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ScienceDirect
Genomics 88 (2006) 675–681
GENOMICS
www.elsevier.com/locate/ygeno

X chromosome gene expression in human tissues: Male and female comparisons

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Received 4 May 2006; accepted 31 July 2006
Available online 1 September 2006

Abstract

About 25% of X-linked genes may escape inactivation at least to some degree. However, in vitro results from somatic cell hybrids may not reflect what happens in vivo. Therefore, we analyzed the female/male (F/M) gene fold expression ratio for 299 X-linked and 7795 autosomal genes from 11 different tissues from an existing in vivo microarray database. On average 5.1 and 4.9% of genes showed higher expression in females compared with 7.4 and 7.9% in males, respectively, for X-linked and autosomal genes. A trend was found for F/M gene fold ratios greater than 1.5 for several X-linked genes indicating overexpression in females among multiple tissues. Nine X-linked genes showed overexpression in females in at least 3 of the 11 studied tissues. Of the 9 genes, 6 were located on the short arm and 3 on the long arm of the X chromosome. Six of the 9 genes have previously been reported to escape X inactivation. However, in general, no consistent pattern was seen for the expression of X-linked genes between in vitro and in vivo systems. This study indicates that factors other than the X-inactivation process may impact on the expression of X-linked genes resulting in an overall similar gender expression for both X-linked and autosomal genes.

Keywords: X inactivation; Gene expression; In vivo systems; In vitro systems

Dosage compensation in mammalian females is a recognized phenomenon whereby inactivation of one X chromosome is achieved in early development leading to equality of X-linked gene products between male and female cells [1]. However, not all X-linked genes are inactivated. Recently, an inactivation profile of 624 X-linked transcripts using a fibroblast-based rodent – human hybrid system retaining only the inactive human X chromosome was reported by Carrel and Willard [2]. In this in vitro hybrid system, at least 25% of X-linked genes escaped inactivation in all or in a significant subset of X chromosomes tested, with the majority located on the human Xp chromosome. Subsequently, Lyon [3] noted that the report by Carrel and Willard [2] enhanced our knowledge about X-chromosome inactivation, a process that is not "all-or-none." She also raised questions on whether the study of cultured skin fibroblast cells in their hybrid system reflects what happens in vivo. On the other hand, microarray gene expression technology has been used by Craig et al. [4] to analyze in vivo the inactivation status of 772 probes representing human X-linked genes in lymphocytes. They found 36 X-linked targets detected in significantly higher levels in females, suggesting these loci escaped, at least partly, from inactivation [4].

To address the inactivation status of X-linked genes in an extended scale, we further examined gender differences in gene expression from expression profiles recently reported [5] from multiple normal human tissues and kindly provided by Dr. J. Khan at Web site http://www.genome.org/cgi/content/full/15/3/443/DC1.

Results and discussion

A relatively similar pattern of expression was seen in males and females for both X-linked ($n=299$) and autosomal ($n=7795$) genes in nine tissues with about 90% falling within the middle category (female/male (F/M) gene fold ratio of 1.4–0.8), but a wider pattern of gene expression was seen for both

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doi:10.1016/j.ygeno.2006.07.016

adrenal and cerebral tissues (Table 1 and Fig. 1). Furthermore, box plots demonstrating interquartile ranges (IQR) for distribution of F/M gene fold ratios are shown in Fig. 2. No statistical differences were detected comparing IQR between X-linked and autosomal genes per tissue. To explore if utilizing IQR would provide enough statistical power and sensitivity to detect differences between two F/M gene fold ratio sets, we examined differences in the distribution of IQR among different tissues for X-linked and autosomal genes separately. Since we used data from 11 tissues, we had 55 possible comparisons to be calculated. Therefore, to apply Bonferroni correction, the calculated randomization p values were multiplied by 55. As expected most of the comparisons between different tissues showed significant differences for the IQR of F/M gene fold ratios indicating tissue specificity; that is, significant differences for 48 of 55 different comparisons for autosomal genes were detected. For X-linked genes 25 of these 48 comparisons were significantly different. Detection of less tissue specificity for X-linked versus autosomal genes could be a reflection of sample size (299 and 7795 genes, respectively).

