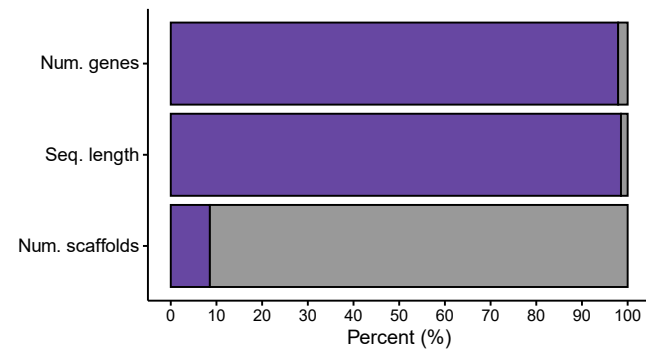
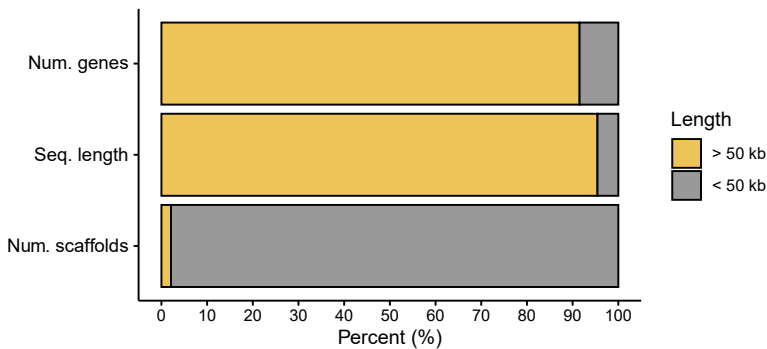
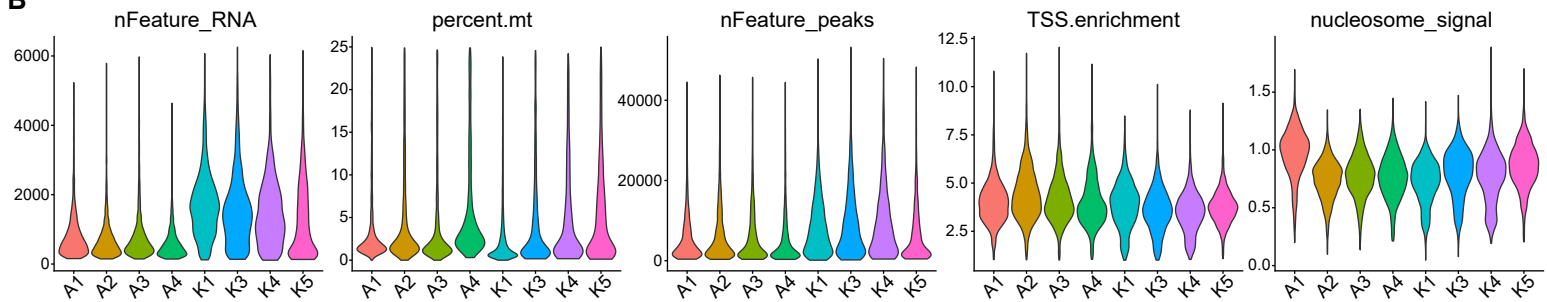
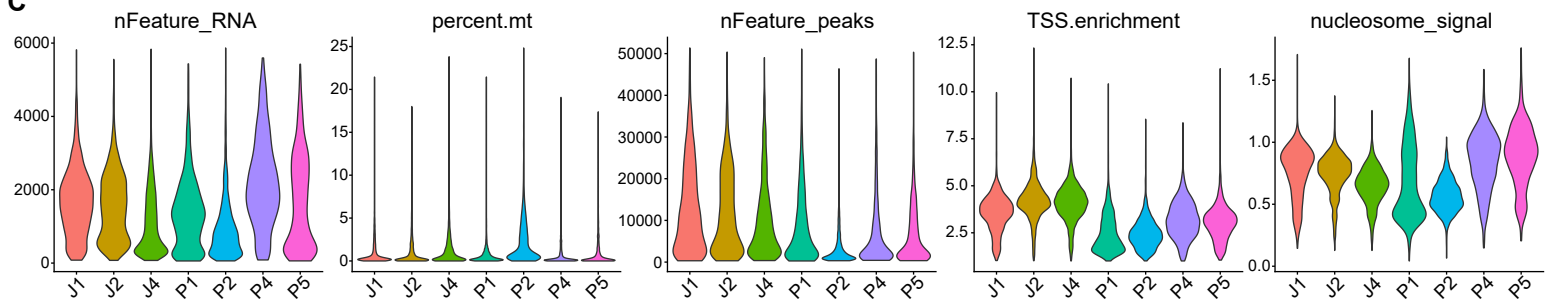
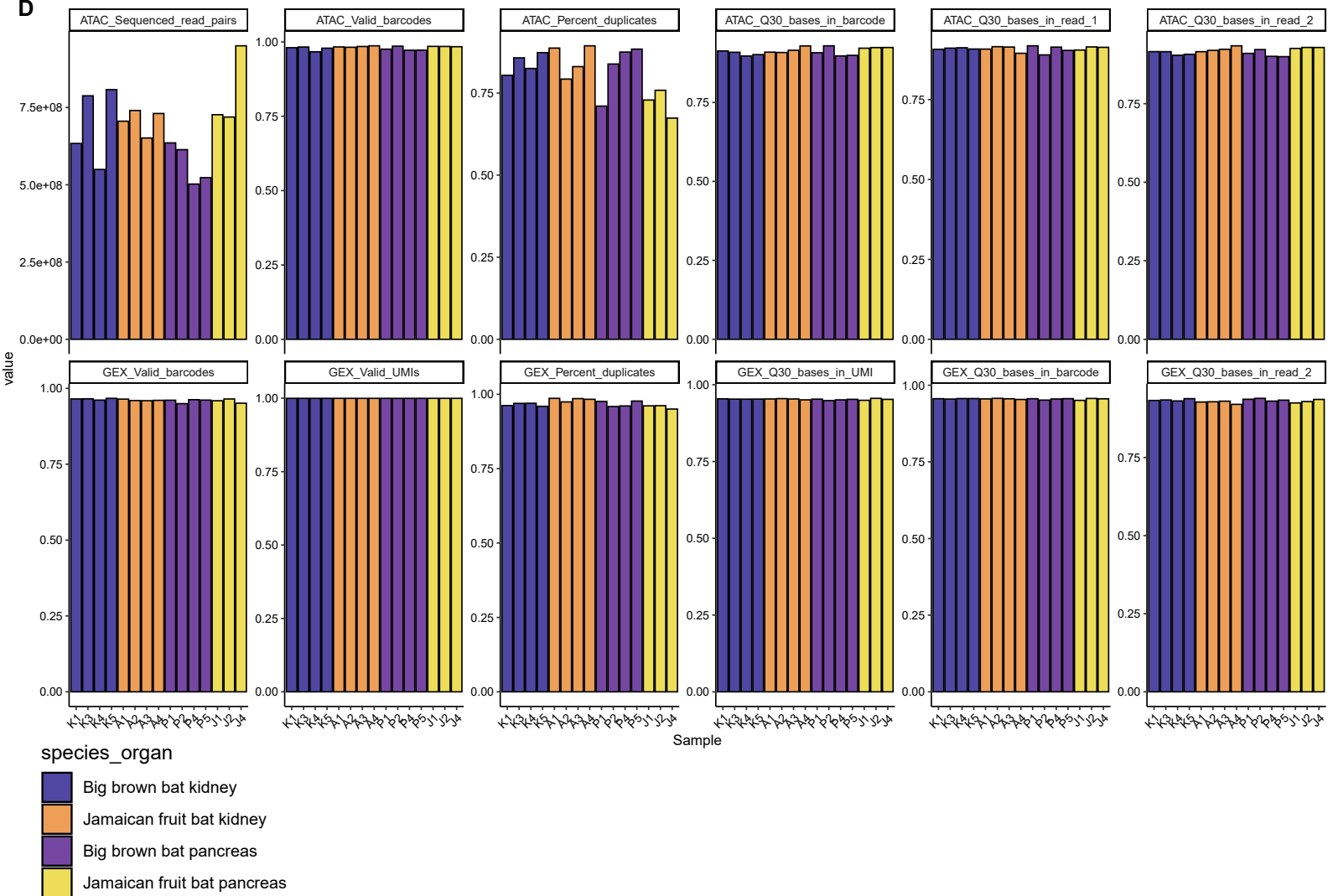
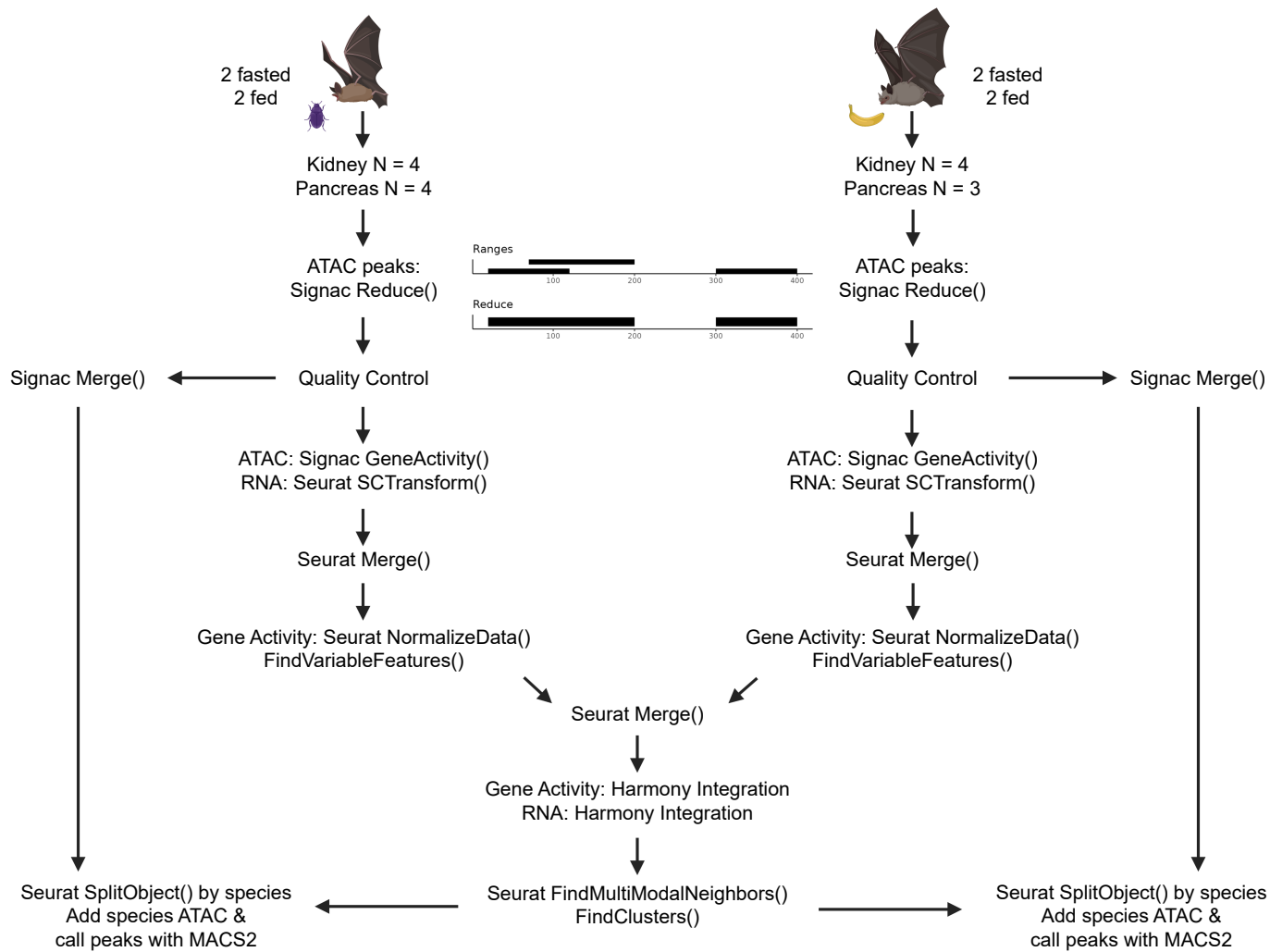


