Comparative Genomic Maps of Kidney Proximal Tubules and medullary Thick Ascending Limbs between Humans and Rats reveal Enrichment for Human Blood Pressure Associated Polymorphisms

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GWAS has identified >1,000 blood pressure (BP)-associated sentinel SNPs, most of which (>90%) are intronic and intergenic. How they regulate BP-relevant genes remains a critical question within the field. We hypothesized many SNPs would reside within *cis*-regulatory elements specific to nephron segments critical to sodium resorption such as proximal tubule (PT) and thick ascending limb (TAL). To address this hypothesis, we developed chromatin state (ATAC-seq) and transcriptome (RNA-seq) maps from manually dissected human and rat PT and medullary TAL (mTAL) segments. Half the identified chromatin-accessible regions were shared between these segments in both species. Interestingly, in humans the shared chromatin-accessible regions resided more frequently in promoters, whereas segment-unique open regions were more often found in distal introns or intergenic regions, suggesting they lie within enhancers. However, the majority of the chromatin-accessible regions in rats were enriched in the distal intergenic and intronic regions, and consistent with humans, a larger fraction of the shared open chromatin regions falls at the promoter compared to the segment-unique accessible regions (**Figure 1**). When comparing across species, the shared chromatin accessible regions between PT and mTAL showed the highest degree of overlap, with far lower overlap for segment-specific accessible regions. To better compare the accessible regions across species, we developed the JBrowser2 tool to visualize the integrated comparative genome view between humans and rats with their conserved epigenetic signatures. As an example, a BP-relevant locus, the intergenic region between *NPR3* and *TARS1* from both species is shown in **Figure 2**, which holds a statistically significant correlation with the ATAC-peaks intensity between humans and rats mTAL and PT.

We hypothesized these open regions would be enriched for BP-relevant SNPs. We curated 26,585 bp-associated SNPs and detected their enrichment of a significant fraction (approximately 4%) on the chromatin-accessible regions of mTAL and PT in humans and rats. In addition, half the segment-specific chromatin-accessible bpSNPs in rats were shared by their human counterparts (**Figure 3**). Thus, we conclude that these novel tissue-specific chromatin maps in both rats and humans can be used to identify potential mechanisms by which SNPs influence gene expression and BP. Additional studies will be needed to demonstrate both causality and molecular mechanisms.

Figure 1

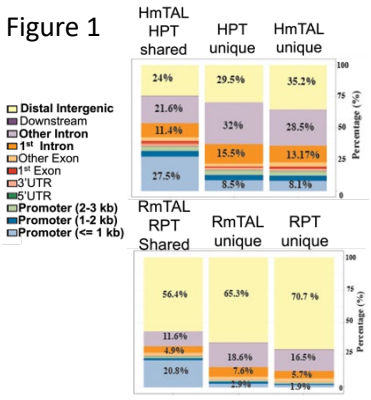

Figure 2

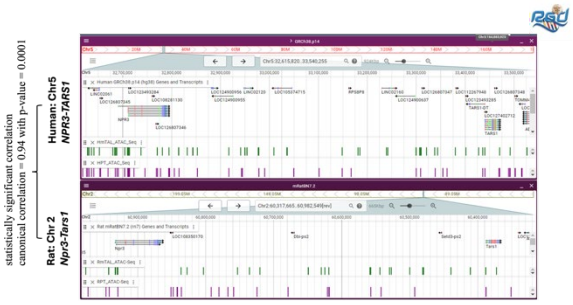

Figure 3