

Supplementary Materials

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Table S1. WGCNA analysis for human glomeruli expression.

Table S2. SE called for human glomeruli.

Table S3. CRC TF members called for human glomeruli.

Table S4. Differential expression analysis for mice *Foxc1/2* KO transcriptome.

Table S5. Gene sets from public data.

Table S6. GO analysis of differential expression in *Foxc1/2* KO podocyte.

Table S7. Reads number and features for ChIP-seq.

Table S8. Peaks coordination and GREAT annotation for FOXC1 and FOXC2 ChIP-seq.

Table S9. Target genes annotated for FOXC1 or FOXC2 sites using Homer or Cistrom.

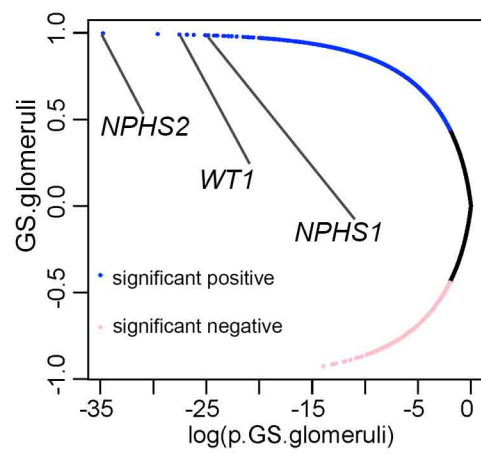
Table S10. Enrichment of podocyte-specific genes in FOXC1/2 target genes.

Table S11. Clinical characteristics of patient cohort used in Figure 5.

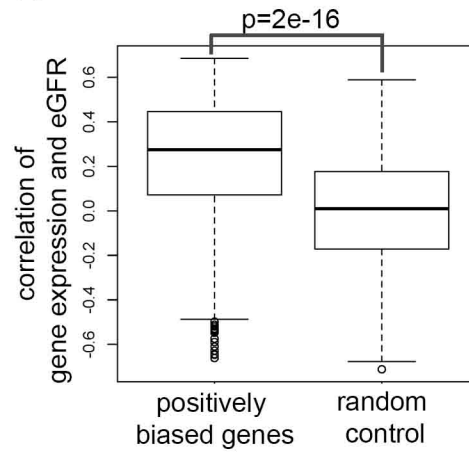
Table S12. Primers and probes.

Figure S1

A



B



C

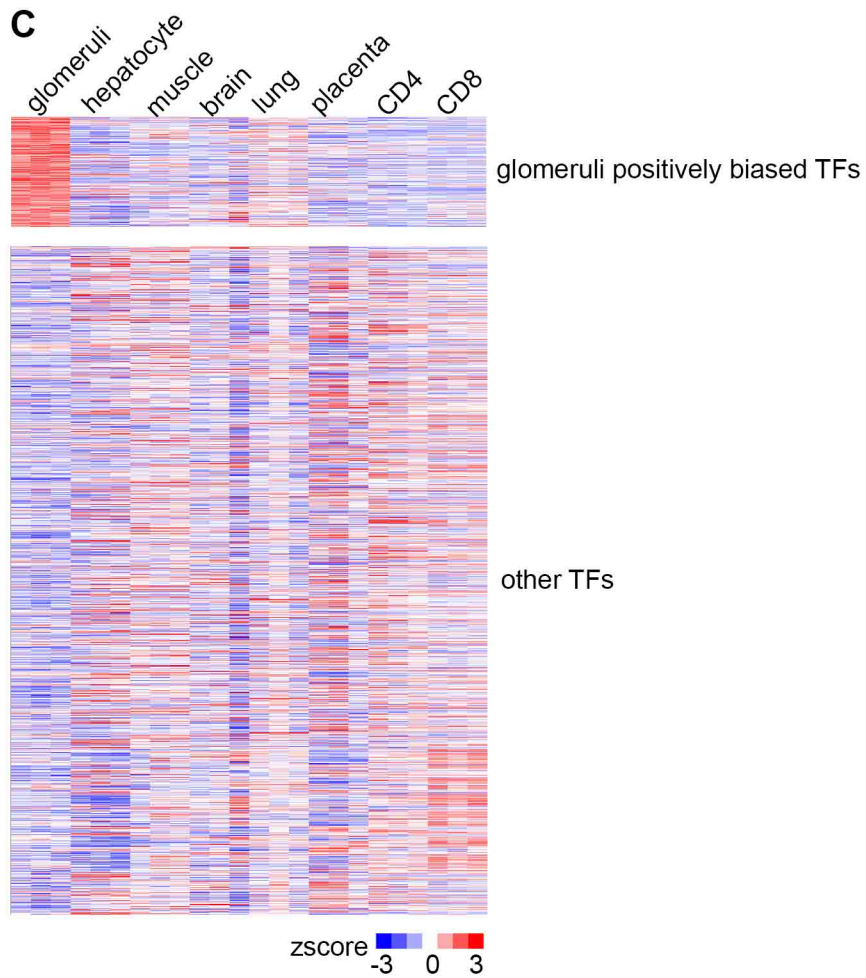


Figure S1. Glomeruli-biased expression in human. (A) Distribution of GS.glomeruli and p.GS.glomeruli of all genes. Podocyte markers as *NPHS1*, *NPHS2*, *WT1* are highlighted. Blue dots indicate glomeruli positively biased genes, and pink dots indicate glomeruli negatively biased genes. (B) Correlation between gene expression and eGFR are calculated for positive biased genes or randomly selected genes. (C) Heatmap of TF genes expressions. Glomeruli positively-biased TFs are those TF genes with WGCNA output $GS.glomeruli > 0$ and $p.GS.glomeruli < 0.01$.