We expected that the majority of genes previously reported to escape X inactivation using somatic cell hybrids [2] would be found in our first category (i.e., F/M gene fold expression ratio ≥ 1.5). However, no specific pattern was detected between results generated for the 217 X-linked genes studied in the somatic cell hybrid system [2] and the F/M gene fold ratio calculated from our existing analyzed microarray database (Fig. 3 and Supplementary Table 1). No consistent correlation was detected for the F/M gene fold ratios across tissues per gene. However, a trend was found for similar F/M gene fold ratios for several genes within multiple tissues. For example, 9 X-linked genes showed overexpression in females in at least 3 of the 11 studied tissues (Table 2). Of the 9 genes, 6 were located in the short arm and 3 on the long arm of the X chromosome. Six of the 9 genes have previously been reported to escape X inactivation [2,6].

The tip of the short arm of the X and Y chromosomes compromises the PAR1 pseudoautosomal region, which is 2.7 Mb in length [7]. A second pseudoautosomal region, PAR2, is shorter (330 kb) and located at the tip of the long arm of the sex chromosomes [7]. The majority of genes in these homologous regions (present in two copies in both males and females) is thought to escape inactivation [7]. Six genes from the PAR1 region (i.e., *PLCXD1, GTPBP6, CSF2RA, IL3RA, ASMTL,* and *XG*) and one gene from the PAR2 region (i.e., *SYBL1*) were present in the existing microarray database. Overall, equal gene expression levels (i.e., F/M gene fold ratio of 1.4–0.8) were seen for these pseudoautosomal genes in tissues studied between males and females. However, a higher expression of the *PLCXD1* and *CSF2RA* genes was found in females compared with males for only the stomach and lung tissue, respectively. The degree of sequence homology between the X- and the Y-chromosome copies should be considered particularly when interpreting pseudoautosomal gene microarray data. If such a sequence homology is very high, we may not distinguish gene expression from the X- and Y-chromosome copies (in male subjects) using microarray analysis. Therefore, for male subjects a combined expression of the X and Y pseudoautosomal genes may be present. A highly specific gene expression assay distinguishing the expression patterns from the X- and Y-chromosome copies of the pseudoautosomal genes would be needed to evaluate precisely gender expression differences for these genes.

Among genes subject to inactivation according to the somatic cell hybrid system [2], several genes showed gender expression differences in our study. From this group, we found 23 and 12 genes, respectively, with significantly (t test; $p < 0.05$) higher expression levels in females or males, in at least 1 of 11 tissues. For these genes with gender expression differences but silenced in the somatic hybrid system [2], there was evidence for sex hormonal influences for only 5 of 23 genes (22%), *PIM2* [8], *NONO* [9], *TCEAL1* [10], *BGN* [11], and *GDI1* [12], that were overexpressed in females. Furthermore, 3 of 12 genes (25%), *SLC35A2* [13], *ARR3* [14], and *FLNA* [15], were overexpressed in males and influenced by sex hormones.

Carrel and Willard [2] also used a quantitative assay to measure allelic expression of 94 X-linked genes from the inactive X chromosome relative to the active X in nonrandomly inactivated human female fibroblasts. Since only female

Table 1
Female/male (F/M) gene fold ratio calculated for (A) autosomal ($n=7795$) and (B) X-linked ($n=299$) genes from 11 different tissues

	Adrenal	Cerebrum	Colon	Ileum	Kidney	Liver	Lung	Sk muscle	Spleen	Stomach	Ureter	Average (%)
Female/male (n)	5/4	4/3	3/5	3/5	5/4	6/4	5/4	5/4	5/4	5/5	3/5	
Average age (years)	19.3/19.2	24.7/22.1	15.9/19.6	9.4/23.3	15.6/19.1	21.3/19.8	15.6/19.1	15.6/19.1	15.6/19.1	15.5/17.3	12.3/21.8	
(A) F/M gene fold ratio: Autosomal genes ($n=7795$)												
≤ 0.7 (higher expression in M)	15%	15%	8%	6%	5%	4%	7%	5%	7%	7%	8%	7.9
0.8–1.4	78%	75%	88%	91%	91%	93%	85%	90%	90%	86%	88%	87.2
≥ 1.5 (higher expression in F)	6%	10%	4%	3%	4%	2%	7%	5%	3%	7%	3%	4.9
(B) F/M gene fold ratio: X-linked genes ($n=299$)												
≤ 0.7 (higher expression in M)	18%	17%	5%	7%	5%	3%	4%	6%	6%	4%	6%	7.4
0.8–1.4	75%	73%	89%	92%	90%	94%	89%	92%	89%	89%	90%	87.5
≥ 1.5 (higher expression in F)	7%	10%	6%	1%	5%	3%	7%	2%	4%	7%	4%	5.1

