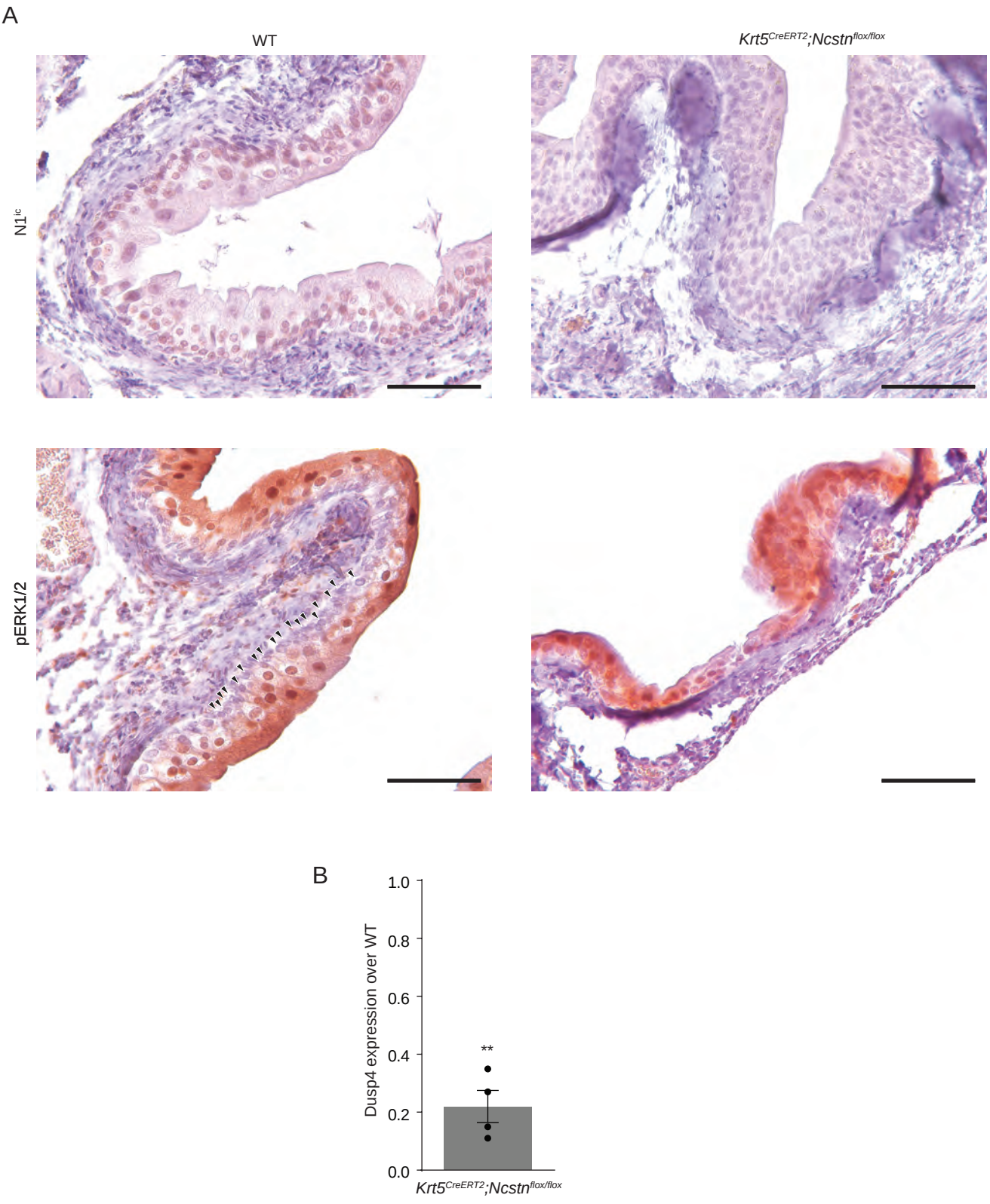
