SUPPLEMENTARY METHODS

Breeding of murine lines and tissue collections

All mice were maintained on a mix genetic background of C57BL/6J and 129. For embryonic analyses, the morning of vaginal plug detection was considered as E0.5. For fertility test, males were mated each night with two females for fifteen days. Harvested testes were either frozen in liquid nitrogen or fixed in 4% PFA. For the BTB integrity analysis, intratesticular injection of EZ-Link Sulfo-NHS-LC-Biotin (15µl, 7.5mg/mL) was performed in the left testis (21335, Thermo Scientific). Testes were harvested 30 min after injection and fixed in 4% PFA.

Histology

Immunohistochemistry and TUNEL staining were performed according to conditions described in table S3. Images were acquired with a Zeiss Axioplan 2, Zeiss AxioImager or Zeiss Axioscan Z1 slide scanner and were minimally processed for global levels with ZEN. Images settings and processing were identical across genotypes. Tumor scoring was performed on H&E stained sections. Testis was noted (1) either normal if any modification of stromal cell number has been observed (2) either hyperplastic if cell number is increased and (3) either tumoral if testis developed stromal nodules representing at least 20% of total section area. 25 random ST were counted to assess the percentage of ST with spermatozoa, with vacuoles, with biotin or filled of germ cells in mice; or the number of G9A+, SYCP3+, ZBTB16+ or TUNEL+ per ST in mice. Epithelium thickening and CLDN11 expression domain were measured in 25 ST per mouse. 500 stromal cells were counted to assess the PCNA proliferation index. Mast cells were detected following toluidine blue staining and were counted in a whole testis section. In human samples, the number of germ cell per tubule and the CLDN11 expression domain were quantified in 50 ST whereas 200 ST were counted to assess the percentage of ST with spermatozoa or with vacuoles.

Micro-array analyses

Gene expression was normalized by RMA (Affy R package) and genotype comparisons were performed using the Limma package. All p-values were adjusted by the Benjamini-Hochberg correction method. Genes with adjusted p-value<0.05 were considered significantly deregulated and highly deregulated if abs(Log2FC)>1.0 (Datafiles S1). Heatmaps were generated with R and represent colour-coded individual median centered gene expression levels. Gene set enrichment analyses were conducted using GSEA 4.0.2 with MSigDB or custom gene sets (Datafiles S2). Permutation were set to 1000 and were performed on gene sets. Enrichment analyses of GO and KEGG terms were conducted using DAVID 6.8 (Datafiles S3). Dotplot and Volcanoplot were generated with R.

Hormonal measurements

For the testosterone assay, we used the commercial LDN ELISA kit AR E-8000. Specificity: the lowest analytical detectable level of testosterone that can be distinguished from the standard A is 0,066ng/ml at the 2SD confidence limit. Reproducibility: Intra-assay: for one sample Mean: 3,23 ng/ml (20 replicate within one run), CV%=6,50; Inter-assay: variation determined by duplicate measurement of one sample over 10 days: Mean 1,23 ng/ml, CV%= 9,3 (n=10). LH and FSH levels were determined by multiplex assay MPTMAG-49K, Merck, Millipore. Sensitivity for LH in our conditions: min DC= 1,34pg/ml. Reproducibility precision intra assay: %CV<15, inter assay <20. Sensitivity for FSH in our conditions: min DC= 6,40 pg/ml. Reproducibility precision intra assay: %CV<15, inter assay <20.

SUPPLEMENTARY FIGURES

Figure S1 related to Figure 1. (**A** and **B**), *Prkar1a* floxed alleles were deleted in SF1+ cells. GFP is expressed from the R26R^{mTmG} locus following Sf1:Cre-mediated recombination from E10.5 in both WT (*Sf1:Cre,mTmG,Prkar1a*$^{+/+}$) and prKO testis (*Sf1:Cre,mTmG,Prkar1a*$^{fl/fl}$). (**C**), Immunohistochemical detection of GFP localized in SF1+ derived cells in 2-mo-old WT and prKO testes. White arrowheads, Sertoli cells (SC); yellow arrowheads, peritubular myoid cells (PMC); red arrowheads, Leydig cells (LC). Scale bars, 100µm and 50µm. (**D**), RTqPCR analysis of mRNAs levels encoding *Prkar1a* in 1-d, 2-wk, 2-mo, 4-mo-old WT and prKO testes. Statistical analysis was performed using Student's t-test or Welch's t-test. (**E**), Plasma testosterone concentration in 3-mo-old prKO mice compared with WT mice. (**F** and **G**), Plasma FSH and LH concentrations in 3-mo-old prKO mice compared with WT mice. Statistical analysis was performed using Mann-Whitney's test. (**H**), Immunohistochemical detection of LAMB in 4-mo-old WT and prKO testis. **(I)** TCM staining in 4-mo-old prKO testis and human CNC-LCCSCT. **(J),** Immunohistochemical analysis of PCNA in 2-wk and 4-mo-old WT and prKO testes. (**K**), HE staining of central tumor in 4-mo-old prKO testis (already presented in figure 1A). Bars represent the mean per group ± SD. Scale bars, 100µm (inset 50µm, (K) 500µm). ns, not significant, **p<0.05, **p<0.01, ***p<0.001*.

Figure S2 related to Figure 1. (**A**), *Prkar1a* floxed alleles were deleted in SF1+ cells and *Prkaca* heterozygosity context (noted as prKO/*Prkaca*$^{+/-}$, *Sf1:Cre,Prkar1a*$^{fl/fl}$,*Prkaca*$^{+/-}$). (**B**), HE staining of 2-mo-old WT, *Prkaca*$^{+/-}$, prKO and prKO/*Prkaca*$^{+/-}$ testis. Dashed black lines delineate tumor developed in prKO testis, blue arrowheads show restored spermatozoa differentiation in prKO/*Prkaca*$^{+/-}$ testis and black lines limit seminiferous epithelium thickness. Ø, absence of spermatozoa. Scale bars, 100µm. (**C**), Relative proportion of testicular hyperplasia and tumor in 2-mo-old *Prkaca*$^{+/-}$, prKO and prKO/*Prkaca*$^{+/-}$ testes. (**D** and **E**),

Percentage of ST with elongated spermatids (D) and epithelium thickness (E) quantified following HE staining in 2-mo-old WT, *Prkaca*$^{+/-}$, prKO and prKO/*Prkaca*$^{+/-}$ testes are restored in prKO/*Prkaca+/-* testis. Bars represent the mean value per group ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey multiple correction test. ****p<0.001*.