Figure S2

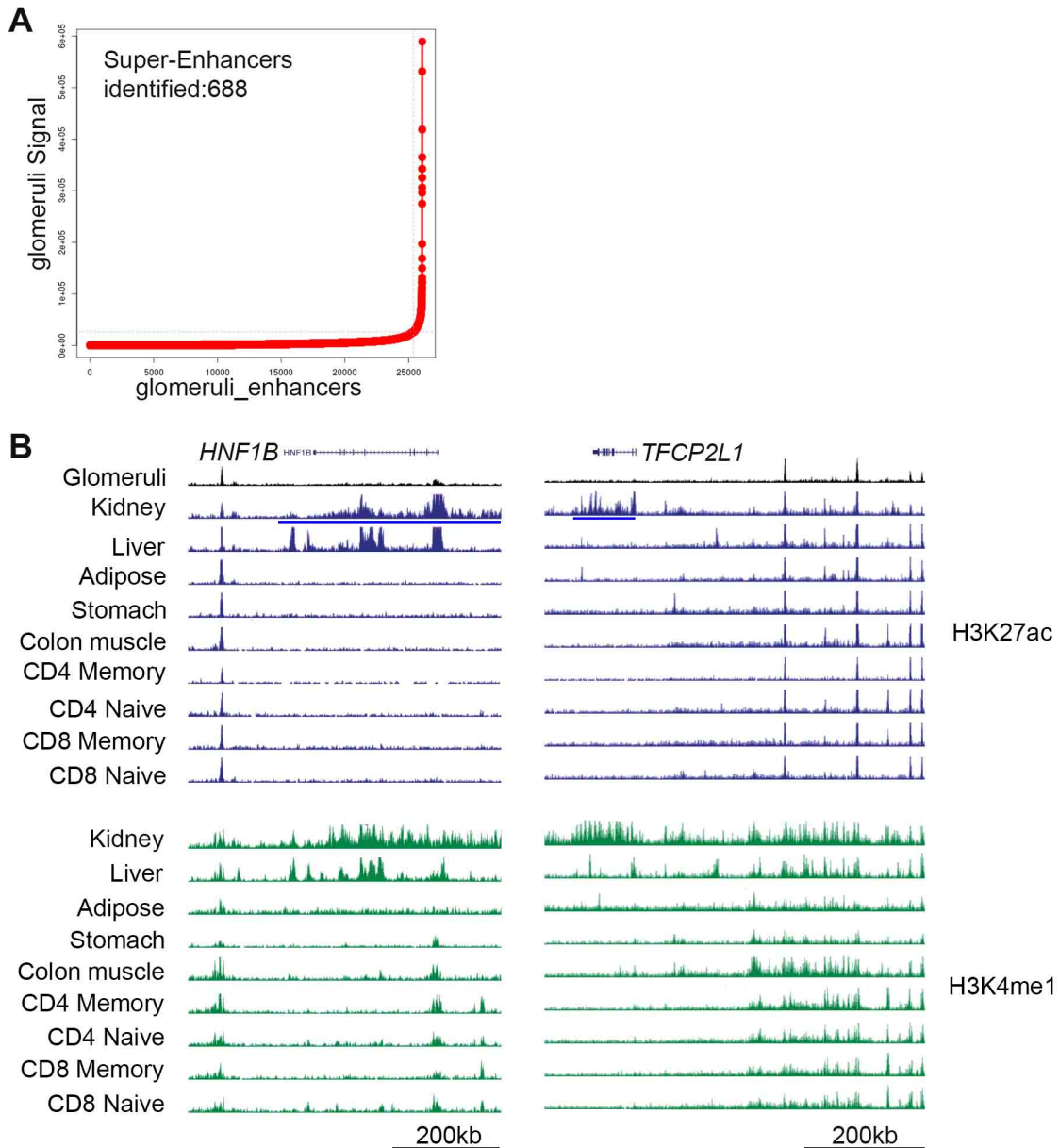


Figure S2. Super enhancer in adult human glomeruli. (A) Super enhancers called on H3K27ac in isolated human glomeruli. Grey line indicates the cutoff for accumulated H3K27ac signal intensity and rank determined by ROSE. Red dots in right up corner are called as super enhancers. (B) H3K27ac distribution at tubule-specific gene loci (*HNF1B* and *TFCEP2L1*) in glomeruli, kidney and other tissue or cell types on UCSC genome

browser. Blue bars indicated SE called on H2K27ac from whole human kidney but not from human glomeruli.

SE	AIRE	→	○
SE	BCL6B	→	○
SE	E2F4	→	○
SE	ERF	→	○
SE	ETS1	→	○
SE	FLI1	→	○
SE	FOS	→	○
SE	FOSL2	→	○
SE	FOXC1	→	○
SE	FOXC2	→	○
SE	FO XK1	→	○
SE	GATA3	→	○
SE	GLIS2	→	○
SE	HOXC6	→	○
SE	HOXD8	→	○
SE	KLF13	→	○
SE	KLF7	→	○
SE	LMX1B	→	○
SE	MEF2D	→	○
SE	MYOG	→	○
SE	NR4A1	→	○
SE	RARA	→	○
SE	RREB1	→	○
SE	RXRA	→	○
SE	SMAD3	→	○
SE	SNAI1	→	○
SE	SOX13	→	○
SE	TBX2	→	○
SE	TEF	→	○
SE	WT1	→	○
SE	ZBTB16	→	○

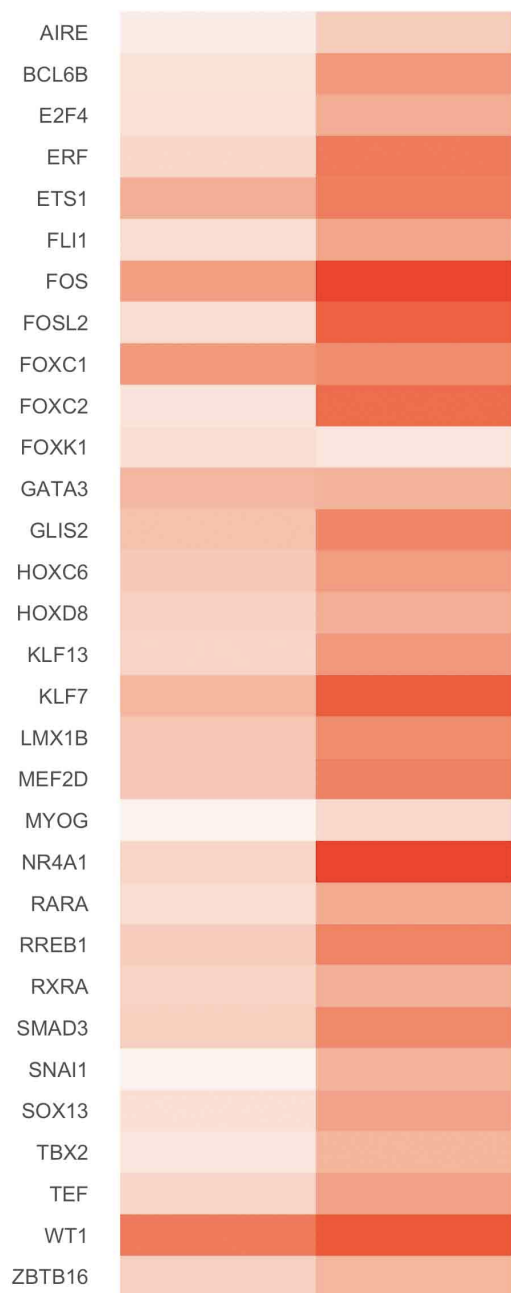


Figure S3. The TFs in top1 CRC called using crcmapper. The regulatory relationship determined by crcmapper (left). The expression of these TF genes in human glomeruli and mice podocyte (right).

