

Supplementary Figure Legends

Supplementary Figure S1. Cyld is expressed in mouse skin and hair follicles.

Frozen tissue sections of newborn and 1-month old mice back skin were immunostained with a rabbit anti-Cyld antibody (Ab-H419, Santa Cruz Biotechnology) followed by detection with a donkey anti-rabbit secondary antibody conjugated with Alexa-555 [orange]. Nuclei [blue, Hoechst 32258]. Scale bars: 100 μ m.

Supplementary Figure S2. K14-Cre mediated knock-in expression of Cyld^m in mice.

(A) Schematic representation of *Cyld*^{flx} allele and Cre-recombined *Cyld*^{E49} allele and the location of the primers used for genotyping by PCR and RT-PCR. **(B-C)** Confirmation of K14-Cre-mediated deletion of *Cyld* exon 9 by PCR and RT-PCR with genomic DNA and total RNA isolated from epidermal cells. PCR-amplified DNA and cDNA were analyzed on 1.2% agarose gel. **(D)** Immunoblotting of mouse skin extracts with antibodies against Cyld (Ab-H419) and Actin (SC1616, Santa Cruz Biotechnology). **(E)** Immunoblotting of mouse skin extracts with antibodies against pI κ B α (S32) and p-c-Jun(S73) (#2859 and #9164, Cell Signaling Technology), I κ B α and Actin (SC847 and SC1616, Santa Cruz Biotechnology).

Supplementary Figure S3. Hair defects of *Cyld*^{E49/49} mice. **(A)** Normal representation of different hair types. A total of 300-400 hairs were counted from 3 mice of each genotype. Graph represents the percentages of each hair type +/- SD. **(B)** Microscopic images of each hair type. Note the reduced thickness of *Cyld*^{E49/49} hairs.

Supplementary Figure S4. Sebaceous gland hyperplasia in adult in *Cyld*^{E49/49} mice skin. **(A-B)** H&E staining of back skin tissues from newborn and 18-day old mice. **(C)**

Oil red staining of epidermal whole mount of the tail skin. Tail skin pieces of 1-month old mice were treated with dispase overnight at 4 °C to separate epidermis from dermis. The epidermal sheets were stained with 0.18% oil red in PBS. (D) H&E staining of eyelid tissue sections of 1-month old mice. (E) Oil red staining of an eyelid skin section. Arrowheads mark sebaceous glands. Scale bars: 50 μm.

Supplementary Figure S5. TPA-treatment enhances epidermal and sebaceous gland hyperplasia in *Cyld*^{EΔ9/Δ9} mice. The back skin of WT, *Cyld*^{EΔ9/+} and *Cyld*^{EΔ9/Δ9} mice (n=3) were treated with TPA twice weekly for 2 weeks. Skin tissues were collected for H&E staining. Scale bar: 40 μm.

Supplementary Figure S6. Tumors induced on *Cyld*^{EΔ9/Δ9} and control mice are highly proliferative. Immunostaining of the frozen tissue sections of tumors developed on WT, *Cyld*^{EΔ9/+} and *Cyld*^{EΔ9/Δ9} mice with primary antibodies against (A) Ki-67 (SP6, ThermoFisher Scientific) and (B) cleaved caspase 3 (C. caspase 3) (D175, Cell Signaling Technology). Ki-67 and C. caspase 3 [orange]; Nuclei [blue, Hoechst 32258]. Scale bar: 100 μm.

Supplementary Figure S7. Tumors induced on *Cyld*^{EΔ9/Δ9} and control mice express epithelial cell markers. Immunostaining of the frozen tissue sections of tumors developed on WT, *Cyld*^{EΔ9/+} and *Cyld*^{EΔ9/Δ9} mice with primary antibodies against (A) cytokeratin 5 (K5) (PRB-160P, Covance), (B) cytokeratin 17 (K17) (AB53707, Abcam) and (C) E-cadherin (24E10, Cell Signaling Technology). K5, K17 and E-cadherin [orange]; Nuclei [blue, Hoechst 32258]. Scale bar: 100 μm.