A*E. Fuscus* Genome*A. Jamaicensis* Genome**B****C****D**

Supplementary Fig.1: Joint scRNA and scATAC design and processing in bat tissues.

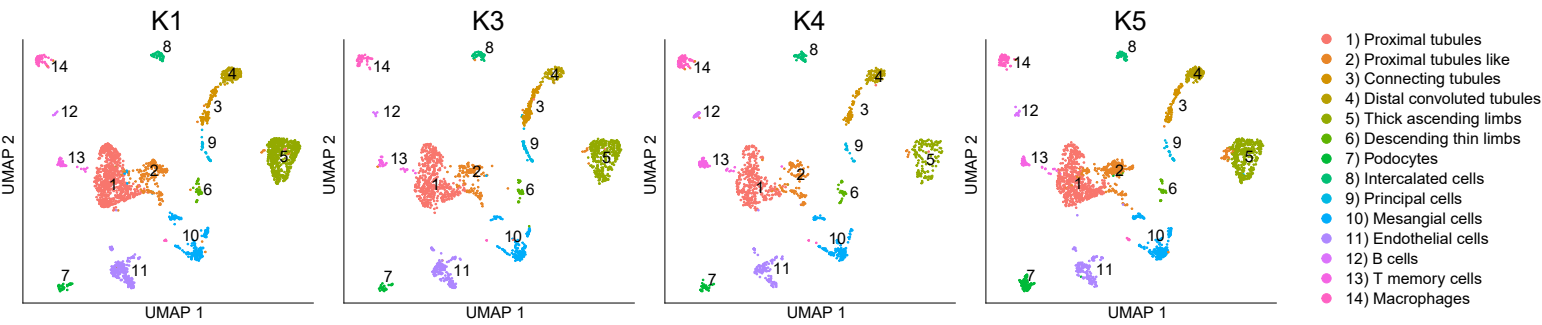
a, Bar chart showing that the number of genes and the genome sequence length captured by the number of scaffolds > 50 kb is > 90% for both bat genomes used in this study. **b-d**, QC metrics for single-cell multiome on bat kidneys and pancreases. A1-2 = fasted Jamaican fruit (JF) bat kidneys, A3-4 = treated Jamaican fruit (JF) bat kidneys, K1-3 = treated big brown (BB) bat kidneys, K4-5 = fasted big brown (BB) bat kidneys, J1-2 = fasted Jamaican fruit (JF) bat pancreases, J4= treated Jamaican fruit (JF) bat pancreas, P1-2 = treated big brown (BB) bat pancreases, P4-5 = fasted big brown (BB) bat pancreases. **b-c**) Violin plots of QC metrics Num. RNA features (nFeature_RNA), mitochondrial percentage (percent.mt), Num. ATAC features (nFeature_peaks), transcription start site enrichment (TSS.enrichment), and nucleosome signal **d**, Bar plots of QC metrics in **Supplementary Data 1**.



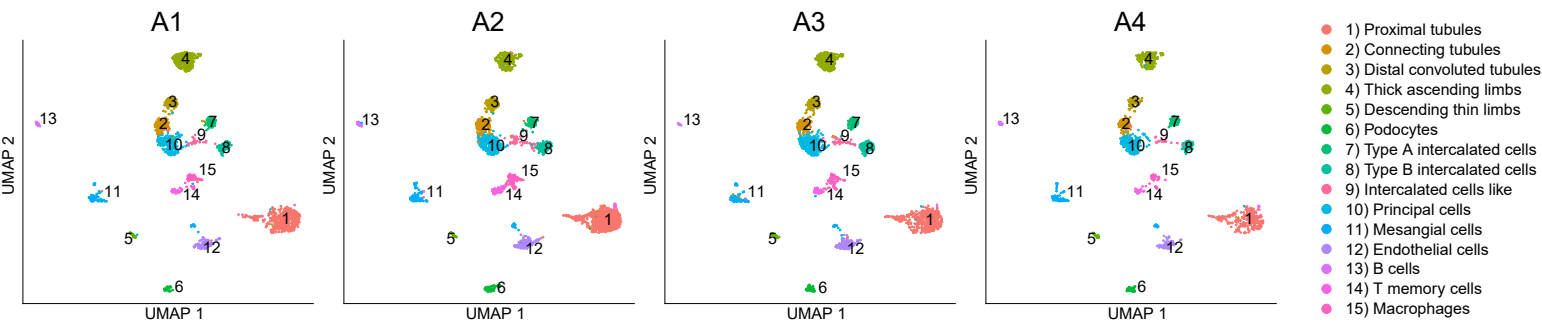
Supplementary Fig.2: Schematic for cross species integration of multi-omic data.

E. fuscus denoted by big brown (BB) bat on the left, and *A. jamaicensis* denoted by Jamaican fruit (JF) bat on the right (ranges and reduce image adapted from Signac¹; created with BioRender.com).