Figure S4

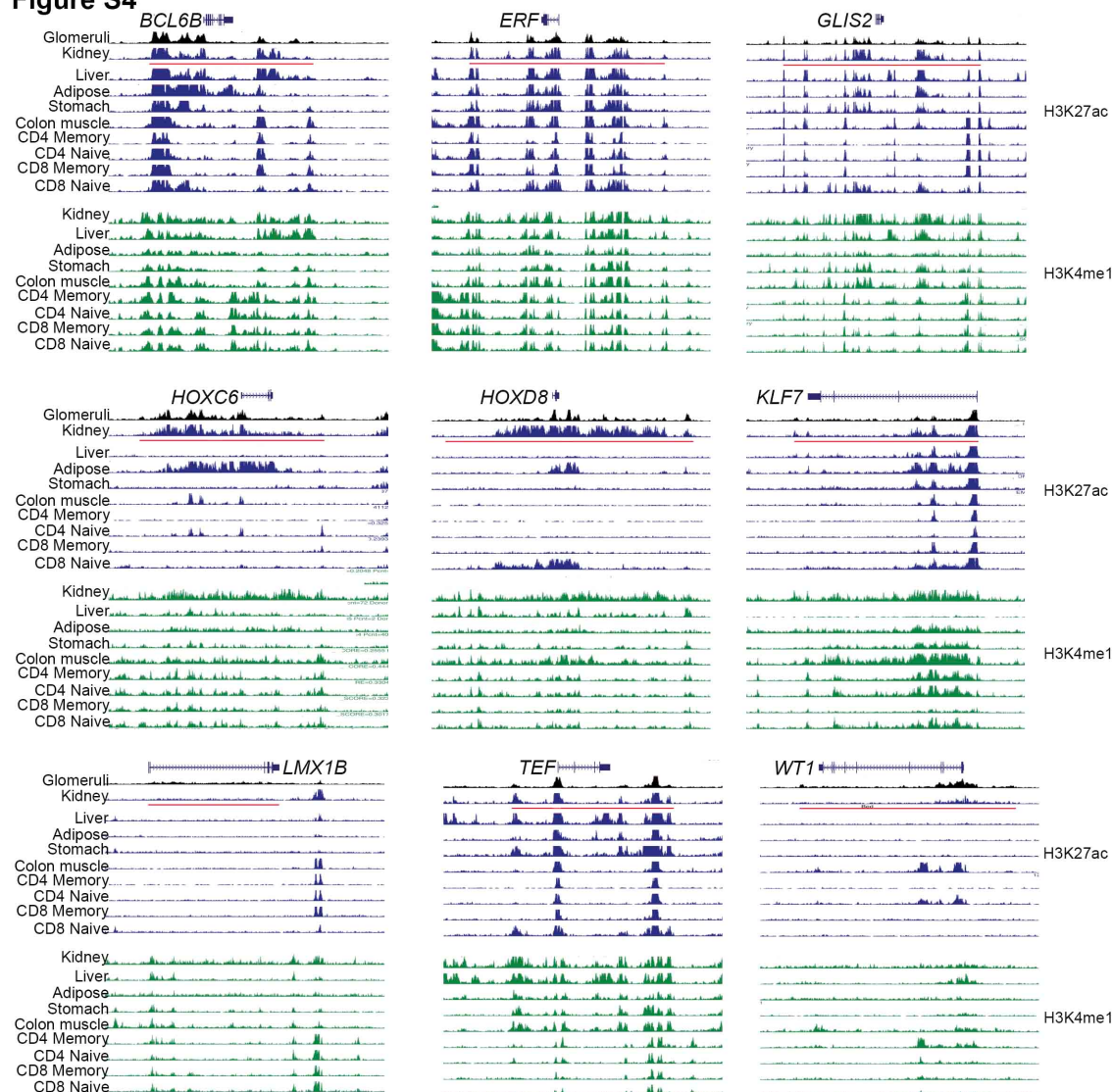


Figure S4. H3K27ac and H3K4me1 distribution at CRC TF gene loci except FOXC1 and FOXC2. Red bars indicate super enhancers called using ROSE on H3K27ac from human glomeruli. Blue tracks are H3K27ac signals and green tracks are H3K4me1 signals. The tissue types which are best matches of those used in WGCNA analysis are displayed.

Figure S5

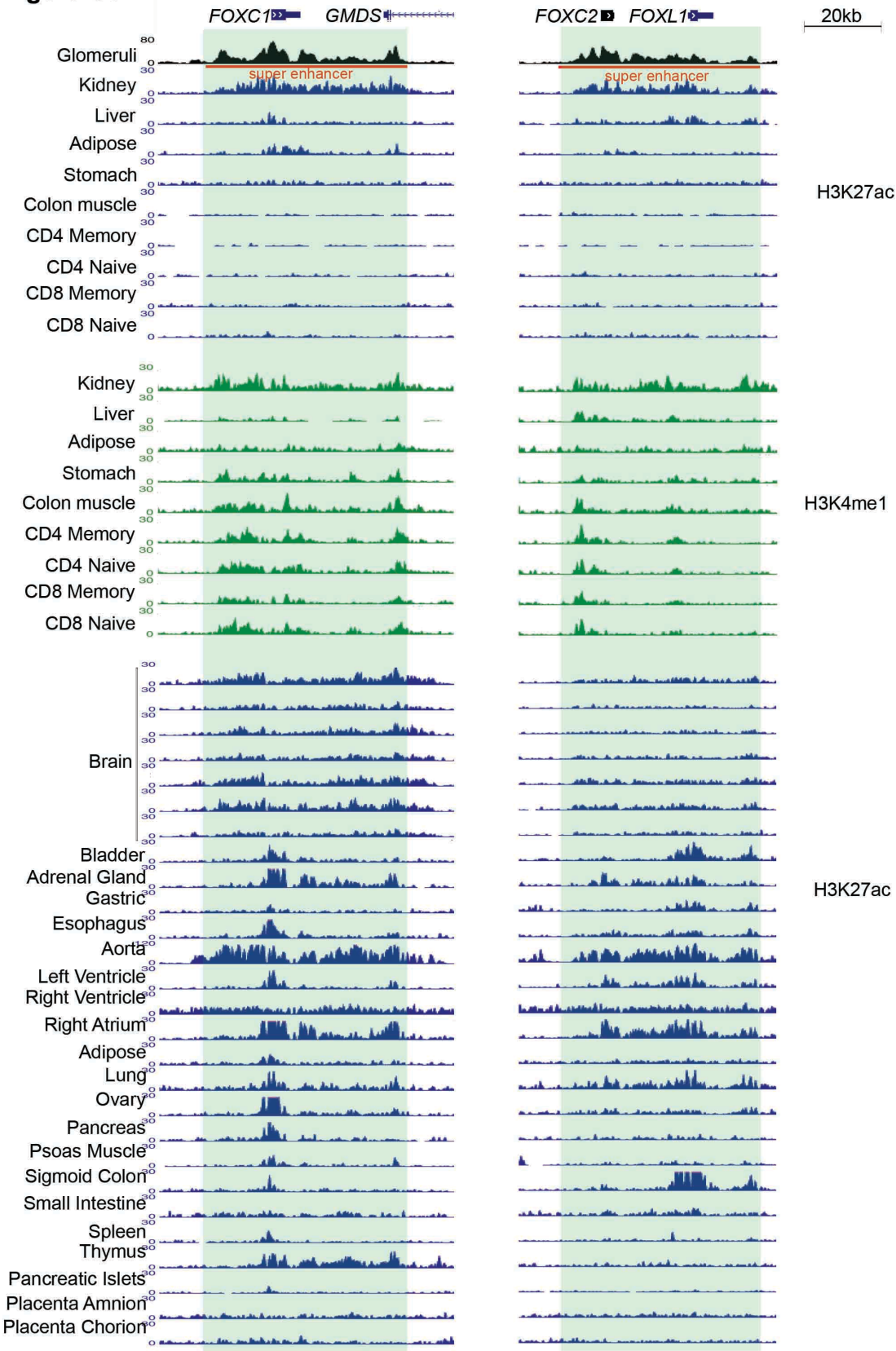


Figure S5. H3K27ac and H3K4me1 distribution at *FOXC1* and *FOXC2*. Red bars and green shades indicate super enhancers called using ROSE on H3K27ac from human glomeruli. Blue tracks are H3K27ac signals and green tracks are H3K4me1 signals. Tissue types that are best match for those used in WGCNA analysis are displayed on top for both H3K27ac and H3K4me1. All additional tissue types that are available in Roadmap are displayed for H3K27ac at bottom.