Figure S3 related to Figure 1. HE staining of reconstituted normal adult human testis (a) and human LCCSCT biopsy sections. Dashed lines delineate primary tumor mass. CNC-LCCSCT 3 section presents two distinct tumor masses (T1, T2) and is devoid of ST. Blue square, tumor; red square, ST. Blue arrowheads, spermatozoa; Ø, disorganized ST devoid of spermatozoa. Scale bars reconstituted biopsies, 1mm; scale bars insets, 100µm.

Figure S4 related to Figure 2. (**A** and **B**), *Prkar1a* floxed alleles were deleted in AMH+ cells (A) or CYP11A1+ cells (B). GFP is expressed from the R26R^{mTmG} locus following Amh:Cre-mediated recombination from E14.5 in srKO testis (*Amh:Cre,mTmG,Prkar1a*$^{fl/fl}$) or following Cyp11a1:Cre-mediated recombination from E15.0 in lrKO testis (*Cyp11a1:Cre,mTmG,Prkar1a*$^{fl/fl}$). (**C** and **D**), Immunohistochemical detection of GFP localized in AMH+ derived cells (Sertoli cells) in 2-mo-old srKO testis (C) and in CYP11A1+ derived cells (Leydig cells) in 2-mo-old lrKO testis (D). (**E** and **F**), Number of fertile males (E) and pups per litter (F) in 2-mo-old lrKO male mice. (**G**), Plasma testosterone concentrations in 2-mo-old WT, srKO and lrKO mice. Bars represent the mean per group ± SD. Statistical analysis was performed using Kruskal-Wallis' test followed by Dunn's multiple correction test. (**H**), HE staining of 12-mo old WT, srKO and lrKO testes showing the absence of tumor in all three genotypes. ****p<0.001*. Scale bars, 100µm.

Figure S5 related to Figure 3. (**A**), HE staining and immunohistochemical detection of ZBTB16, G9A, SYCP3 in 2-wk and 5 wk-old WT and srKO testes. Blue arrowheads, spermatozoa. (**B**), Quantification of ZBTB16, G9A and SYCP3 based on the number of positive cells per tube. Statistical analysis was performed using Student's test or Welch's t-test. (**C**) WT and *Prkar1a* mutant testis weight from 3-wk to 4-mo. Welch's one-way ANOVA was followed by Games-Howell multiple correction test. (**D**), Representative HE of 5-wk-old WT and srKO sections. (**E**), Quantification of full tubules represented as a percentage of positive tubules quantified following HE staining in 5-wk-old WT and srKO testes. Statistical analysis was performed using Mann-Whitney's test.

Figure S6 related to Figure 3

(**A**) Immunohistochemical detection of SOX9 in 2-wk, 5-wk and 7-wk-old WT and srKO testes. (**B**), Quantification of SOX9 based on the number of positive cells per tube. Statistical analysis was performed using Student's test or Welch's t-test. *$p<0.05$, **$p<0.01$, ***$p<0.001$. Bars represent the mean per group ± SD. Scale bars, 100µm.

Figure S7 related to Figure 4. (**A**), HE staining of 2-wk, 5-wk-old (already presented in figure S5A) 6-wk and 2-mo-old WT, prKO and srKO testes. Arrowheads indicate vacuoles. Black dashed lines delineate multinucleated giant cells at 6-wk resulting in vacuole formation (black arrowhead) at 2-mo. (**B**), ST magnification from normal adult human and CNC-LCCSCT HE staining already presented in figure S3. (**C** and **D**), Quantification of vacuolized tubules represented as a percentage of positive tubules quantified following HE staining of normal adult human testis, LCCSCT CNC (C), 2-wk-old, 5-wk-old and 2-mo-old WT, prKO and srKO testes (D). Statistical analysis was performed using Welch's t-test. (**E**), RTqPCR analysis of mRNAs levels encoding genes involved in cell junction assembly (*Cdh5*, *Cldn11*, *Ctnna1*, *F11r*, *Gja1*,

Itgav, *Jup*, *Ocln*, *Pvrl2*, *Tubb3*, *Vcl*, *Vim*) in 2-mo-old WT, srKO and prKO testes. Bars represent the mean per group ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey multiple correction test, Welch's one-way ANOVA followed by Games-Howell multiple correction test or Kruskal-Wallis' test followed by Dunn's multiple correction test. **p<0.05, **p<0.01, ***p<0.001*. (**F**), Immunohistochemical detection of TUBB3 and VIM in 5-wk-old WT, prKO and srKO testes. White line delineates VIM expression domain. (**G**), RTqPCR analysis of *Dpt* transcripts in 2-wk and 2-mo-old WT, srKO and prKO testes. Welch's one-way ANOVA was followed by Games-Howell multiple correction test. Bars represent the mean per group ± SD. **p<0.05, ***p<0.001*. Scale bars, 100µm.

