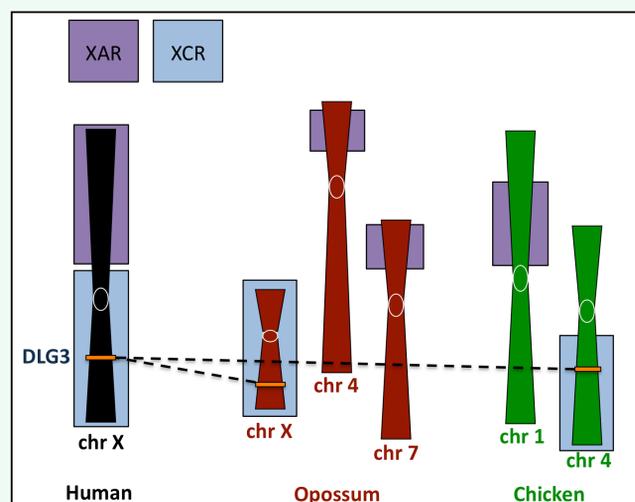


Figure 2. Existence of a gene in homologous regions across species was used as evidence for the presence of that gene on the ancestral X.

Comparing Classes

For each gene data was collected on several possible predictive features including expression intensity and expression breadth across 79 human tissues (Su *et al.*, 2004), GO functional categories, association with human disease in Online Mendelian Inheritance of Man, and selective constraint at nucleotide sites.

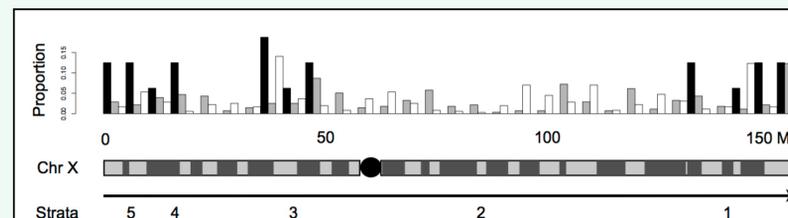


Figure 3. Proportion of X-linked genes with functional (black), pseudogenized (grey), or lost (white) Y homologs along chrX in 5Mb windows.

For each feature, each class of genes was compared using a permutation test with 1000 iterations to detect differences between the classes. There were no significant differences between any classes with respect to function, expression or selective constraint.

X-chromosome Inactivation

In humans one of the two X chromosomes in females is inactivated, but some genes on the inactive X escape inactivation (Carrel and Willard, 2005; Figure 4). If X chromosome inactivation (XCI) evolves in response to loss of gene content on the Y chromosome, then XCI status should be a strong predictor of the status of Y-linked homologs.

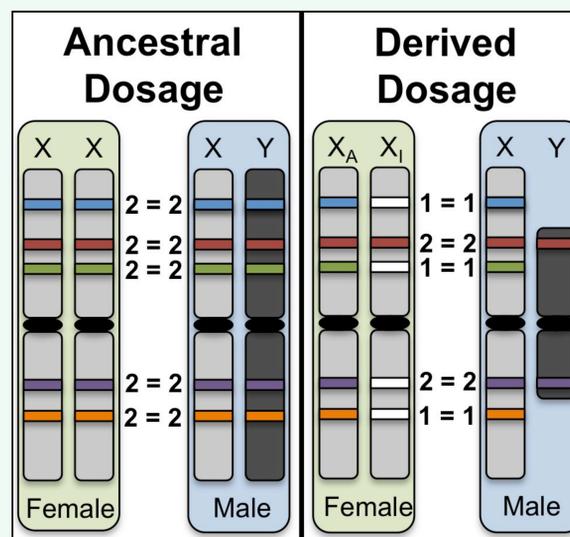


Figure 4. X-inactivation in females mirrors gene loss on the Y chromosome in males.

Predicting Y retention and loss

Using a linear discriminant analysis (LDA) with XCI status as the sole predictor, the model successfully predicts whether an X-linked gene has a functional Y homolog or has lost its Y homolog, with intermediate success predicting whether the Y is a pseudogene (Figure 5 and Table 1).

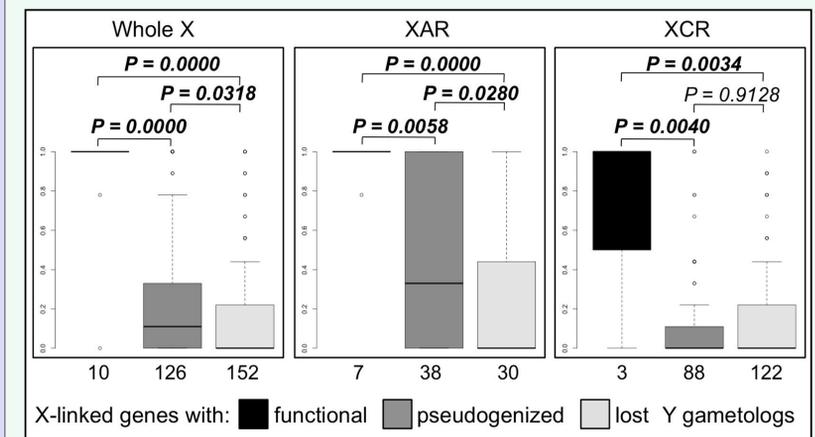


Figure 5. Significant differences in X-inactivation status between classes of X-linked genes.

X-linked gene class	Correct LDA Classification
Functional Y homolog	85%
Pseudogenized Y homolog	56%
Lost Y homolog	92%

Table 1. Results of LDA.

Conclusions

- Current function, expression and selective constraint of X-linked genes were not significantly different between any of the classes. It may be that the signals have diminished over time.
- X-chromosome inactivation results from gene loss on the Y.
- XCI status can correctly predict the status of Y-linked homologs

References

Carrel and Willard (2005) Nature, 434(7031): 400-4.
Lahn and Page (1999) Science, 286(5441): 964-7.
Su *et al.* (2004) PNAS, 101(10): 6062-7.

Acknowledgments

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