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# Nonrandom Representation of Sex-Biased Genes on Chicken Z Chromosome

**R. Storchová, P. Divina**

Institute of Molecular Genetics, Academy of Sciences of the Czech Republic and Center for Applied Genomics, Vídeňská 1083, CZ-142 20, Prague 4, Czech Republic

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**Abstract.** Several lines of evidence suggest that the X chromosome of various animal species has an unusual complement of genes with sex-biased or sex-specific expression. However, the study of the X chromosome gene content in different organisms provided conflicting results. The most striking contrast concerns the male-biased genes, which were reported to be almost depleted from the X chromosome in *Drosophila* but overrepresented on the X chromosome in mammals. To elucidate the reason for these discrepancies, we analysed the gene content of the Z chromosome in chicken. Our analysis of the publicly available expressed sequence tags (EST) data and genome draft sequence revealed a significant underrepresentation of ovary-specific genes on the chicken Z chromosome. For the brain-expressed genes, we found a significant enrichment of male-biased genes but an indication of underrepresentation of female-biased genes on the Z chromosome. This is the first report on the nonrandom gene content in a homogametic sex chromosome of a species with heterogametic female individuals. Further comparison of gene contents of the independently evolved X and Z sex chromosomes may offer new insight into the evolutionary processes leading to the nonrandom genomic distribution of sex-biased and sex-specific genes.

**Key words:** Comparative genomics — Chicken — Dosage compensation — Evolution — Gene expression — Sex chromosomes — Z chromosome

*Correspondence to:* R. Storchová; *email:* radkas@biomed.cas.cz

## Introduction

Several studies have shown that the X chromosome, a homogametic sex chromosome in male heterogametic organisms, differs from autosomes by a nonrandom content of genes with sex-biased or sex-specific expression (the genes expressed preferentially or exclusively in one sex). However, the direction of the biases in the location of sex-biased and sex-specific genes is not consistent across species. Thus, in humans, the genes related to sex and reproduction as well as the genes connected with brain and muscle functions were enriched on the X chromosome relative to autosomes (Bortoluzzi et al. 1998; Hurst and Randerson 1999; Lercher et al. 2003; Saifi & Chandra 1999; Zechner et al. 2001). In mice, the genes preferentially expressed in ovary, placenta, testicular somatic cells, and premeiotic germinal cells were more abundant on the X chromosome (Divina et al. 2005; Khil et al. 2004; Wang et al. 2001), whereas the genes expressed in the male germ line during meiosis were underrepresented (Divina et al. 2005; Khil et al. 2004). In *Caenorhabditis elegans*, the genes expressed in spermatogenic and oogenic cells were underrepresented on the X chromosome (Reinke et al. 2004), and in *Drosophila*, the male-biased genes were nearly absent from the X chromosome regardless of whether their expression was preponderant in germinal or in somatic tissues (Parisi et al. 2003; Ranz et al. 2003).

Two main hypotheses exist concerning the possible mechanisms causing the nonrandom representation of sex-biased and sex-specific genes on the homogametic sex chromosome. According to the hypothesis of sexual antagonism (Hurst 2001; Rice 1984), an unusual homogametic sex chromosome gene content reflects a

nonrandom accumulation of sexually antagonistic mutations (those favouring one sex, although being detrimental to the other) on this chromosome. This is caused by the different time that the homogametic sex chromosome has spent in the two sexes and by its hemizygous exposure in the heterogametic sex. The other hypothesis concerns the epigenetic modifications of the sex chromosomes associated with meiotic sex chromosome inactivation and dosage compensation (Khil et al. 2005; Parisi et al. 2003; Reinke et al. 2004; Rogers et al. 2003). Although the effect of the meiotic sex chromosome inactivation on the homogametic sex chromosome gene content has been well documented (Betran et al. 2002; Divina et al. 2005; Emerson et al. 2004; Khil et al. 2004; Reinke 2004), the role of dosage compensation and sexual antagonism remains elusive.

