

Supplementary Table 1. Genes with significantly altered expression in *slc4a11*^{-/-} mouse cornea. Genes with increased expression are written in green text and red indicates decreased expression. Genes in the table are ordered from most to least altered in both the increased and decreased categories. Fold changes indicate change of expression in *slc4a11*^{-/-} mice relative to *slc4a11*^{+/+}. Genes with adjusted P-values (Bonferroni-Hochberg adjustment for multiple comparisons) less than 0.05 and over 1.5-fold change in either direction were selected as differentially expressed. In the gene product function column, products of differentially expressed genes are written in upper case for consistency and not in italic. * indicates genes not identified as expressed in human CEC (on the basis of genes expressed in isolated human CEC^{1,2}) and thus likely expressed in corneal epithelial cells. One of these studies measured transcript abundance in 15 human CEC samples². In this case, we considered genes as expressed in CEC if they were found in 10/15 samples.

Entrez_id/ gene	Adjusted P-value	<i>log</i> ₂ Fold Change	Fold Change	Gene Product Function
14394/ <i>gabra1</i>	*8.5 x 10 ⁻⁶	4.1	18	• Gamma-aminobutyric acid receptor (GABAR)³. • GABA is an inhibitory neurotransmitter causing Cl⁻ influx cell hyperpolarization.
14401/ <i>gabrb2</i>	*3.0 x 10 ⁻⁴	2.8	6.7	• GABA receptor subunit⁴.
NA/ <i>gv2c</i>	*3.6 x 10 ⁻⁹	2.3	4.8	• Synaptic vesicle glycoprotein 2⁵. • Involved in Ca²⁺ dependent synaptic vesicle exocytosis.
NA/ <i>kcnj13</i>	*4.0 x 10 ⁻⁴	2.0	4.1	• Inwardly rectifying K⁺ channel⁶.
70945/ <i>mmrn1</i>	*2.1 x 10 ⁻²	2.0	4.0	• Multimerin (MMRN) is involved in endothelial cell adhesion. • Aids in extracellular matrix elasticity. • Binds outer surface of endothelial cells and extracellular matrix (ECM) (including collagen) to aid in adhesion⁷.
14201/ <i>fhl3</i>	6.0 x 10 ⁻³	1.9	3.8	• Four-and-a-half LIM domains 3 (FHL3) inhibits regulates epithelial-mesenchymal transition (EMT)⁸. • Regulator of myoblast differentiation- acts as a transcriptional activator or repressor⁹.
102954/ <i>nudt11</i>	2.5 x 10 ⁻²	1.9	3.8	• Nucleoside diphosphate attached moiety 'X'-type (NUDT) is a phosphohydrolase that hydrolyses 5-phosphoribosyl 1-pyrophosphate (PRPP) to generate glycolytic activator, ribose 1,5 bisphosphate¹⁰.

66042/ <i>sostdc1</i>	*7.0 x 10 ⁻⁴	1.9	3.8	• Sclerostin domain containing 1 (SOSTDC1) is a bone morphogenetic protein (BMP) antagonist and Wnt pathway antagonist, regulating BMP signaling during cellular proliferation, differentiation and programmed cell death^{11,12}.
226075/ <i>glis3</i>	6.6 x 10 ⁻¹⁶	1.9	3.7	• GLI-Similar protein 3 (GLIS3) is a Krüppel-like zinc finger transcription factor^{13,14}. • Regulator of embryonic development and cell migration.
243931/ <i>tshz3</i>	3.4 x 10 ⁻²	1.9	3.6	• Teashirt zinc finger homeobox family member 3 (TSHZ3; also known as ZNF537) encodes a zinc finger transcription factor upregulated upon oxidative damage^{15,16}. • TSHZ3 overexpression in myoblasts inhibited myogenic differentiation and decreased Myog, a transcription factor that induces myogenesis, expression.
NA/ <i>nt5e</i>	1.53 x 10 ⁻⁷	1.8	3.6	• Ecto-5'-nucleotidase (NT5E) catalyzes the conversion of extracellular nucleotides to nucleosides. • The preferred substrate of the enzyme is AMP¹⁷.
12296/ <i>cacnb2</i>	1.5 x 10 ⁻²	1.8	3.5	• CACNb2 is the β2 subunit of the L-type calcium channel, involved in positive regulation of presynaptic cytosolic calcium levels¹⁸.
319211/ <i>nol4</i>	1.7 x 10 ⁻⁶	1.8	3.5	• Nucleolar protein 4 (NOL4) is involved in determining cell specificity. • Abundant in malignant cells¹⁹.
72432/ <i>spink5</i>	5.2 x 10 ⁻⁷	1.8	3.5	• <i>Serine peptidase inhibitor</i> Kazal type 5 (<i>SPINK5</i>) is associated with dermatitis and asthma²⁰⁻²².
22153/ <i>tubb4a</i>	1.5 x 10 ⁻³	1.7	3.3	• <i>TUBB4A</i> encodes beta-tubulin isotype, beta-tubulin 4A, a core tubulin protein that forms microtubules, a structural constituent of the cytoskeleton^{23,24}.
21928/ <i>tnfaip2</i>	9.6 x 10 ⁻³	1.7	3.3	• Tumor necrosis factor alpha induced protein (TNFAIP) is Involved in cell determination and organ formation. • Involved in regulating inflammation and apoptosis of tumor cells²⁵.
117600/ <i>srgap1</i>	2.3 x 10 ⁻¹⁰	1.7	3.3	• Slit-Robo GTPase-activating protein 1 (SRGAP1) negatively regulates neuronal migration by regulating Rac activity. • SRGAP1 limits Rac1 activity, decreasing cell migration^{26,27}.
242122/ <i>vtcn1</i>	*4.9 x 10 ⁻⁶	1.7	3.2	• VTCN1 (V-set domain containing T-cell activation inhibitor 1) proteins are present on the surface of antigen-presenting cells and interact with ligand bound to receptors on the surface of T cells.

				Decreases cytokine production and decreases T-cell proliferation²⁸.
16980/ <i>lrrn2</i>	3.7×10^{-2}	1.6	3.1	- Leucine rich repeat neuronal 2(LRRN2) LrRRN2 is a cell adhesion molecule and signal transduction receptor with a type III fibronectin domain in its extracellular domain. - Lrrn2 possesses ww domains in the short intracellular region-these mediate protein–protein interactions²⁹.
243312/ <i>elfn1</i>	$*6.0 \times 10^{-3}$	1.6	3.1	Extracellular leucine rich repeat and fibronectin Type III domain containing 1. (ELFN1) is important in synapse formation, neuronal adhesion and synapse differentiation by recruiting pre/postsynaptic proteins^{30,31}.
16682/ <i>krt4</i>	$*1.8 \times 10^{-8}$	1.6	3.0	Keratin 4 (KRT4) forms intermediate filaments, a structural component of the cytoskeleton in all epithelial cells³².
14086/ <i>fscn1</i>	1.6×10^{-4}	1.6	3.0	- Fascin (FSCN1) is an actin binding and bundling protein that directly interacts with to control focal adhesions. - Fascin is also required for the stability of parallel bundles of F-actin. - Fascin–actin binding plays a role in regulating cell adhesion³³.
13380/ <i>dkk1</i>	3.7×10^{-7}	1.5	2.9	- Dickkopf-related protein 1 (DKK1) is a Wnt pathway antagonist. - A regulator in local cell adhesion, Dkk1 localizes to the plasma membrane, to adhesion complexes, and regions of high actomyosin. - It is a repressor of cell polarization and cell-cell adhesion. - Prevents the localization of β-catenin³⁴.
106565/ <i>dlk2</i>	3.6×10^{-6}	1.5	2.8	- Delta-like 2 (DLK2) is a negative regulator of Notch signaling pathway. - Notch signaling plays an important role in proliferation³⁵.
12818/ <i>col14a1</i>	4.1×10^{-2}	1.5	2.7	<i>COL14a1</i> encodes the alpha chain of type XIV collagen, a component of ECM. <i>col14a1</i>^{-/-} mice displayed delayed corneal endothelial maturation, had thicker cornea suggesting that collagen XIV plays a role in corneal thinning needed to maintain corneal clarity and also had delayed endothelial junction maturation³⁶.
107146/ <i>glyat</i>	$*3.0 \times 10^{-2}$	1.4	2.7	- Glycine-N-acyltransferase (GLYAT) plays a role in conjugating glycine with mitochondrial acyl-CoA. - Reduced expression of GLYAT causes hyperglycemia meaning it is an important regulator in energy metabolism. - Overexpression of GLYAT decreases glucose levels³⁷.