Figure S6

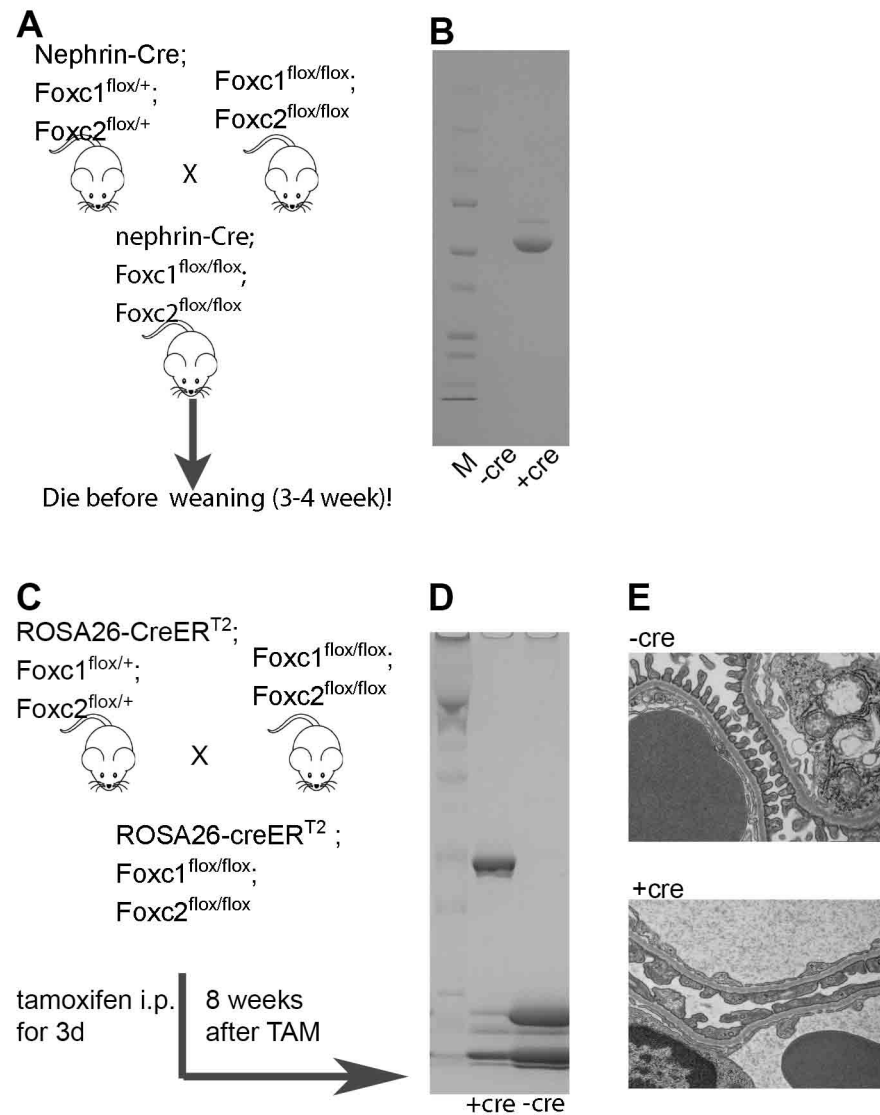


Figure S6. *Foxc1/2* KO in mice. (A) Scheme outline for podocyte specific KO of *Foxc1/2* under Nephrin-cre. (B) Electrophoresis of urea protein under Nephrin-cre mediated *Foxc1/2* KO. (C). Outline for conditional knockout of *Foxc1/2* in adult mice. (D). Electrophoresis of urea protein. (E). Electron microscope of podocyte focal foot process.

Figure S7

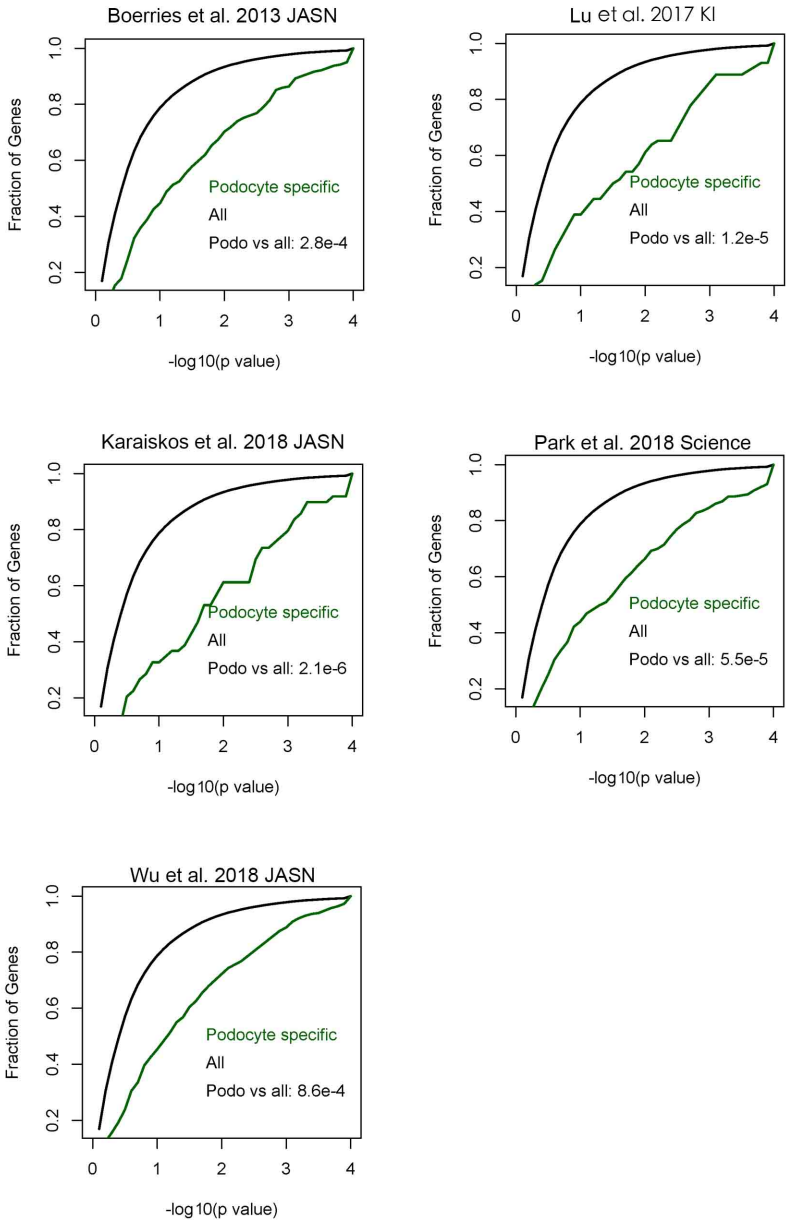
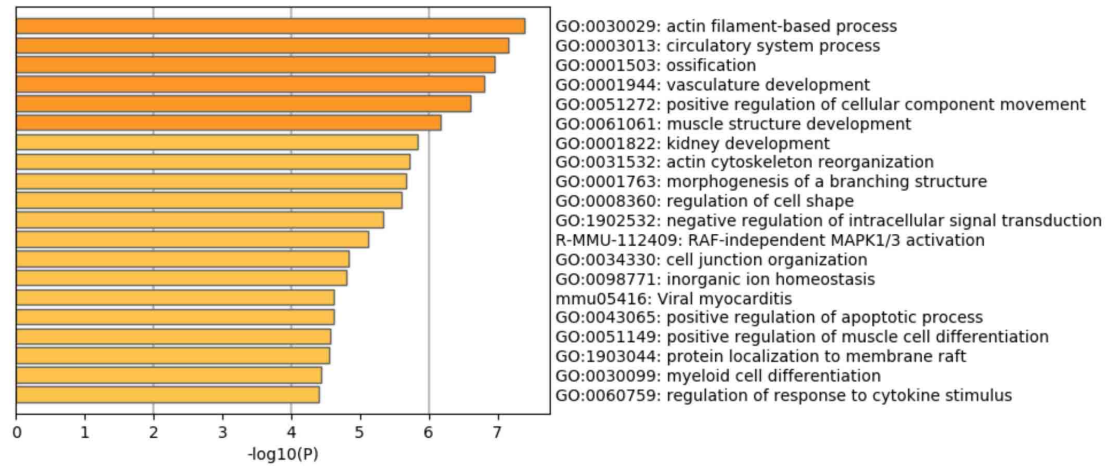


Figure S7. Cumulative curve of $-\log_{10}(\text{p value})$ for differential expression analysis from Table S4. Podocyte specific are extracted from previous studies and listed in Table S5. t-test is performed for statistics.