The mechanisms responsible for the nonrandom representation of sex-biased and sex-specific genes on the homogametic sex chromosome may be clarified by analysing the gene content of the Z chromosome, a homogametic sex chromosome in heterogametic female organisms. Although the X chromosome occurs more frequently in female individuals, the Z chromosome spends more time in male individuals. If sexually antagonistic selection were the primary mechanism affecting the sex chromosome gene content, we would expect the opposite trend in the representation of sex-biased and sex-specific genes on the X and Z chromosomes. Other evolutionary processes also shape the gene content of the X and Z chromosomes in slightly different ways. For example, because the Z chromosome occurs more frequently than the X chromosome in male individuals, it is exposed to a higher mutation rate, which provides more material for selection to act on (Axelsson et al. 2004; Ellegren & Fridolfsson 1997; Kirkpatrick & Hall 2004; Montell et al. 2001). The Z chromosome has also been suggested to be more responsive to sexual selection than the X chromosome (Reeve and Pfennig 2003). Therefore, the Z chromosome would be expected to show more profound differences in gene composition, relative to autosomes, than the X chromosome. Here we present the first analysis of the gene content of the Z chromosome in chicken. We show that chicken Z chromosome gene content is characterized by underrepresentation of ovary-specific genes and, to a lesser extent, of the brain-expressed female-biased genes, whereas the brain-expressed male-biased genes are significantly overrepresented on the Z chromosome.

## Materials and Methods

### *EST Data*

We used publicly available chicken EST data from NCBI UniGene database (build no. 24, October 14, 2004) (Wheeler et al. 2005). To analyse the distribution of tissue-specific genes on autosomes and the Z chromosome, we selected 68 chicken EST libraries containing at least 500 ESTs that were prepared from bulk tissues and were not annotated as diseased or embryonic. These libraries were sorted into 14 groups representing different tissue types (Supplementary Table 1). To get enough data for the analysis, we used both nonnormalized and normalized EST libraries (each tissue type was represented by at least one nonnormalized EST library). In the normalized libraries, the quantitative information about gene expression is biased, but the qualitative information about gene expression, or at least the distribution of genes among the chromosomes, should be preserved, and this was a sufficient condition for our analysis. Indeed, the proportion of Z-linked genes in the nonnormalized and normalized libraries did not show any significant difference for each of the examined tissues ($p > 0.05$, Fisher's Exact test). The tissue-specific genes were defined as the genes present in the libraries from one tissue type but not the others. For subsequent analysis of the distribution of male- and female-biased genes on autosomes and the Z chromosome, we used three nonnormalized EST libraries prepared from male brain (total 4230 ESTs) and female brain (total 8399 ESTs). The corresponding EST library IDs were 16171, 15560, and 15561.

**Table 1.** The proportion of Z-linked tissue-specific genes in 14 different tissues

| Tissue | ChrA | ChrZ | % Z-linked |
|---|---|---|---|
| Brain | 1135 | 40 | 3.40 |
| Limbs | 446 | 18 | 3.88 |
| Chondrocytes | 527 | 28 | 5.05 |
| Heart | 130 | 3 | 2.26 |
| Kidney and adrenal | 280 | 6 | 2.10 |
| Small intestine | 235 | 6 | 2.49 |
| Liver | 153 | 7 | 4.38 |
| Pancreas | 36 | 2 | 5.26 |
| Muscle | 156 | 8 | 4.88 |
| Fat | 42 | 1 | 2.33 |
| Bursal lymphocytes | 134 | 7 | 4.96 |
| Spleen | 42 | 2 | 4.55 |
| All somatic | 3316 | 128 | 3.72 |
| Testis | 363 | 16 | 4.22 |
| Ovary | 620 | 11 | 1.74 |

ChrA, autosomes; ChrZ, Z chromosome.