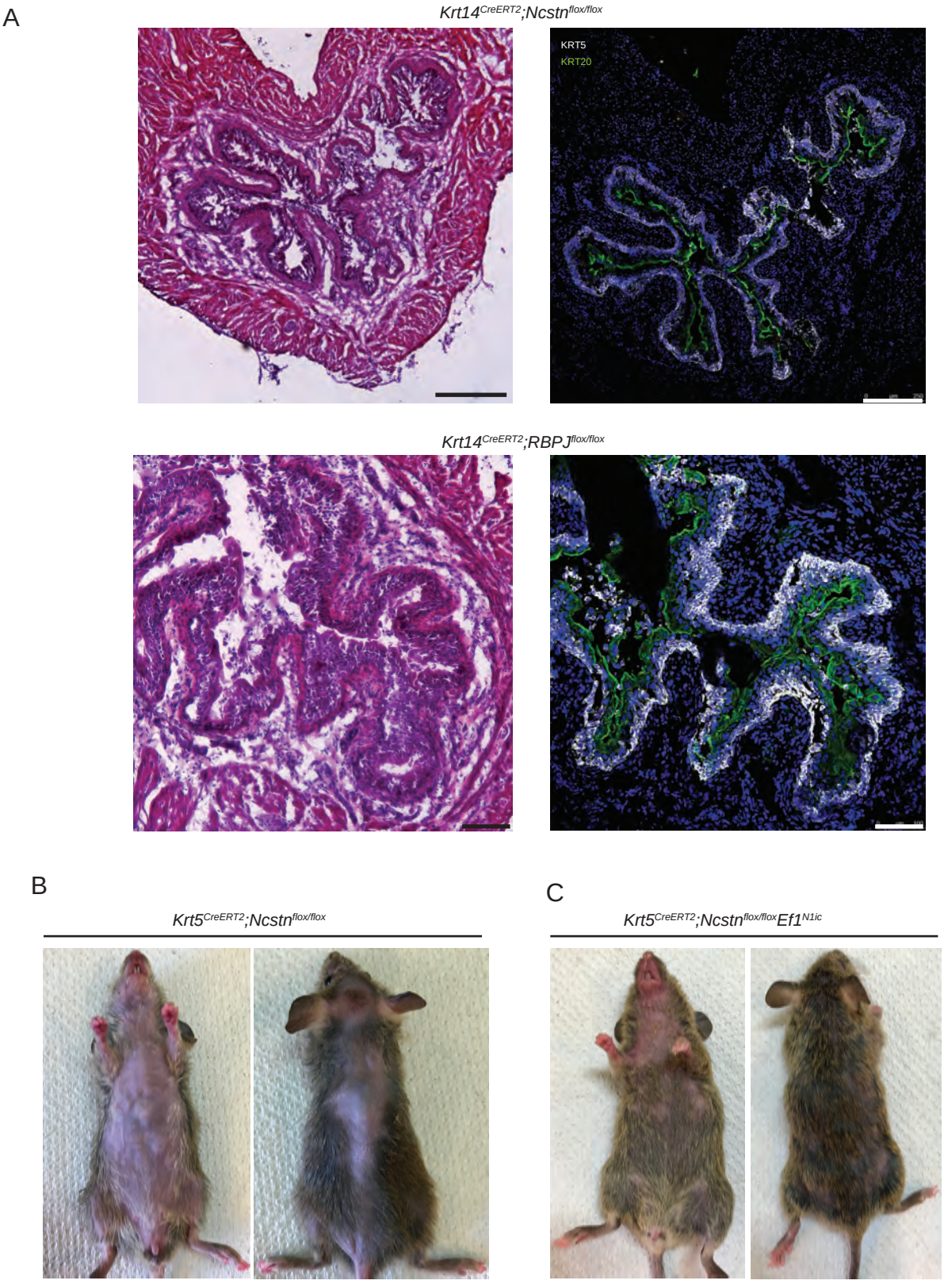
Supplemental Fig 1