Figure S8 related to Figure 5. (**A** and **B**), *Prkar1a* and *Wnt4* floxed alleles were deleted in SF1+ cells (noted as prwKO, *Sf1:Cre,Prkar1a*$^{fl/fl}$,*Wnt4*$^{fl/fl}$) (A) or in AMH+ cells (noted as srwKO, *Amh:Cre,Prkar1a*$^{fl/fl}$,*Wnt4*$^{fl/fl}$) (B). (**C**). Immunohistochemical analysis of WNT4 in 4-mo-old WT, prKO and prwKO testes. (**D**). Immunohistochemical analysis of WNT4 in 2-mo-old WT, srKO and srwKO testes. (**E**), HE staining of 2-mo-old WT, Wnt4 somatic progenitor cell knockout (noted as pwKO, Sf1:Cre,Wnt4fl/fl) and Wnt4 Sertoli cell knockout testis (noted as swKO, Amh:Cre,Wnt4fl/fl). (**F**), RTqPCR analysis of mRNAs levels encoding *Ddx4* in 4-mo-old WT, prKO and prwKO testes. Bars represent the mean expression per group ± SD. Statistical analysis was performed using Welch's one-way ANOVA followed by Games-Howell multiple correction test. (**G**), TCM staining of 2-mo-old WT, prKO and prwKO testes. *p<0.05, **p<0.01, ***p<0.001. Scale bars, 100µm.

Acronyme	Description		Color code
	Target cell type	Target gene(s)	
prKO	**P**rogenitor cell conditional	***R1a* KO**	
prKO, *Prkaca*$^{+/-}$	**P**rogenitor cell conditional	***R1a* KO** and *Prkaca*$^{+/-}$	
***Prkaca*$^{+/-}$**		*Prkaca*$^{+/-}$	
srKO	**S**ertoli cell conditional	***R1a* KO**	
lrKO	**L**eydig cell conditional	***R1a* KO**	
pwKO	**P**rogenitor cell conditional	***Wnt4* KO**	
swKO	**S**ertoli cell conditional	***Wnt4* KO**	
prwKO	**P**rogenitor cell conditional	***R*1a and *Wnt4* KO**	
srwKO	**S**ertoli cell conditional	***R*1a and *Wnt4* KO**	

Table S1. Mouse models developed for the study

	CNC-LCCSCT 1	CNC-LCCSCT 2	CNC-LCCSCT 3
Identification number	BH14 16096	SI-109-208	N518-740
Associated center	Rouen, France	Bethesda, USA	Bethesda, USA
Carney complex	Yes	Yes	Yes
Prkar1a mutation	Yes	Yes	*PRKAR1A* genetic testing was indeterminate, due to lack of peripheral DNA testing.
	ex7, c.695dup, p.Arg233LysfsX15	c.891+3A>G p.Glu297Glu	
Age	25 years	7 years	6 years
Orchiectomy	Partial - right testis	Bilateral Orchiectomy (left orchiectomy at age 7 and right orchiectomy at age 10)	Partial – left testis
CNC associated manifestations	LCCSCT Cardiac myxomas Cutaneous myxomas Pituitary microadenomas Thyroid nodules	LCCSCT Cardiac myxomas Lentigines and conjunctival pigmentation PPNAD	LCCSCT Pigmentary lesions
Hormonal manifestations	LH 4UI/l (N: 1.7-8.6) FSH 3.8UI/l (N: 1.5-12.4) Testosterone 3.77ng/ml (N : 3-9) Estradiol 20pg/ml (N : 10-60) TeBG 26nmol/l (N : 17-34) Delta4androstenedione 2.3ng/ml (N : 0.9-2.4).	LH 0.1 U/L FSH <0.1 U/L Testosterone 1.14 ng/mL (Tanner II) Estradiol <10 pg/mL	Not available

Table S2. Clinical data of CNC patients

IHC							
Antibody	**Supplier**	**Reference**	**Host**	**Dilution**	**Unmasking (boiling = 25 min.)**	**Amplification**	
						Antibody	**Substrat**
CLDN11	Invitrogen	36-4500	Rabbit	1/500	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
β-catenin	BD Biosciences	610153	Mouse	1/500	Vector Unmasking Solution H-3300, Vector Laboratories	ImmPRESS Polymer Detection Kit MP-2400, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
DDX4	Abcam	ab13840	Rabbit	1/500	Vector Unmasking Solution H-3300, Vector Laboratories	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
G9A	Cell Signaling	3306S	Rabbit	1/100	Tris 10mM, EDTA 1mM, pH 9.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
GFP	Abcam	ab5450	Goat	1/1000	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7405, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
HIF2A	R&D Systems	NB100-132	Mouse	1/200	Tris 10mM, EDTA 1mM, pH 9.0	ImmPRESS Polymer Detection Kit MP-2400, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
LAMB	Novus	L9393	Rabbit	1/200	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
p4EBP1	Cell Signaling	2855	Rabbit	1/200	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	Vector NovaRED Kit SK-4800, Vector Laboratories
pERK	Cell Signaling	4370	Rabbit	1/50	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
PCNA	Santa Cruz	sc-56	Mouse	1/500	Sodium Citrate 10mM, Tween 0.05%, pH 6.0		
SOX9	Milipore	AB5535	Rabbit	1/5000	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
SYCP3	Abcam	ab97672	Mouse	1/2000	Sodium Citrate 10mM, Tween 0.05%, pH 6.0		
SYCP3	Abcam	ab150292	Rabbit	1/1000	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
TUBB3	Sigma	T2200	Rabbit	1/5000		ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
VIM	Cell Signaling	5741	Rabbit	1/500	Tris 10mM, EDTA 1mM, pH 9.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
WNT4	Abcam	Ab91226	Rabbit	1/200	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
ZBTB16	R&D Systems	AF2944	Goat	1/1000	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7405, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen
ZBTB16	Santa Cruz	sc-22839	Rabbit	1/1000	Sodium Citrate 10mM, Tween 0.05%, pH 6.0	ImmPRESS Polymer Detection Kit MP-7401, Vector Laboratories	TSA Alexa-coupled Kit Invitrogen