### *Chromosomal Location*

For the purpose of our analyses, each UniGene cluster represented a "gene." To determine the chromosomal location we aligned the representative sequence for each UniGene cluster to the chicken draft genome assembly (galGal2, February 2004, University of California Santa Cruz [UCSC] Genome Browser) (International Chicken Genome Sequencing Consortium 2004; Karolchik et al. 2003) using BLAT (Kent Informatics, Santa Cruz, CA, USA) (Kent 2002). BLAT was run with parameters used to build the UniGene track of the UCSC Genome Browser (minimum sequence identity of 95%, at least 20% coverage of the query sequence, at least 96.5% alignment ratio, and scores within 0.2% of the best-in-genome). The hits to multiple locations in the genome were discarded as were the hits to the W chromosome. Using these criteria, we mapped 79% (16,795 of the 21,447) UniGene clusters to unique positions in the genome.

### *Statistics*

To control for the effects of tissue specificity (Lercher et al. 2003), we compared the proportions of Z-linked genes specific for testis

**Table 2.** The proportion of the tissue-specific genes expressed in testis and ovary on the Z chromosome and comparison with tissue-specific genes expressed in somatic tissues

| Tested tissue | Observed gene counts | | Expected gene counts | | % Z-linked (observed) | $p$ value[a] (two tailed) |
|---|---|---|---|---|---|---|
| | Tested tissue | Somatic tissues | Tested tissue | Somatic tissues | | |
| Testis | | | | | | |
| ChrA | 363 | 2676 | 365.5 | 2673.5 | | |
| ChrZ | 16 | 96 | 13.5 | 98.5 | 4.22 | 0.537 |
| Ovary | | | | | | |
| ChrA | 620 | 2676 | 611.2 | 2684.8 | | |
| ChrZ | 11 | 96 | 19.8 | 87.2 | 1.74 | 0.027 |

[a]The $p$ value (two tailed) corresponds to the proportion of permutations producing the gene counts greater or equal (for testis) and lower or equal (for ovary) to the observed gene counts in the tested tissue and the Z chromosome multiplied by two.
ChrA, autosomes; ChrZ, Z chromosome.

and ovary with the proportions of Z-linked tissue-specific genes in the pool of 12 somatic tissues by permutation test. All genes were randomly reassigned to chromosomes while keeping fixed the total gene count, the total count of genes in each group, and the total number of genes on autosomes and the Z chromosome. To assess significance, fractions of permutations producing the gene counts "lower or equal" and "greater or equal" to the observed gene counts in the tested tissue and the Z chromosome were determined. The $p$ value (two tailed) was defined as the smaller of these fractions multiplied by two.

The genes with preferential expression in male or in female brain were sorted out using the R statistic, which was devised previously for comparison of transcript abundances in cDNA libraries (Stekel et al. 2000). The R statistic was computed for each gene expressed in the brain, and the genes exceeding a given R threshold were considered as preferentially expressed in male or female brain. Fisher's Exact test was used to compare the proportions of male- and female-biased genes located on the Z chromosome.

## Results

First, we assessed the allocation of the tissue-specific genes (the genes expressed exclusively in one tissue) between autosomes and the Z chromosome. For this purpose, we compared the proportions of the Z-linked tissue-specific genes in 14 different tissues (12 somatic tissues, testis and ovary; Table 1). Because these proportions did not differ significantly among the 12 somatic tissues ($p > 0.05$, Fisher's Exact test), we combined the EST data of all somatic tissues into one pool. Then we analysed whether the proportions of the Z-linked tissue-specific genes in testis (male specific) and ovary (female specific) differ from those in somatic tissues (Table 2). Of the 379 testis-specific genes, 4.2% mapped to the Z chromosome, a proportion comparable with 3.5% of the Z-linked tissue-specific genes present in the pool of 12 somatic tissues ($p > 0.05$, two tailed, 100,000 permutations). In ovary, 631 tissue-specific genes were detected, but only 11 of them (1.7%) mapped to the Z chromosome, which is a significant decrease compared with the Z-linked tissue-specific genes in the pool of 12 somatic tissues ($p = 0.027$, two tailed, 100,000 permutations). To confirm that the paucity of ovary-specific genes concerns only the Z chromosome, we further examined the distribution of ovary-specific genes among individual autosomes. Although the proportion of ovary-specific genes on the autosomes containing at least 500 genes (Chr: 1 to 10 and 14) was uneven (2.7% to 5.9%), it was in all cases higher than on the Z chromosome, which contained only 1.7% ovary-specific genes of the total number of 653 Z-linked genes. This represents a significant decrease ($p < 0.01$, Chi-square test) compared with the average proportion of ovary-specific genes on autosomes (3.8% or 620 of 16142). A list of the 11 Z-linked ovary-specific genes obtained in this analysis is provided in Supplementary Table 2.

