Chromatin accessibility analysis and architectural profiling of human kidneys reveal key cell types and a regulator of diabetic kidney disease

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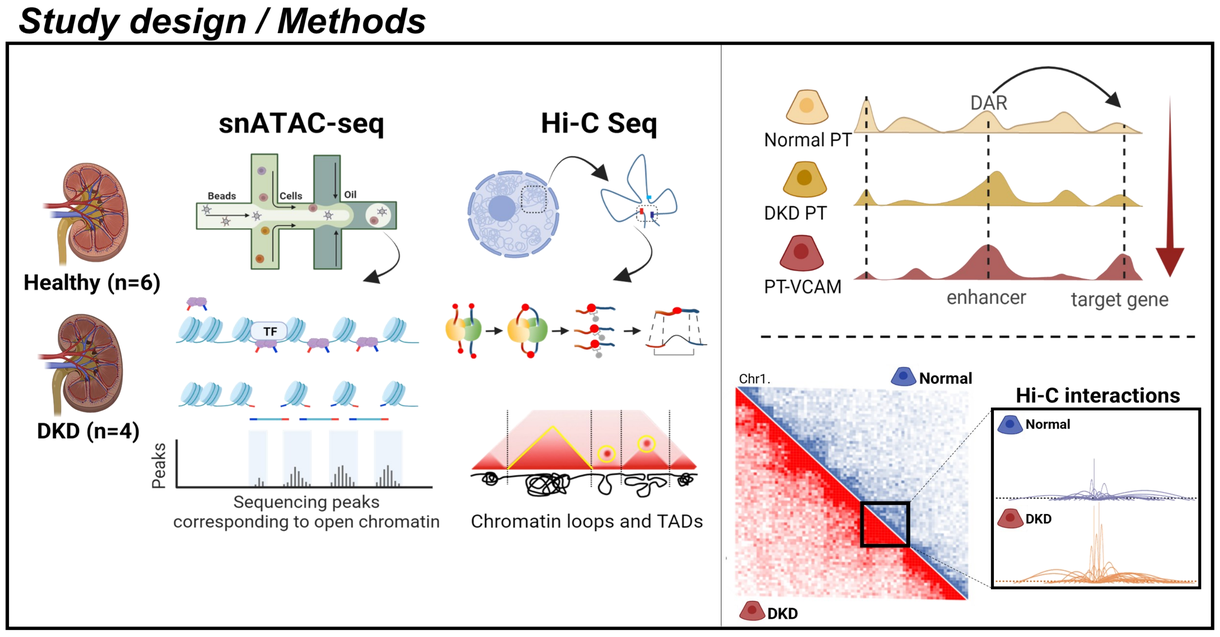
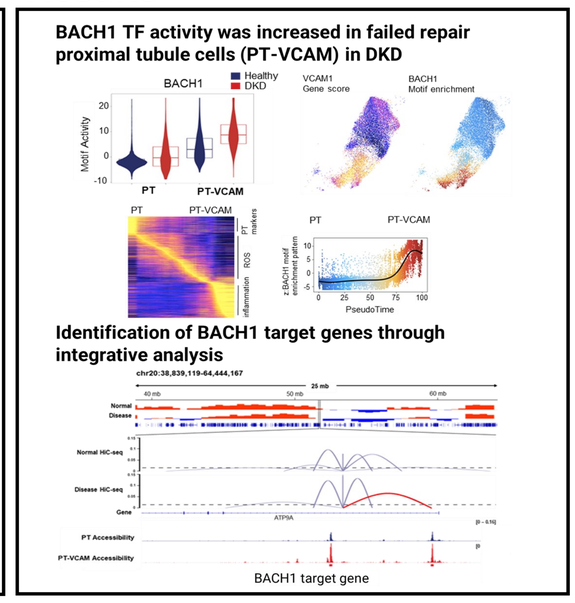
ABSTRACT