WB				
Antibody	**Supplier**	**Reference**	**Host**	**Dilution**
4EBP1	Cell Signaling	9644	Rabbit	1/1000
Actin	Sigma	A2066	Rabbit	1/5000
β-catenin (active)	BD Biosciences	610153	Mouse	1/1000
β-catenin (total)	Cell Signaling	8814	Rabbit	1/500
ERK	Cell Signaling	9102	Rabbit	1/1000
GAPDH	Sigma	G9545	Rabbit	1/5000
p4EBP1	Cell Signaling	2855	Rabbit	1/1000
pERK	Cell Signaling	9106	Mouse	1/2000
pS6K	Cell Signaling	9208	Rabbit	1/1000
S6K	Cell Signaling	9202	Rabbit	1/1000

Table S3. Antibodies and conditions for immunohistochemistry and western blot

	Forward	Reverse
Actb	TCATCACTATTGGCAACGAGC	AGTTTCATGGATGCCACAGG
Axin2	ATGGGGAGTAAGAAACAGCTCC	CCAGCTCCAGTTTCAGTTTCTC
Calb2	GGAAGCACTTTGATGCTGACG	TCTCCAGCTCCTGGAAGAAGT
Ccdc80	AGGCATGCAATTTTGGTCTGC	ACATCTTCCCGCTCAACGAT
Cdh5	ATTGGCCTGTGTTTTCGCAC	CACAGTGGGGTCATCTGCAT
Cldn11	CAGGCTTGTAGAGCCCTCAT	GTGGGCACATACAGGAAACC
Ctnna1	CAGTTCGCTGCAGAAATGAC	CAGCCAAAACATGGGCCTTC
Ctnnb1	AGTGCAGGAGGCCGAGG	GAGTAGCCATTGTCCACGCA
Ddx4	AGAGGGTTTTCCAAGCGAGG	CTGAATCACTTGCTGCTGGTTT
Dpt	TGCCGCTATAGCAAGAGGTG	CTTCCACTGGCGATCCCTTT
Egf	TGGAACCCAGTGGAATCACG	TGGGATAGCCCAATCCGAGA
F11r	TTGGCGTCTGGTTTGCCTAT	CACTTCGAGTACTGGGCTGG
Fgf2	CGCGAGAAGAGCGACCCACAC	GGCACACACTCCCTTGATAGACACAA
Gja1	AGGAGTTCCACCACTTTGGC	AGCGAAAGGCAGACTGTTCA
Hif1a	AGATGACGGCGACATGGTTT	GATGTTCATCGTCCTCCCCC
Hif1b	GGCGACTACAGCTAACCCAG	GGCAAACCGCTCTTTGTCATT
Hif2a	GGAGCTACTTGGACGCTCTG	GTTGCGGGGGTTGTAGATGA
Igf1	CTGGACCAGAGACCCTTTGC	CCGGAAGCAACACTCATCCA
Inha	TCCTGGTAGCCCACACTAGG	GAAACTGGGAGGGTGTACGA
Itgav	CGTCCTCCAGGATGTTTCTCC	CCAAACCACTGGTGGGACTT
Jup	GTCCCTTTGCCTTTTGTTCGG	ACCTTGATGGGCTGCTCAAT
Ki67	AGTCTCTTGGCACTCACAGC	ATGGATGCTCTCTTCGCAGG
Kitl	ACGTCTGAGTGCTGAAAACCC	CACCATCCAGGCTGAAATCTAC
Myc	GGCTGGATTTCCTTTGGGCG	CGGAGTCGTAGTCGAGGTCA
Nr0b1	GGTCCAGGCCATCAAGAGTTT	CCGGATGTGCTCAGTAAGGAT
Ocln	ACGGACCCTGACCACTATGA	TCCTGCAGACCTGCATCAAA
Prkar1a	CGGGAATGCGAGCTCTATGT	CTCGAGTCAGTACGGATGCC
Pvrl2	GCGTCAAGGTCACGTGTAGA	ATAGTCTGTGGGCTCTGGGT
S100a1	AGGTCGGTAGGGAAAGACGA	CCAGCTCAGAGCCCATTTCA
Tgfb1	AGGGCTACCATGCCAACTTC	CCACGTAGTAGACGATGGGC
Tgfb2	GGGTCTTCCGCTTGCAAAAC	GAAGGAGAGCCATTCACCCT
Tgfb3	AGCGCTACATAGGTGGCAAG	CCATTGGGCTGAAAGGTGTG
Tubb3	TTGGACACCTATTCAGGCCC	ACTCTTTCCGCACGACATCT
Vcl	CCTCCTCCACCAGACCTTGA	TGTCATTGCCCTTGCTAGACC
Vim	GGATCAGCTCACCAACGACA	AAGGTCAAGACGTGCCAGAG
Wnt4	CCCTGTCTTTGGGAAGGTGGTG	CACCTGCTGAAGAGATGGCGTATAC
Wnt5a	CGCCCAGGTTGTTATAGAAGCTAATTCTTG	GGCTGCAGAGAGGCTGTGCAC

Table S4. Primers used for RTqPCR

Data files S1. Common and specific deregulated gene lists extracted from microarray analysis

Data files S2. Gene sets used for GSEA and Heatmap analyses

Data files S3. GO and KEGG analyses

Figure S1 related to Figure 1.