The important question for interpreting our results is whether the nonrandom distribution concerns only the genes expressed in ovary, composed of both somatic and germinal cells, or also the genes expressed in pure somatic tissues. To answer this question, we performed an analysis of the sex-biased genes expressed in brain, for which the nonnormalized EST libraries were created separately from male and female individuals. The genes preferentially expressed in either male or female brain (male biased or female biased) were sorted out using different thresholds of the R statistic (Stekel et al. 2000). When the preferentially expressed genes with $R > 1$ were selected, 5.6% (58 of 1029) of male-biased genes were located on the Z chromosome. In comparison, only 1.3% (4 of 314) of female-biased genes were found on the Z chromosome, representing a highly significant difference ($p < 0.001$, Fisher's Exact test). For more relaxed thresholds ($R > 0.5$ and $R > 0$), the difference in proportion of male-biased and female-biased genes on the Z chromosome was smaller but still highly significant (Fig. 1).

We were also interested whether the male- or female-biased genes expressed in the brain were enriched or impoverished on the Z chromosome. For that reason we compared the proportions of the male-biased and female-biased Z-linked genes to the overall proportion of Z-linked genes expressed in

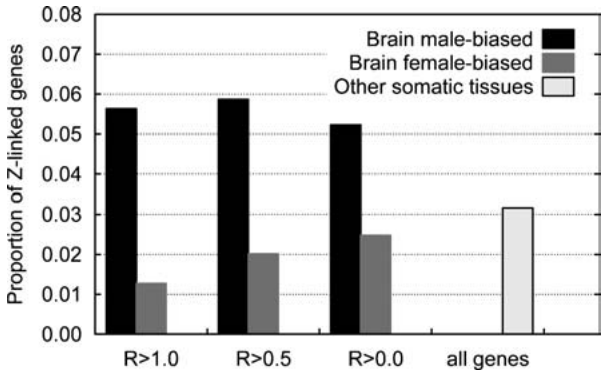


**Fig. 1.** The proportions of Z-linked genes with male- and female-biased expression in brain for different thresholds of the R statistic. The R statistic (Stekel et al. 2000) was used as a measure of sex-biased expression. For all thresholds of the R statistic, the male-biased genes were significantly more abundant on the Z chromosome than the female-biased genes. Compared with the genes expressed in other somatic tissues, the male-biased genes were significantly enriched on the Z chromosome, whereas the female-biased genes displayed an indication of underrepresentation on the Z chromosome.

the pool of 11 other somatic tissues. The male-biased genes expressed in the brain were 1.8-fold more abundant on the Z chromosome than the genes expressed in other somatic tissues, which is a highly significant difference ($p < 0.0001$, Fisher's Exact test). Significant overrepresentation (1.6-fold) was also observed for more stringent threshold, $R > 2$ ($p < 0.05$, Fisher's Exact test). Using this threshold, we sorted out 421 male-biased genes from which 22 mapped to the Z chromosome. In contrast, the female-biased genes expressed in the brain were 2.5-fold less abundant on the Z chromosome than the genes expressed in other somatic tissues. However, this difference was not significant at the 5% level because of the low number of female-biased genes ($p = 0.052$, Fisher's Exact test) (Fig. 1). A list of the Z-linked genes preferentially expressed in male brain (58 genes) and female brain (4 genes) is available in Supplementary Table 3. Admittedly, the majority of these genes are annotated as unknown transcripts.