Diabetes is the leading cause of kidney disease that progresses to end-stage kidney disease. However, the key molecular and cellular pathways involved in diabetic kidney disease (DKD) pathogenesis are largely unknown. We performed a comparative analysis of adult human kidneys by examining single-nucleus chromatin accessibility by single-nucleus ATAC-seq (snATAC-seq) and analyzing three-dimensional chromatin architecture via Hi-C of paired samples. We mapped the cell type-specific and DKD-specific open chromatin landscape and found that genetic variants associated with kidney diseases were significantly enriched in the proximal tubule- (PT) and injured PT-specific open chromatin regions in DKD samples. BACH1 was identified as a core transcription factor of injured PT cells; its binding target genes were highly associated with fibrosis and inflammation, which were also key features of injured PT cells. In addition, Hi-C analysis revealed global chromatin architectural changes in DKD, accompanied by changes in local open chromatin patterns. Moreover, combining the snATAC-seq and Hi-C data identified direct target genes of BACH1, and indicated that BACH1 binding regions showed increased chromatin contact frequency with promoters of their target genes in DKD. Our multi-omics analysis revealed BACH1 target genes in injured PTs and highlighted the role of BACH1 as a novel regulator of tubular inflammation and fibrosis. Our findings will help identify novel genes and cellular pathways involved in the development of DKD and offer new clinical insights.