Figure S8
A



B

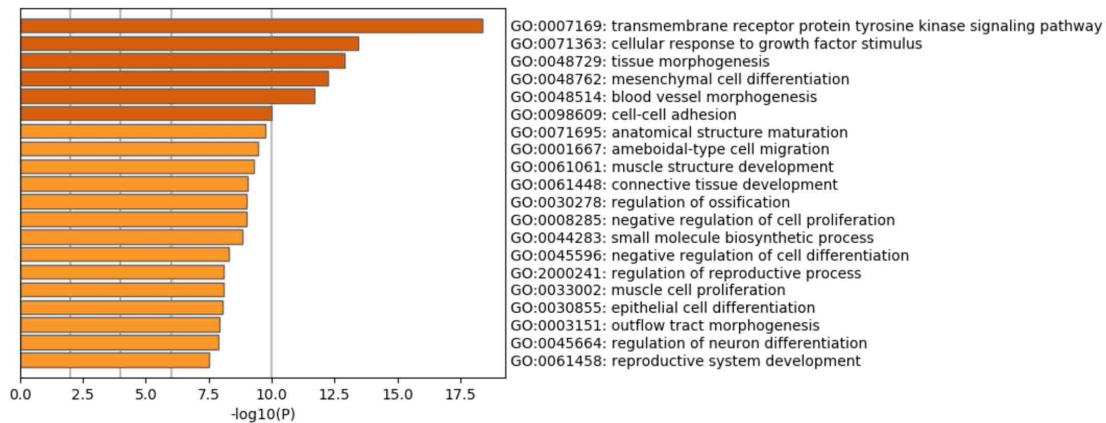


Figure S8. Gene ontology analysis of differential expressed genes in *Foxc1/2* cKO. (A) Top GO terms enriched for down-regulated genes. (B) Top GO terms enriched for up-regulated genes.

Figure S9

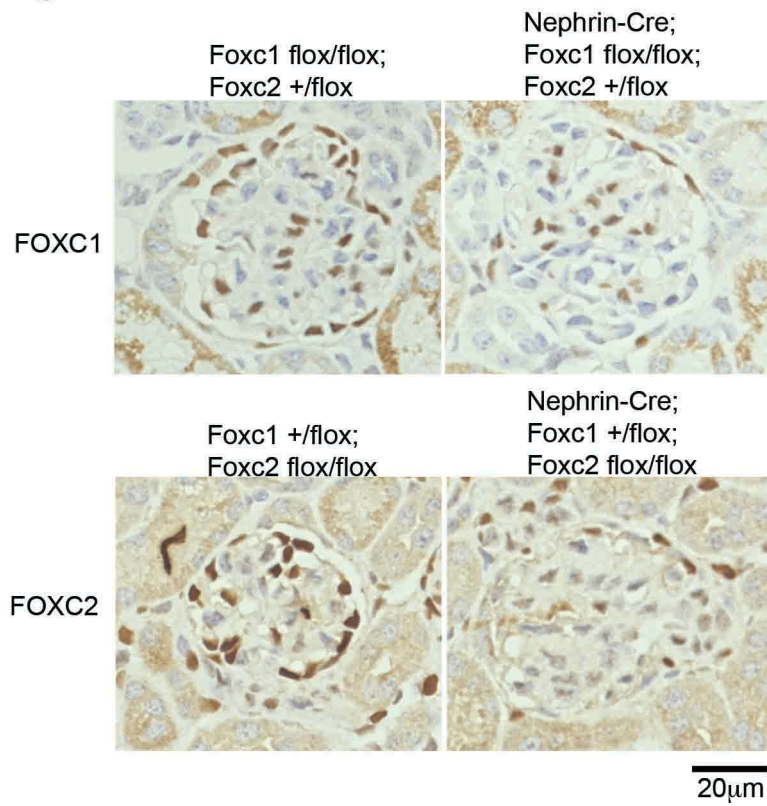


Figure S9. Validation of FOXC1 and FOXC2 antibodies.

Figure S10

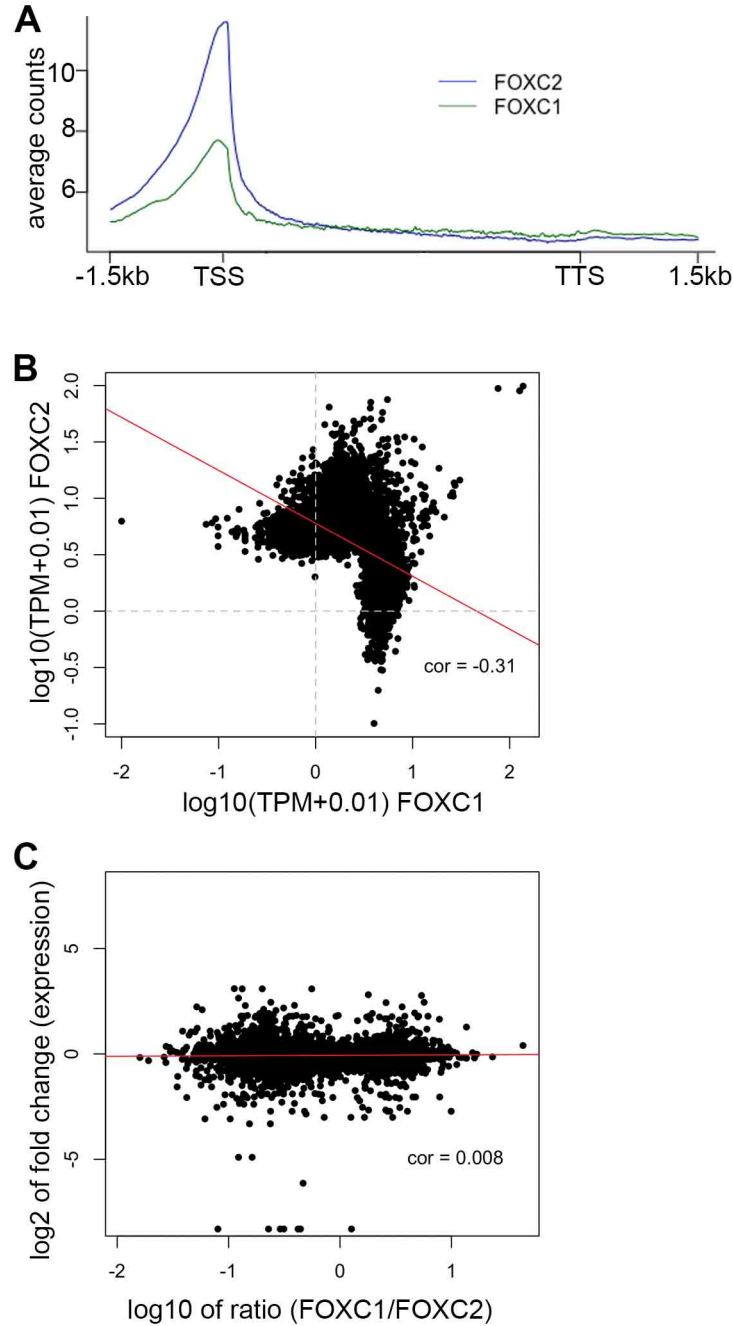


Figure S10. Features of FOXC1/2 binding. (A) Metagene plot of FOXC1 and FOXC2 ChIP-seq signal. (B) Scatter plot of FOXC1 versus FOXC2 signal at combined FOXC1/2 binding sites. (C) Scatter plot of expression fold change from FOXC-associated genes versus FOXC1/FOXC2 signal ratio of these FOXC sites.