Percentage of the genes overexpressed in either females or males is shown for each tissue. Number of subjects and average age for each gender are indicated per tissue.

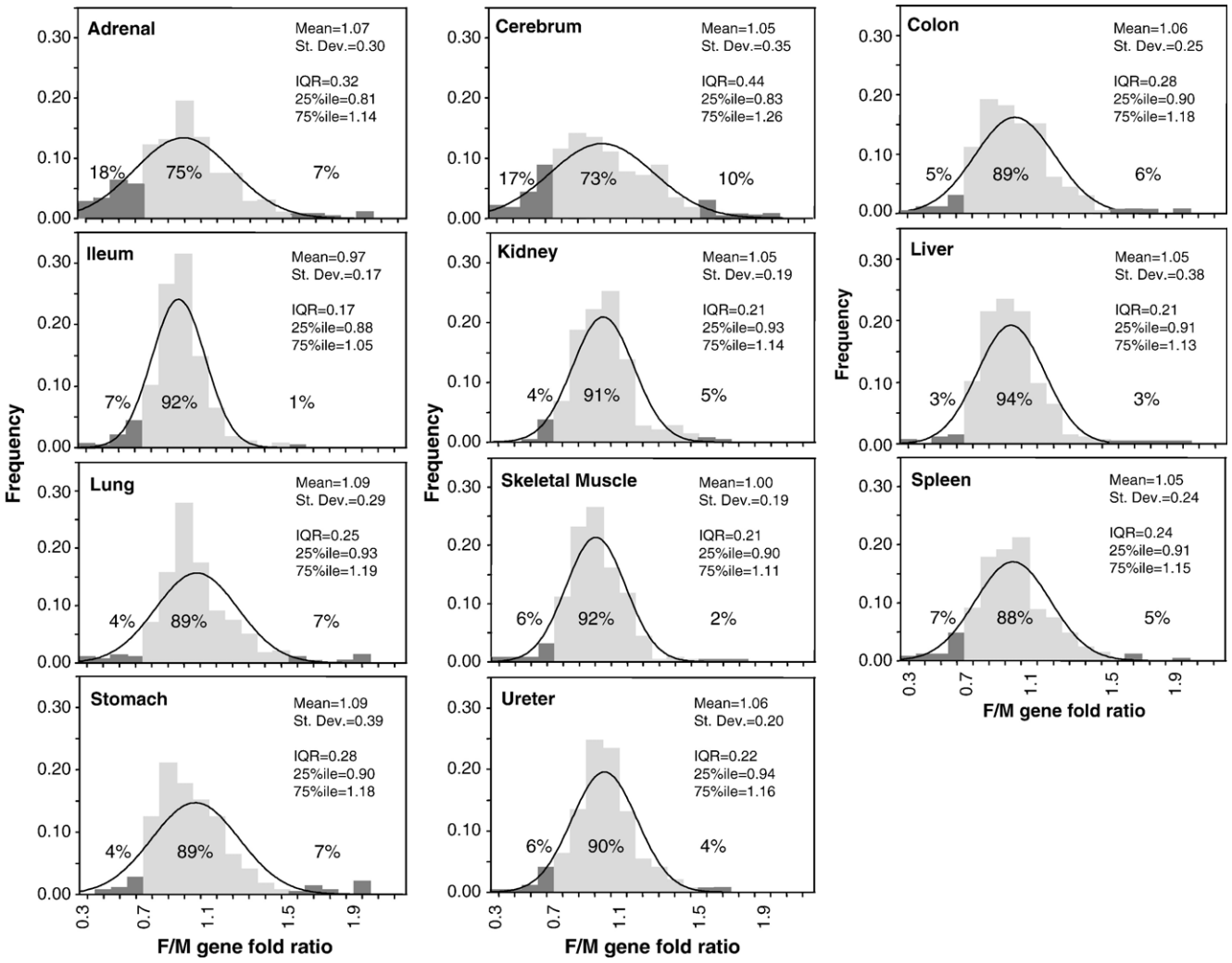