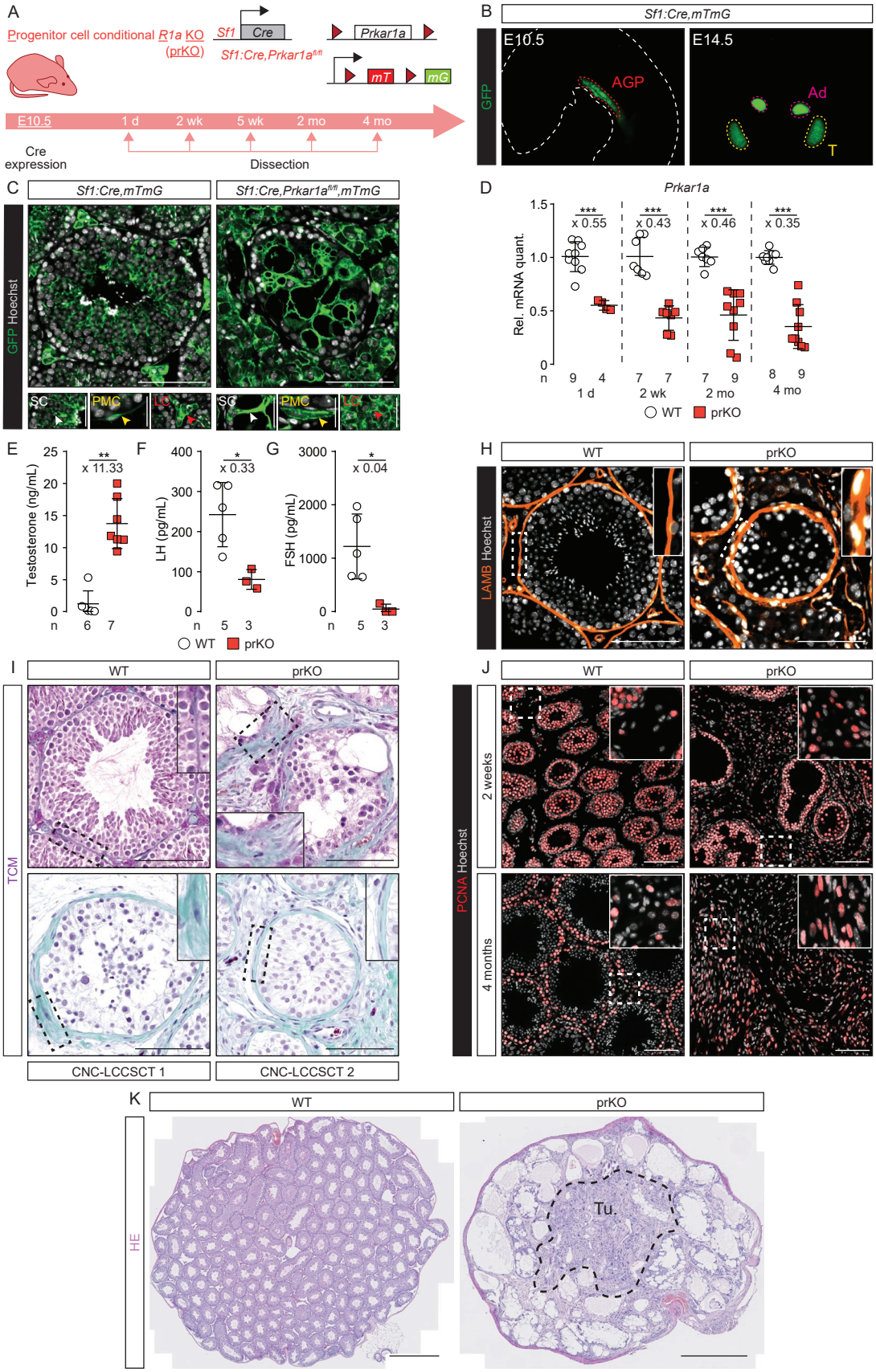

Figure S2 related to Figure 1.

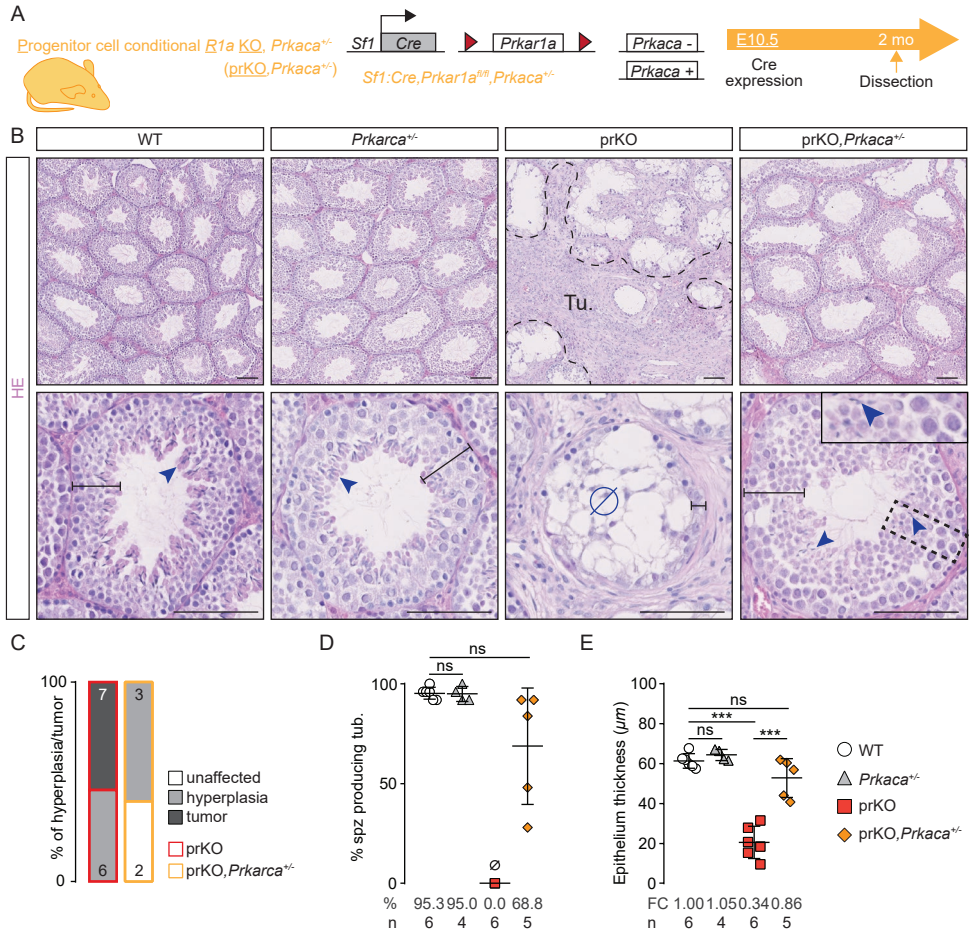

Figure S3 related to Figure 1.