225288/ <i>fhod3</i>	1.5×10^{-8}	1.4	2.6	• Formin Homology 2 Domain Containing 3 (FHOD3) is an actin associated protein that plays a role in actin organization. • Formins direct the formation of straight actin filaments such as stress fibers³⁸.
11839/ <i>areg</i>	3.0×10^{-3}	1.4	2.6	• Amphiregulin (AREG) binds to and regulates epidermal growth factor receptor (EGFR) and acts as an autocrine growth factor to promote epithelial cell growth. • Important in the regulation of the EMT in pancreatic cancer. • Silencing of AREG causes keratinocyte growth arrest^{39,40}.
16664/ <i>krt14</i>	$*1.1 \times 10^{-26}$	1.3	2.5	• Keratin 14 (KRT14) is a constituent of the cytoskeleton, forming part of intermediate filaments⁴¹⁻⁴³.
17918/ <i>myo5a</i>	4.2×10^{-8}	1.3	2.5	• Myosin gene superfamily member 5A (MYO5A) is one of the three myosin V heavy-chain genes, part of an actin-based motor protein. • Myo5a can dissociate from the ribosome complex to release ribosomes from the actin cytoskeleton⁴⁴.
50918/ <i>myadm</i>	8.4×10^{-12}	1.3	2.5	• Myeloid associated differentiation marker (MYADM) is a transmembrane protein at the plasma membrane where it co-localizes with actin and cell-cell junctions. • When MYADM was silenced it caused disruption of the endothelial monolayer and caused disorganization of cell-cell junctions. • MYADM organizes plasma membrane domains and regulates the connection with cytoskeleton^{45,46}.
18599/ <i>padi1</i>	$*2.5 \times 10^{-2}$	1.3	2.5	• Peptidylarginine deiminases (PADIs) catalyze deamination of proteins by converting arginine into citrulline. • Histone citrullination turns off gene expression and is an antagonist to histone arginine methylation^{47,48}.
17755/ <i>map1b</i>	4.8×10^{-11}	1.3	2.4	• Microtubule associated protein 1b (MAP1B) is important in microtubule assembly⁴⁹.
20677/ <i>sox4</i>	1.1×10^{-3}	1.3	2.4	• SRY-box transcription factor 4 (SOX4) is involved in the regulation of embryonic development and determination of cell fate. • Functions in the apoptosis pathway⁵⁰.
16665/ <i>krt15</i>	1.6×10^{-26}	1.3	2.4	• Keratins, like keratin 15 (KRT15) are intermediate filament proteins that are responsible for the structural integrity of epithelial cells.
19228/ <i>pth1r</i>	2.0×10^{-3}	1.3	2.4	• PTH type 1 receptor (PTH1R) is a G-protein coupled receptor involved in calcium homeostasis.

				• PTH1R activation increases cAMP levels via adenylate cyclase activity⁵¹.
19224/ <i>ptgs1</i>	6.6×10^{-16}	1.3	2.4	• Cyclo-oxygenase 1 (COX-1) (encoded by <i>PTGS1</i>) converts arachidonic acid into prostaglandins⁵².
53416/ <i>stk39</i>	6.0×10^{-5}	1.3	2.4	• STE20 (sterile 20-like)-related proline-alanine-rich kinase (SPAK) is encoded by <i>STK39</i>. • STE20 kinases are important in osmotic stress signaling. • SPAK is ubiquitously expressed and modulates ion and fluid homeostasis through phosphorylation of chloride transporters and p38 MAPK pathway activation⁵³.
12560/ <i>cdh3</i>	4.0×10^{-8}	1.2	2.3	• Cadherin3 (CDH3) is a calcium-dependent cell-cell adhesion protein⁵⁴.
NA/ <i>krt90</i>	$*1.0 \times 10^{-3}$	1.2	2.3	• Member of the keratin family of intermediate filament proteins.
12554/ <i>cdh13</i>	2.5×10^{-10}	1.2	2.3	• Cadherin13 (CDH13) is a member of cadherin family of cell adhesion proteins.⁵⁵.
94352/ <i>lox12</i>	5.5×10^{-6}	1.2	2.3	• Lysyl oxidase 2 (LOXL2) is an extracellular amine oxidase that catalyzes the formation of crosslinks between collagen and elastin to remodel ECM. • LOXL2 mediated deamination of tropoelastin increases resistance to degradation and stiffness of elastin^{56,57}.
13131/ <i>dab1</i>	$*3.9 \times 10^{-5}$	1.2	2.3	• Disabled 1 (DAB1) is an intracellular adaptor protein of the Reelin signaling pathway • Causes a signaling cascade of actin and microtubules. • If DAB1 is phosphorylated, it activates the Crk pathway, which plays an important role in cell adhesion to fibronectin and regulates nectins and N-cadherin trafficking, important in cell-cell interactions⁵⁸.
19224/ <i>ptges</i>	6.6×10^{-16}	1.2	2.2	• Prostaglandin E Synthase (PTGES) is downstream of COX-2 in the prostaglandin signaling pathway. • PTGES is induced by hypoxic conditions. • PTGES contributes to collagen induced arthritis as determined by knockout mice studies^{59,60}.
16858/ <i>lgals7</i>	$*1.3 \times 10^{-11}$	1.1	2.2	• Galectins (encoded by LGALS genes) modulate cell-cell and cell-matrix interactions. • Galectin-7 binds to the extracellular domain of E-cadherin^{61,62}.

76898/ <i>b3gat1</i>	*6.0 x 10 ⁻³	1.1	2.2	• β-1,3-glucuronyltransferase 1 (B3GAT1), a key enzyme in the glucuronyl transfer reaction is important in integrin signaling and cell motility^{63,64}.
104111/ <i>adcyl3</i>	3.6 x 10 ⁻⁴	1.1	2.2	• ADCY3 is an adenylate cyclase that catalyzes the synthesis of cAMP from ATP. • ADCY3 has a role in metabolism and regulation of glucose homeostasis and protects from type 2 diabetes when it is upregulated⁶⁵.
22271/ <i>upp1</i>	1.8 x 10 ⁻¹⁴	1.1	2.1	• Uridine phosphorylase 1 (UPP1) catalyzes the phosphorylation of uridine to uracil. • Plays an important role in uridine homeostasis⁶⁶.
55963/ <i>slc1a4</i>	1.6 x 10 ⁻⁰⁸	1.1	2.1	• Solute carrier family 1 member 4 (SLC1a4) is a sodium-dependent neutral amino acid transporter that transports glutamine into the cell to be used for glutaminolysis^{67,68}.
NA/ <i>krt19</i>	2.0 x 10 ⁻¹⁰	1.1	2.1	• Part of the keratin family which are intermediate filaments involved in maintaining structural integrity of epithelial cells. • Interact with various proteins and effector molecules to regulate cell growth, migration and apoptosis^{69,70}.
17181/ <i>matn2</i>	8.7 x 10 ⁻⁵	1.0	2.1	• Matrilin2 (MATN2) is important in ECM organization. • Interacts with ECM molecules using a von Willebrand Factor A- like domain. • Forms ECM filaments by interacting with itself or other ECM constituents, including collagens and fibronectin. • Matrilin2 binds to cells using α1β1 integrin⁷¹.
240888/ <i>gpr161</i>	1.6 x 10 ⁻²	1.0	2.0	• A G-protein coupled receptor (GPCR) that increases intracellular cAMP levels. • Suppresses Shh signaling. • Shh signaling is important in embryonic cell differentiation⁷².
68655/ <i>fndc1</i>	2.5 x 10 ⁻¹³	1.0	2.0	• Fibronectin type III domain containing 1 (FNDC1) is a major structural domain of fibronectin, part of ECM. • Fndc1 expression levels may be an important biomarker for gastric cancer and is involved in regulating tumorigenesis⁷³.
76448/ <i>ppp1r18</i>	2.5 x 10 ⁻²	1.0	2.0	• Protein phosphatase 1 regulatory subunit 18 (PPP1r18) overexpression negatively regulates actin ring formation. • Suppresses actin elongation by directly binding to actin⁷⁴.
319757/ <i>smo</i>	1.4 x 10 ⁻⁹	1.0	2.0	• Smoothened (SMO) is a G protein-coupled receptor involved with patched proteins in the Hedgehog signaling pathway located on the plasma membrane where Hh signal is transduced.