## Discussion

Previous studies have shown that the X chromosome of various animal species harbours nonrandom proportions of genes with sex-biased or sex-specific expression. However, selective forces responsible for this phenomenon remain mostly elusive. Our results indicate that nonrandom proportions of sex-biased and sex-specific genes also characterise the Z chromosome in chicken. Comparing the gene contents of the independently evolved X and Z chromosomes may help decide which mechanisms are mostly responsible for the nonrandom genomic distribution of sex-biased and sex-specific genes. These mechanisms could involve sexually antagonistic selection and/or epigenetic modifications of the X/Z chromatin such as meiotic sex chromosome inactivation and dosage compensation.

According to the hypothesis of sexual antagonism (Hurst 2001; Rice 1984), dominant mutations favouring the homogametic sex but not the heterogametic sex should accumulate on the X/Z chromosome because this chromosome spends two thirds of its time in the homogametic sex but only one third of its time in the heterogametic sex. Indeed, it was observed that the female-specific and/or female-biased genes are enriched on the X chromosome in mice and *Drosophila* (Khil et al. 2004; Parisi et al. 2003; Ranz et al. 2003), although this was not confirmed in humans (Lercher et al. 2003). In chicken, we have found a significant overrepresentation of the genes expressed preferentially in the male brain on the Z chromosome, which is in agreement with the theory of sexually antagonistic selection. The question still remains why the testis-specific genes are not enriched on the chicken Z chromosome as well.

The role of sexually antagonistic selection in the distribution of genes favouring the heterogametic sex is more complicated because it depends on the proportion of dominant and recessive mutations that emerge in the population (or on the average dominance of new mutations) (Rogers et al. 2003). If the majority of mutations are dominant, we should expect underrepresentation of genes favouring the heterogametic sex on the X/Z chromosome because it spends only one third of its time in the heterogametic sex. However, if the majority of mutations are recessive, the reverse effect should be expected. The reason is that the recessive mutations favouring the heterogametic sex have a greater chance to be fixed on the hemizygous X/Z chromosome where they are exposed to selection. Studies on the X/Z chromosome gene content in different organisms provided conflicting results. The genes that are preferentially expressed in the male somatic tissues are enriched on the X chromosome in mammals (Divina et al. 2005; Khil et al. 2004; Lercher et al. 2003; Wang et al. 2001). In contrast, the male-biased genes in *Drosophila* (Parisi et al. 2003; Ranz et al. 2003) and the female-biased genes in chicken seem to be underrepresented on the X/Z chromosome. Assuming that the proportion of dominant and recessive mutations does not differ among taxa, the sexually antagonistic selection is unlikely to explain the discrepancies in the X/Z chromosome gene content in different species.

Another mechanism affecting sex chromosome gene content concerns the epigenetic modifications of the X/Z chromatin, such as meiotic sex chromosome inactivation and dosage compensation. The meiotic sex chromosome inactivation occurs in germinal cells in heterogametic male individuals, but it has not been

observed in heterogametic female individuals (Jablonka & Lamb 1990) and hence is unlikely to affect the complement of genes on the Z chromosome. In contrast, the dosage compensation occurs in somatic cells and has been observed in both heterogametic male and female organisms. Different species, however, use different mechanisms to achieve dosage compensation (Avner & Heard 2001; Baker et al. 1994; Ellegren 2002; Gupta et al. 2006; Kelley 2004; Meyer 2000). Interestingly, recent findings suggest that dosage compensation in chicken may be achieved by the same mechanism as in *Drosophila*, i.e., by transcriptional upregulation of the single X/Z chromosome in heterogametic sex (Bisoni et al. 2005). According to the hypothesis of Pomiankowski et al. (Rogers et al. 2003), this mechanism of dosage compensation could lead to the paucity of genes upregulated in the heterogametic sex on the X/Z chromosome. The reason is that the overall overactivation of the single X/Z chromosome could constrain further increase of transcription in the heterogametic sex. If dosage compensation is really achieved by the same mechanism in *Drosophila* and birds, our data could support this hypothesis.

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