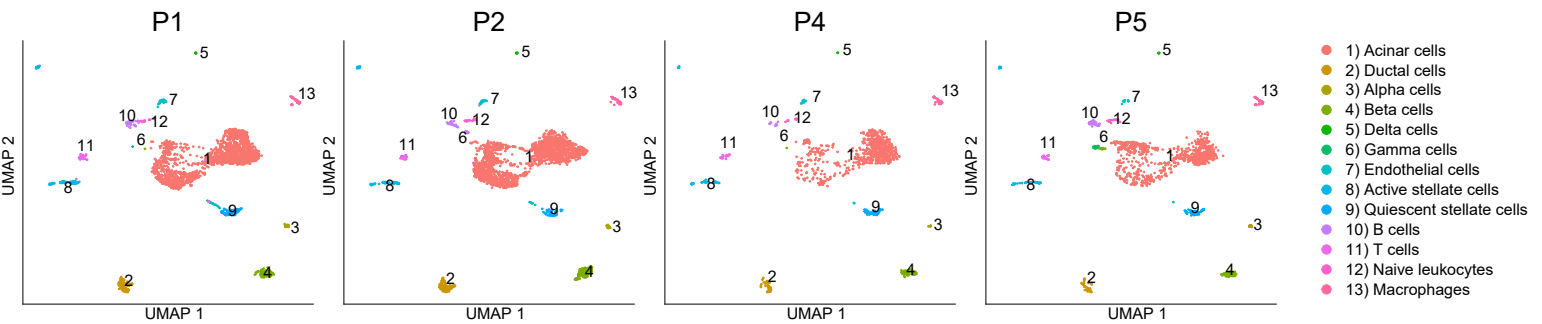
Big brown bat kidney



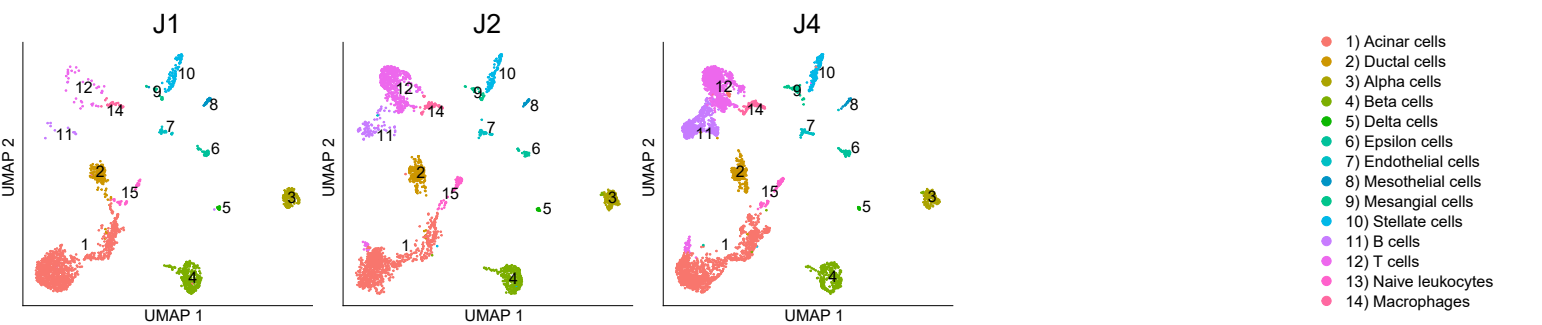
Jamaican fruit bat kidney



Big brown bat pancreas



Jamaican fruit bat pancreas

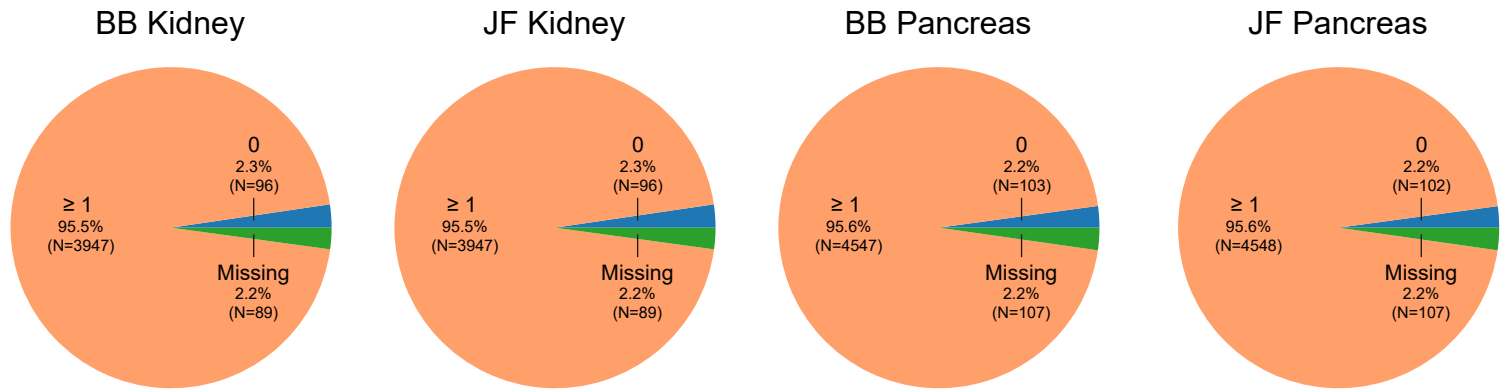


Supplementary Fig.3: Cell-type annotations across samples within each tissue of each species.

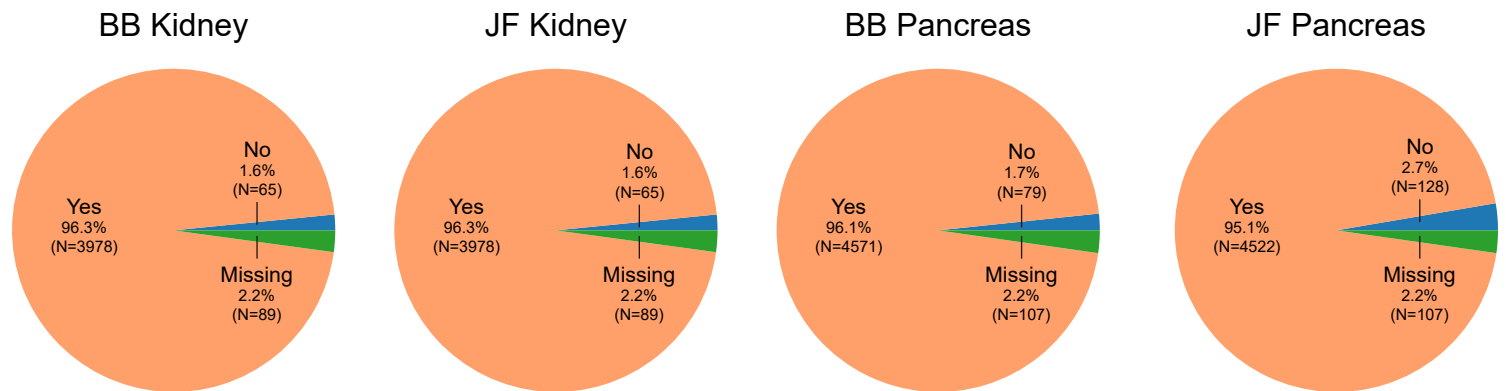
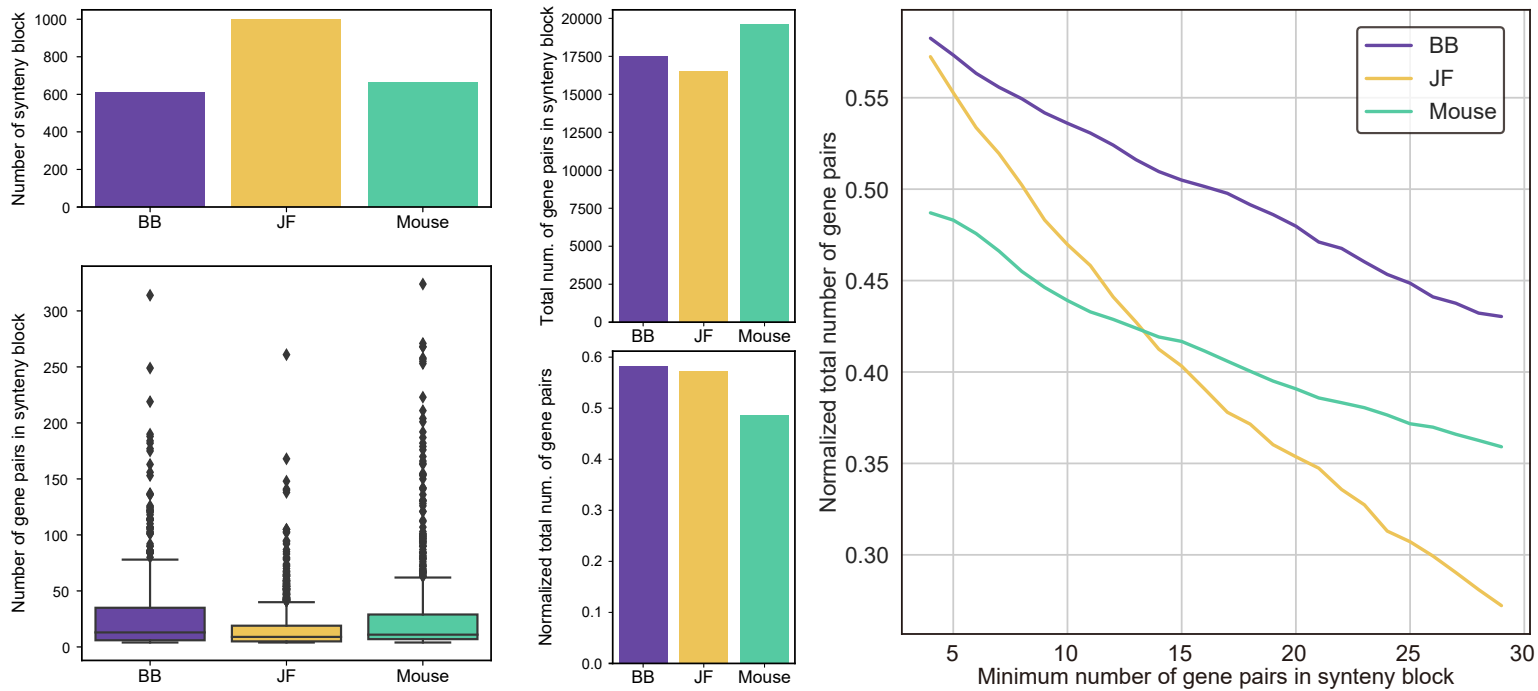
K1-3 = treated big brown (BB) bat kidneys, K4-5 = fasted big brown (BB) bat kidneys, A1-2 = fasted Jamaican fruit (JF) bat kidneys, A3-4 = treated Jamaican fruit (JF) bat kidneys, P1-2 = treated big brown (BB) bat pancreases, P4-5 = fasted big brown (BB) bat pancreases, J1-2 = fasted Jamaican fruit (JF) bat pancreases, J4= treated Jamaican fruit (JF) bat pancreas.

A

Predicted ortholog
TOGA DEG orthologs
(ref: hg38)

