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Poster Submissions

Poster Title

Chromatin state patterns and sequence motif analysis at sex-biased transcription factor binding sites provide insights into the hierarchical regulation of sex-biased gene expression in mammalian liver

Authors and their Affiliation

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Please describe the extent of your work in this research

GMB carried out the computational analyses

Abstract Submission

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Would you like your abstract to be considered for an oral presentation (students and post docs only)?

No

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Chromatin state patterns and sequence motif analysis at sex-biased transcription factor binding sites provide insights into the hierarchical regulation of sex-biased gene expression in mammalian liver

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Sex differences in liver gene transcription are extensive and are regulated by the sex-differential stimulation of hepatocytes by male versus female plasma patterns of growth hormone (GH). These actions of GH are mediated by combinatorial interactions of several GH-responsive liver transcription factors (TFs), including STAT5 and HNF6, whose sex-biased binding to liver chromatin correlates strongly with the sex-biased expression of neighboring genes. Here, we examine the hypothesis that this sex-biased TF binding is determined by sex-differential chromatin accessibility in combination with sex-biased histone marks and sex-biased binding by cofactors. We used chromatin state maps based on chromatin accessibility and a set of 6 histone marks in male and female mouse liver to cluster sex-biased STAT5 and HNF6 binding sites according to the sex bias of their local chromatin state. Clusters comprised of a subset of sex-biased STAT5 and HNF6 sites were localized to genomic regions in a sex-differential chromatin state, notably, enhancer states in the sex where TF binding is stronger, and inactive or bivalent states in the sex where TF binding is weaker. Whereas the sex-biased STAT5 binding sites were often associated with sex-differences in chromatin accessibility, the sex-biased HNF6 binding sites were frequently associated with differences in chromatin state, without differences of chromatin accessibility. Further, a substantial fraction (58-64%) of sex-biased STAT5 binding is associated with an enhancer state in both male and female liver, in many cases with a sex bias in chromatin accessibility. However, with HNF6, only 20-34% of sex-biased binding is associated with an enhancer state in both male and female liver, and often without a sex bias in chromatin accessibility. Further, a subset (10-17%) of sex-biased STAT5 and HNF6 binding sites localized within enhancer states, and a subset of female-biased HNF6 sites (13%) localized within transcribed-like states and are not in regions of accessible chromatin. This association of sex-biased STAT5 and HNF6 binding at genomic regions in a sex-independent chromatin state suggests that factors other than chromatin accessibility and

local chromatin state can confer sex bias in TF binding. Sequence motifs differentially enriched near the sex-biased TF binding sites in a sex-independent chromatin state include binding sites for factors associated with chromatin opening, including GATA2 and TAL1 as potential collaborators of sex-biased STAT5 in male but not female liver, and the REST repressor associated with STAT5 in female liver but not male liver. Additionally, we identified the factor HOXO9 associated with both STAT5 and HNF6 in male but not female liver, and LHX3, SOX5, FOXI1 in association with STAT5 in male liver only, which are factors associated with binding at pre-existing accessible chromatin states. These findings highlight the utility of using chromatin marks to identify functional genomic elements, and provide insights into the hierarchy of TF binding interactions that mediate sex-specific gene regulation in mouse liver. *Supported in part by NIH grant DK33765 (to DJW).*