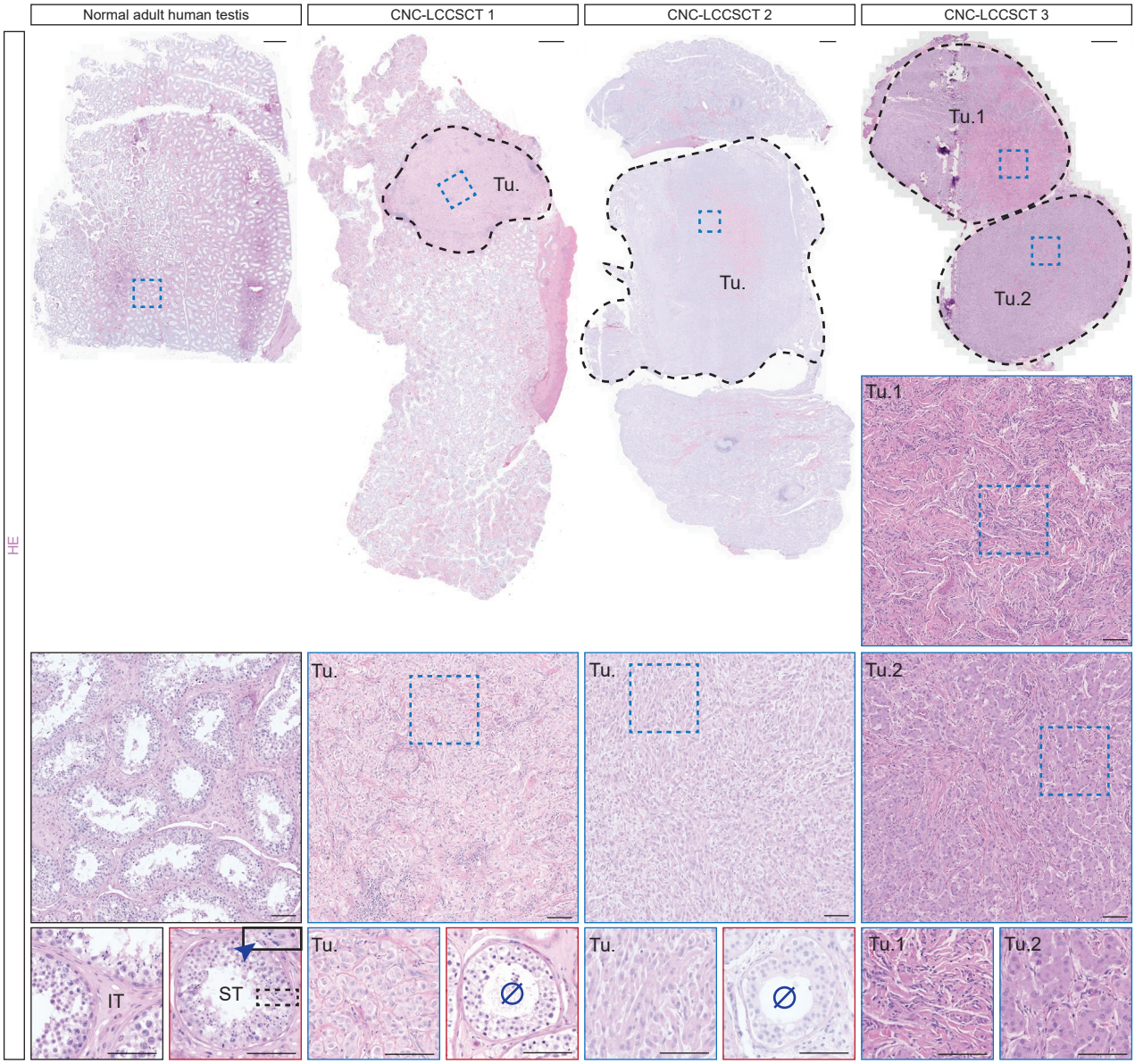

Figure S4 related to Figure 2.