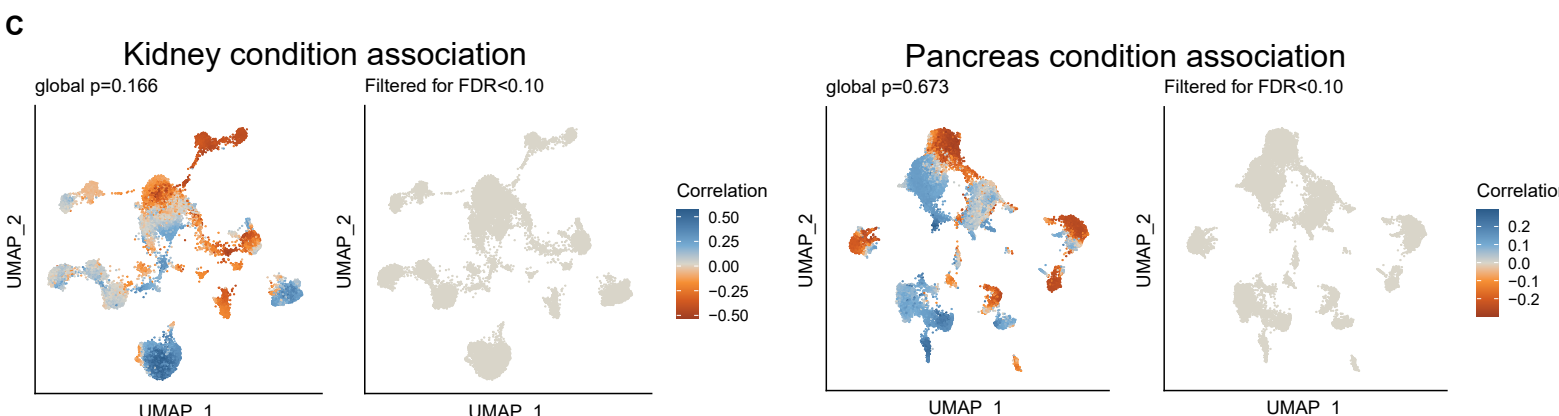
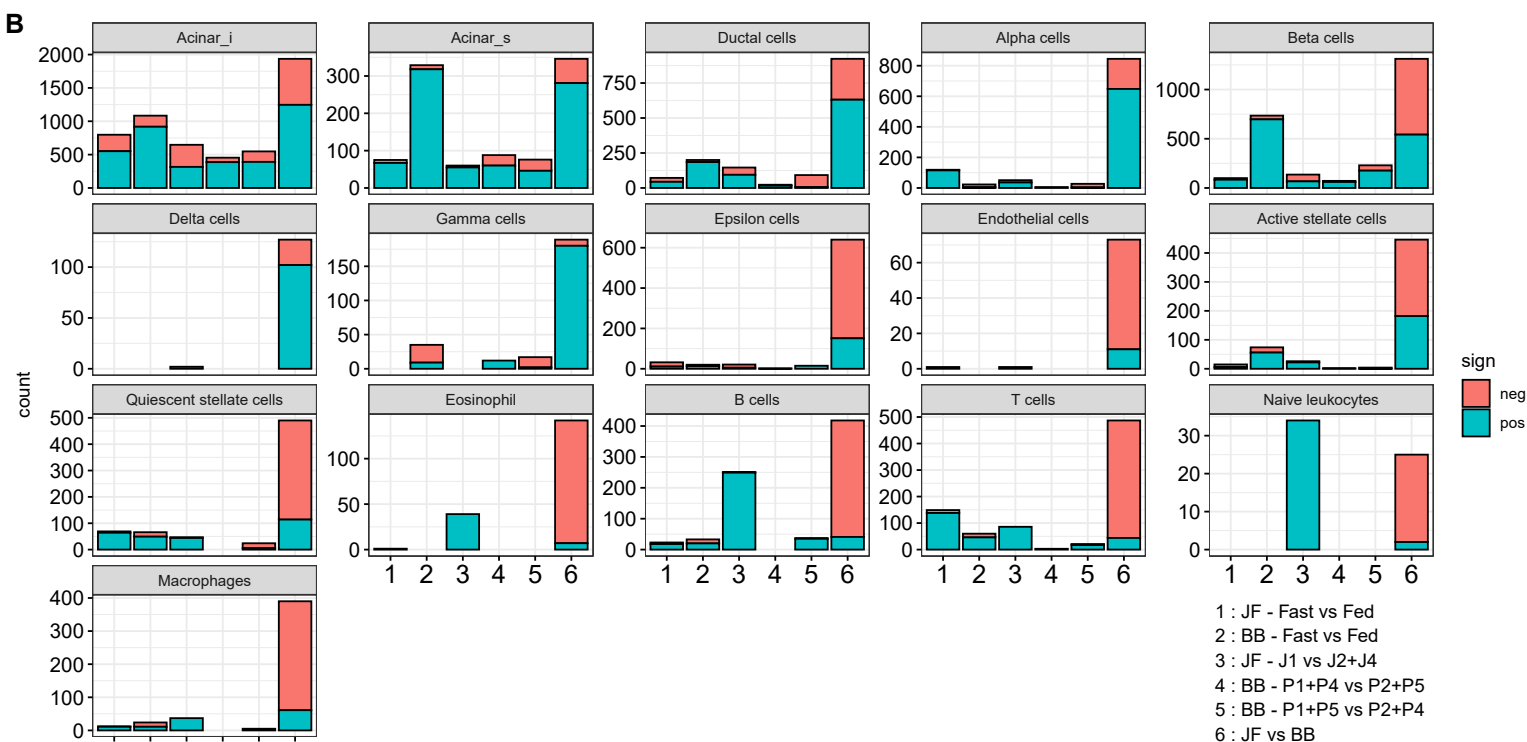
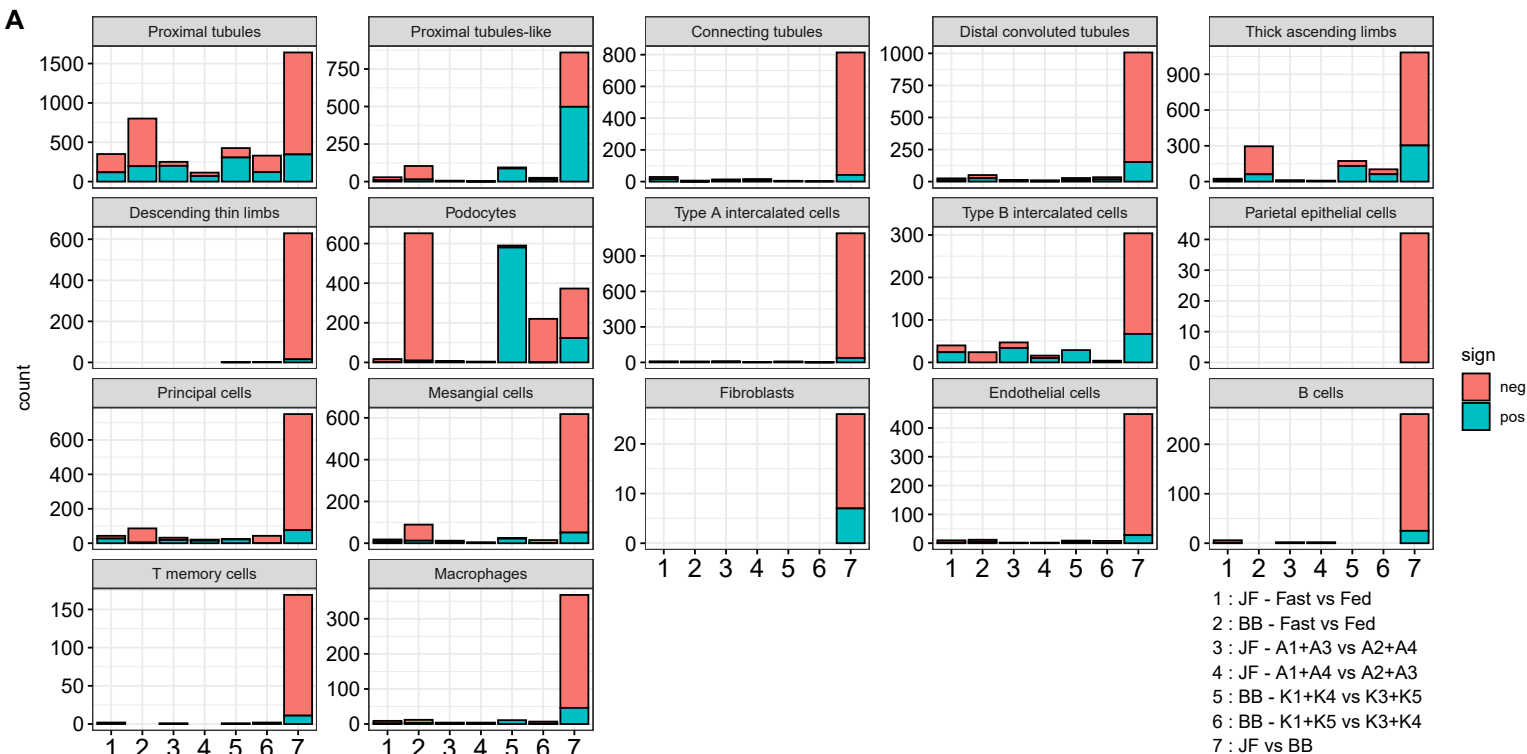
**B**

Intact/partially intact transcript
TOGA DEG orthologs
(ref: hg38)

**C**

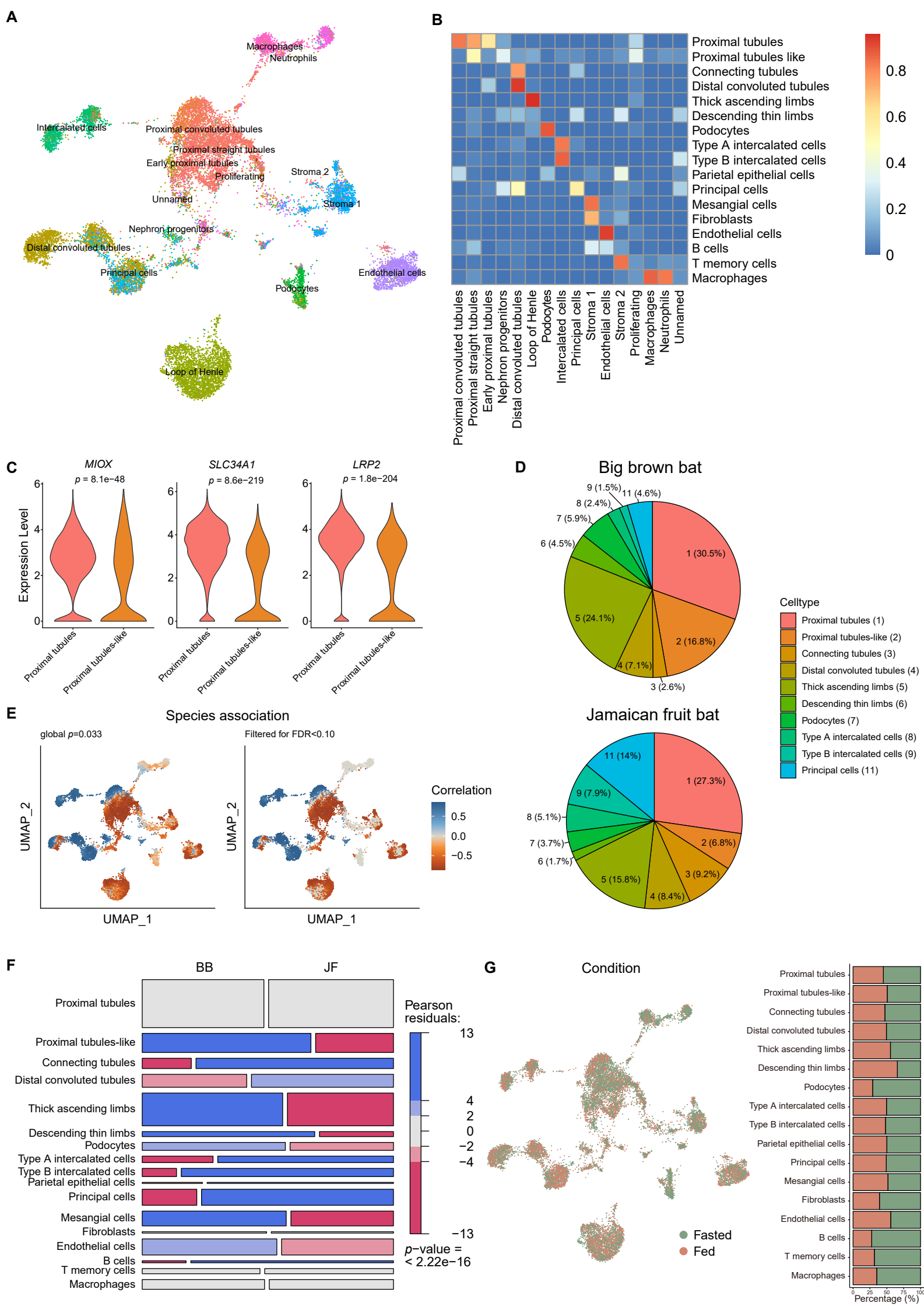
Supplementary Fig.4: Evaluation of gene orthology and synteny between bats and humans.