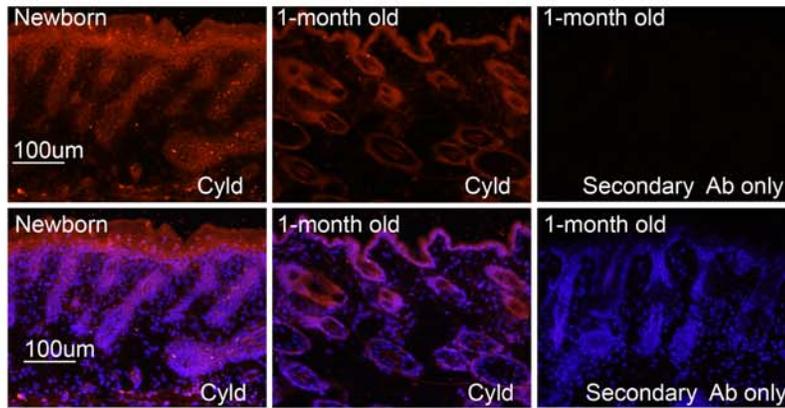
Supplementary Figure S8. Expression of CDK4, β -catenin and Gli1 in tumors

induced on $Cyld^{E49/\Delta 9}$ and control mice. Immunostaining of the frozen tissue sections of tumors developed on WT, $Cyld^{E49/+}$ and $Cyld^{E49/\Delta 9}$ mice with primary antibodies against **(A)** β -catenin (A00407, Genscript), **(B-C)** CDK4 and Gli1 (SC260 and SC20687, Santa Cruz Biotechnology). β -catenin, CDK4 and Gli1 [orange]; Nuclei [blue, Hoechst 32258]. Scale bar: 100 μ m.

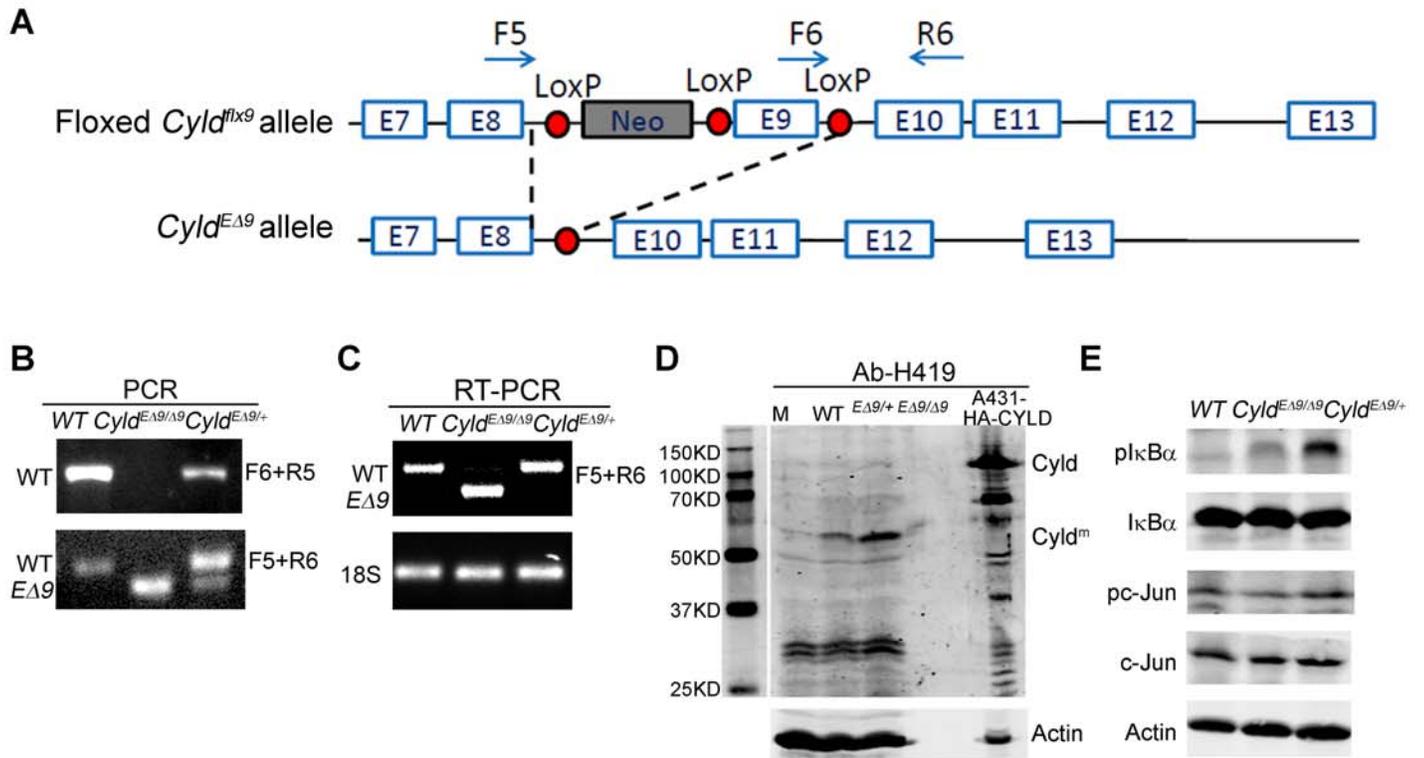
Supplementary Figure S9. Expression of β -catenin and CDK4 in WT and $Cyld$