Fig. 1. Histograms showing distribution of F/M gene fold ratios for X-linked genes. Gene fold ratios (F/M) for 299 X-linked genes analyzed are shown for 11 different tissues.

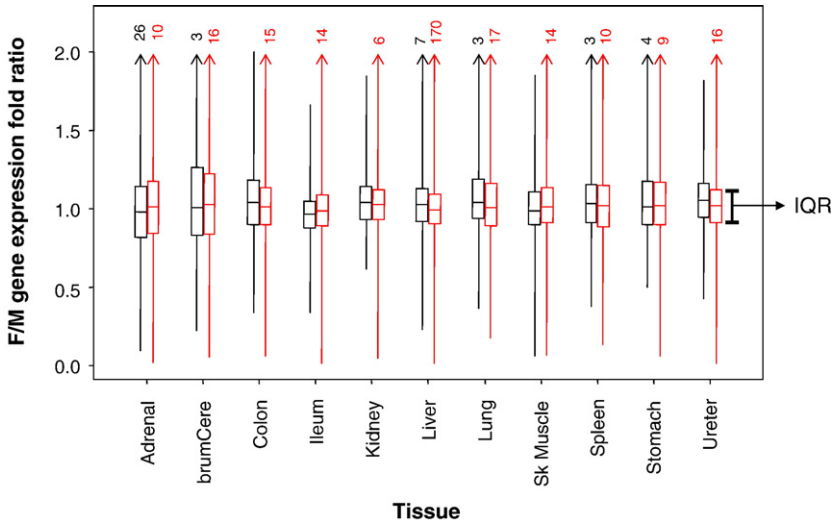
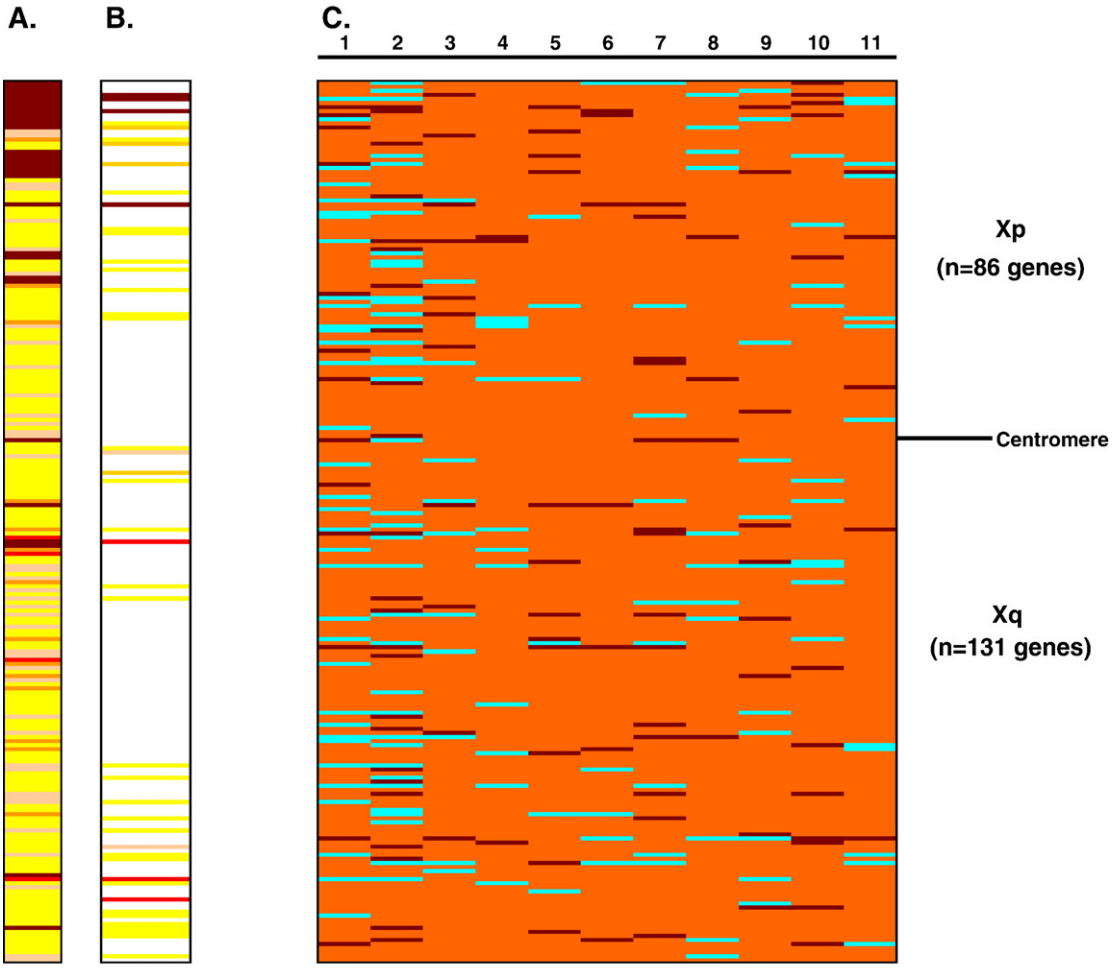