Figure S11

A Motif2



Enrichment: $p=1e-83$
WT1 (Homer) similarity: 0.88

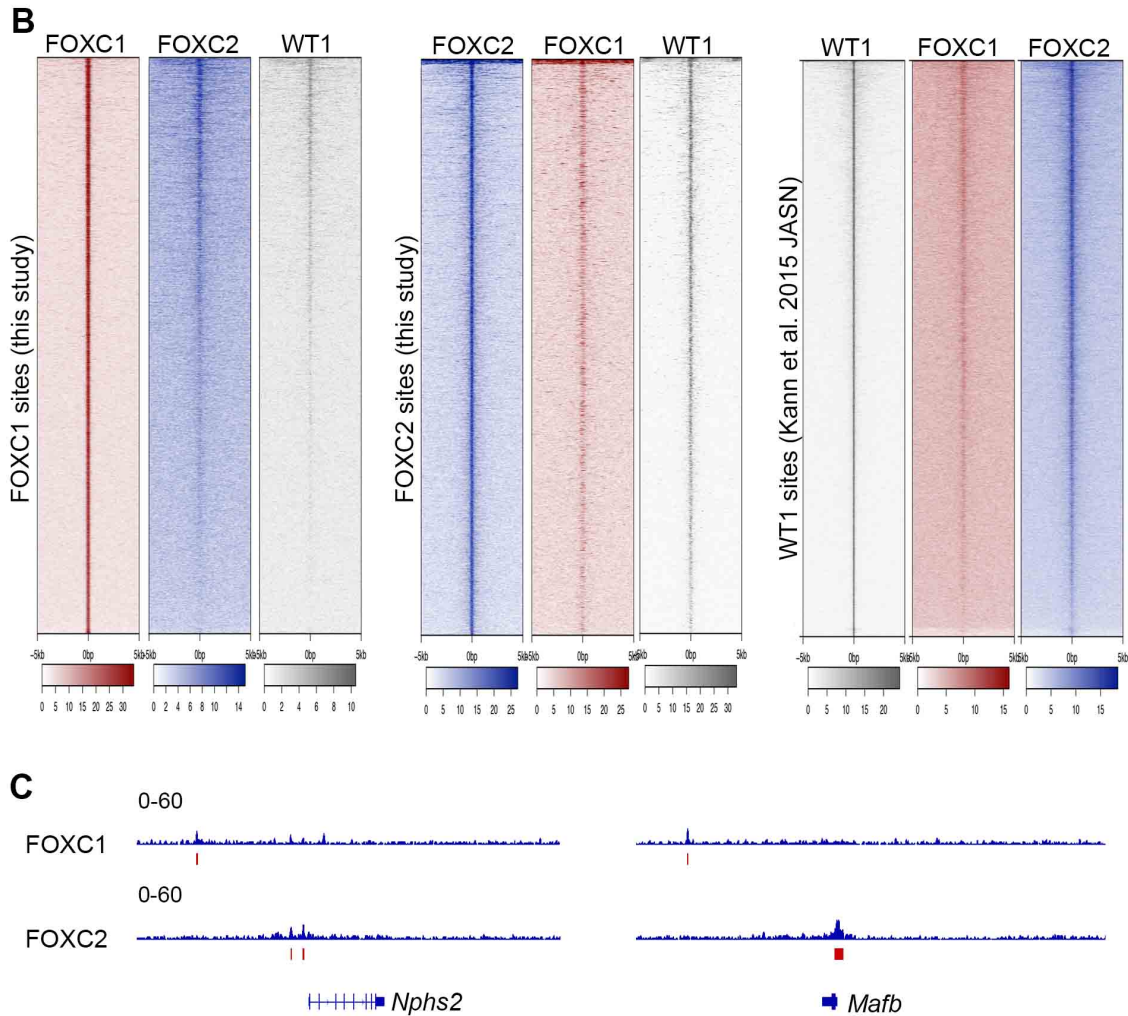
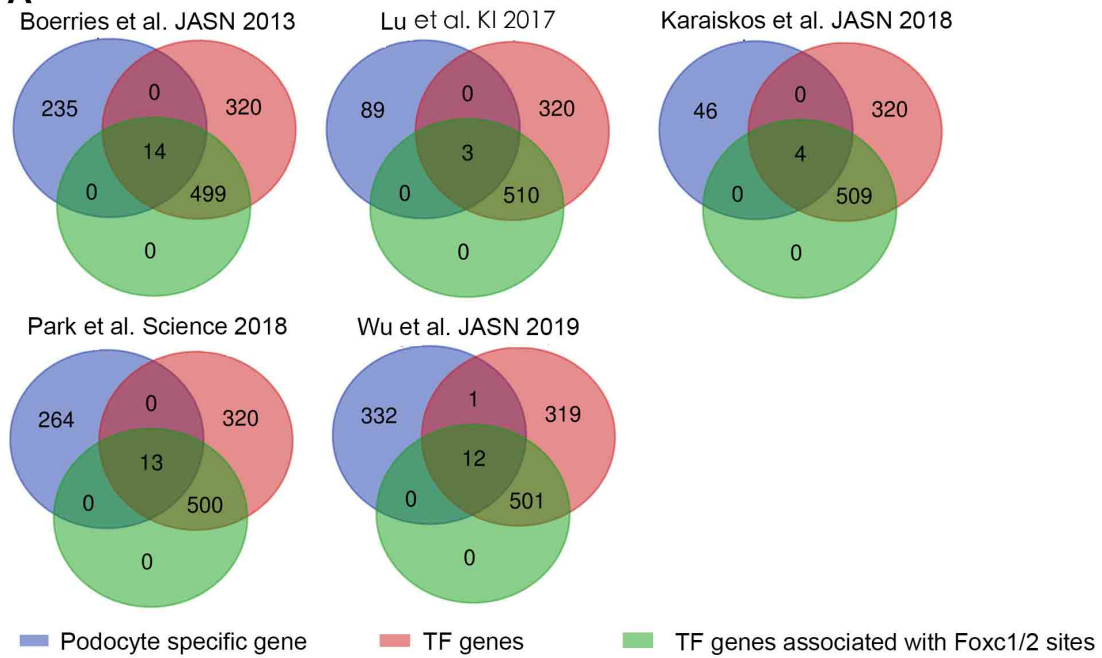


Figure S11. Distribution of FOXC1 and FOXC2 on genome. (A) Top 2nd motifs discovered at FOXC1/2 binding site. (B) Heatmap of signal from FOXC1, FOXC2 and WT1 ChIP-seq at FOXC1, FOXC2 or WT1 (Kann 2015) sites. (C) IGV tracks show

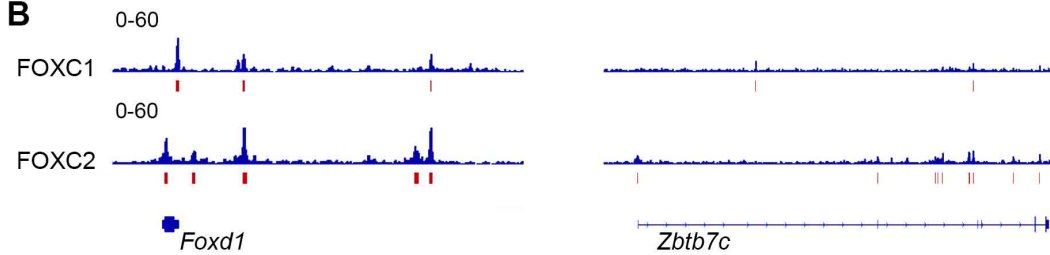
FOXC1 and FOXC2 distribution at *Nphs2* and *Mafb* loci. Red bars indicate the binding peaks.