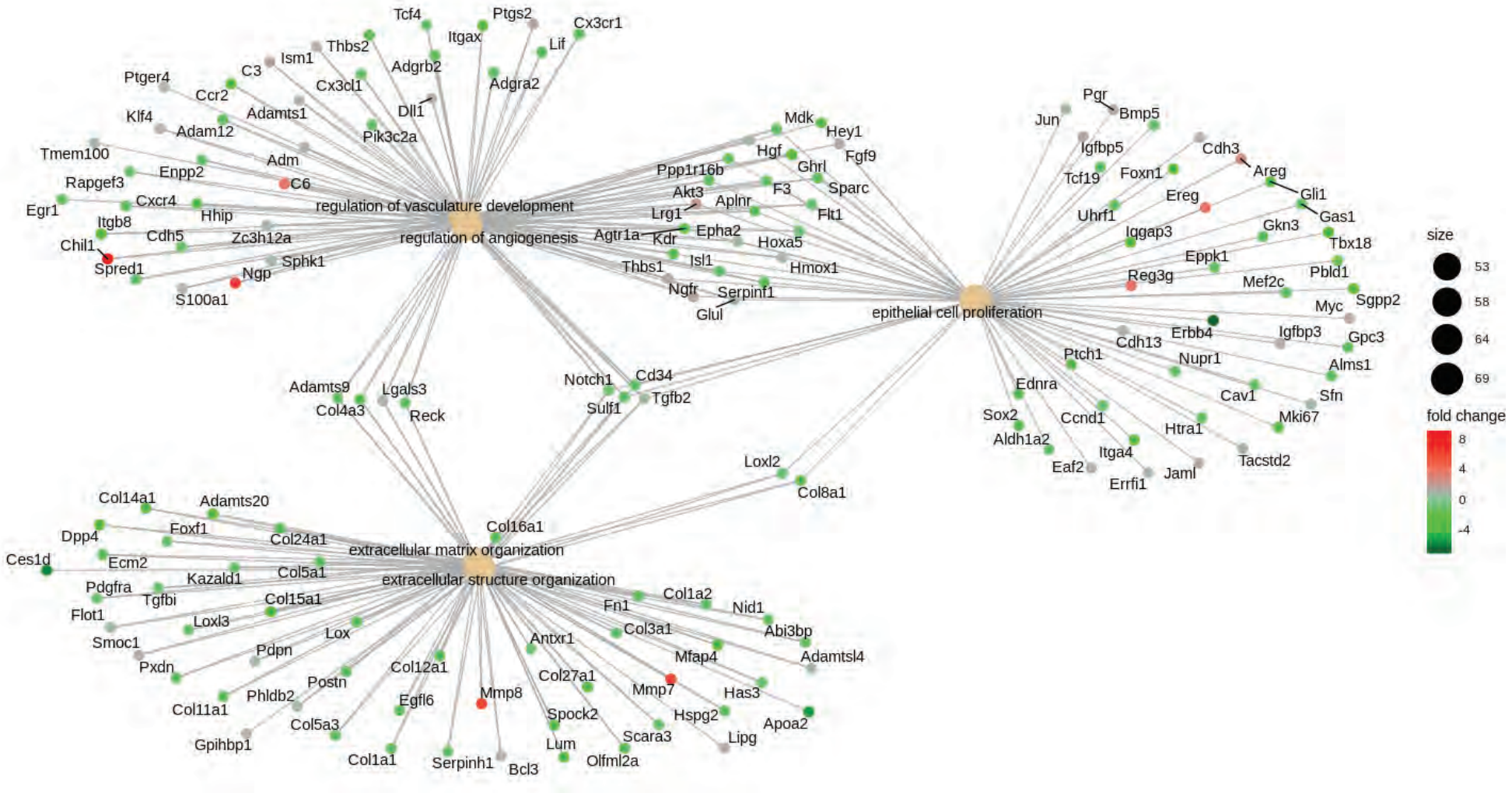
Supplemental Fig 1. Genetic inactivation of the Notch pathway leads to loss of nuclear N1 signal and elevation of activated ERK1/2. (A) Immunohistochemistry with antibodies against the nuclear form of NOTCH1 (N1ic; top) and phosphorylated ERK1/2 (pERK1/2; bottom) in WT and Notch deficient (in this case *Krt5^{CreERT2};Ncstn$^{flox/flox}$*) mice. Note the obvious lack of intracellular NOTCH1 and pERK1/2 in basal cells (black arrowheads). Scale bars indicate 100 μm. (B) Quantitative RT-PCR analysis of *Dusp4* from urothelial cell RNA of *Krt5^{CreERT2};Ncstn$^{flox/flox}$* mice (n=4). Expression is presented as ratio over WT mice (n=4). ** indicates $p<0.01$. Student's t test was used.