Fig. 2. Box plots showing the interquartile range. Box plots representing interquartile range (IQR) and median (horizontal line shown inside each IQR box) demonstrating distribution of the F/M gene fold ratio for 299 X-linked genes (shown in black) and 7795 autosomal genes (shown in red) in 11 different tissues are presented. The F/M gene fold ratios are within 0 to 2, otherwise the maximum data point is indicated following an arrow line.



F/M gene fold ratio	1	2	3	4	5	6	7	8	9	10	11	
≥ 1.5	7	9	7	2	4	3	4	2	3	5	3	Xp
	6	15	4	1	8	4	10	2	6	7	2	Xq
1.4-0.8	170	156	195	203	199	205	194	202	197	195	200	Xp & Xq
≤ 0.7	15	18	3	4	3	1	3	4	3	4	7	Xp
	19	19	8	7	3	4	6	7	8	6	5	Xq

Number of genes represented on chromosome Xp and Xq per F/M gene fold ratio categories.

Fig. 3. Comparison of in vitro and in vivo results for expression of X-linked genes. (A) X-inactivation gene expression data from human – mouse somatic cell hybrid system [2]. (B) Expression from inactive X chromosome using allelic expression assay in human fibroblasts [2]. (C) X-linked genes (n=217) analyzed from microarray gene expression database in 11 tissues [5]. The female/male (F/M) gene fold expression ratio (in vivo) from Son et al. [5] is shown for 217 X-linked genes in 11 tissues (1, adrenal; 2, cerebrum; 3, colon; 4, ileum; 5, kidney; 6, liver; 7, lung; 8, skeletal muscle; 9, spleen; 10, stomach; and 11, ureter). In (A) the X-inactivation status of the same 217 X-linked genes using nine somatic cell hybrids (in vitro) reported by Carrel and Willard [2] and demonstrated by a color code is also presented. Expression of a specific gene in 9/9 cell hybrids denotes significant gene expression for that gene from the inactive X (escaped inactivation), while 0/9 hybrids represented completely silenced genes. In general, no specific pattern was seen between the in vivo and the in vitro results. Relative expression levels of 43 of these genes from the inactive X chromosome in female human fibroblasts [2] are also shown by a color code (B).

samples with a complete nonrandom inactivation were used for this assay, genes that showed biallelic expression must have escaped from inactivation. In our analyzed database, we found expression data for 43 of these 94 genes. Relative expression in fibroblasts from the inactive X chromosome (using this allelic expression assay) is shown by color coding in Fig. 3 for these 43 X-linked genes. Overall no consistent pattern was seen between the results generated by (1) the somatic cell hybrid system, (2) the allelic expression assay in female human fibroblasts, and (3) F/M gene fold expression ratios in our 11 tissues. However, a pattern was noticed for a subset of these genes; for example, 9 genes with no expression from the inactive X chromosome in the hybrid system (i.e., subject to inactivation) showed almost no expression from the inactive X in human fibroblasts [2]. Furthermore, relatively equal expression was detected in males and females in 11 tissues analyzed in our study.