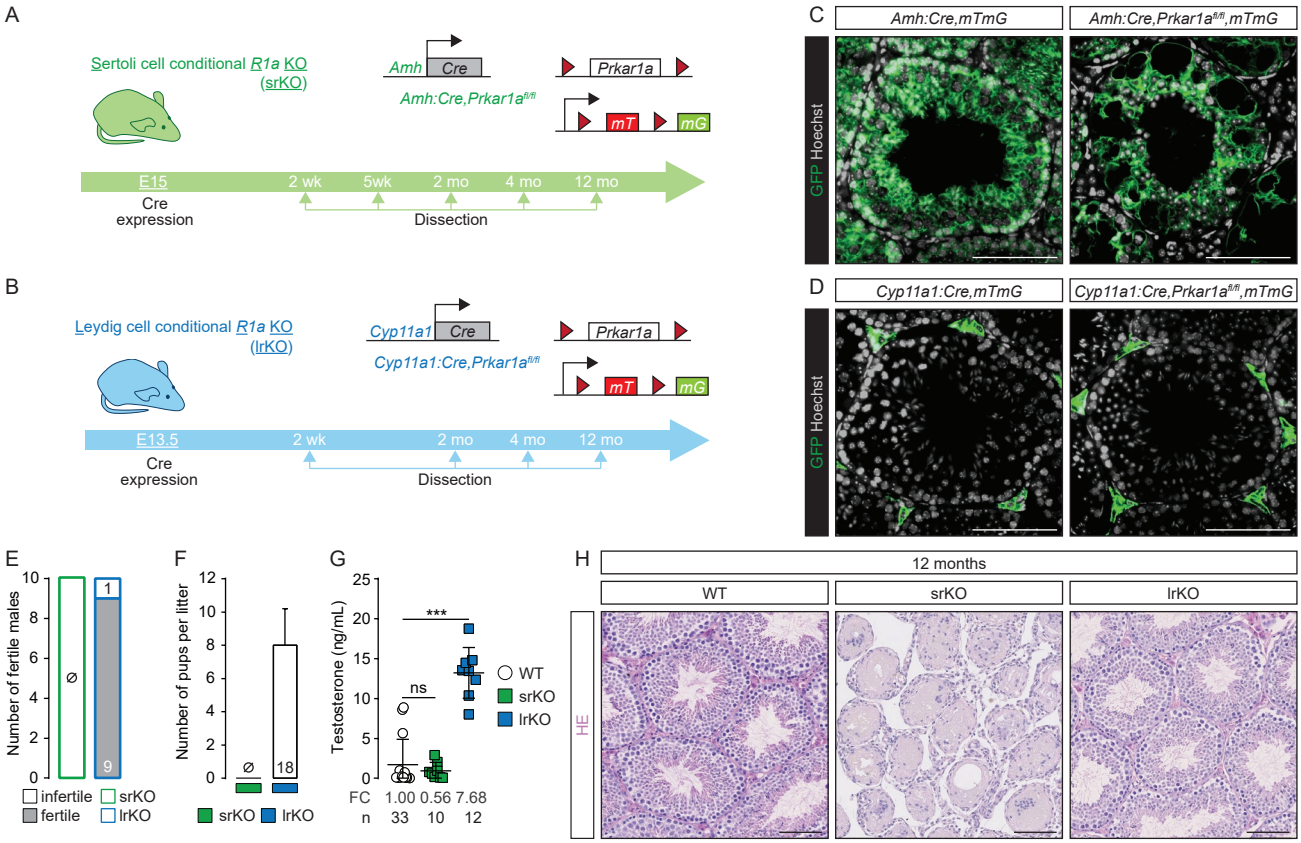

Figure S5 related to Figure 3.

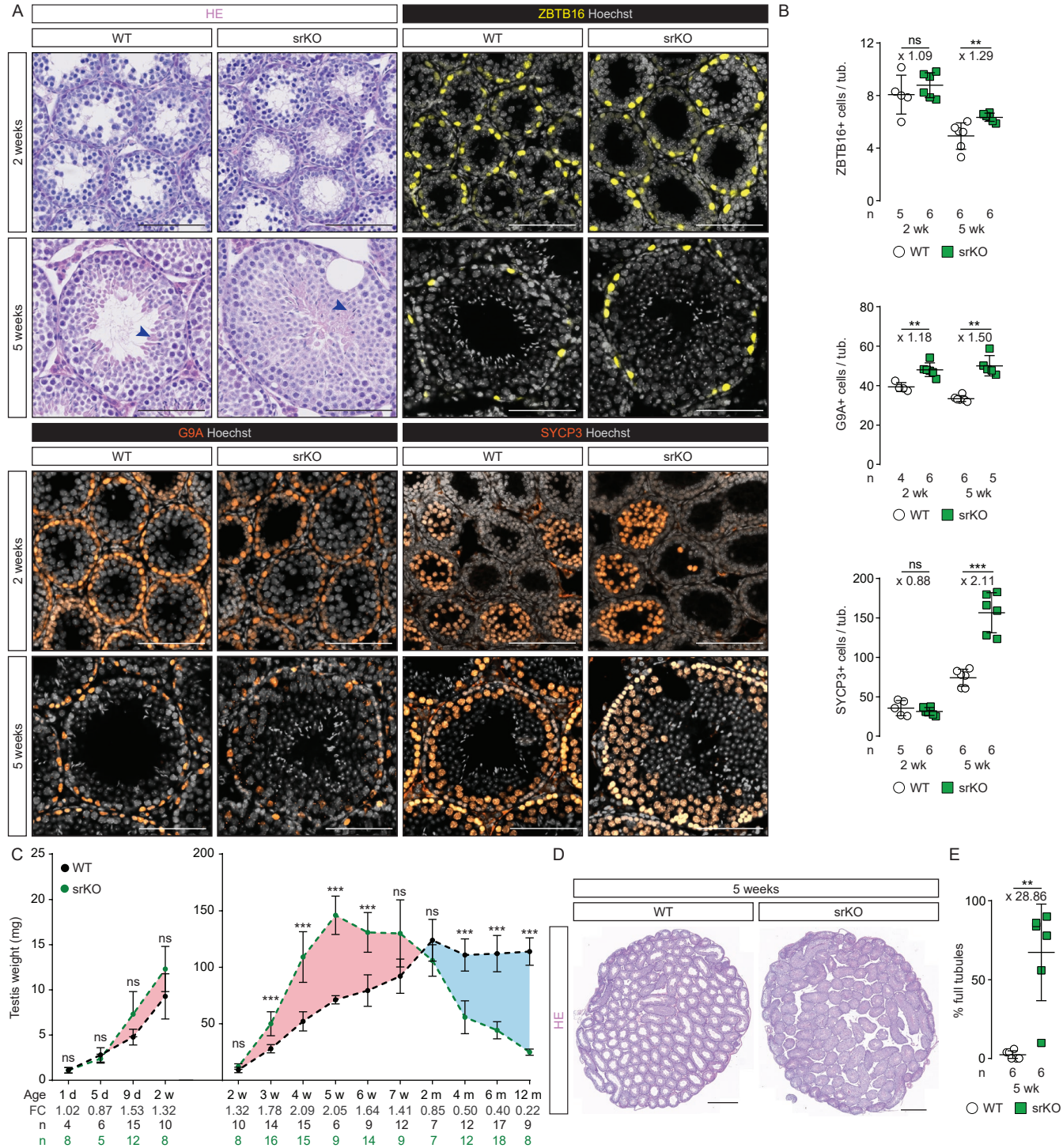

Figure S6 related to Figure 3.

