Whole Transcriptome Analysis Reveals Gene Expression Differences Between Sexes, Possible Sex Specific Regulation and Contribution to Differential Disease Prevalence Between Sexes

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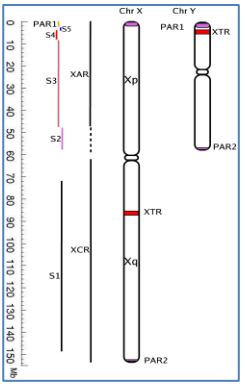
Background and aims

Although sex is often not taken into account in the genetic studies of human diseases, sex is known to play a role in affecting disease risk, prevalence, severity and subtype. An intermediate phenotype that may help us elucidate gender based differences is gene expression, and we used whole transcriptome data to comprehensively investigate gender based gene expression differences.

Methods

Using RNA seq gene expression data from a lymphoblastoid cell line, we tested for gene expression differences between sexes on 216 males and 246 females. As one mechanism of differentially expressed genes is X inactivation, we investigated whether the differentially expressed genes on the X chromosome tend to be genes that have escaped X inactivation. As another possible mechanism of differential gene expression is differential regulation between sexes, we investigated whether differentially expressed genes (DEGs) are also sex specific expression quantitative trait loci (sex specific eQTLs). Lastly, we performed pathway analysis on DEGs to test for enrichment of these DEGs in known disease gene sets.



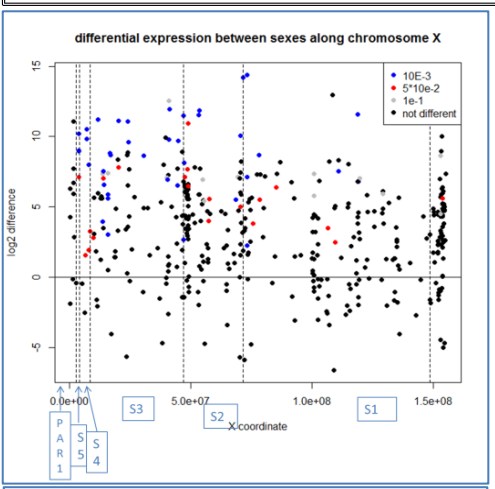


Fig 1. Gene expression differences between sexes, colored by the p value for significance of difference. If a gene undergoes X inactivation, then it would reach similar expression value in male and females. More differential gene expression occur near the older strata, co-located with more genes that have escaped X inactivation, implying X inactivation as a main mechanism for differential gene expression on the X chromosome.

Results and Conclusion

- One thousand sixty six differentially expressed genes between sexes were found throughout both autosomes and sex chromosomes (pvalue adjusted <0.05).
- In general, differentially expressed genes on the X chromosome tended to be genes that have escaped X inactivation or located near genes that have escaped X inactivation.
- Some genes appeared to be regulated in a sex specific manner as they presented as sex specific eQTLs.
- Pathway analysis revealed that diseases that were previously known to have different disease prevalence between sexes also showed signs of having enrichment of genes that were differentially expressed between sexes. These pathways and diseases include: Systemic lupus erythematosus (SLE), serotonergic receptor, prostate cancer, breast cancer.

Table 1: Top 5 sex specific expression quantitative trait (eQTLs) from Dimas et al. matched to differentially expressed genes by sex (DEG) in current dataset.

rs_ID	-log10(pvalue) for eQTL	% FDR	Population source	ENSEMBL	SYMBOL	MALE expression (RPKM)	FEMALE expression (RPKM)	Log2 fold difference in gene expression	Multiple test corrected Pvalue for DEG	Chr	Coord
rs2872507	5.963	17	CEU_F	ENSG00000186075	ZPBP2	63.778	43.61	-0.5484	2.15E-11	17	38024469
rs7201780	9.6329	14	CHB_F	ENSG00000102882	MAPK3	1424.352	1587.13	0.156115	0.000293	16	30134827
rs11673399	7.5078	13	JPT_M	ENSG00000104946	TBC1D17	904.139	1007.419	0.156047	0.00414	19	50380682
rs1683570	8.053	14	CHB_F	ENSG00000175221	MED16	1619.75	1874.02	0.210365	0.006485	19	893218
rs1683570	6.164	13	JPT_M	ENSG00000175221	MED16	1619.75	1874.02	0.210365	0.006485	19	893218

References:

Dimas, A. S., et al. (2012). "Sex-biased genetic effects on gene regulation in humans." Genome research **22**(12): 2368-2375

Lappalainen, T., et al. (2013). "Transcriptome and genome sequencing uncovers functional variation in humans." Nature.