a, Number of differentially expressed genes between bats in each tissue that were predicted by TOGA² to have ≥ 1 human orthologs, 0 human orthologs, or no prediction (“Missing”). b, Number of differentially expressed genes between bats in each tissue that were predicted by TOGA² to have at least one human orthologous transcript that is intact or partially intact (“Yes”), not intact or partially intact (“No”), or no prediction (“Missing”). c, (Left) Number of synteny blocks and number of gene pairs in synteny blocks between each genome and human detected by MCscan³ (see Methods). (Middle) Total number of gene pairs in synteny blocks and normalized total number of gene pairs in synteny blocks. (Right) Normalized total number of gene pairs by minimum number of gene pairs in synteny blocks. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels. Source data are provided as a **Source Data** file.



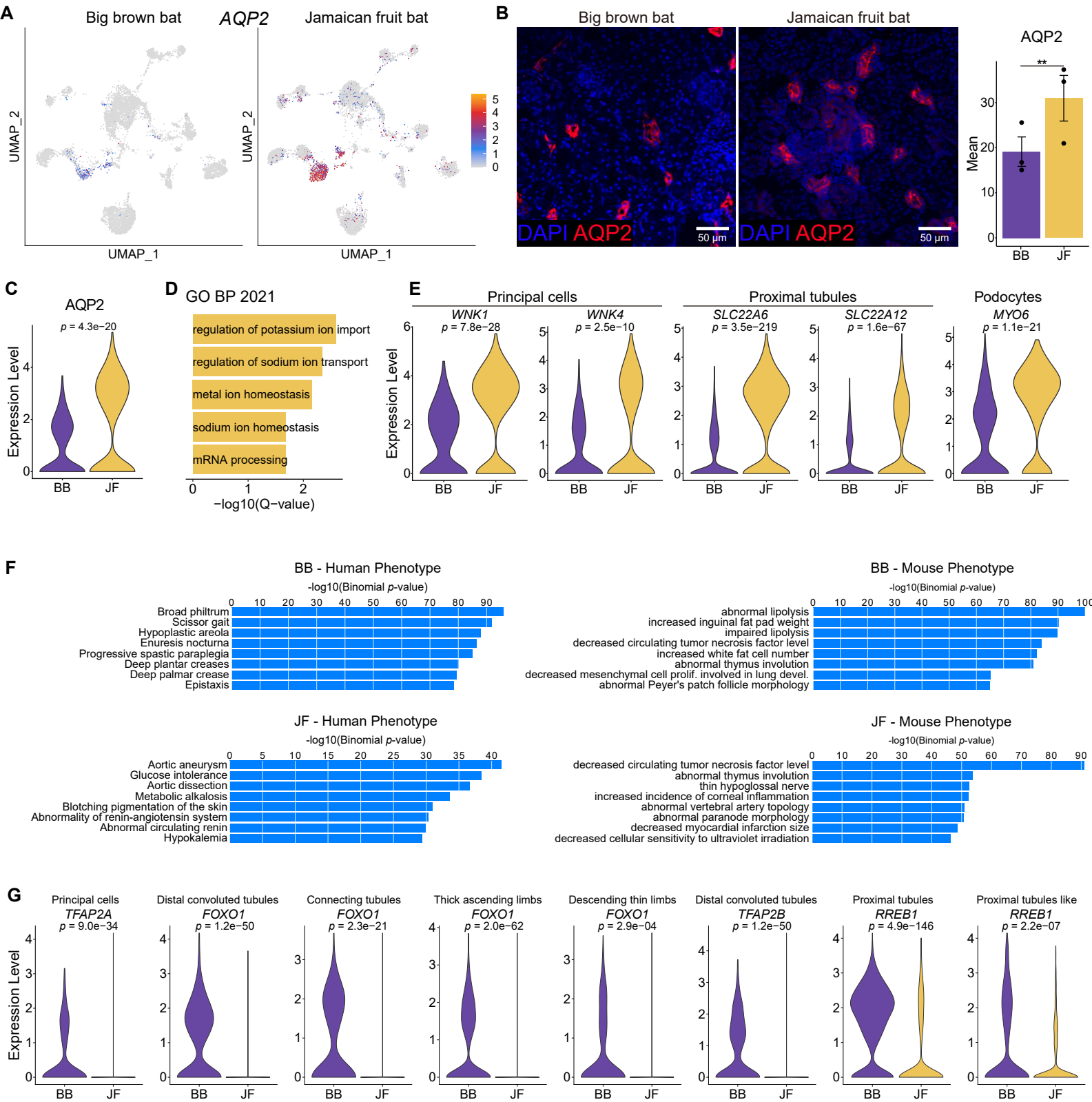
Supplementary Fig.5: Differential expressed gene (DEG) counts by condition and by species in bat kidney and pancreas.

a, Bar charts of DEG counts in bat kidneys (legend notation: pos. vs neg.). A1-2 = fasted Jamaican fruit (JF) bats, A3-4 = treated Jamaican fruit (JF) bats, K1-3 = treated big brown (BB) bats, K4-5 = fasted big brown (BB) bats. (B) Bar charts of DEG counts in bat pancreases (legend notation: pos. vs neg.). J1-2 = fasted Jamaican fruit (JF) bats, J4= treated Jamaican fruit (JF) bats, P1-2 = treated big brown (BB) bats, P4-5 = fasted big brown (BB) bats. (C) (Left) CNA of condition associations to cell-types in bat kidney. (Right) CNA of condition associations to cell-types in bat pancreas. Global p -value calculated with permutation in CNA package. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels.



Supplementary Fig.6: Single-cell composition analysis of bat kidney.

a, UMAP of bat kidney cell-types automatically annotated with mouse kidney single-cell reference data from Azimuth⁴. b, Overlap coefficients of auto-annotations in A (horizontal) with our integrated species annotations in Fig.1d (vertical). c, Violin plots of proximal tubule marker gene expression in bat proximal tubules and proximal tubules-like cells. *P*-values calculated with two-sided Wilcoxon rank-sum test and the Bonferroni correction. d, Pie charts of cell-type percentages across renal epithelial cells. e, CNA of species associations to cell-types. Global *p*-value calculated with permutation in CNA package. f, Pearson residuals visualized by mosaic plot of all cell-types identified in bat kidneys. *P*-value calculated with chi-square test. g, UMAP of bat kidney cell-types by condition. The bar chart shows the proportion of conditions for each cell-type. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels.

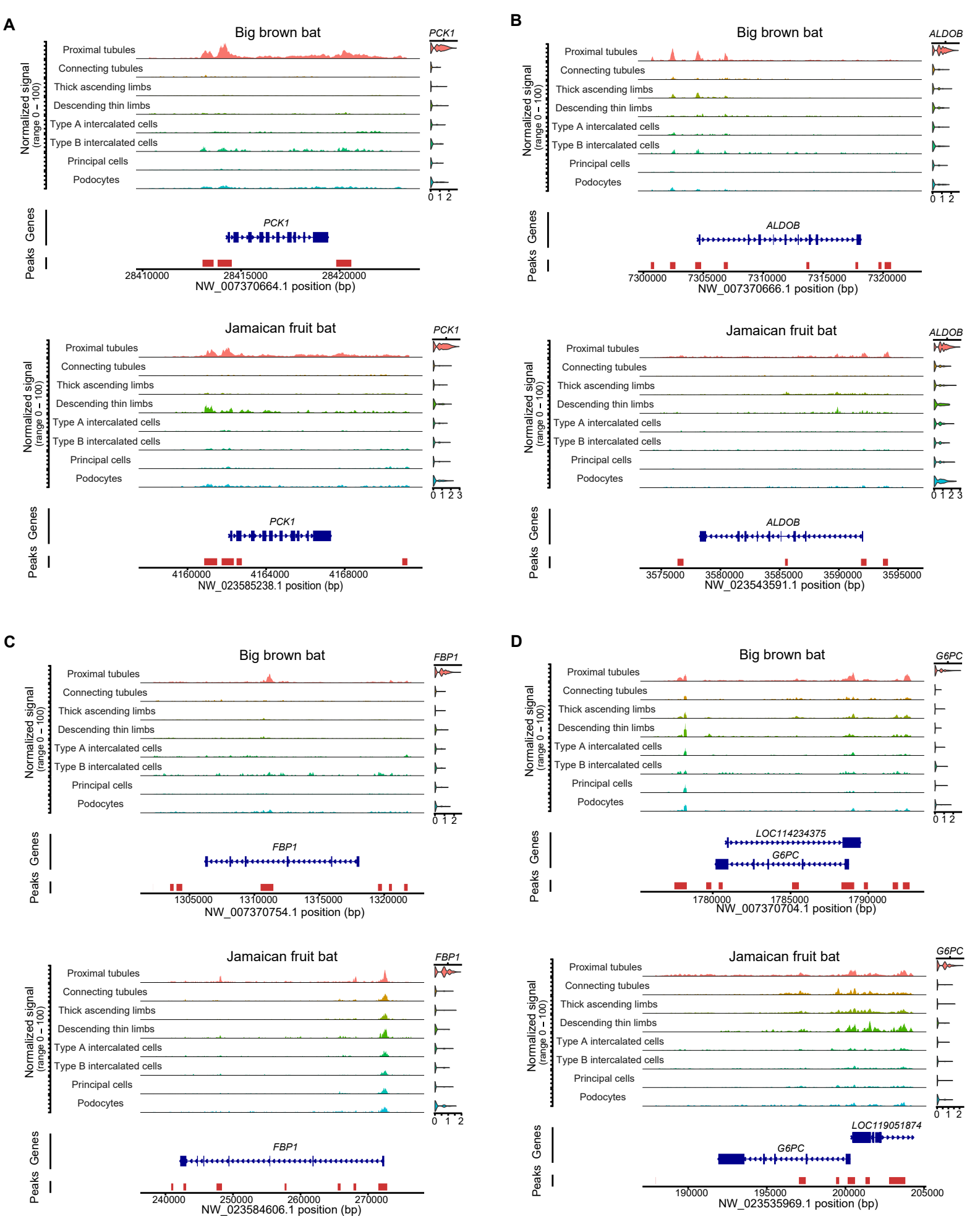


Supplementary Fig.7: scRNA-seq and scATAC-seq analysis of bat kidney.