Table 2
X-linked genes found to be overexpressed in females in at least 3 of 11 tissues

Symbol	Chromosome band	Carrel and Willard [2]	Adrenal	Cerebrum	Colon	Ileum	Kidney	Liver	Lung	Sk muscle	Spleen	Stomach	Ureter
HDHD1A	Xp22.32	8/9	1.8 *	1.5	1.2	1.2	1.9*	1.4*	1.4	1.1	1.6*	1.3	1.2
PNPLA4	Xp22.3	9/9	1.8*	1.1	1.1	1.0	1.3	1.6*	1.1	0.8	1.1	1.8*	1.2
AP1S2	Xp22.2	9/9	1.4	1.3	1.1	0.9	1.5	1.3	1.1	0.9	1.5	0.8	1.5
ZFX	Xp21.3	9/9	0.9	1.0	1.5*	1.1	1.3	1.8*	1.5	1.2	1.5*	1.4*	1.3
RPGR	Xp11.4	0/9	0.9	1.0	1.4	1.6	1.2	1.1	1.4	1.5	1.3*	0.9	1.6
UTX	Xp11.2	Escapes inactivation [a]	1.0	0.9	1.8*	1.2	1.7*	1.6*	1.8*	1.3*	1.4*	1.7*	1.3
RPS4X	Xq13.1	9/9	1.2	1.1	1.7*	1.0	1.7*	1.7	1.4	1.1	1.3	1.2	1.0
ACSL4	Xq22.3	0/5	1.5	1.7*	0.9	1.0	1.5	6.6	1.6	0.9	1.4	1.2	1.2
CDR1	Xq27.1	2/9	0.9	2.0	0.9	1.0	1.2	1.0	1.6*	1.0	1.1	1.6	0.9
		Total	3	3	3	1	5	5	4	1	2	3	2
			33%	33%	33%	11%	56%	56%	44%	11%	33%	33%	22%

At least 3 of 11 tissues showed gene overexpression in females (≥1.5 F/M gene fold ratios), indicating escape from inactivation for the X-linked gene. Of the nine X-linked genes with evidence of escaping X inactivation, six are located on the short arm and three on the long arm. Six of the nine genes were also reported to have escaped X inactivation by Carrel and Willard [2] (e.g., expressed from the inactive X in 8/9 or 9/9 cell hybrids) and Greenfield et al. [6].

[a] Greenfield et al. [6].

* F/M gene fold ratios indicating significantly higher expression in females than in males (*t* test; $p<0.05$).

Two genes (*TBL1X* and *SH3BGRL*), which should have escaped from inactivation according to the hybrid system, had equal gender expression in our 11 tissues analyzed and none or little expression (≤15%) from the inactive X in fibroblasts. Three genes (*GPR143, PIR,* and *IKBKG*), which escaped from inactivation based on the somatic cell hybrid system, had less than 10% expression from the inactive X in fibroblasts but a variable expression level in the 11 tissues evaluated in our study. The last group of genes (i.e., *GYG2, STS,* and *ZFX*), which escaped from inactivation in the hybrid system assay, had also relatively high expression levels (between 20 and 65%) from the inactive X chromosome in fibroblasts. On the other hand, while equal gene expression was seen for these genes in some of the tissues that we examined, higher expression was seen in females than in males in at least 2 of these 11 tissues. In particular, *ZFX,* a zinc finger protein, was markedly expressed from the inactive X in fibroblasts (almost 65% relative to the expression from the active X chromosome). Expression of the *ZFX* gene was also significantly higher (*t* test; $p<0.05$) in 5 of the 11 tissues that we examined.