Supplemental Fig 2



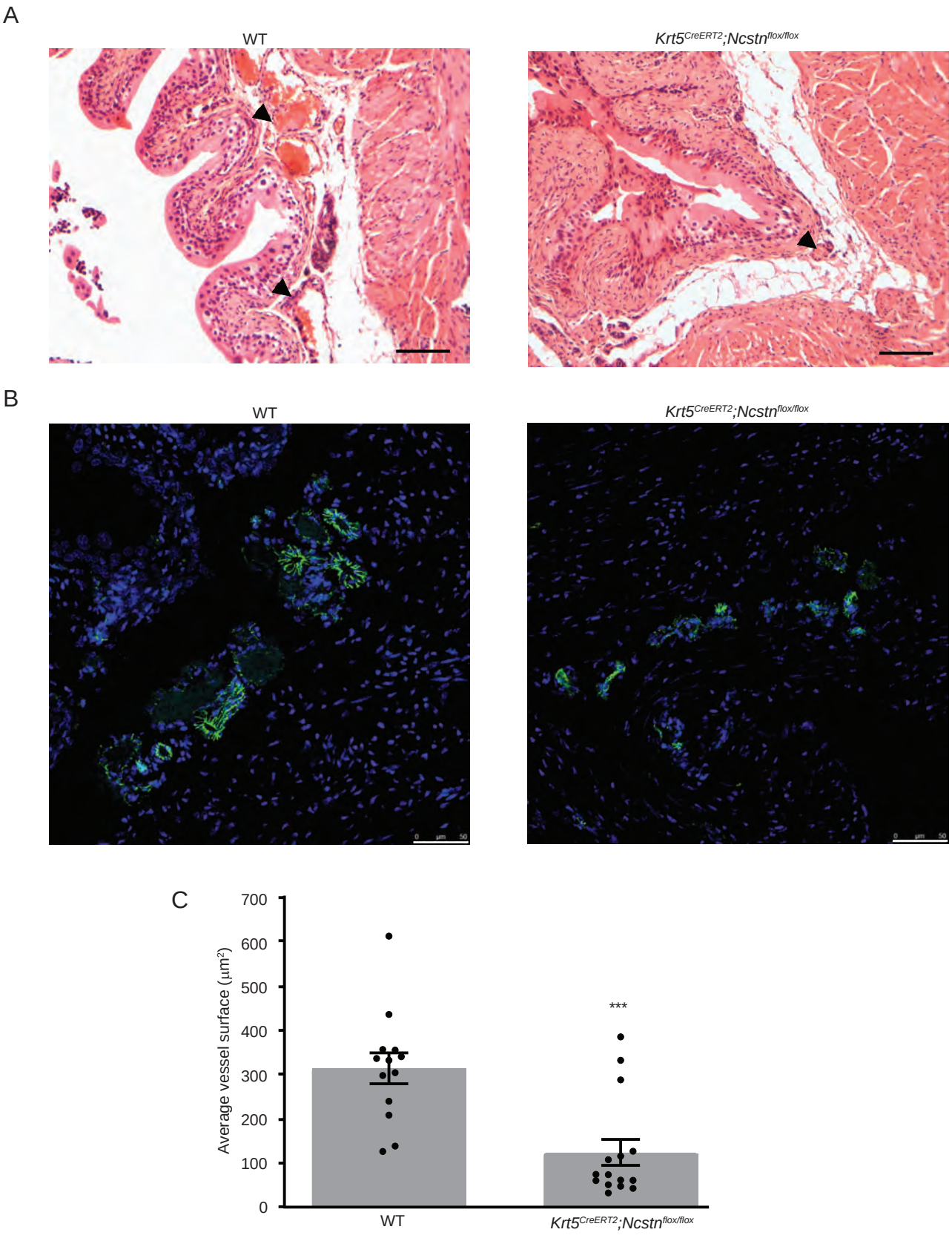
Supplemental Fig 2. Genetic inactivation of the Notch pathway leads to bladder and skin abnormalities. (A) H&E staining and immunofluorescence with the indicated antibodies on bladder sections from *Krt14^{CreERT2};Ncstn$^{flox/flox}$* or *Krt14^{CreERT2};RBPJ$^{flox/flox}$* mice. Scale bars indicate 250 μm (top) and 100 μm (bottom). Mice shown here do not carry the Tomato transgene. DAPI has been used as nuclear counterstain. (B) Images of *Krt5^{CreERT2};Ncstn$^{flox/flox}$* mice indicating severe skin defects. (C) Images of *Krt5^{CreERT2};Ncstn$^{flox/flox}$;Ef1^{N1ic}* mice showing serious amelioration of the Notch loss-induced skin phenotype.