mutant mouse skin. **(A-B)** Immunostaining of 3-month old adult back skin sections with primary antibodies against (A) β -catenin and (B) CDK4. β -catenin and CDK4 [orange]; Nuclei [blue, Hoechst 32258]. Scale bar: 100 μ m. Asterisks mark hair follicles and sebaceous glands. CDK4 appeared increased in sebaceous glands of $Cyld^{E49/\Delta 9}$ skin.

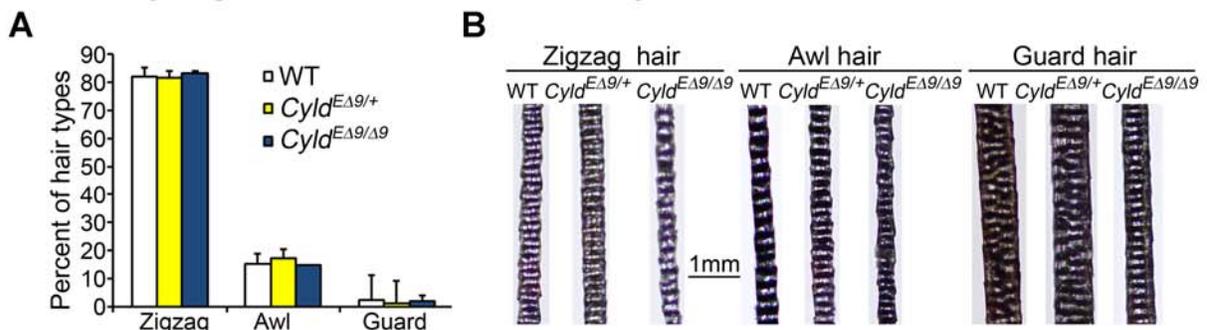
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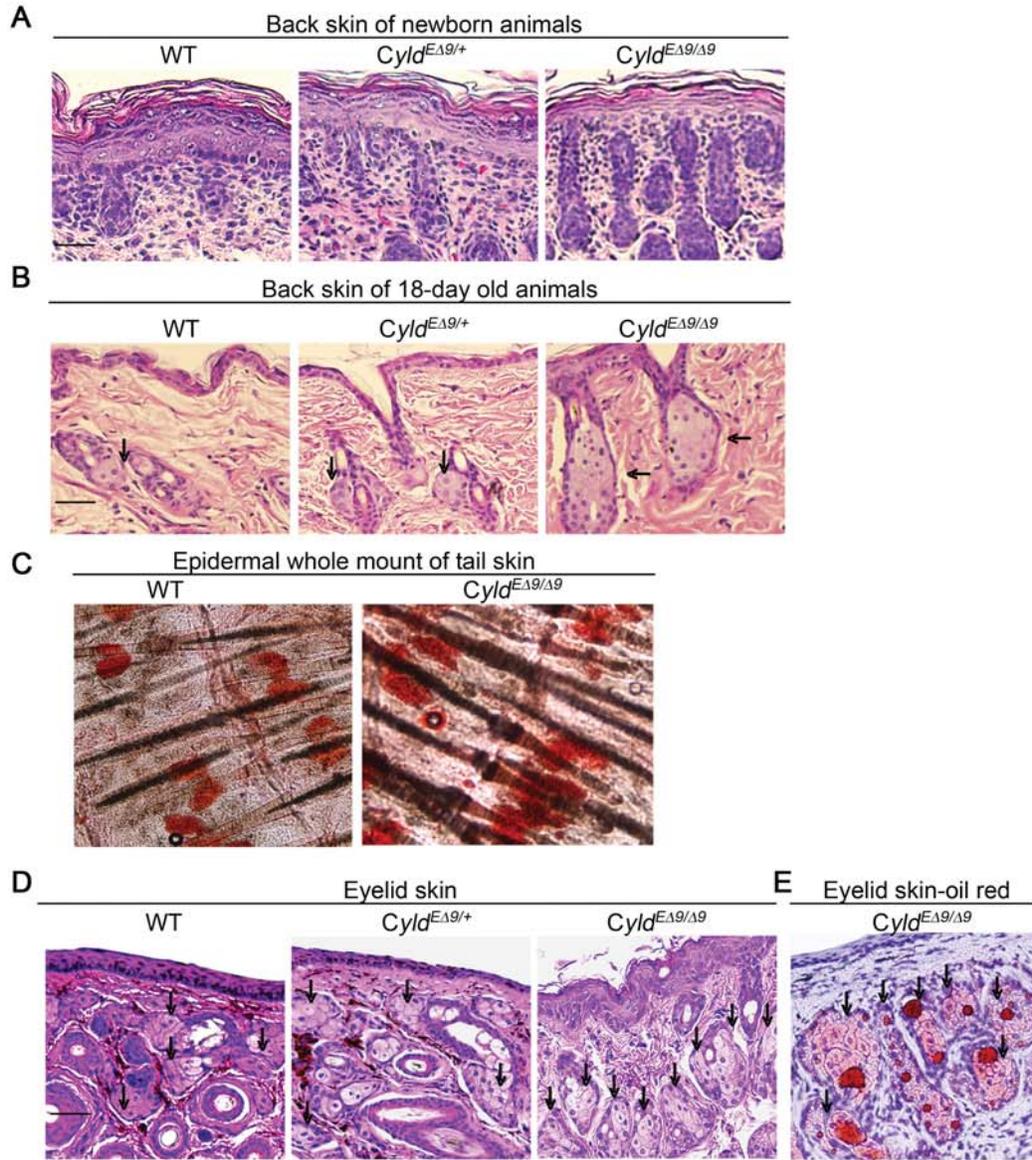
Supplementary Figure S2. K14-Cre mediated knock-in expression of *Cyld^m* in mice.