Twenty-seven of the 36 genes identified by Craig et al. [4] as having higher expression in females than in males using microarray data from lymphocytes were later studied in a somatic cell hybrid system [2]. Strong agreement between the two earlier studies was found for only 9 (33%) genes (i.e., genes expressed from the inactive X in 5/9 through 9/9 cell hybrids), moderate agreement for 6 (22%) genes (i.e., genes expressed from the inactive X in 3/9 through 1/9 hybrids), and strong disagreement for 12 (44%) genes (i.e., genes expressed from the inactive X in 0/9 hybrids). Seventeen of the 25 genes reported by Craig et al. [4] and Carrel and Willard [2] were also found in our analyzed dataset but only 6 genes (35%) were overexpressed in females (in at least 1 of our 11 analyzed tissues). In the hybrid system [2], 2 of these genes were expressed in 9/9 hybrids, while the other 4 genes showed expression in 0/9 through 3/9 hybrids.

More recently, genome-wide microarray expression data were utilized by Nguyen and Disteche [16] to determine whether X-chromosome expression differed between sexes in human heart, liver, muscle, spleen, and brain tissues. Using X/autosome expression ratios for a given tissue, overall they reported no significant differences among the tissues between the sexes. In particular, for the 27 X-linked genes previously reported by Carrel and Willard [2] to escape inactivation (i.e., using the somatic cell hybrid system), Nguyen and Disteche [16] found a significant increase in expression in females for only a few of these escaped genes. Because of a paucity of female to male gene expression ratios in the tissues reported by Nguyen and Disteche [16], we were unable to correlate our female to male expression data with their dataset for these genes. However, the lack of significant overexpression in females for the genes escaping from inactivation is in agreement with our overall finding (i.e., absence of a definite agreement between results generated by the somatic cell hybrid system and in vivo gene expression data).

In conclusion, we analyzed an existing genome-wide microarray expression profiling dataset generated from multiple normal tissues to examine gender differences in expression of X-linked genes with the objective to determine if higher expression levels were detectable in females representing genes that apparently escape X inactivation. We compared the expression of X-linked genes with autosomal genes and among different tissues. In each tissue, about 13% of our analyzed X-linked genes demonstrated greater than 1.5-fold change in expression between males and females; most were genes not previously identified in recent gene expression studies [2,4].

To evaluate if gender differences in gene expression were influenced by the sex chromosome, we utilized a randomization test to compare F/M gene expression fold ratios between X-linked and autosomal genes. This statistical analysis indicated that overall gender gene expression was not significantly different comparing X-linked genes with autosomal genes as a group. For the X-linked genes, no consistent pattern was seen between the results from the somatic cell hybrid system, allelic expression of the inactive X chromosome in female fibroblasts [2], and microarray gene expression data in 11 tissues that we examined. However, strong agreement was seen for only a few genes; for example, significantly higher expression levels were found for *UTX* in colon, kidney, lung, skeletal muscle, spleen, and stomach.

Furthermore, *ZFX* showed significantly higher expression in females in 5 tissues (i.e., colon, kidney, liver, spleen, and stomach). Both genes were also reported to have significantly higher expression for females in lymphocytes [2], which is in agreement with the previous finding using the somatic hybrid system [2,6]. However, even for these two genes with considerable compatibility between in vitro and in vivo results, their expression in other tissues did not confirm the X-inactivation result from the somatic cell hybrid system, which further emphasizes the impact of tissue specificity.

Therefore, our study suggests that previous in vitro gene expression analysis of X-linked genes [2] may not necessarily concur with in vivo activity. Factors other than the X-inactivation process (e.g., sex hormone influence, subject's age, tissue specificity and composition, and other factors that may alter the amount of mRNA production or degradation in a cell [17]) may impact on expression outcome of X-linked genes. Furthermore, microarray analysis provides a general expression profile that needs to be confirmed for each gene with a more sensitive technique such as quantitative RT-PCR. As evidence, we studied expression of an X-linked gene, *NLGN4,* previously reported to escape from inactivation by the somatic hybrid system [2], but found monoallelic expression of this X-linked gene in about 80% of females [18] using SNPs at the 3′ untranslated region of this gene. Furthermore, as Carrel and Willard [2] demonstrated in their study, gene expression levels for a distinct gene that escapes from inactivation might be as low as 25% in the inactive X compared with the active X chromosome. X-linked genes, in particular, are of great interest for their involvement in neurodevelopmental disorders such as mental retardation and autism with unequal gender prevalence. Our findings emphasize the need to uncover further the impact of the X-chromosome inactivation phenomenon at the gene expression level. Undoubtedly, other factors impacting on expression of X-linked genes remain to be explored.