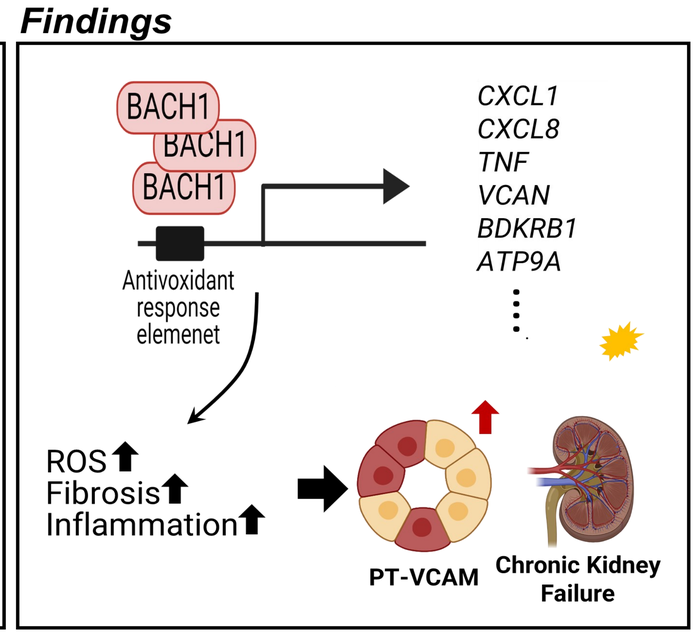
Study design / Methods



Results



Findings



RESULT

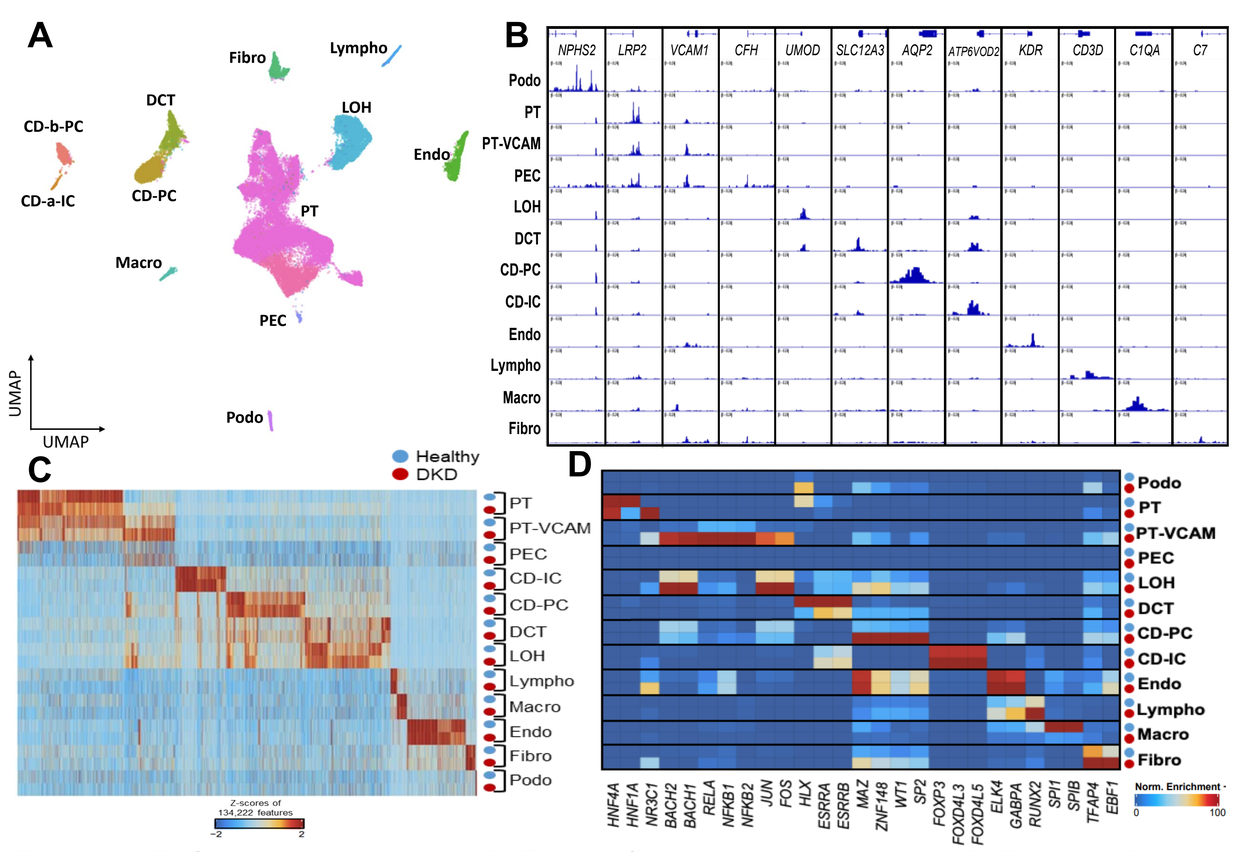


Fig 1. snATAC-seq clustering and DKD specific epigenetic changes. **A**. The UMAP plot displays 12 major cell clusters in kidney tissue. **B**. Genome browser shows accessibilities of marker genes. **C** and **D**. The heatmaps illustrates differential accessible regions (**C**), and Transcription Factors (**D**) for each cell types divided by conditions.