				• SMO activation and activation of Cubitus interruptus (Ci)/Gli family of zinc finger transcription factors which then causes expression of Hh target genes⁷⁵.
208439/ <i>klhl29</i>	1.0×10^{-3}	1.0	2.0	• Kelch-like (<i>KLHL</i>) proteins are substrate-specific adapters for cullin E3 ubiquitination⁷⁶. There is no literature on member 29.
237175/ <i>adgrg2</i>	$*2.0 \times 10^{-2}$	1.0	2.0	• Adhesion G-protein coupled receptor G2 (<i>ADGRG2</i>) is a member of the adhesion family of GPCRs involved in cell-cell communication and cell-matrix interaction⁷⁷⁻⁷⁹.
108043/ <i>chrbn3</i>	$*1.0 \times 10^{-11}$	-4.9	0.03	• Cholinergic receptor nicotinic beta 3 subunit (<i>Chrbn3</i>) is part of a superfamily of ligand-gated ion channels at synapses that mediate neuronal signals^{80,81}.
21892/ <i>tll1</i>	$*7.4 \times 10^{-6}$	-3.3	0.10	• Tolloid-like protein 1 (<i>TLL1</i>) negatively regulates hepatic differentiation of human iPS cells via upregulation of TGFβ signaling. • Down regulation of <i>Tll1</i> increased cell differentiation⁸².
329872/ <i>frem1</i>	2.4×10^{-14}	-3.2	0.11	• FRAS1-related extracellular matrix 1 (<i>FREM1</i>) controls adhesion of the developing epidermis. • <i>FREM1</i> mutation contributes to basement membrane fragility and blistering maybe by reduced PDGFC signaling leading to impaired ECM function. • <i>FREM1</i> may bind directly to growth factor A (PDGFA), fibroblast growth factor FGF2, and collagens V and VI^{83,84}.
238377/ <i>gpr68</i>	1.9×10^{-5}	-3.0	0.12	• G-protein-coupled receptor 68 gene (<i>GPR68</i>) is an acid-sensing receptor⁸⁵. • <i>GPR68</i> requires the presence of protons to sense stress to activate receptor^{86,87}.
13081/ <i>cyp24a1</i>	1.4×10^{-6}	-3.0	0.12	• Member of the cytochrome P450 superfamily of enzymes. • Enzymatic pathway for cholesterol, steroids, and lipids^{22,88,89}.
20452/ <i>st8sia4</i>	3.8×10^{-4}	-2.2	0.22	• <i>ST8SIA4</i> is a polysialyltransferase that catalyzes polycondensation of alpha-2,8-linked sialic acid. • <i>ST8SIA4</i> delays oligodendrocyte differentiation, and plays a role in re-myelination^{90,91}.
53417/ <i>hif3a</i>	1.7×10^{-2}	-2.1	0.24	• Hypoxia inducible Factor 3 Alpha Subunit (<i>HIF3A</i>) is involved in response to hypoxia, including transition to anaerobic metabolism. • Promotes glucose uptake by activating the transcription of transporters GLUT1 and GLUT3.

				• Inhibits PDH (pyruvate dehydrogenase) complex and blocks conversion of pyruvate into acetyl-CoA⁹².
333315/ <i>frem3</i>	$*7.5 \times 10^{-39}$	-2.0	0.25	• FRAS-related extracellular matrix 3 (FREM3) is an ECM protein associated with epithelial–mesenchymal cohesion during embryonic development in mammals. • FREM3 is an integral membrane protein containing numerous CSPG (chondroitin sulfate proteoglycan element) repeats and Calx-beta domains^{83,84}.
56226/ <i>espn</i>	5.7×10^{-3}	-2.0	0.25	• Espin (ESPN) is a multifunctional actin-bundling protein. With a major role in regulating the organization, dimensions, dynamics, and signaling capacities of the actin filament rich. • ESPN interacts with F-actin to mediate the formation and extension of protrusion structure⁹³.
13395/ <i>dlx5</i>	$*2.4 \times 10^{-2}$	-1.9	0.28	• Distal-Less Homeobox 5 (DLX5) is a transcription factor with a role in bone formation, neurogenesis and hematopoiesis as part of the bone morphogenetic protein (BMP) signaling pathway. • In ovarian cancer, DLX5 promotes cell proliferation by increased stimulation of AKT signaling by transactivation of insulin receptor substrate 2⁹⁴.
18208/ <i>ntn1</i>	1.0×10^{-15}	-1.8	0.29	• Netrin-1 (NTN1) is an axonal guidance molecule that also promotes angiogenesis. - NTN1 upregulation inhibits apoptosis induced via its dependence and possible cross-linking to on DCC (deleted in colorectal cancer (DCC) protein) and UNC5H. • NTN1 is upregulated in in Type 2 brittle cornea syndrome (BCS2) studying mutations in the transcription factor PR domain containing 5 (PRDM5). • Dysregulated PRDM5-target genes reveal enrichment for extracellular matrix (ECM) genes supporting vascular integrity and development⁹⁵⁻⁹⁸.
110095/ <i>pygl</i>	6.4×10^{-37}	-1.8	0.29	• Glycogen phosphorylase L (PYGL) catalyses breakdown of glycogen to glucose. • Mutations can cause liver phosphorylase deficiency, which may result in glycogenolysis disorder like Hers Disease^{99,100}.
26971/ <i>pla2g2f</i>	$*3.3 \times 10^{-2}$	-1.8	0.29	• Phospholipase 2g2f (PLA2G2F) is a secreted enzyme hydrolyzing phospholipids into free fatty acids and lysophospholipids, with a role in epidermal barrier function¹⁰¹. • In humans and mice, PLA2G2F causes release of arachidonic acid, interleukin-1 and microsomal prostaglandin E synthase.

171531/ <i>mlph</i>	2.5×10^{-9}	-1.7	0.31	• Melanophilin (<i>MLPH</i>) is a critical component of the melanosome transport machinery and may be part of a transport complex with Rab27a and MyoVa^{102,103}.
108017/ <i>fxyd4</i>	6.0×10^{-4}	-1.6	0.32	• FXD4 is a member of a family of Na⁺-K⁺-ATPase stimulators^{104,105}.
76074/ <i>gbp8</i>	$*3.2 \times 10^{-2}$	-1.6	0.33	• Guanylate binding proteins (GBPs) are GTPases up-regulated by proinflammatory cytokines and toll-like receptor agonists^{106,107}.
252838/ <i>tox</i>	9.9×10^{-12}	-1.6	0.33	• Thymocyte Selection-Associated High Mobility Group Box (TOX) is a transcription factor with uncharacterized roles in the nervous system. • TOX is regulated by calcineurin/Nfat signalling¹⁰⁸.
18383/ <i>tnfrsf11b</i>	7.7×10^{-6}	-1.6	0.33	• Tumor necrosis factor receptor superfamily member 11B (<i>TNFRSF11B</i>) encodes osteoprotegerin, a decoy receptor for receptor activator of NF-κB ligand (RANKL)^{109,110}.
83672/ <i>syt13</i>	1.1×10^{-3}	-1.6	0.34	• Synaptotagmin (Syt)-like protein (Slp) (SYTL) is involved in vesicle trafficking¹¹¹.
433619/ <i>kprp</i>	$*1.0 \times 10^{-2}$	-1.5	0.35	• Keratinocyte Proline-Rich Protein (KPRP) is involved in keratinocyte differentiation. • KPRP is expressed exclusively in stratified squamous epithelial layers¹¹².
12268/ <i>c4b</i>	4.5×10^{-2}	-1.5	0.35	• Complement component 4 (C4) is a part of host defense against microbes. • Patients deficient in this protein have compromised immunity¹¹³.
234356/ <i>csgalnact1</i>	1.5×10^{-13}	-1.5	0.36	• Chondroitin sulfate N-acetylgalactosaminyltransferase-1 (CSGalNAcT1) is involved in chondroitin sulfate lengthening in proteoglycans. • Required for normal cartilage development, brain development, mechanical properties of connective tissue, and aggrecan metabolism. • Component of the extracellular matrix^{114,115}.
219134/ <i>shisa2</i>	3.9×10^{-5}	-1.5	0.36	• Single transmembrane segment protein acting as a protein-protein interaction partner, regulating signaling pathways. • Involved in downregulation of pathways of fibroblast growth¹¹⁶.