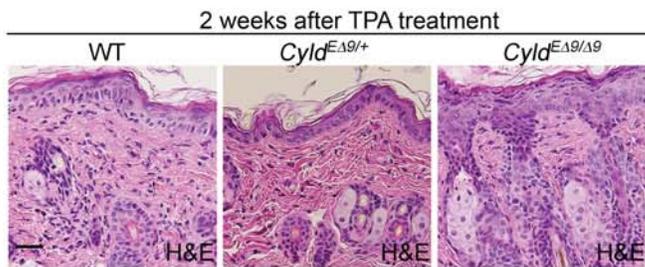
Supplementary Figure S3. Hair defects of *Cyld^{EΔ9/Δ9}* animals.



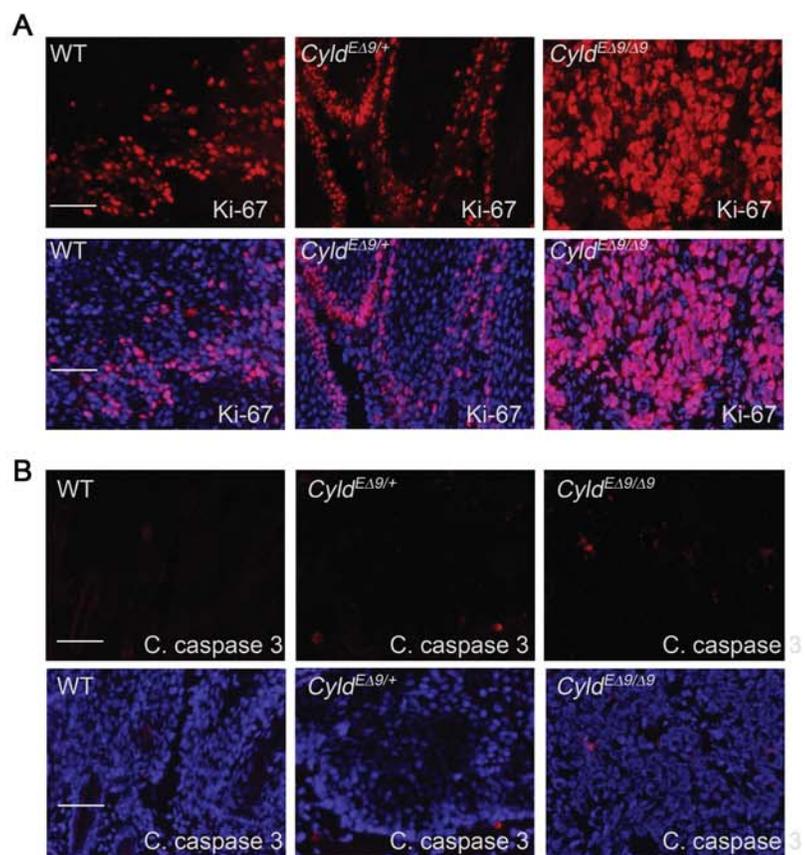
Supplementary Figure S4. Sebaceous gland hyperplasia in adult *Cyld*^{EΔ9/Δ9} animals.