Figure S12

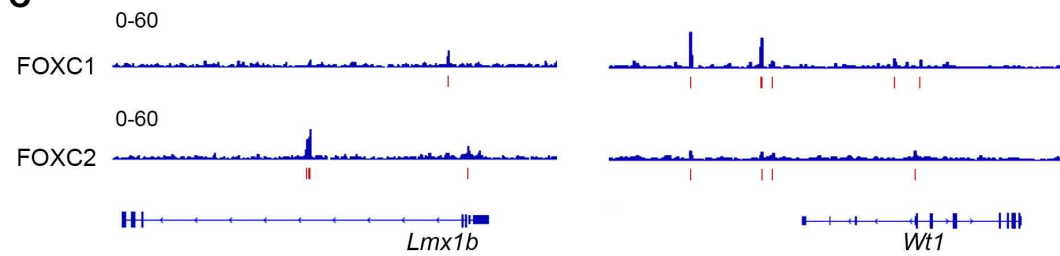
A



B



C



D

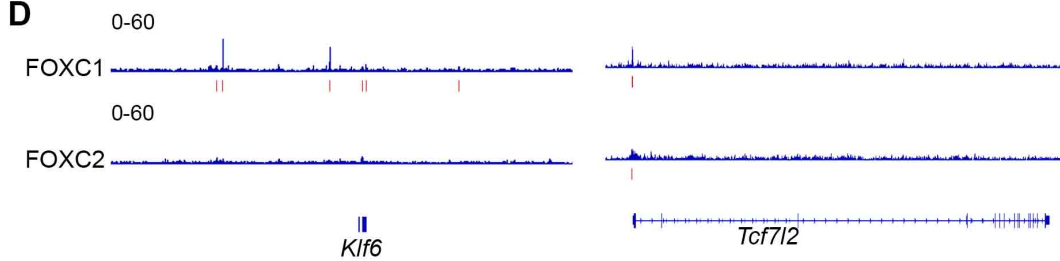
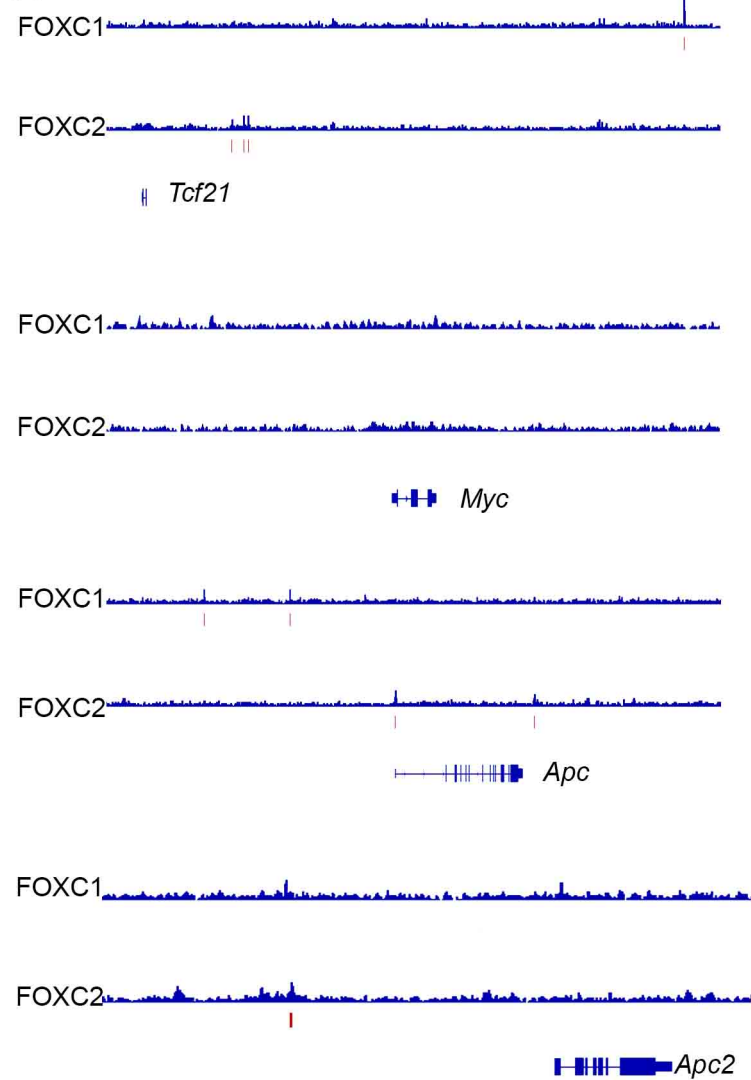


Figure S12. Target genes of FOXC1 and FOXC2 binding sites. (A) Venn diagram for overlapping among podocyte-specific genes (Table S5), TF genes in mouse genome, and FOXC1/2 target genes (annotated using Cistrom). (B) FOXC1 and FOXC2 binding at podocyte-specific TF genes (*Foxd1* and *Zbtb7c*). Red bars indicate the binding peaks. (C) FOXC1 and FOXC2 binding at other CRC members *Lmx1b* and *Wt1*. (D) FOXC1 and FOXC2 binding at reported TF genes important for podocyte homeostasis (*Klf6* and *Tcf7l2*).

Figure S13

A



B

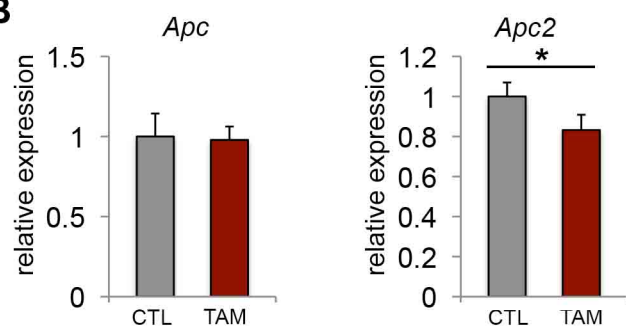


Figure S13. FOXC1 and FOXC2 distribution at *Tcf21*, *Myc*, *Apc* and *Apc2*. (A) FOXC1 and FOXC2 signal at *Tcf21*, *Myc*, *Apc* and *Apc2*. Red bars indicate the binding peaks. (B) Relative expression of *Apc* and *Apc2* mRNA. * stands for $p < 0.05$.