a, UMAPs of principal cell marker gene *AQP2* expression in each species. b, (Left) Representative images of SLC26A4 immunofluorescence (red) in bat kidneys. Nuclei are stained with DAPI (blue). (Right) Quantification of AQP2 immunofluorescence normalized to nuclei in bat kidneys. Results represent arbitrary units of fluorescence (AU) mean $\pm$ standard error of the mean (SEM) derived from 3 big brown (BB) bats and 3 Jamaican fruit (JF) bats (n = 3/phenotype, n = 10 images/individual [see Methods]). Mixed effects model (two-sided) $**p$ -value = .001. c, Violin plot of *AQP2* expression in principal cells. *P*-values calculated with two-sided Wilcoxon rank-sum test and the Bonferroni correction. d, Bar plots showing GO Biological Process 2021 terms enriched in Jamaican fruit (JF) bat principal cells. *Q*-values calculated with one-sided Fisher's exact test and corrected with the Benjamini-Hochberg method. e, Violin plots of differentially expressed genes in bat kidney cells. *P*-values calculated with two-sided Wilcoxon rank-sum test and the Bonferroni correction. f, Bar plots showing GREAT human and mouse phenotypes enriched in big brown (BB) bat and Jamaican fruit (JF) bat kidneys. g, Violin plots of differentially expressed TFs in bat renal epithelial cells. *P*-values calculated with two-sided Wilcoxon rank-sum test and the Bonferroni correction. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels. Source data are provided as a **Source Data** file.

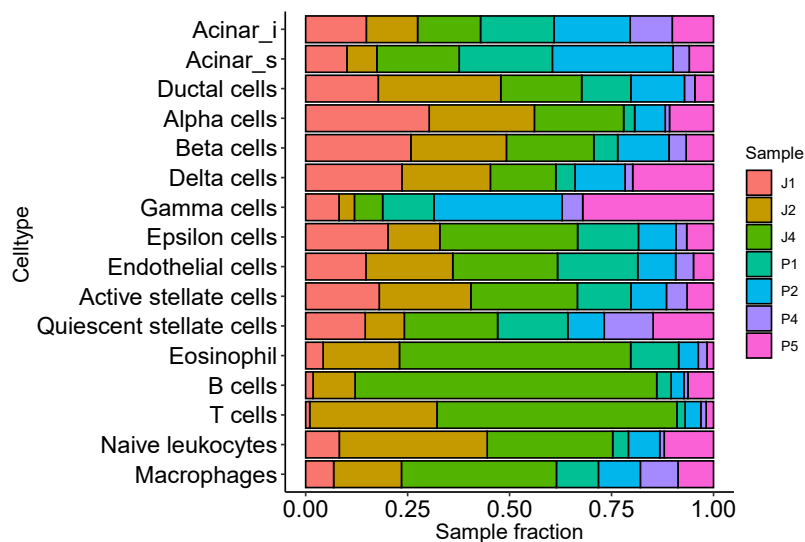
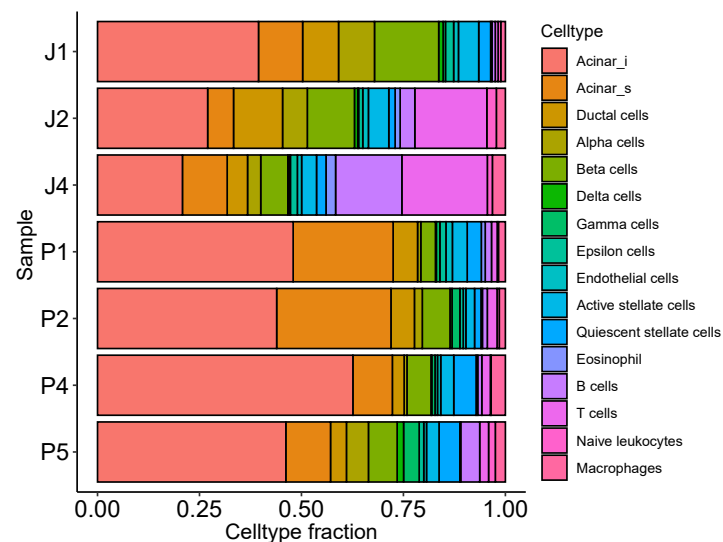
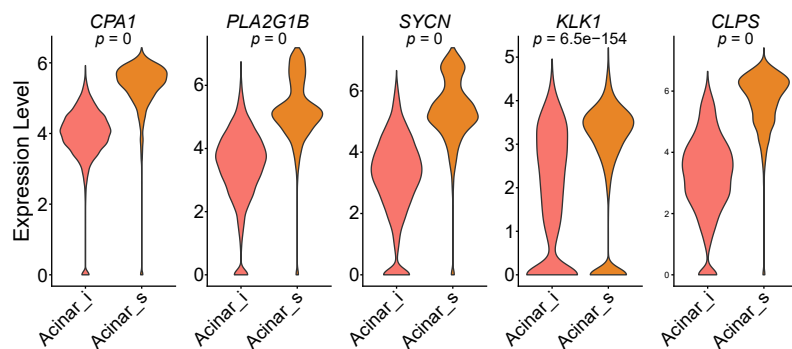
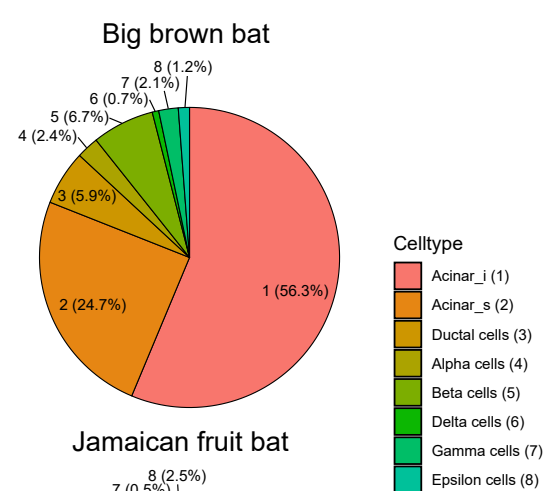
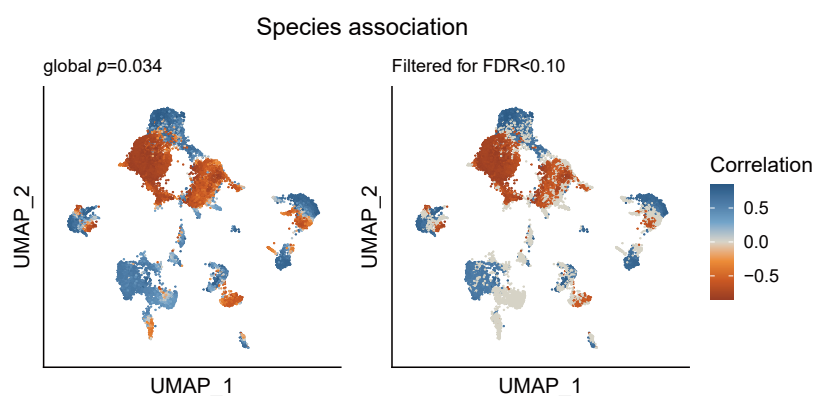
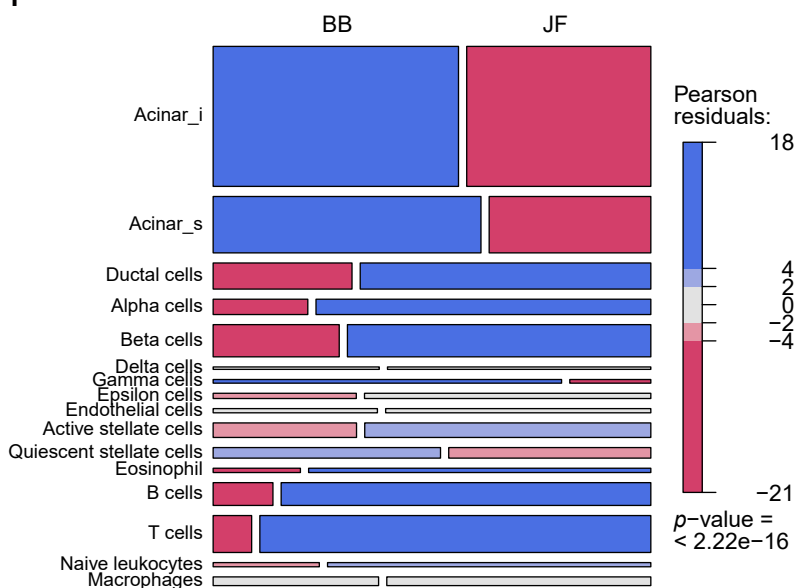
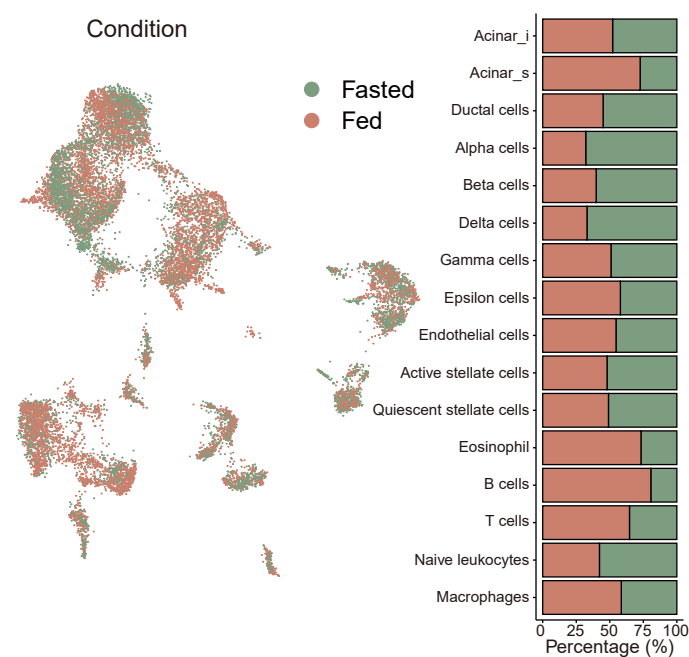
Supplementary Fig.8: Multi-omics GRN analyses of bat kidneys.