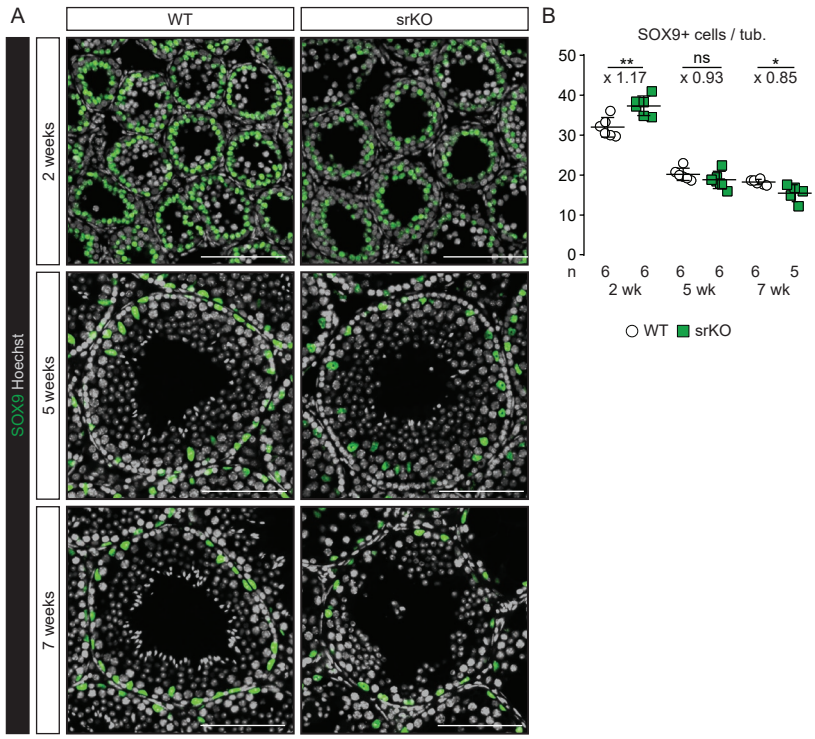

Figure S7 related to Figure 4.

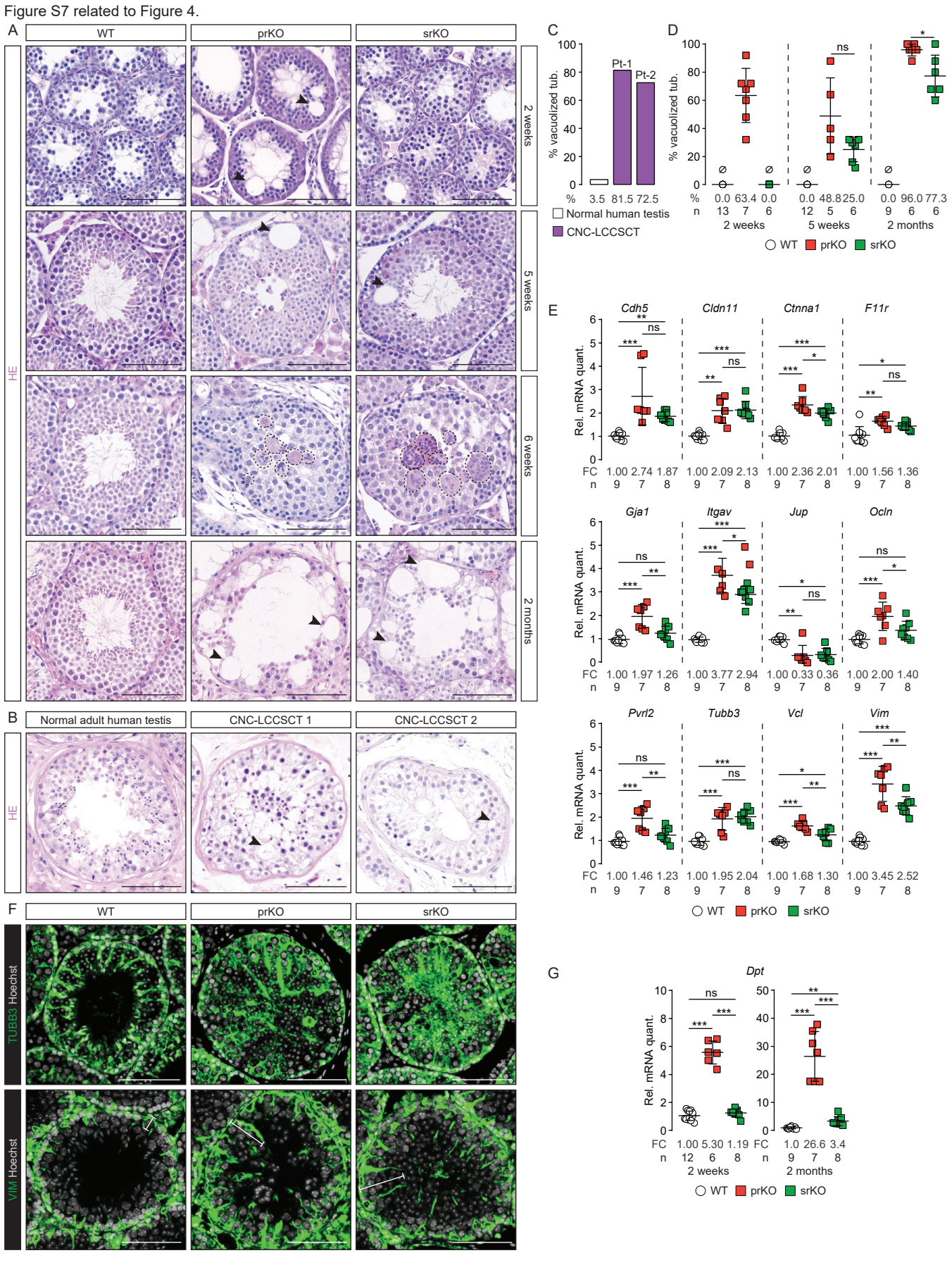

Figure S8 related to Figure 5.