381310/ <i>stum</i>	$*3.3 \times 10^{-2}$	-1.4	0.37	• <i>Drosophila</i> mutants of <i>STUM</i> stumble, hence the gene name. Gene may be responsible for the generation of the proper proprioceptive responses in <i>stum</i>-expressing neurons • Essential for converting cell stretch of dendrites into cellular responses¹¹⁷.
407795/ <i>smim31</i>	$*1.1 \times 10^{-5}$	-1.4	0.39	• Small integral membrane protein 31 (SMIM31) promoted cell proliferation and repressed cell apoptosis in head and neck squamous cell carcinoma cells¹¹⁸.
12804/ <i>cntfr</i>	$*3.1 \times 10^{-2}$	-1.4	0.39	• Ciliary neurotrophic factor receptor (CNTFR) promotes differentiation and survival of a wide range of nervous cells. Also promotes motor neurons viability by preventing their degeneration¹¹⁹.
70809/ <i>cllec2g</i>	$*6.2 \times 10^{-6}$	-1.3	0.39	• C-type lectin 2G (SLEG2G) has been proposed to have a role in epithelial stratification or cornification^{120,121}.
68339/ <i>ccdc88c</i>	3.9×10^{-2}	-1.3	0.40	• CCDC88C encodes DAPLE, a regulator of epithelial cell polarity^{122,123}.
239559/ <i>a4galt</i>	1.5×10^{-5}	-1.3	0.40	• α-1,4-galactosyltransferase (A4GALT) is required for globotriaosylceramide (GB3) synthesis. GB3 is found on the surface of epithelial and endothelial cells where it acts as a protein receptor^{124,125}.
22361/ <i>vnn1</i>	$*1.6 \times 10^{-12}$	-1.2	0.43	• Vanin-1 (VNN1) is anchored to the cell surface by glycosylphosphatidylinositol and hydrolyzes pantetheine to pantothenic acid and cysteamine. • In oxidative phosphorylation, Vnn1 permits restoration of CoA pools thus controlling ATP production. • VNN1 limits the Warburg effect and promotes mitochondrial function^{126,127}.
56808/ <i>cacna2d2</i>	3.5×10^{-2}	-1.2	0.44	• Voltage-gated calcium channel auxiliary subunit alpha2delta 2 gene (CACNA2D2) controls calcium currents¹²⁸.
329628/ <i>fat4</i>	7.3×10^{-3}	-1.2	0.44	• FAT is a protocadherin that binds the protein, DCHS, on adjacent cells to regulate planar cell polarity¹²⁹.
NA/ <i>lce3a</i>	$*3.5 \times 10^{-3}$	-1.2	0.45	• Late cornified envelope 3a (LCE3A) is involved in keratinization and skin repair. • Loss of LCE3 function may compromise ability of psoriatic lesions to heal¹³⁰.
104174/ <i>glc</i>	4.4×10^{-17}	-1.2	0.45	• Glycine dehydrogenase (GLDC) decarboxylates glycine and moves a one-carbon unit into folate metabolism. • GLDC reduction causes abnormal tissue folate profiles, slow

				growth, and lessened cellular proliferation GLDC pathways include glyoxylate metabolism and glycine degradation¹³¹.
193385/ <i>ripor2</i>	3.8×10^{-6}	-1.1	0.46	- RHO family interacting cell polarization regulator 2 (RIPOR2, previously known as FAM65B) is an essential protein required in human hearing, that acts as an inhibitor of the small G protein RhoA¹³². - Regulates abundance and post translational modifications of proteins expressed in the kinocilium.
NA/ <i>ccn3</i>	$*4.5 \times 10^{-3}$	-1.1	0.46	Cellular communication network factor 3 (CCN3) interacts with extracellular and transmembrane proteins to regulate expression of ECM genes^{133,134}.
100129/ <i>gpr153</i>	2.2×10^{-4}	-1.1	0.47	- G-protein coupled receptor primarily expressed in CNS. - Mutations are associated with neuropsychiatric diseases (schizophrenia, autism). - Related to serotonin receptors that are involved in body weight homeostasis¹³⁵.
192198/ <i>lrrc4</i>	1.6×10^{-5}	-1.1	0.47	- LRRC4/NGL-2 (Leucine rich repeat containing 4/Netrin-G ligand-2) is important in neural development and glioma formation. - LRRC4 inhibits glioblastoma cell proliferation by downregulating pleiotropic cytokines^{136,137}.
77462/ <i>tmem116</i>	1.7×10^{-2}	-1.1	0.47	TMEM116 is a transmembrane protein of unknown function.
235320/ <i>zbtb16</i>	2.1×10^{-5}	-1.1	0.48	ZBTB16 is a zinc-finger family transcription factor¹³⁸.
68939/ <i>rasl11b</i>	1.2×10^{-4}	-1.0	0.49	- Ras-like protein family member 11B (RASL11B) is a GTPase. - Upregulated RASL11B inhibits cell proliferation, invasion, and migration; induce G0/G1 cell cycle arrest and promotes cell¹³⁹.
69219/ <i>ddah1</i>	8.7×10^{-11}	-1.0	0.50	Dimethylarginine dimethylaminohydrolase 1 (DDAH-1) hydrolyses methylarginine to produce dimethylamine and citrulline. Its down regulation is associated with hypoxia and its inhibition blocks NO synthesis¹⁴⁰⁻¹⁴².

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Suppl. Table 2. Oligonucleotide primers and expected amplicon size used for qReal Time RT-PCR analysis.

Genes	Primers - 5'→3'	Amplicon size
<i>pygl</i>	Forward: GCCTGGAACACAATGGTACT Reverse: GGACTCGTTGGATAGGGAAATC	135
<i>espn</i>	Forward: CAAAGTGAGAGTCCTGAGACAC Reverse: CGCCTTTATCTCAGCCAGAA	97
<i>tubb4a</i>	Forward: ATGAGGCCACAGGTGGAAAC Reverse: CTCGGTGTAGTGACCCTTGG	169
<i>frem3</i>	Forward: GGCCGACTGTGAGGCTTTTAT Reverse: GCATGGGCACATAGTCCCTG	100
<i>st8sia4</i>	Forward: GGTGGACCATCTGCACTATAAG Reverse: GATGAGTTGCGTCTCTTGGT	92
<i>tll1</i>	Forward: CGTGCAAAGCTGCTGTGTTT Reverse: GCATGCCATGGTCTCCAAAG	146
<i>glyat</i>	Forward: TGAGAGGAGCCAGAGATTCA Reverse: CTCTCCAGTTTGGTCCATTAGAG	112
<i>mmrn1</i>	Forward: GCCCTTACAGCGATTCTCTAAA Reverse: CACCTGGGAAGTGGTTTCAT	90
<i>tcf4</i>	Forward: GTTTGAGCTATCCATCCCCTC Reverse: GCAGGAAGAGGGTGTCTGTAAT	104
<i>slc4a11</i>	Forward: CTGTGCTGTATGGGCTCTTT Reverse: GGTATGATGTCTGCTCCTTGAG	102
<i>col8a2</i>	Forward: CACCTACACGTACGACGAATAC Reverse: TCGGTGGAGTAGAGACCATT	135
<i>lamc1</i>	Forward: GTTACCGACTGGTGAAGGATAAG Reverse: TGTCTCAAAGGCTTGATCTG	120
<i>col14a1</i>	Forward: GAAGTGGTAGGAACGGTTATGG Reverse: GACGCCTTCTCCAACAGTATAG	120
<i>gapdh</i>	Forward: AACAGCAACTCCCACTCTTC Reverse: CCTGTTGCTGTAGCCGTATT	110

Suppl. Table 3. Altered gene expression in *slc4a11*^{-/-} mice and human FECD corneas. The 1556 genes with altered expression level in human FECD corneas¹ were compared to altered genes found in the present manuscript. Genes with significantly altered expression in both studies are listed in the table.

Mouse gene	Human Gene	Gene function
<i>ccdc88c</i>	<i>CCDC80</i>	CCDC88C encodes DAPLE, a regulator of epithelial cell polarity ^{122,123}
<i>ripor2 (also called fam65b)</i>	<i>FAM65B</i>	RHO family interacting cell polarization regulator 2 (RIPOR2, previously known as FAM65B) is an essential protein required in human hearing, that acts as an inhibitor of the small G protein RhoA ¹³² . Regulates abundance and post translational modifications of proteins expressed in the kinocilium.
<i>fhl3</i>	<i>FHL2</i>	Four-and-a-half LIM domains 3 (FHL3) inhibits regulates epithelial-mesenchymal transition (EMT) ⁸ . Regulator of myoblast differentiation- acts as a transcriptional activator or repressor ⁹ .
<i>krt4</i>	<i>KRT8</i>	Keratin 4 (KRT4) forms intermediate filaments, a structural component of the cytoskeleton in all epithelial cells ³² .
<i>map1b</i>	<i>MAP7D1</i>	Microtubule associated protein 1b (MAP1B) is important in microtubule assembly ⁴⁹ .
<i>myo5a</i>	<i>MYO18A</i>	Myosin gene superfamily member 5A (MYO5A) is one of the three myosin V heavy-chain genes, part of an actin-based motor protein. Myo5a can dissociate from the ribosome complex to release ribosomes from the actin cytoskeleton ⁴⁴ .
<i>nol4</i>	<i>NOL3 and NOLC1</i>	Nucleolar protein 4 (NOL4) is involved in determining cell specificity. Abundant in malignant cells ¹⁹ .
<i>nudt11</i>	<i>NUDT4</i>	Nucleoside diphosphate attached moiety 'X'-type (NUDT) is a phosphohydrolase that hydrolyses 5-phosphoribosyl 1-pyrophosphate (PRPP) to generate glycolytic activator, ribose 1,5 biphosphate ¹⁰ .
<i>ppplr18</i>	<i>PPPLR7</i>	Protein phosphatase 1 regulatory subunit 18 (PPP1r18) overexpression negatively regulates actin ring formation. Suppresses actin elongation by directly binding to actin ⁷⁴ .
<i>stk39</i>	<i>STK16</i>	STE20 (sterile 20-like)-related proline-alanine-rich kinase (SPAK) is encoded by <i>STK39</i> . STE20 kinases are important in osmotic stress signaling. SPAK is ubiquitously expressed and modulates ion and fluid homeostasis through phosphorylation of chloride transporters and p38 MAPK pathway activation ⁵³ .
<i>tnfrsf11b</i>	<i>TNFRSF25</i>	Tumor necrosis factor receptor superfamily member 11B (<i>TNFRSF11B</i>) encodes osteoprotegerin, a decoy receptor for receptor activator of NF-κB ligand (RANKL) ^{109,110} .
<i>tshz3 (also called znf537)</i>	<i>ZNF207, ZNF219, ZNF638</i>	Teashirt zinc finger homeobox family member 3 (TSHZ3; also known as ZNF537) encodes a zinc finger transcription factor upregulated upon oxidative damage ^{15,16} . TSHZ3 overexpression in myoblasts inhibited myogenic differentiation and decreased Myog, a transcription factor that induces myogenesis, expression.