Supplemental Fig 3



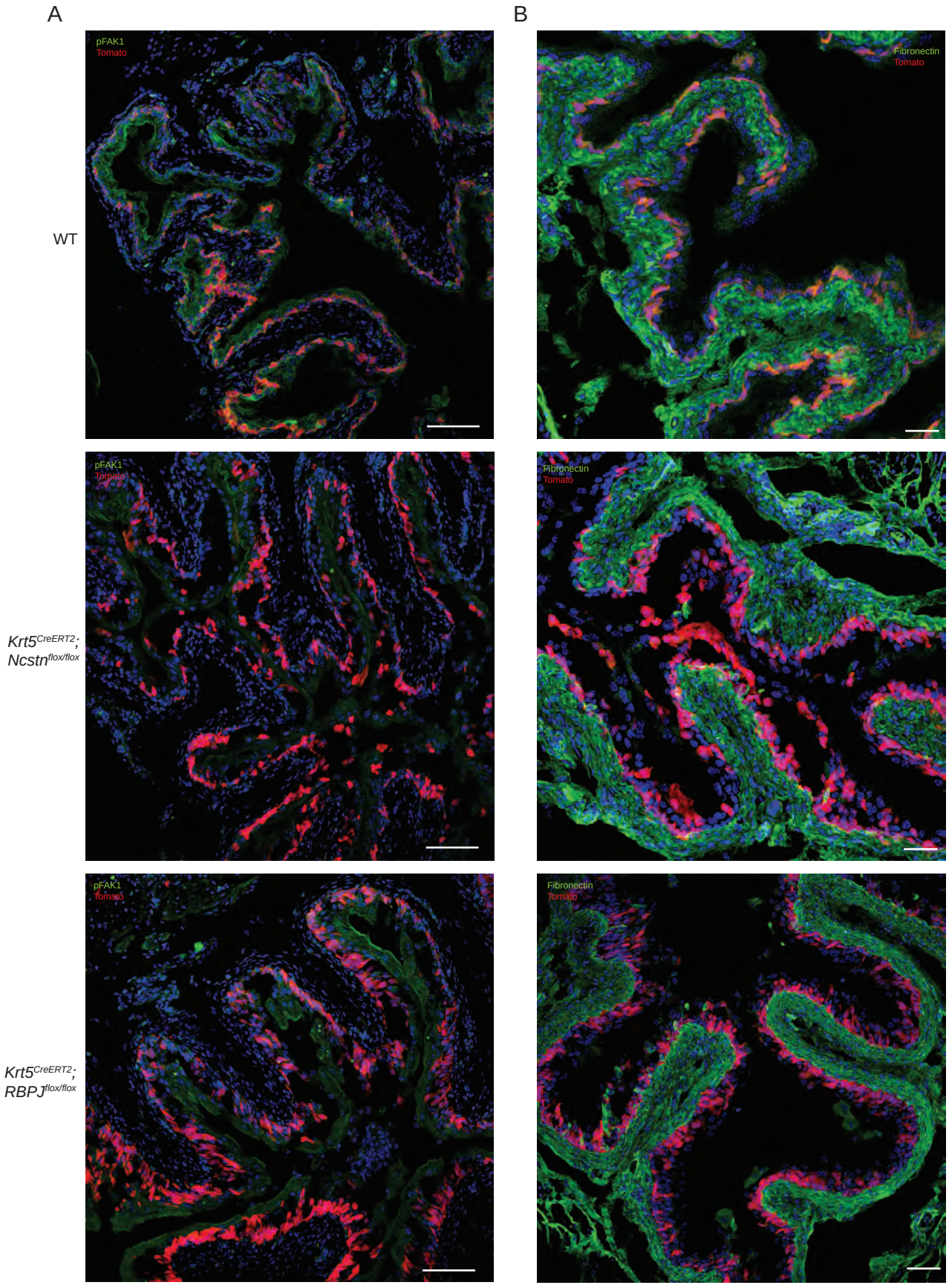
Supplemental Fig 3. Gene Ontology annotation network. The plot depicts the linkages of genes amongst the top biological concepts (GO terms) as a network. The size of every biological process is defined by the number of implicated genes. Expression levels of the genes are represented through a continuous scale of green to red color transition. For statistical analysis see Methods section.