a, Big brown (BB) bat and Jamaican fruit (JF) bat GRNs determined by Pando⁵. b, Scatter plots of the percentile rank of species difference by the difference in percentile rank of strength centrality for all nodes (top) and shared nodes (bottom). c, Heatmap of enriched pathways in each species GRN. *Q*-values calculated with one-sided Fisher's exact test and corrected with the Benjamini-Hochberg method. d, *NR3C2* subnetworks in each species. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels. Source data are provided as a **Source Data** file.



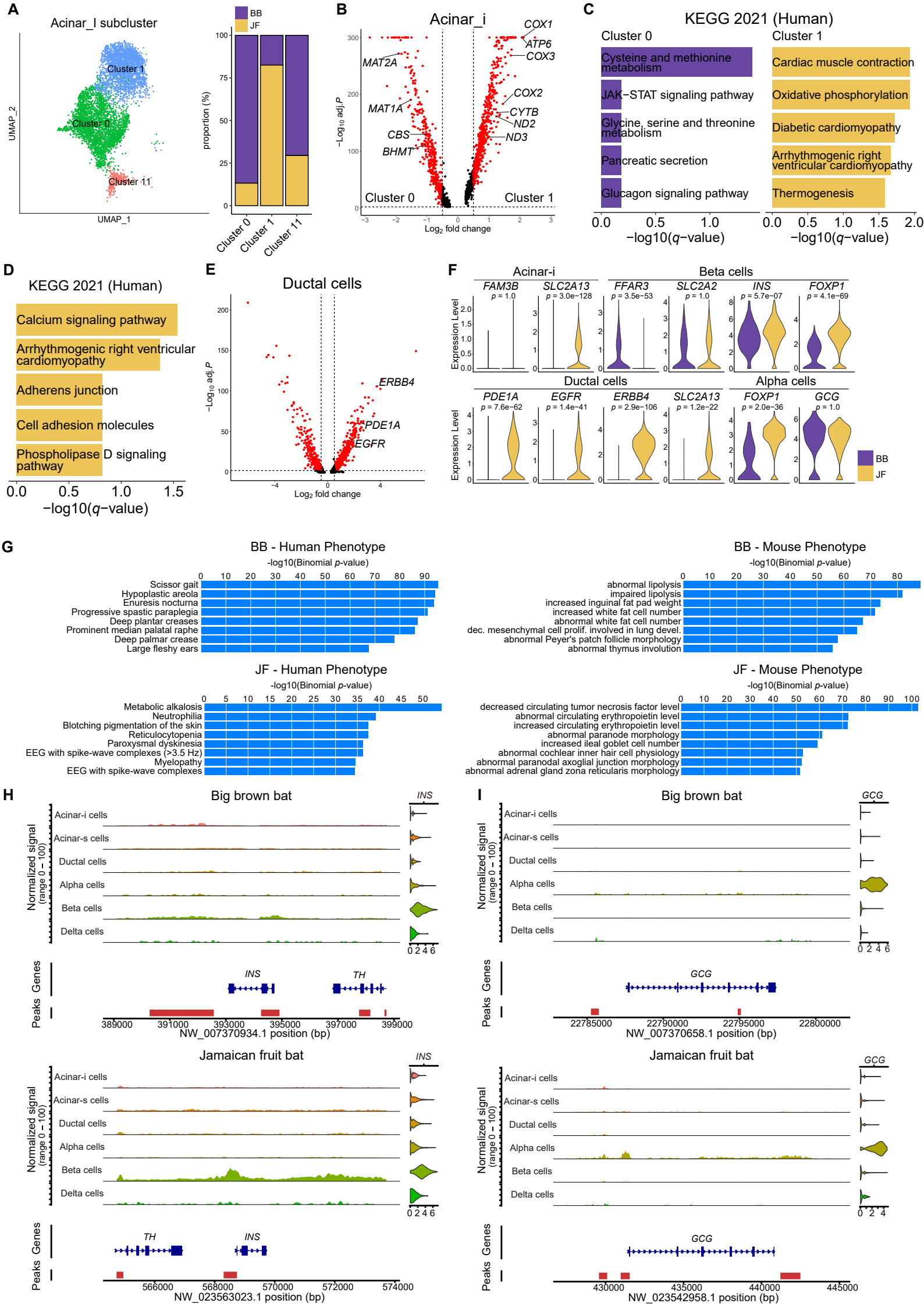
Supplementary Fig.9: scATAC-seq coverage plots of diabetes-associated genes in bat kidneys.

a-d, scATAC-seq coverage plots of *PCK1* (a), *ALDOB* (b), *FBP1* (b) and *G6PC* (d) in bat kidneys. SCTransform-normalized expression plot visualized on the right by cell-type.

A**B****C****D****E****F****G**

Supplementary Fig.10: Single-cell composition analysis of bat pancreas.

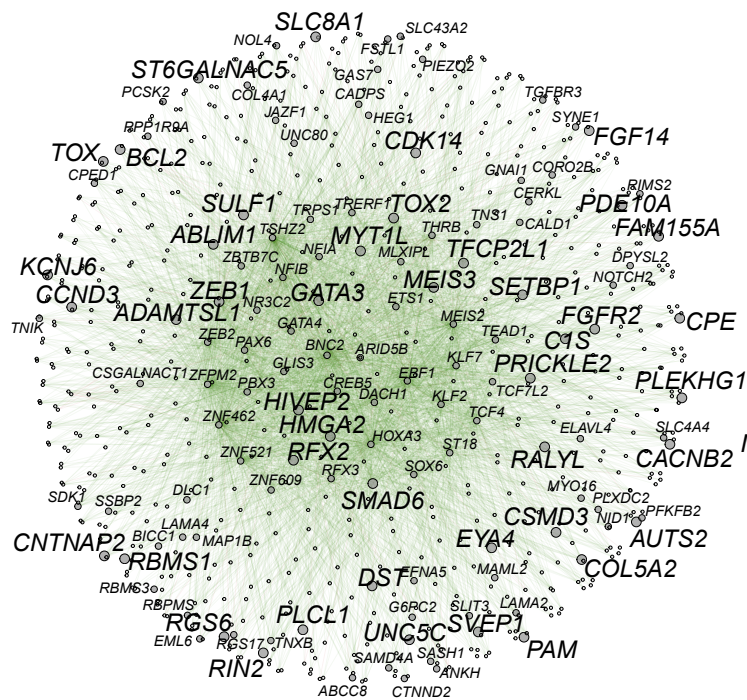
a-b, a) Sample fraction across cell-type and b) Cell-type fraction across samples. J1-2 = fasted Jamaican fruit (JF) bats, J4= treated Jamaican fruit (JF) bat, P1-2 = treated big brown (BB) bats, P4-5 = fasted big brown (BB) bats. c, Violin plots of proximal tubule marker gene expression in bat proximal tubules and proximal tubules-like cells. d, Pie charts of cell-type percentages across renal epithelial cells. e, CNA of species associations to cell-types. Global p -value calculated with permutation in CNA package. f, Pearson residuals visualized by mosaic plot of all cell-types identified in bat pancreases. P -value calculated with chi-square test. g, UMAP of bat pancreases cell-types by condition. Bar chart shows the proportion per condition for each cell-type. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels.