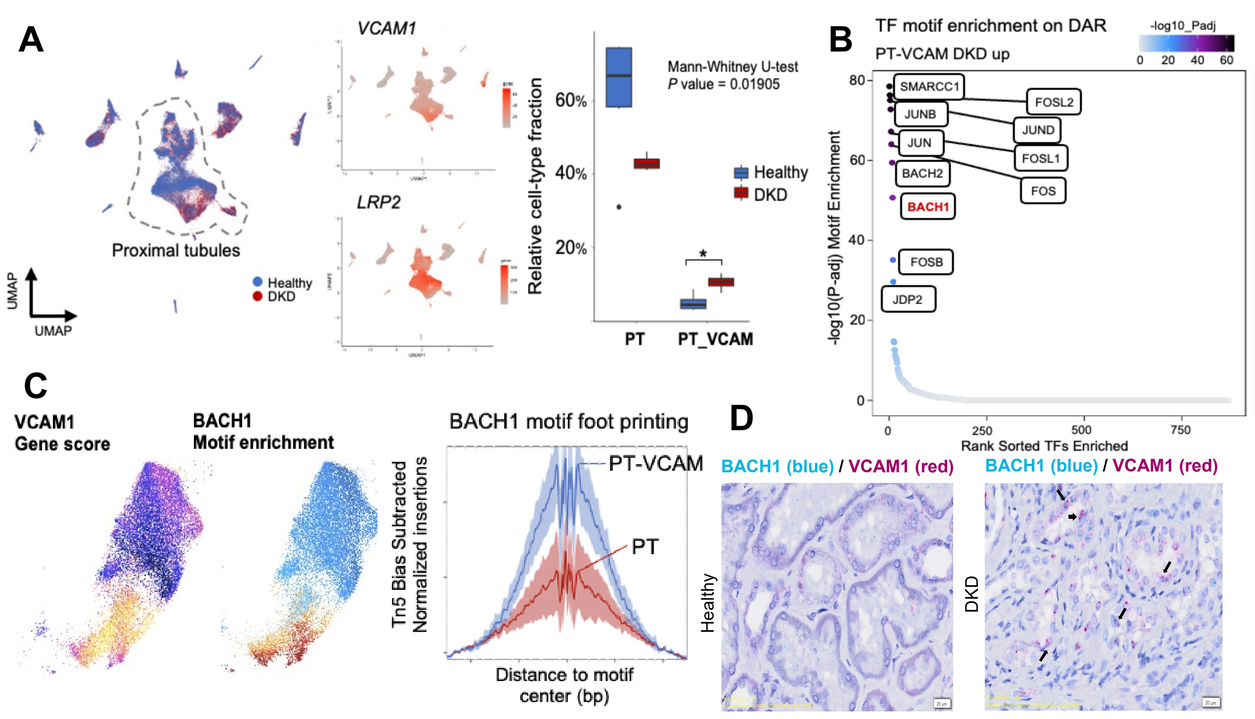


Fig 2. Identification of CKD associated proximal tubule subtype, PT-VCAM and its characterization. **A**. Distribution of condition and expressions of the kidney injury related genes nominated VCAM1 expressing proximal tubule subtype (PT-VCAM) and boxplot shows PT-VCAM is significantly enriched on the patients. **B** and **C**. Increased BACH1 TF activity (**B**) and gene expression (**C**) in PT-VCAM. **D**. Representative images show in situ hybridization of BACH1 (blue) and VCAM1 (red) in both healthy and DKD samples.

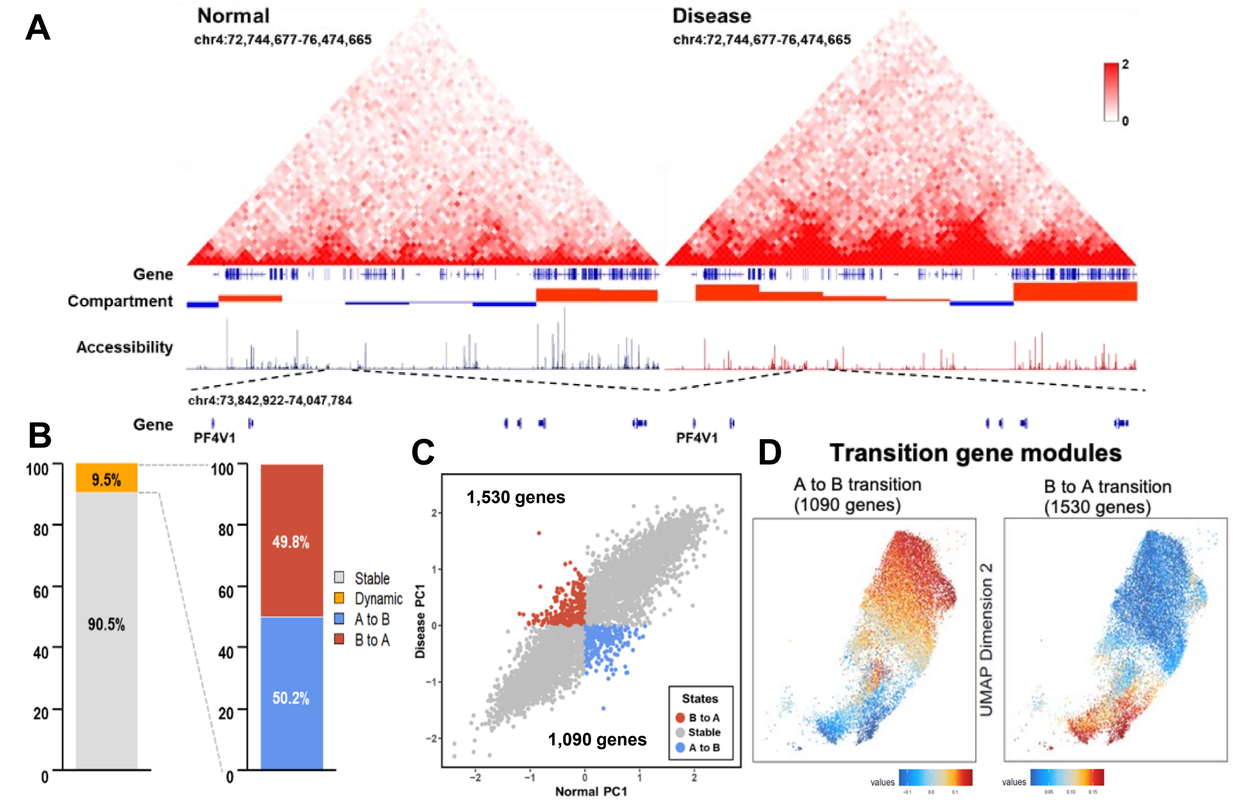


Fig 3. Chromatin conformation changes in kidneys are associated with cell state and chromatin accessibility. **A** Triangular contact heatmap showing large-scale chromatin interaction change for each conditions **B**. Distribution plot of compartment changes from normal to DKD samples. **C**. Scatter plot showing the genes located in the DKD compartment transition regions. **D**. Feature plots showing the snATAC-seq gene module scores of genes in the transient compartments for each samples.