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Supplementary Figure Legends

Supplementary Figure 1. Distribution of normalized and variance stabilized expression values across individual sequencing libraries for three mice (M1-M3) of each respective genotype. A, Gene expression estimated as expected number of Fragments Per Kilobase of transcript $\times 10^6$ Mapped reads (FPKM, box plot). The box plot for each region indicates five statistics (top to bottom: maximum, upper quartile, median, lower quartile and minimum). B, Principal component analysis (PCA). Corneal RNA gene expression from three mice (M1-M3) of each respective genotype, *slc4a11*^{+/+} and *slc4a11*^{-/-}, was subjected to PCA. Results of exploratory analysis were visualized as principal component plots. PCA was performed on the 1500 of genes with the highest median absolute deviation.

Supplementary Figure 2. Differentially expressed genes in mouse cornea. Cluster analysis (hierarchical clustering) of expression patterns of differentially expressed genes between corneas of *slc4a11*^{+/+} and *slc4a11*^{-/-} mice. Heatmap represents normalized and variance stabilized values of differentially expressed genes (adjusted p value < 0.05 and log2 fold change > 0.59). Both columns (samples) and rows (genes) underwent hierarchical non-supervised clustering using Euclidean distance and ward.D clustering method. Magnitude of expression differences (Row Z-score) are indicated by different colors in the heat map from red (large increase in relative expression) to green (large decrease in relative expression).

Supplementary Figure 3. Gene clustering for *slc4a11*^{+/+} and *slc4a11*^{-/-} mice. Cluster analysis of expression patterns of differentially expressed genes for three mice (M1-M3) of each indicated

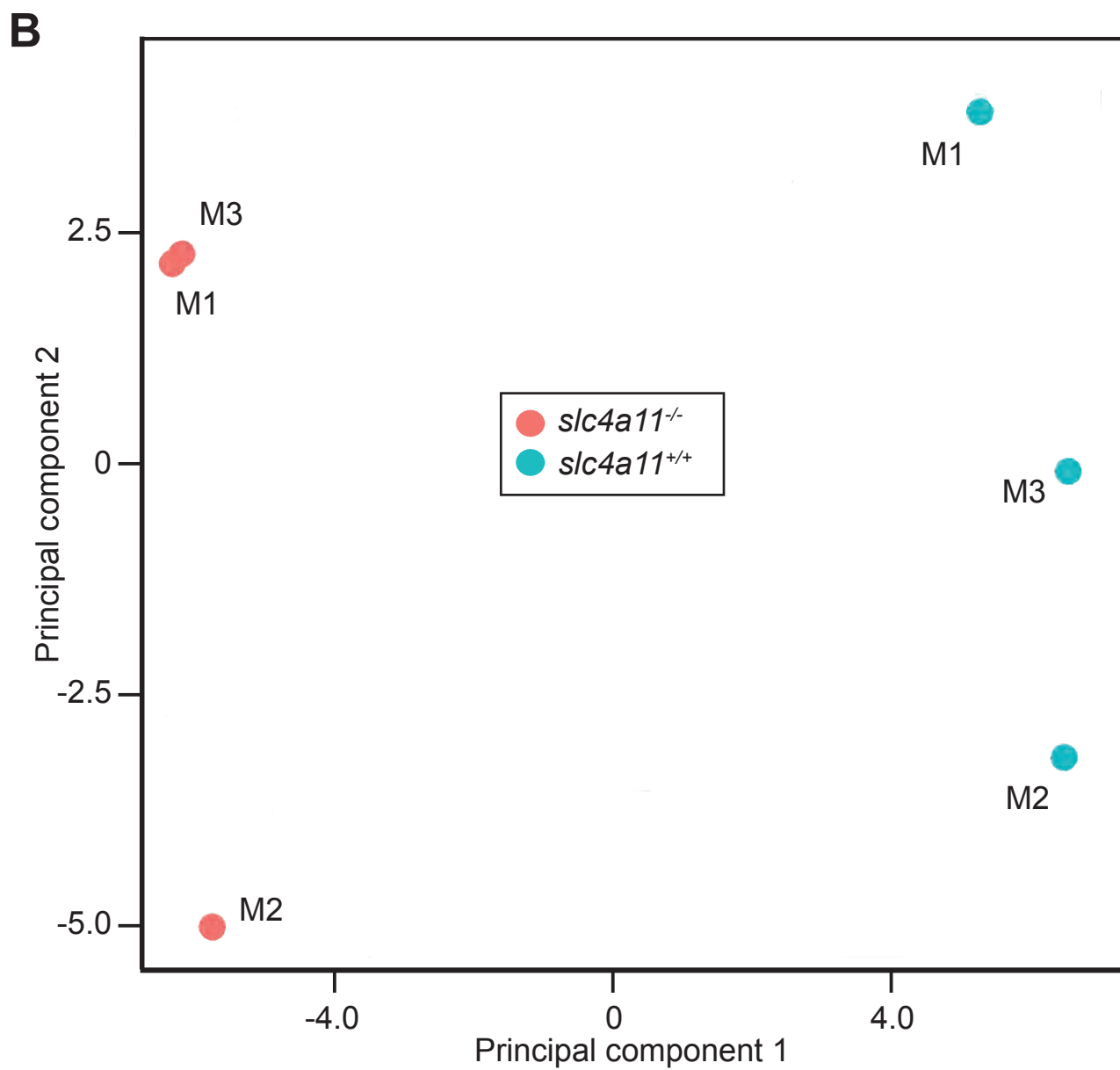
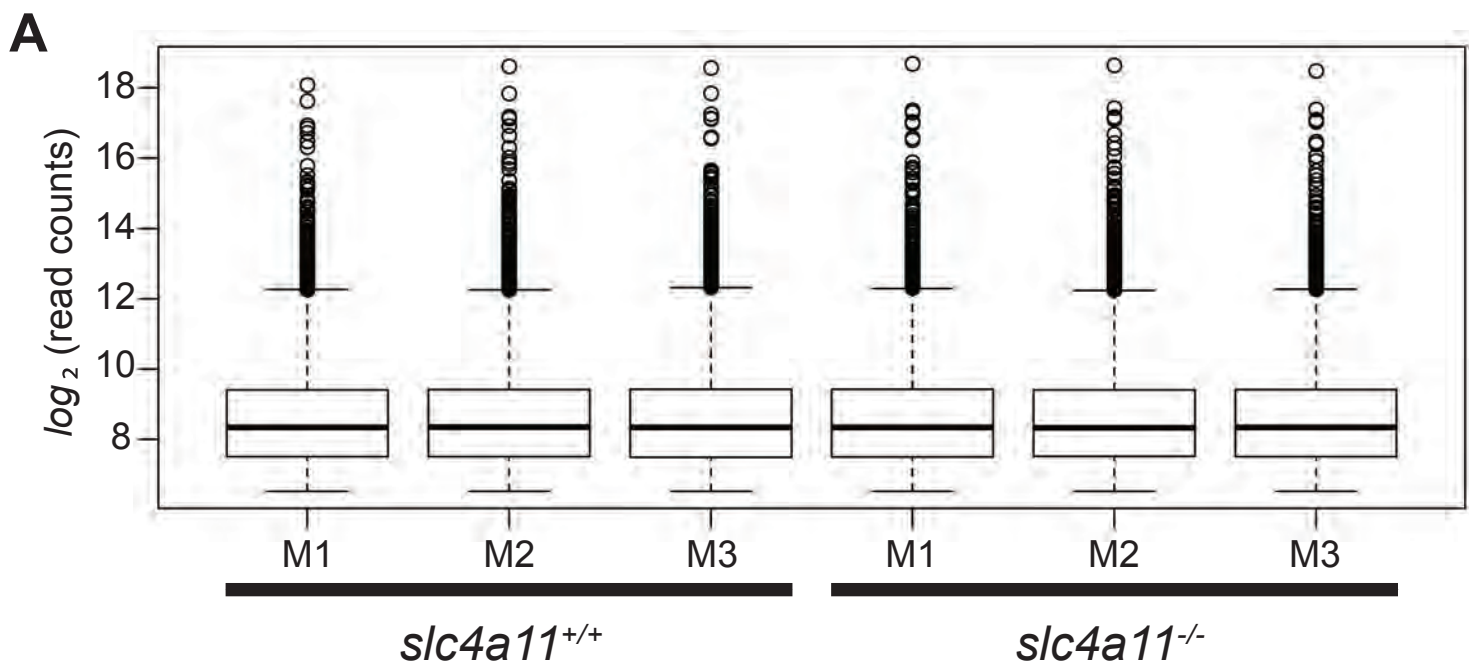
genotype. The non-supervised hierarchical clustering of the top 1500 genes detected with the highest median absolute deviation is shown by heat map. Expression changes were represented by the indicated color scale. Dendrograms corresponding to different groups are presented by brackets (*top*).