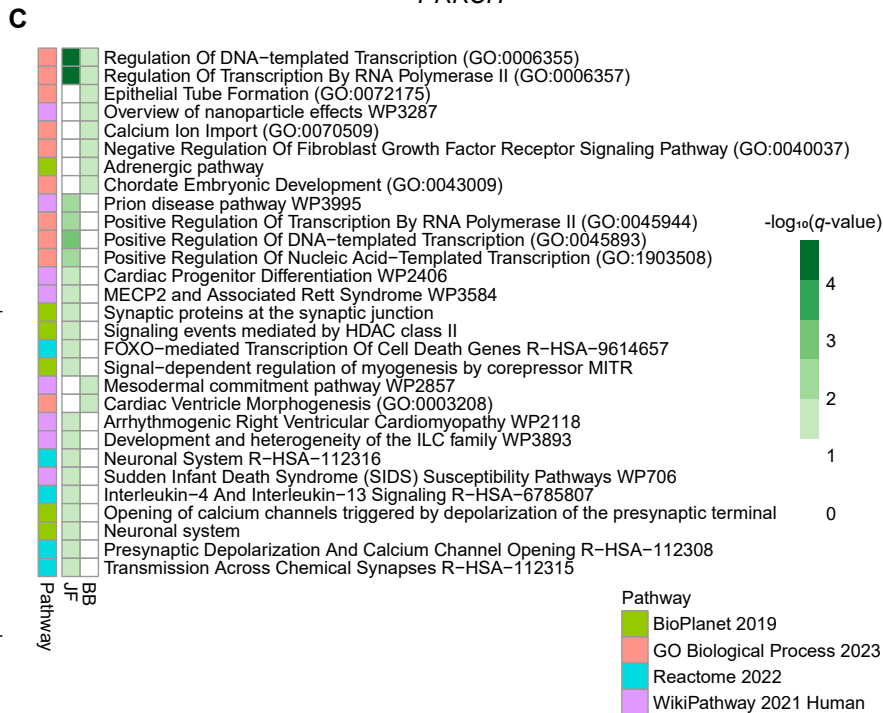
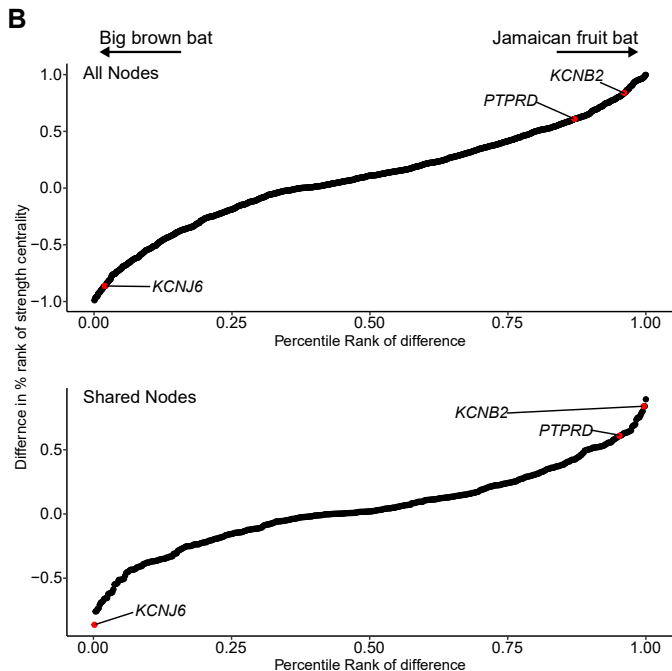
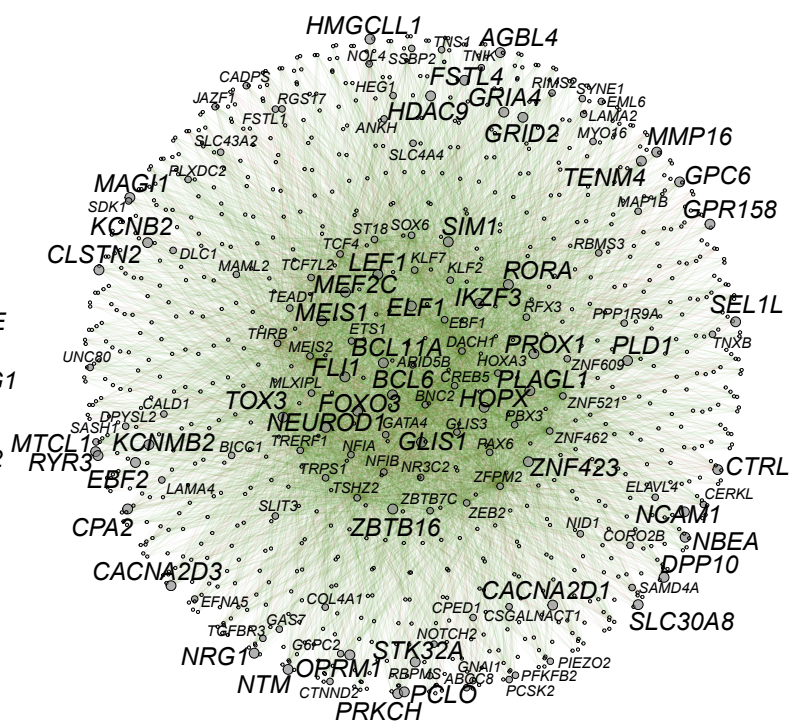
Supplementary Fig.11: scRNA-seq and scATAC-seq analysis of bat pancreas.

a, (Left) UMAP of acinar-i subclusters. (Right) Proportion of species in each acinar-i subcluster. b, Volcano plot showing differentially expressed genes between acinar-i subcluster 0 (big brown (BB) bat-enriched) and subcluster 1 (Jamaican fruit (JF) bat-enriched). c, Bar plots showing KEGG Human 2021 pathways enriched in acinar-i subcluster 0 (big brown (BB) bat-enriched) and subcluster 1. *Q*-values calculated with one-sided Fisher's exact test and corrected with the Benjamini-Hochberg method. d, Bar plots showing KEGG Human 2021 pathways enriched in Jamaican fruit (JF) bat ductal cells. *Q*-values calculated with one-sided Fisher's exact test and corrected with the Benjamini-Hochberg method. e, Volcano plot showing differentially expressed genes between species in ductal cells. f, Violin plots of differentially expressed genes, except *FAM3B*, *SLC2A2*, and *GCG*, in bat pancreas cells. *P*-values calculated with two-sided Wilcoxon rank-sum test and the Bonferroni correction. g, Bar plots showing GREAT human and mouse phenotypes enriched in big brown (BB) bat and Jamaican fruit (JF) bat pancreases. h, scATAC-seq coverage plots of *INS* in bat pancreases. SCTransform-normalized expression plot visualized on the right by cell-type. i, scATAC-seq coverage plots of *GCG* in bat pancreases. SCTransform-normalized expression plot visualized on the right by cell-type. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels. Source data are provided as a **Source Data** file.

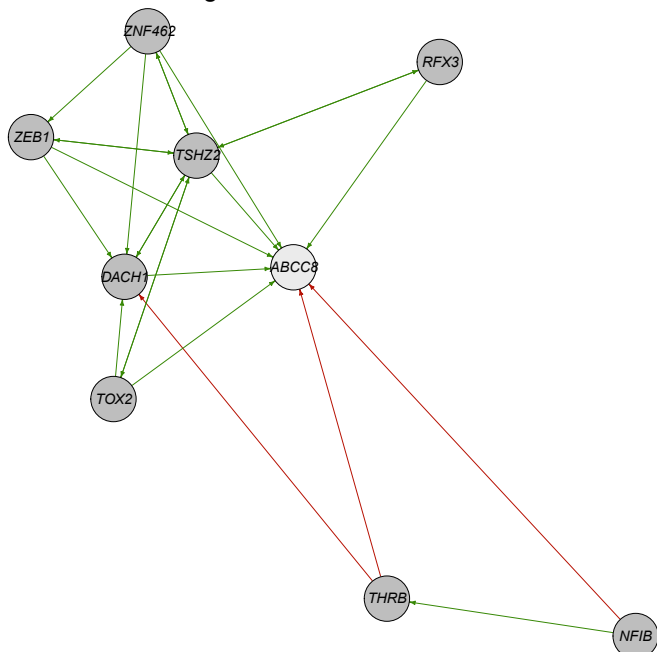
Big brown bat GRN



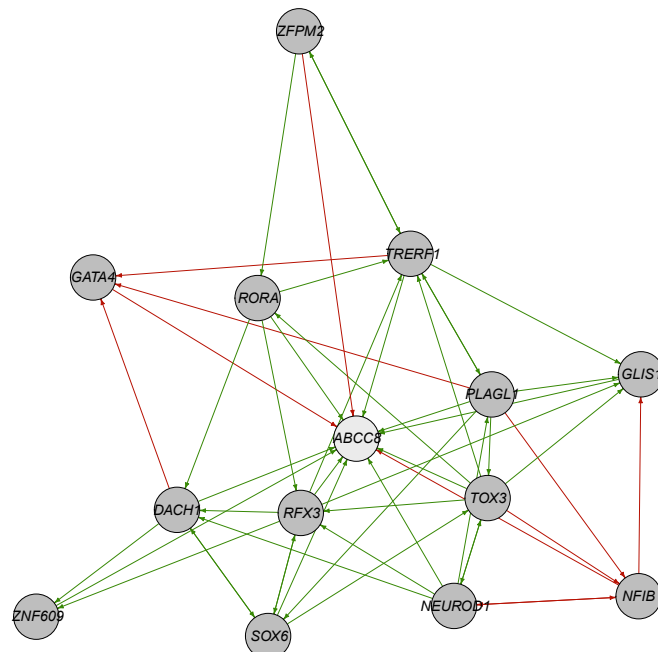
Jamaican fruit bat GRN



Big brown bat subnetwork



Jamaican fruit bat subnetwork



Supplementary Fig.12: Multi-omics GRN analyses of bat pancreases.

a, big brown (BB) bat and Jamaican fruit (JF) bat GRNs determined by Pando⁵. b, Scatter plots of the percentile rank of species difference by the difference in percentile rank of strength centrality for all nodes (top) and shared nodes (bottom). c, Heatmap of enriched pathways in each species GRN. *Q*-values calculated with one-sided Fisher's exact test and corrected with the Benjamini-Hochberg method. d, *ABCC8* subnetworks in each species. Jamaican fruit bat is depicted as JF and big brown bat as BB in the various panels. Source data are provided as a **Source Data** file.

Supplementary Table 1. Immunofluorescence antibodies and epitope matching to bats.

Gene	Thermo Scientific Antibody Catalog #	Big brown bat NCBI protein ID	Big brown bat NCBI Protein Blast % Identity	Jamaican fruit bat NCBI protein ID	Jamaican fruit bat NCBI Protein Blast % Identity
<i>SLC12A1</i>	18970-1-AP	XP_008141339.1	87.01	XP_037012367.1	86.36
<i>AQP2</i>	PA5-78808	XP_008138879.1	100	XP_036992308.1	100
<i>SLC26A4</i>	PA5-115911	XP_008148295.1	85.19	XP_037006378.1	96.3
<i>INS</i>	15848-1-AP	XP_008158493.1	81.82	XP_037012244.1	86.36
<i>GCG</i>	15954-1-AP	XP_027996892.1	78.33	XP_036996293.1	93.33

Supplementary References

1. Stuart, T., Srivastava, A., Madad, S., Lareau, C. A. & Satija, R. Single-cell chromatin state analysis with Signac. *Nat. Methods* **18**, 1333–1341 (2021).
2. Kirilenko, B. M. *et al.* Integrating gene annotation with orthology inference at scale. *Science* **380**, eabn3107 (2023).
3. Tang, H. *et al.* Synteny and collinearity in plant genomes. *Science* **320**, 486–488 (2008).
4. Hao, Y. *et al.* Integrated analysis of multimodal single-cell data. *Cell* **184**, 3573–3587.e29 (2021).
5. Fleck, J. S. *et al.* Inferring and perturbing cell fate regulomes in human brain organoids. *Nature* 1–8 (2022).