Subjects and methods

The existing gene expression dataset utilized in our study was previously normalized and quality filtered by removing those clones with poor quality measurement for more than 20% of all samples (see Son et al. [5] for details about data normalization and quality filtering). Approximately 85% of their clones passed this filtration process. By applying this quality filtering, the genes with low or undetectable expression would have been removed from their dataset. Furthermore, this gene expression database was selected for our analysis because of its proven validation and internal consistency of gene expression profiles. Using principal component analysis plots, Son et al. [5] demonstrated that samples from the same organ but different donors clustered together and were distinct from other organs regardless of age, gender, cause of death, or postmortem interval of individual donors, indicating internal stability of the dataset. In addition, randomly selected subsets of genes (as small as 100) reproduced a hierarchical clustering of the full dataset that strongly indicates consistency of these gene expression data.

The gene expression dataset from Son et al. [5] contained multiple probes for several genes while other genes were standardized with the use of a single probe. For our analysis, we averaged gene expression data between males and females; and, to avoid introducing the calculation of another average, we examined only those genes represented by a single probe. Genes represented by a single probe from this normalized expression dataset were then separated into autosome and X-linked genes (7795 and 299 genes, respectively). Of the 299 X-linked expressed genes, 217 genes were previously examined by Carrel and Willard [2]. Data from 11 different tissues in our study were available for analysis in at least three males and three females, while 4 tissues (kidney, lung, skeletal muscle, and spleen) were available from nine identical subjects (four males and five females). The female/male gene fold expression ratio was calculated for each gene and tissue. An arbitrary ratio of greater than or equal to 1.5 gene fold expression was used as a cutoff indicating higher expression in females, which supports escape from inactivation [4]. Thus, three categories were developed: F/M gene fold ratio ≥ 1.5, F/M gene fold ratio between 1.4 and 0.8 (indicating relatively equal expression in males and females), and F/M gene fold ratio ≤ 0.7 (indicating higher expression in males).

The following tests were conducted for statistical assessment of our analyses. We compared IQR using a randomization test [19] with a Bonferroni correction for multiple tests. The interquartile range is the range of the middle 50% of the data or, more simply, the difference between the 75th percentile and the 25th percentile. This is judged to be a better measure of spread than the standard deviation when comparing values that may be skewed and with numerous outliers such as array gene expression data.

The randomization test comparing F/M gene fold ratios between X-linked and autosomal genes in the same tissue utilized natural pairing of the data during the randomization phase. We then reshuffled the F/M gene fold expression ratios for a random set of genes between the two gene datasets (X-linked and autosomal) and evaluated the ratio of the IQR. This was repeated 10,000 times and the actual ratio of IQR was compared to this distribution. If the actual ratio of IQR was well inside the set of randomized ratios of IQR, this would provide evidence that the result may be due to a sampling error. If instead, the actual ratio of IQR was well outside the distribution of randomized ratios of IQR, then a sampling error was unlikely. The estimated p values from the randomization test were the result of counting the number of randomized ratios of IQR that were more extreme than the actual ratio of IQR and that number was then divided by 10,000. In addition, a Bonferroni-adjusted p value was calculated by multiplying the randomization p value by 11, the number of possible pair-wise comparisons. All statistical calculations used R software version 2.2 [20].

Acknowledgments

We thank Javed Khan (National Cancer Institute) and his colleagues for kindly providing access to their gene expression database. We also thank Douglas C. Bittel (CMH) for helpful discussion during the preparation of the manuscript. Partial funding support for this study was from a Children's Mercy Hospital Physician Scientist Award (01.3905) and the Cure Autism Now Foundation (01.3956).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ygeno.2006.07.016.

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