Supplemental Fig 4



Supplemental Fig 4. Notch loss leads to blood vessel abnormalities. (A) Hematoxylin & Eosin staining on bladder tissue from wild-type (WT) and *Krt5^{CreERT2};Ncstn$^{flox/flox}$* mice indicating smaller size blood vessels (arrowheads). Scale bars indicate 100 µm. (B) Immunofluorescence with antibodies against the vascular endothelial cell marker CD31 indicating smaller size vessels with abnormal structure. Scale bars indicate 50 µm. DAPI has been used as nuclear counterstain. (C) Scatter dot plot indicating average blood vessel surface from WT and *Krt5^{CreERT2};Ncstn$^{flox/flox}$* mice. A total of n=13 and n=15 blood vessels respectively, from 3 different mice from each group, were measured with the use of LAS AF 2.6.0 software. *** indicates $p<0.001$. Student's t test was used.

Supplemental Fig 5



Supplemental Fig 5. Notch loss leads to downregulation of ECM components and integrin signaling. Phosphorylated FAK1 (A) and fibronectin (B) immunofluorescence on bladder sections from wild-type and *Krt5^{CreERT2};Ncstn$^{flox/flox}$* or *Krt5^{CreERT2};RBPJ$^{flox/flox}$* mice. Scale bars indicate 100 μm (A) and 50 μm (B). DAPI has been used as nuclear counterstain.

Supplemental Table 1. List of processes affected in Notch KO mouse bladders and IC patients

Mouse Notch KO	Human non ulcer area (ni)
Cell adhesion molecules (CAMs)	Staphylococcus aureus infection
Phagosome	Viral protein interaction with cytokine and cytokine receptor
Viral myocarditis	Chemokine signaling pathway
Antigen processing and presentation	Cytokine-cytokine receptor interaction
Human T-cell leukemia virus 1 infection	Cell adhesion molecules (CAMs)
Protein digestion and absorption	Intestinal immune network for IgA production
ECM-receptor interaction	Hematopoietic cell lineage
Human papillomavirus infection	Allograft rejection
Graft-versus-host disease	Leishmaniasis
Renin secretion	Type I diabetes mellitus
Type I diabetes mellitus	Graft-versus-host disease
Cellular senescence	Rheumatoid arthritis
Allograft rejection	Th1 and Th2 cell differentiation
Epstein-Barr virus infection	Viral myocarditis
AGE-RAGE signaling pathway in diabetic complications	Inflammatory bowel disease (IBD)
Focal adhesion	Th17 cell differentiation
Gap junction	T cell receptor signaling pathway
Dilated cardiomyopathy (DCM)	Natural killer cell mediated cytotoxicity
Autoimmune thyroid disease	Epstein-Barr virus infection
Metabolism of xenobiotics by cytochrome P450	Autoimmune thyroid disease
Toxoplasmosis	B cell receptor signaling pathway
Inflammatory bowel disease (IBD)	Antigen processing and presentation
MAPK signaling pathway	Asthma
Salivary secretion	NF-kappa B signaling pathway
Pentose and glucuronate interconversions	Osteoclast differentiation
cGMP-PKG signaling pathway	Primary immunodeficiency
Human cytomegalovirus infection	Phagosome
Small cell lung cancer	Systemic lupus erythematosus
Leishmaniasis	Fc gamma R-mediated phagocytosis
Tuberculosis	Toxoplasmosis
Amoebiasis	Chagas disease (American trypanosomiasis)
cAMP signaling pathway	Leukocyte transendothelial migration
Leukocyte transendothelial migration	Tuberculosis
Pathways in cancer	Fc epsilon RI signaling pathway
Colorectal cancer	PD-L1 expression and PD-1 checkpoint pathway in cancer
Cytokine-cytokine receptor interaction	Human T-cell leukemia virus 1 infection
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Malaria
Adrenergic signaling in cardiomyocytes	TNF signaling pathway
Viral protein interaction with cytokine and cytokine receptor	Toll-like receptor signaling pathway
Drug metabolism - cytochrome P450	Complement and coagulation cascades
PI3K-Akt signaling pathway	Human immunodeficiency virus 1 infection
Hematopoietic cell lineage	Pertussis
Insulin secretion	Influenza A
Herpes simplex virus 1 infection	Rap1 signaling pathway
Th1 and Th2 cell differentiation	Aldosterone-regulated sodium reabsorption
Other types of O-glycan biosynthesis	Measles
Hypertrophic cardiomyopathy (HCM)	Legionellosis
p53 signaling pathway	Platelet activation
Aldosterone-regulated sodium reabsorption	Glutathione metabolism
TNF signaling pathway	Fluid shear stress and atherosclerosis
Malaria	Yersinia infection
Proteoglycans in cancer	Amoebiasis
Calcium signaling pathway	Transcriptional misregulation in cancer