Supplementary Figure 4 Principal component analysis clustered the patterns of gene expression by tissue type. Gene expression data from RNAseq were processed to normalize transcripts in mouse cornea. Expression of these genes was compared to expression levels of these genes in a panel of 13 indicated mouse tissues (from tissue expression database, <https://www.omicsdi.org/dataset/arrayexpress-repository/E-MTAB-6081>).

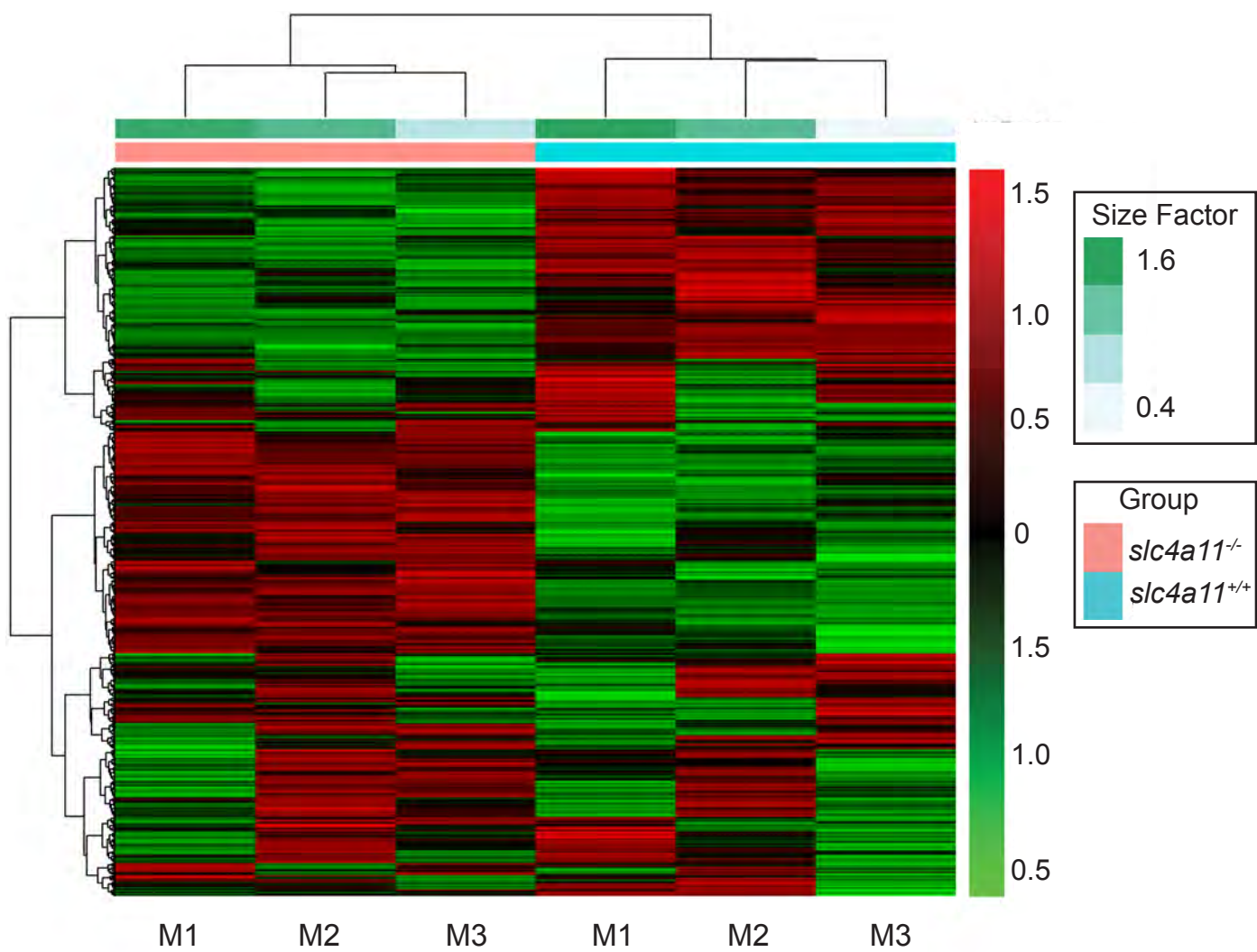
Supplementary Figure 5. Specificity of qReal-time RT-PCR. **A**, Agarose gel (3%) showing amplification of a specific PCR product for each gene tested in this study, for *slc4a11*^{+/+} and *slc4a11*^{-/-} mice corneal cDNA. Samples were run on separate agarose gels, as indicated by white breaks between sections. **B**, Agarose gel (3%) of amplified col14a1 for *slc4a11*^{+/+} and *slc4a11*^{-/-} mice corneal cDNA; **C**, Melting curves analysis of *tubb4a* and *espn* products. The negative first derivative of the change in fluorescence is plotted as a function temperature in °C (-df/dt). Full, uncropped versions of all gels are in Suppl. Fig. 6.

Supplementary Figure 6. Full length, unedited versions of images from Fig. 5. **A**, Agarose gel (3%) showing amplification of a specific PCR product for each gene tested in this study, for *slc4a11*^{+/+}

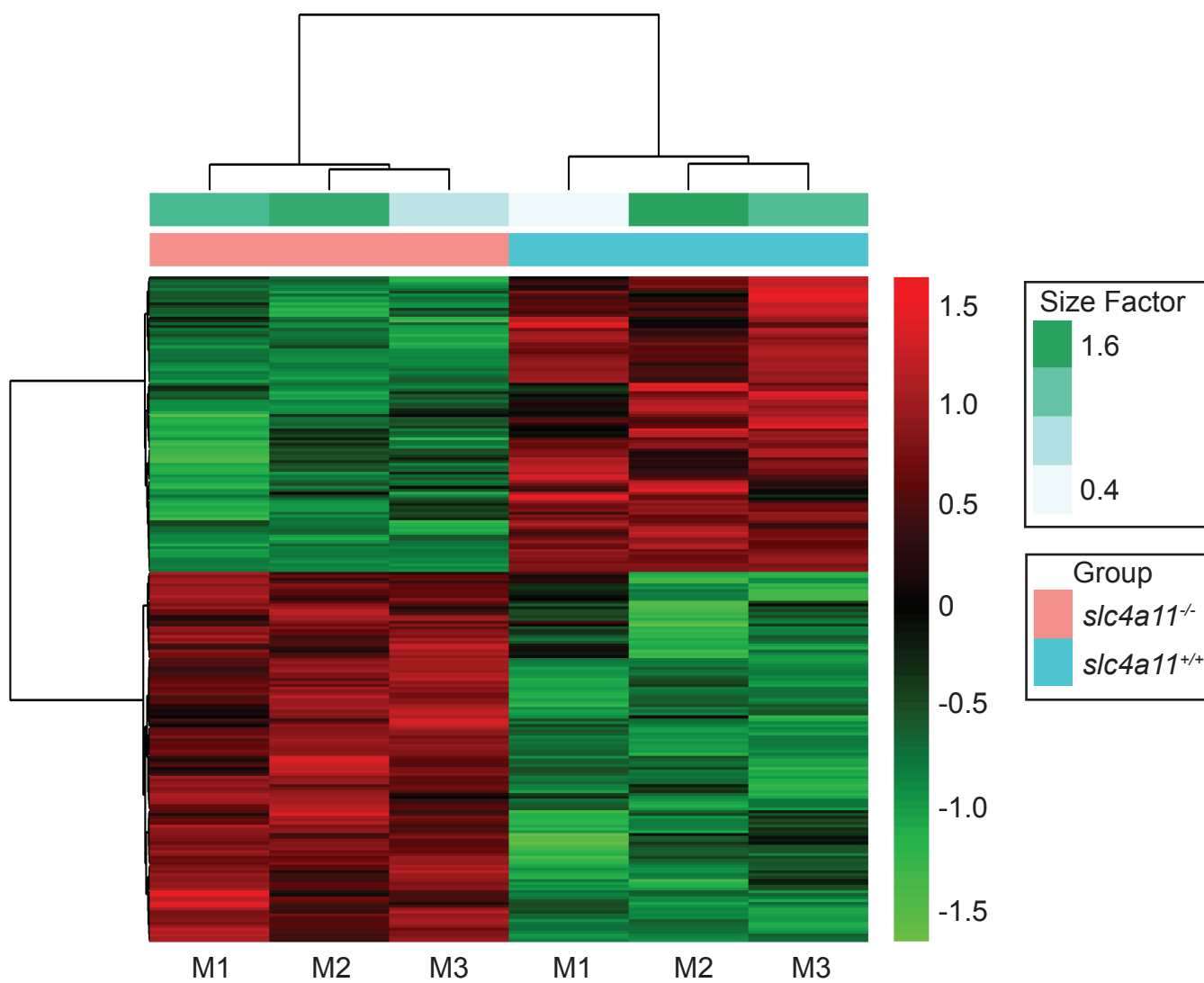
and *slc4a11*^{-/-} mice corneal cDNA. Samples were run on separate agarose gels. **B**, Agarose gel (3%) of amplified *col14a1* for *slc4a11*^{+/+} and *slc4a11*^{-/-} mice corneal cDNA. NRS, non relevant sample (these samples were not analyzed in the current manuscript).