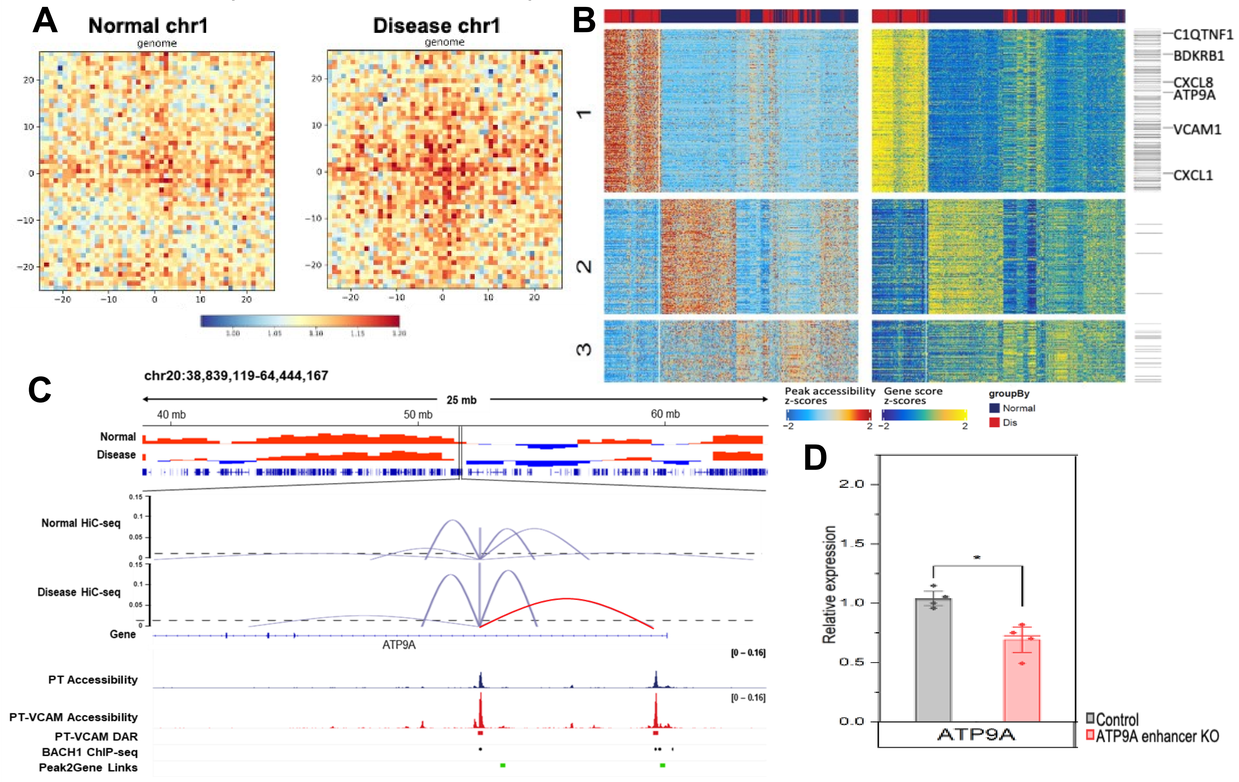


Fig 4. Chromatin accessibility analysis and architectural profiling reveal changes in BACH1 activity in DKD. **A**. Heatmaps showing the contact frequency from the BACH1 binding site. **B**. Correlation heatmap showing peak-to-gene links of BACH1 target genes. **C** Genome browser showing the Hi-C contact link and chromatin accessibility of BACH1 target genes, *ATP9A*. **D**. Boxplot showing *ATP9A* expression levels in control and enhancer-knockout cells.

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