Th17 cell differentiation
ABC transporters
Cell cycle
Kaposi sarcoma-associated herpesvirus infection
Human immunodeficiency virus 1 infection
Chronic myeloid leukemia
Porphyrin and chlorophyll metabolism
Breast cancer
Prion diseases

Human ulcer area (ulcus)

Staphylococcus aureus infection
Viral protein interaction with cytokine and cytokine receptor
Cytokine-cytokine receptor interaction
Rheumatoid arthritis
Hematopoietic cell lineage
Cell adhesion molecules (CAMs)
Chemokine signaling pathway
Intestinal immune network for IgA production
Leishmaniasis
Type I diabetes mellitus
Graft-versus-host disease
Allograft rejection
Complement and coagulation cascades
NF-kappa B signaling pathway
Inflammatory bowel disease (IBD)
Th17 cell differentiation
Asthma
Viral myocarditis
Th1 and Th2 cell differentiation
Leukocyte transendothelial migration
Systemic lupus erythematosus
Osteoclast differentiation
Phagosome
AGE-RAGE signaling pathway in diabetic complications
Autoimmune thyroid disease
Malaria
Amoebiasis
Fc epsilon RI signaling pathway
TNF signaling pathway
Fc gamma R-mediated phagocytosis
B cell receptor signaling pathway
Natural killer cell mediated cytotoxicity
Fluid shear stress and atherosclerosis
Epstein-Barr virus infection
Chagas disease (American trypanosomiasis)
Tuberculosis
T cell receptor signaling pathway
PI3K-Akt signaling pathway
Legionellosis
Toll-like receptor signaling pathway
Aldosterone-regulated sodium reabsorption
Primary immunodeficiency
Antigen processing and presentation
Protein digestion and absorption

Mouse Notch KO and Human ni and ulcus

Cell adhesion molecules (CAMs)
Phagosome
Viral myocarditis
Antigen processing and presentation
Human T-cell leukemia virus 1 infection
Graft-versus-host disease
Type I diabetes mellitus
Allograft rejection
Epstein-Barr virus infection
Autoimmune thyroid disease
Toxoplasmosis
Inflammatory bowel disease (IBD)
Leishmaniasis
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Leukocyte transendothelial migration
Cytokine-cytokine receptor interaction
Viral protein interaction with cytokine and cytokine receptor
Hematopoietic cell lineage
Th1 and Th2 cell differentiation
Aldosterone-regulated sodium reabsorption
TNF signaling pathway
Malaria
Th17 cell differentiation

[Mouse Notch KO] and [Human ni]:

Human immunodeficiency virus 1 infection

[Mouse Notch KO] and [Human ulcus]:

Protein digestion and absorption
ECM-receptor interaction
AGE-RAGE signaling pathway in diabetic complications
Metabolism of xenobiotics by cytochrome P450
MAPK signaling pathway
Pentose and glucuronate interconversions
Drug metabolism - cytochrome P450
PI3K-Akt signaling pathway
Proteoglycans in cancer

[Mouse Notch KO unique]

Human papillomavirus infection
Renin secretion
Cellular senescence
Focal adhesion

Metabolism of xenobiotics by cytochrome P450
Chemical carcinogenesis
Rap1 signaling pathway
Glutathione metabolism
Drug metabolism - cytochrome P450
Ascorbate and aldarate metabolism
Arachidonic acid metabolism
MAPK signaling pathway
Pertussis
Pentose and glucuronate interconversions
Steroid hormone biosynthesis
Influenza A
Transcriptional misregulation in cancer
Arginine and proline metabolism
Toxoplasmosis
Tryptophan metabolism
African trypanosomiasis
Human T-cell leukemia virus 1 infection
Valine, leucine and isoleucine degradation
Platelet activation
VEGF signaling pathway
Inflammatory mediator regulation of TRP channels
Carbohydrate digestion and absorption
Pathogenic Escherichia coli infection
Drug metabolism - other enzymes
EGFR tyrosine kinase inhibitor resistance
Glycosaminoglycan biosynthesis - chondroitin sulfate/dermatan sulfate
ECM-receptor interaction
Proteoglycans in cancer
IL-17 signaling pathway
TGF-beta signaling pathway
Antifolate resistance
PD-L1 expression and PD-1 checkpoint pathway in cancer
Gap junction
Dilated cardiomyopathy (DCM)
Salivary secretion
cGMP-PKG signaling pathway
Human cytomegalovirus infection
Small cell lung cancer
cAMP signaling pathway
Pathways in cancer
Colorectal cancer
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p53 signaling pathway
Calcium signaling pathway
ABC transporters
Cell cycle
Kaposi sarcoma-associated herpesvirus infection
Chronic myeloid leukemia
Porphyrin and chlorophyll metabolism
Breast cancer
Prion diseases

Supplemental Table 2: Quantitative PCR Primer sequence

Primer Name	Sequences (5'—> 3')
Gapdh_ F	CTGCCCAGAACATCATCCCT
Gapdh_ R	ACTTGGCAGGTTTCTCCAGG
Ncstn_F	AGCCAAGCCCAACTCAACTT
Ncstn_R	CAAGCCGTTGCCCAGTTCAT
RBPJ_F	TGGCAACAGCGATGACATTG
RBPJ_R	TCGTTCCTGAAGCAATGCAC
Hey1_F	TGCAGATGACTGTGGATCACC
Hey1_R	AAACCCCAAACTCCGATAGTCC
Itga4_F	GTAGCCGTTGGTGCATTTCA
Itga4_R	TGTAGCCTGGGACCTCTTTG
Itga9_F	TTCCTGCCAGGCTCCATCAA
Itga9_R	CCACATCAGCCGTCAGATTG
Itgb8_F	GCTTTTCTGACTGCTGCACT
Itgb8_R	GGCACAGGAGACCACATTTG
Itga1_F	GGCCAGAAGGGGAGTGAAAA
Itga1_R	GGGCTCACTTGCGATTGATT
Prlc_F	TAGCGGTGACGCATGGGCTG
Prlc_R	CTGCCAGCAGGTCCTCATCA
Bgn_F	CTCTGACTTGGGTCTGAAGACT
Bgn_R	TGCTGGAGGCCTTTGAAGTCAT
Dcn_F	TTCCTACTCGGCTGTGAGTC
Dcn_R	AAGTTGAATGGCAGAACGC
ZO-1_F	CCACCTCTGTCCAGCTCTTC
ZO-1_R	AGTTGGTGGTCTGAAAGTTGCT
Dusp4_F	CGTGCGCTGCAATACCATC
Dusp4_R	CTCATAGCCACCTTTAAGCAGG