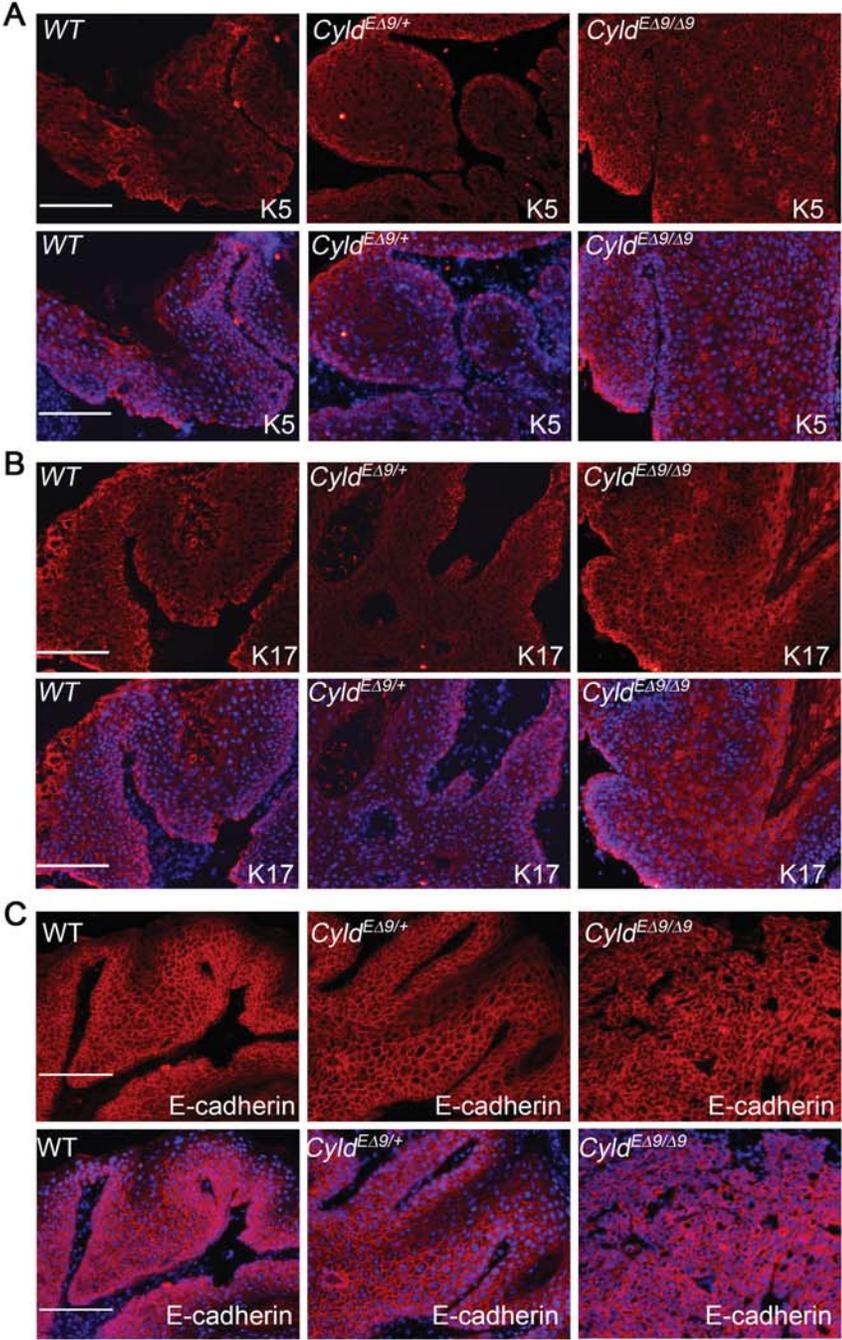
Supplementary Figure S5. TPA-treatment enhances sebaceous gland and epidermal hyperplasia in *Cyld*^{EΔ9/Δ9} mice.