Figure S14

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Foxc2_human  MQARYSVSDPNALGVVPLS-EQNYRA----AGSYGGMASPMGVSG--HPEQYSGMGRSYAPYHHQPAAPKDLVKKPPYSYIALITMAIQNAPDK 91
Foxc2_mouse  MQARYSVSDPNALGVVPLS-EQNYRA----AGSYGGMASPMGVSG--HPEQYSGMGRSYAPYHH-QPAAPKDLVKKPPYSYIALITMAIQNAPDK 90
Foxc1_human  MQARYSVSSPNSLCVVPLYLGGESYRAAAAAAGGTYTAMPAPMSVYSHPAHAQYPPGGMARAYGPYTPQ--PQPKDMVKPPYSYIALITMAIQNAPDK 97
Foxc1_mouse  MQARYSVSSPNSLCVVPLYLGGESYRAAAAAAGGTYTAMPAPMSVYSHPAHAQYPPGGMARAYGPYTPQ--PQPKDMVKPPYSYIALITMAIQNAPDK 97
Foxc1a_danre  MQARYSVSSPNSLCVVPLYSSDQSYRAA--AGGTYTAMPAPMTMYSHAH-DQYPASMARAYGPYTPQ--PQPKDMVKPPYSYIALITMAIQNSPDK 93
Foxc1b_danre  MQARYPVSSQSLGVVPLYPCDQGFYRTA--TGGYTGMPAPMSMYSHATH-EQYPGGMARAYGPYAPA--QQPKDMVKPPYSYIALITMAIQNSDK 93

      **      *      *
KITLNGIYQFIMDRFFYRENKQGWQNSIRHNLSLNECFVKVPRDDKKPGKGSYWTLPDSYNMFENGSLRRRRRFFKKKDVSKKEERHL--KEPPP 188
KITLNGIYQFIMDRFFYRENKQGWQNSIRHNLSLNECFVKVPRDDKKPGKGSYWTLPDSYNMFENGSLRRRRRFFKKKDVSKKEERHL--KEPPS 187
KITLNGIYQFIMDRFFYRDNKQGWQNSIRHNLSLNECFVKVPRDDKKPGKGSYWTLPDSYNMFENGSLRRRRRFFKKKDAYKDEEKDRHLKEPPP 196
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KVTLNGIYQFIMERFFYRDNKQGWQNSIRHNLSLNECFVKVPRDDKKPGKGSYWTLPDSYNMFENGSLRRRRRFFKKKDAYKDEEKDRHLKEPPP 191
KITLNGIYQFIMERFFYRDNKQGWQNSIRHNLSLNECFVKVPRDDKKPGKGSYWTLPDSYNMFENGSLRRRRRFFKKKDVLEKEDRDRQKDNPP--190

AASKG--APATPHLADAPKE--AEKKV---VIKSEASPALPVITKVETLSPESALQG-----SPRSA-A-STPAGSPDGLS-----256
TTAKG--APTGTVPADGPK--AEKKV---VVKSEASPALPVITKVETLSPESALQA-----SPRSA-S-STPAGSPDGLS-----255
P--GRQPPAPP EQADGNAPGQPPPVRIQDIKTENGTCPSP---PQLSPAAALGSGSAAAVPKIESPDSSSSLSGSSPPGSLPSARPLSLDGAD 289
PQAGRQPAPP EQAEGSAPGQPPPVRIQDIKTENGTCPSP---PQLSPAAALGSGSAAATVPKIESPDSSSSLSGSSPPGSLPSARPLSLDAAE 291
-----AQPQAREEQSVPGSQPVRIQDIKTENGTSTPP---QAV-SP-----TLSTVPKIESPDSSSSMS---SGSPHSIPSTRSLSLDSAG 266
-----GQACEQDAQPVKLRDIKTENGACTPP---HDS-TP-----PLSTVPKTESPDSSGSA-----CSG 243

-----PEHHAAPNGLPGFSVENIMTLRTSPGG-ELSPGA-----GRAGLVVPP LALPY-AAAPPAAYGQPCAQGLEA-----323
-----PEHHAAPNGLPGFSVETIMTLRTSPGG-DLSPAA-----ARAGLVVPP LALPY-AAAPPAAYTQPCAQGLEA-----322
SAPPPAP SAPPPHHSQGFSDNIMTSLRGSPQSAAEELSGLLASAAASSRAG-IAPPLALGAYSPGQSSLYSSPCQSTSAGSSGGGGGAGA---383
PAPPP--QPAPPHHSQGFSDNIMTSLRGSPQSAAEELSGLLASAAASSRAG-IAPPLALGAYSPGQSSLYSSPCQSSSAGSSGGGGGGGGGGGS 387
EQH-----HQAPAQGFSDNIMTSLRGSPHSAGE-----LTPSLVAPSRGT-ITPTLSLNYSPNQ--SSVYSSPCSQNIS--334
SPQ-----SQTQQAFSMDTITGLRGSPQHAAE-----LPAS-----RAA-LPGSVSLTSPTPQAHYSPPCQ-----303

-----GAAGGYQCSMRAMSLYTGAERPAHMCVPPAL-----DEALSDHPSGPTSPLSALNLAAGQEGALATGHHQHGHGHHHPQAPPPAPQPQP 410
-----AGSAGYQCSMRAMSLYTGAERPAHVCPVPPAL-----DEALSDHPSGPGSP L G A L N L A A G Q E G A L G A S G H H Q H H G L H P Q A P P P A P 409
--AGGAGGAGTYHCNLQAMSLYAAGERGGHLQAGPAGGAGSAVDDPLPDYSLPPVTSSSSSSLSHGGGGGGGGGGQEGHH-----462
SSAAGTGGATYHCNLQAMSLYAAGERGGHLQAGPAGGAGSAVDDPLPDYSLPPATSSSSSSLSHGG-----GGQEASHH-----462
-----TTSNATYHCNLQAMSLYAGGDRSGHLGT----TATTVDLETLPDYSITTTTSS---LSHGNLSS-----AQEG-----394
-----PATYHCNLQATSLYTGDGRGHG-----DDTLPEYTTNTNASS---ISHPHQSS-----SQES-----351

TPQPGAAAQAASWYLNHSG-DLNHLPG-----HTFAAQQTFFNVREMFNSHRLGIENTSLGESQVSGNASQCLPYRSTPPLRHAAPYSYDCTKY 501
QP-----ATQATSWYLNHGG-DLSHLPG-----HTFATQQTFPNVREMFNSHRLGLDNSSLGESQVS--NASQCLPYRATPSLYRHAAPYSYDCTKY 494
--PAHQGR L TSWYLNQAGDGLHLASAAAAAAGYPPGQQNFHVSREMFESQRI GLNNS-----PVNGNSCQMAFPSSQSLYRTSGAFVYDCSKF 553
--PASHQGR L TSWYLNQAGDGLHLASAAAAAAGYPPGQQNFHVSREMFESQRI GLNNS-----PVNGNSCQMAFPASQSLYRTSGAFVYDCSKF 553
--HHPHQGR L ASWYLNQAG-DIGHLG-----ATYPAGQQNFHVSREMFESQRI GLNNS-----PVNGNSCQMFSPSQPIYRTSGAFVYDCSKF 476
--QHLQNR LAPWYLNQSG-ELGHL-----ASYPGQQNFHAVREMFETQRI ALNNS-----PVTGNSCQMAFPSSQPIYRASGAFVYDCSKF 433

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Figure S14. Conservation of Foxc in human, mice and zebrafish. Red box highlights forkhead domain. Stars highlight DNA binding sites.