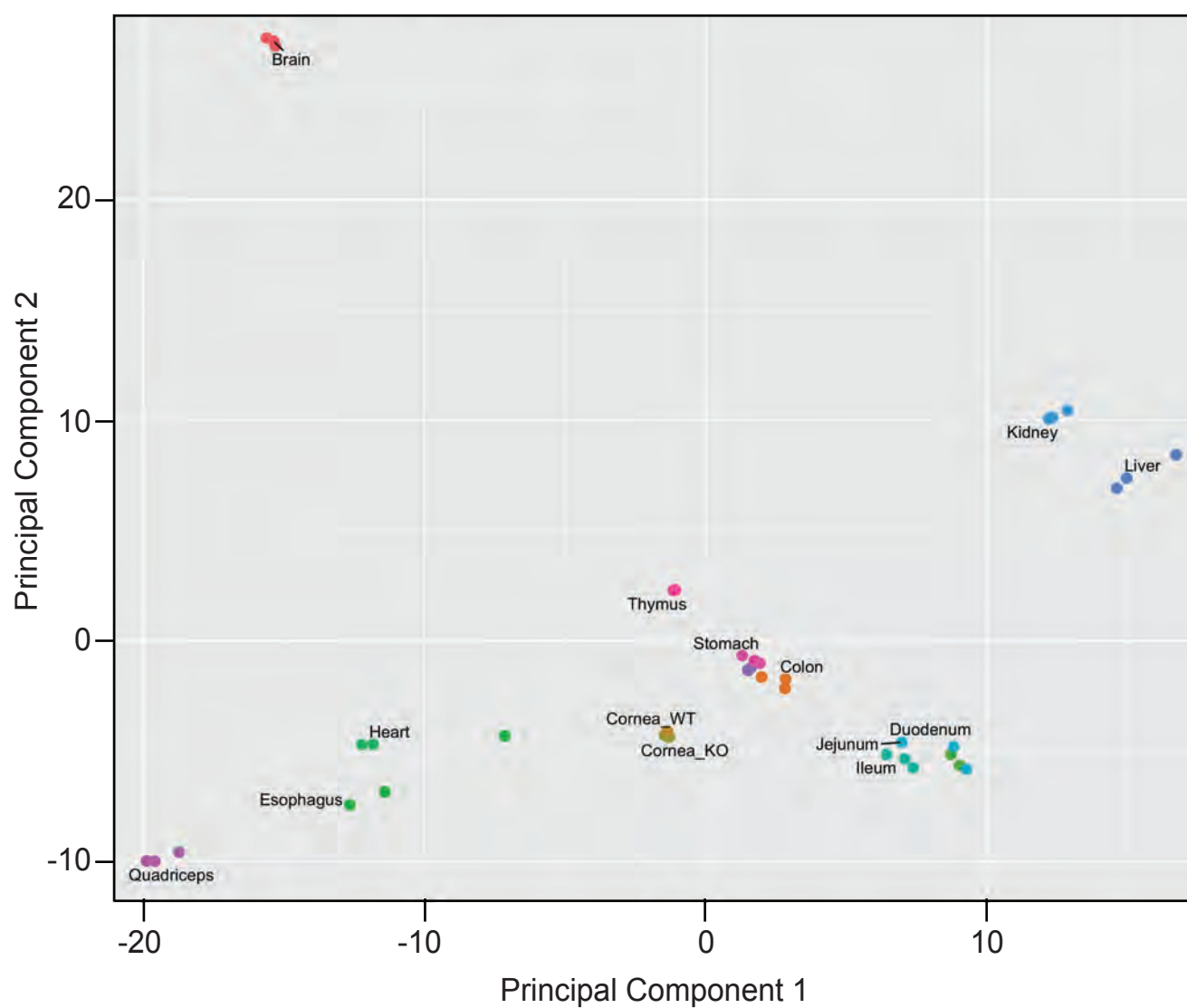
Suppl. Figure 1



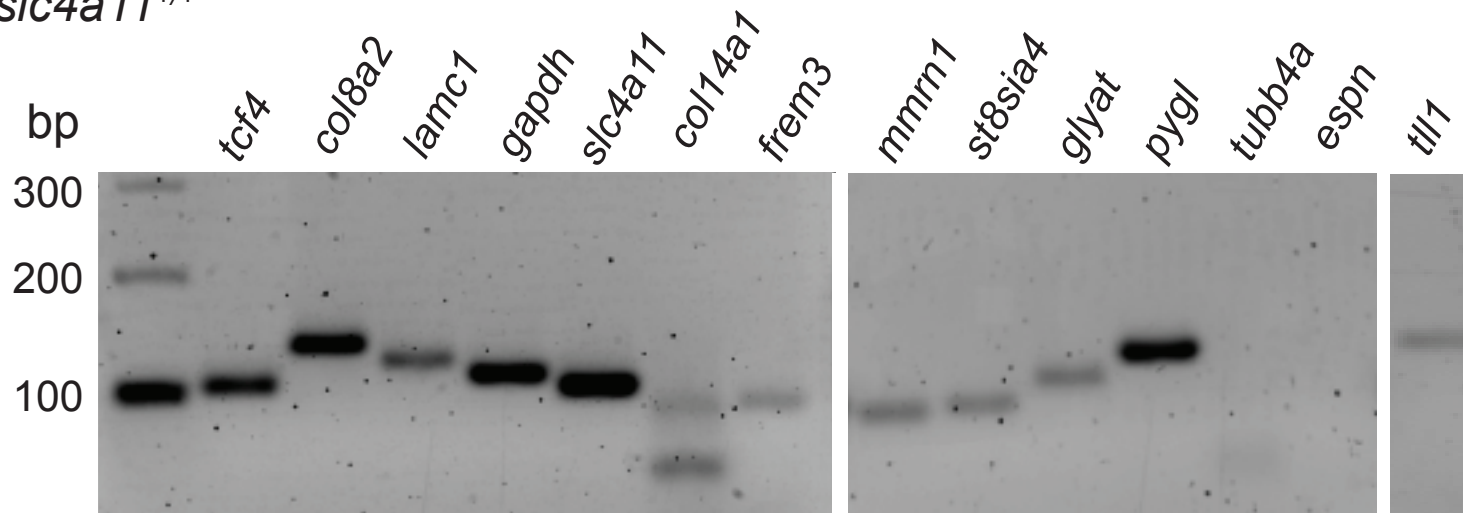
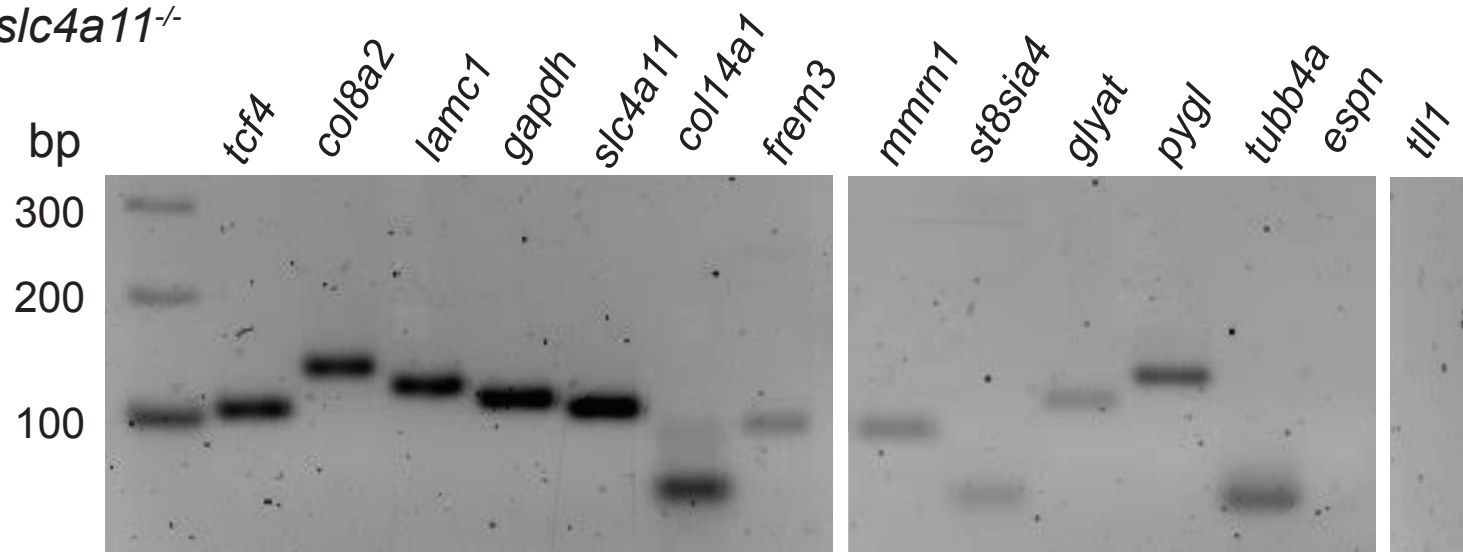
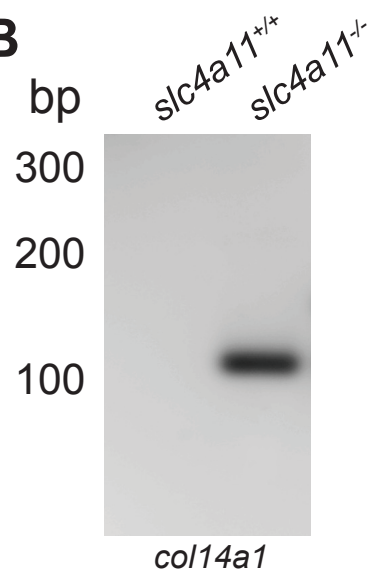
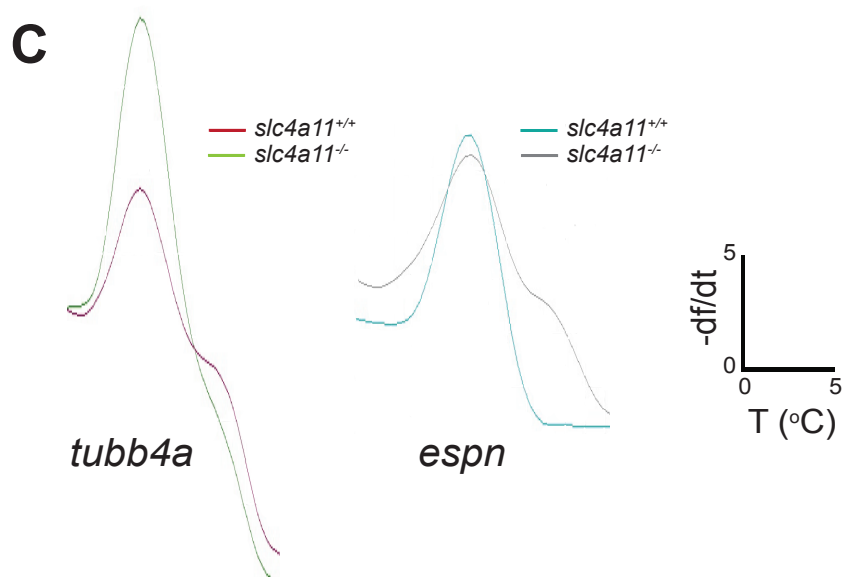