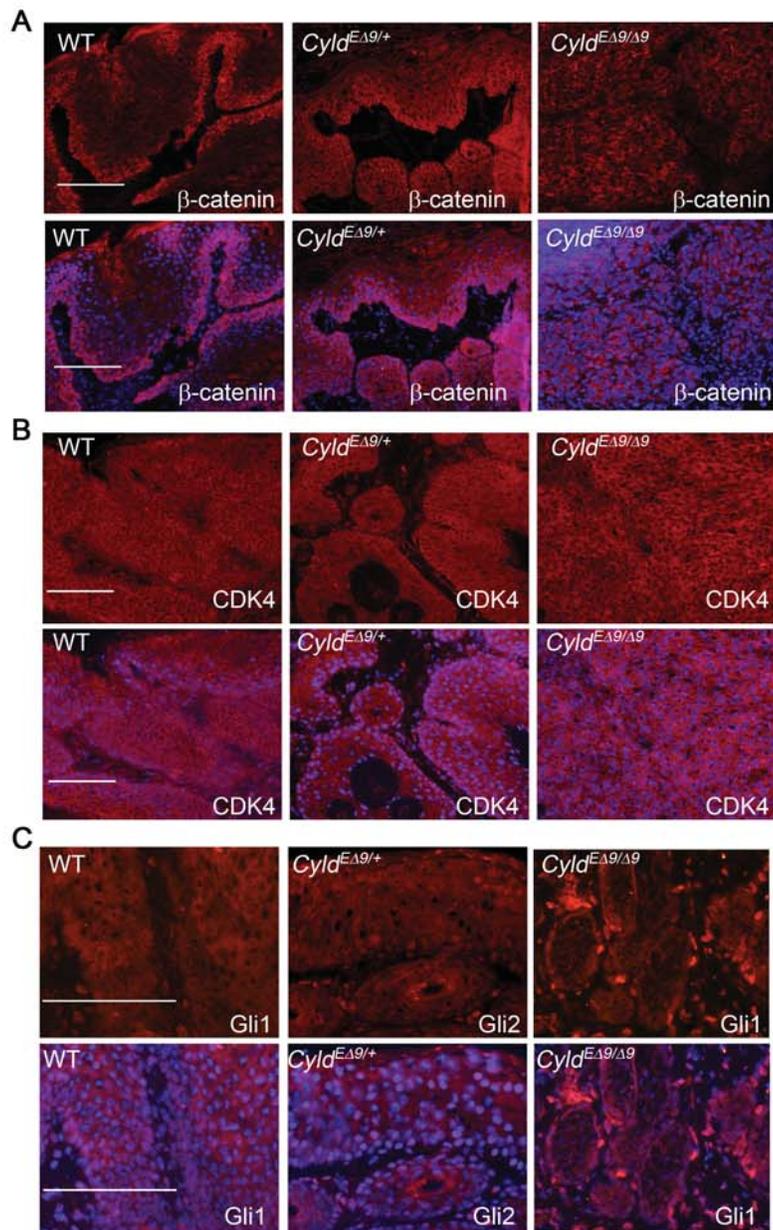
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Supplementary Figure S7. Tumors induced on *Cyld*^{EΔ9/Δ9} and control mice express epithelial cell markers.



Supplementary Figure S8. Expression of CDK4, β -catenin and Gli1 in tumors induced on *Cyld*^{E Δ 9/ Δ 9} and control mice.



Supplementary Figure S9. Expression of β -Catenin and CDK4 in WT and mutant mouse skin.