Suppl. Figure 2

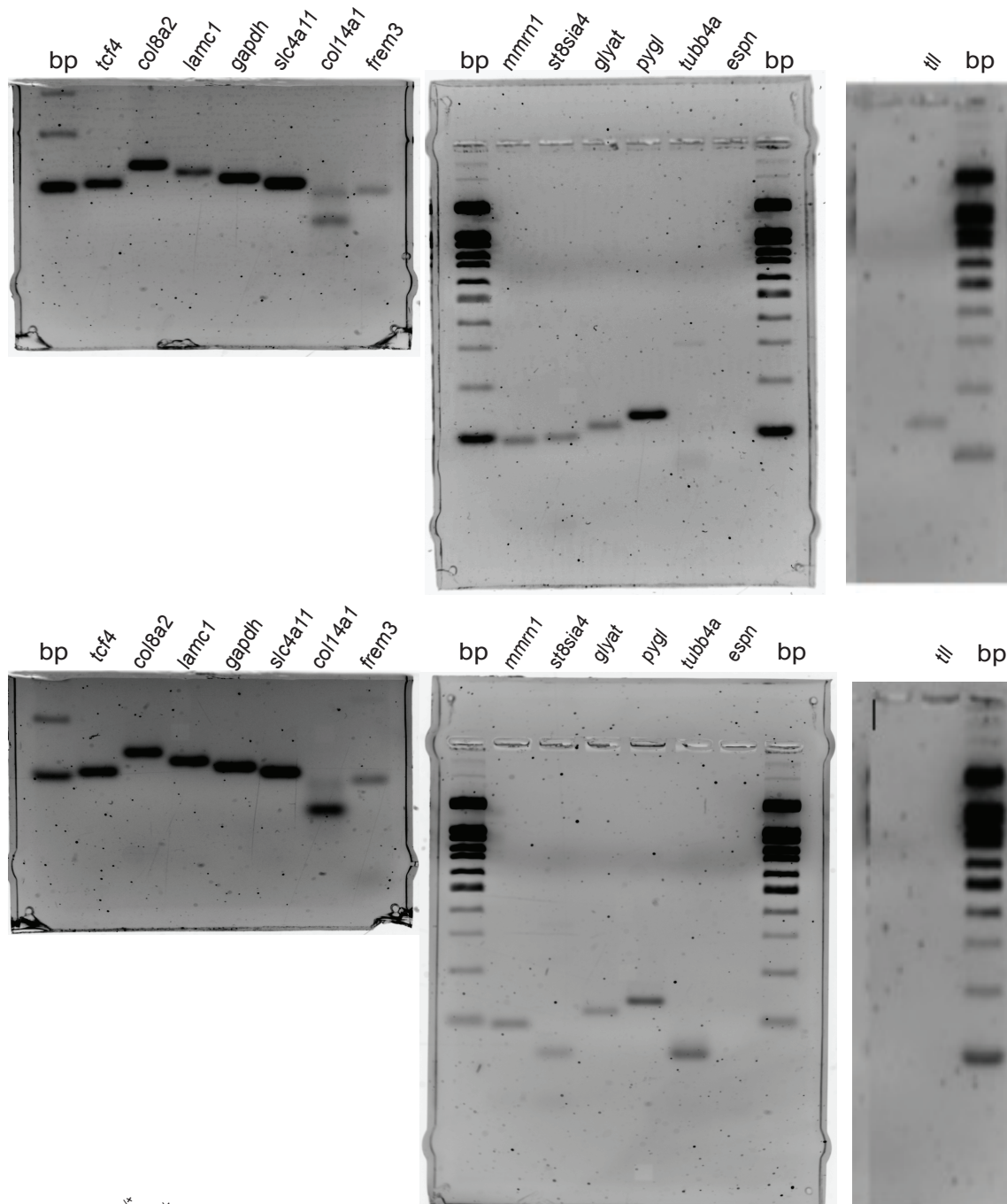
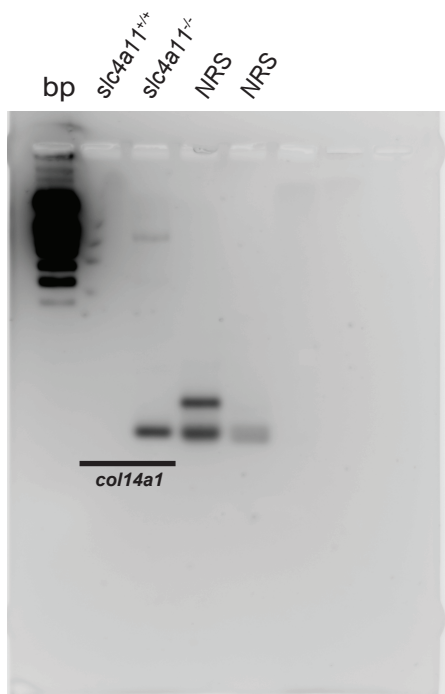


Suppl. Figure 3



Suppl. Figure 4

A*slc4a11*^{+/+}*slc4a11*^{-/-}**B****C****Suppl. Figure 5**

A**B****Suppl. Figure 6**