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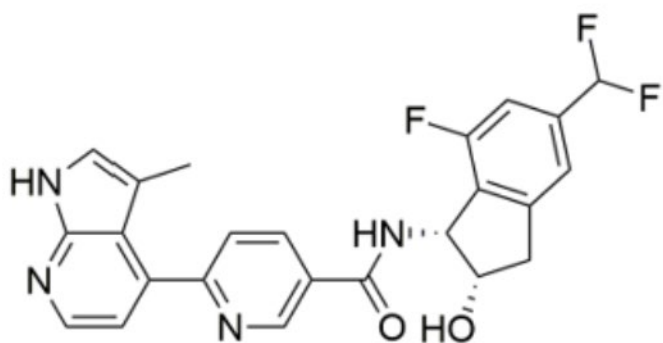
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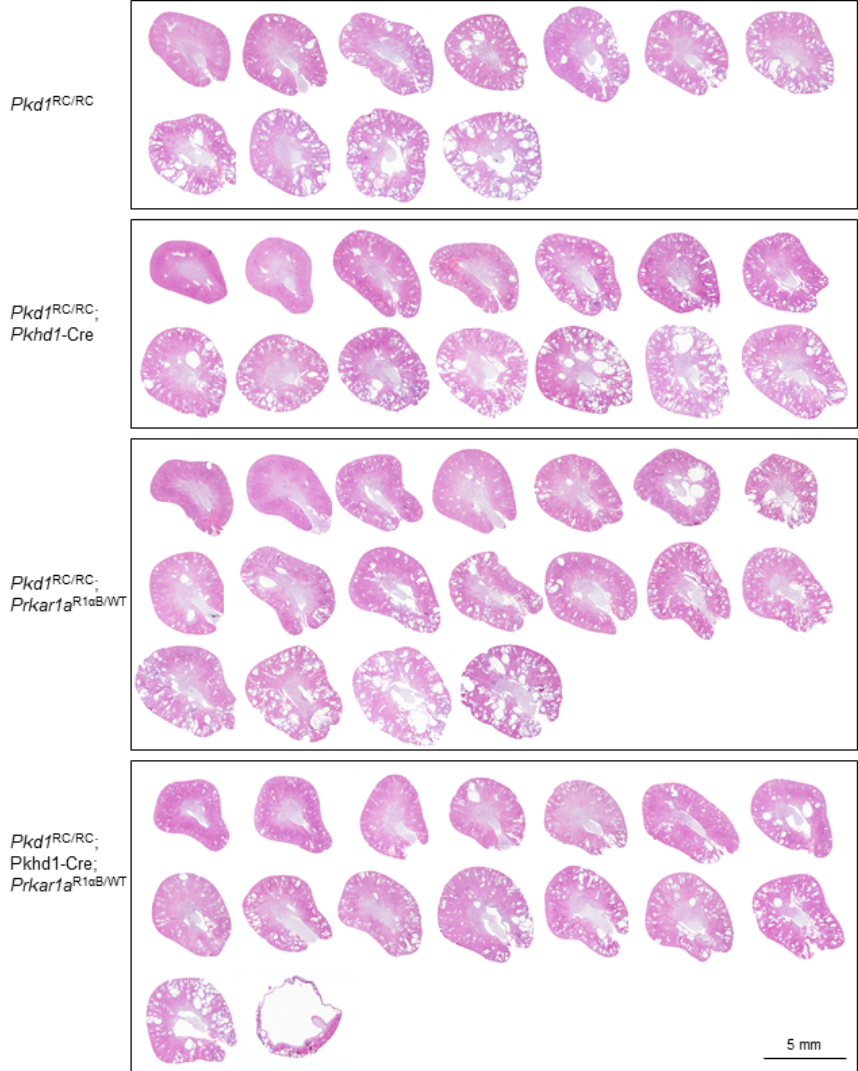
SUPPLEMENTAL MATERIAL

Supplemental Figure 1.

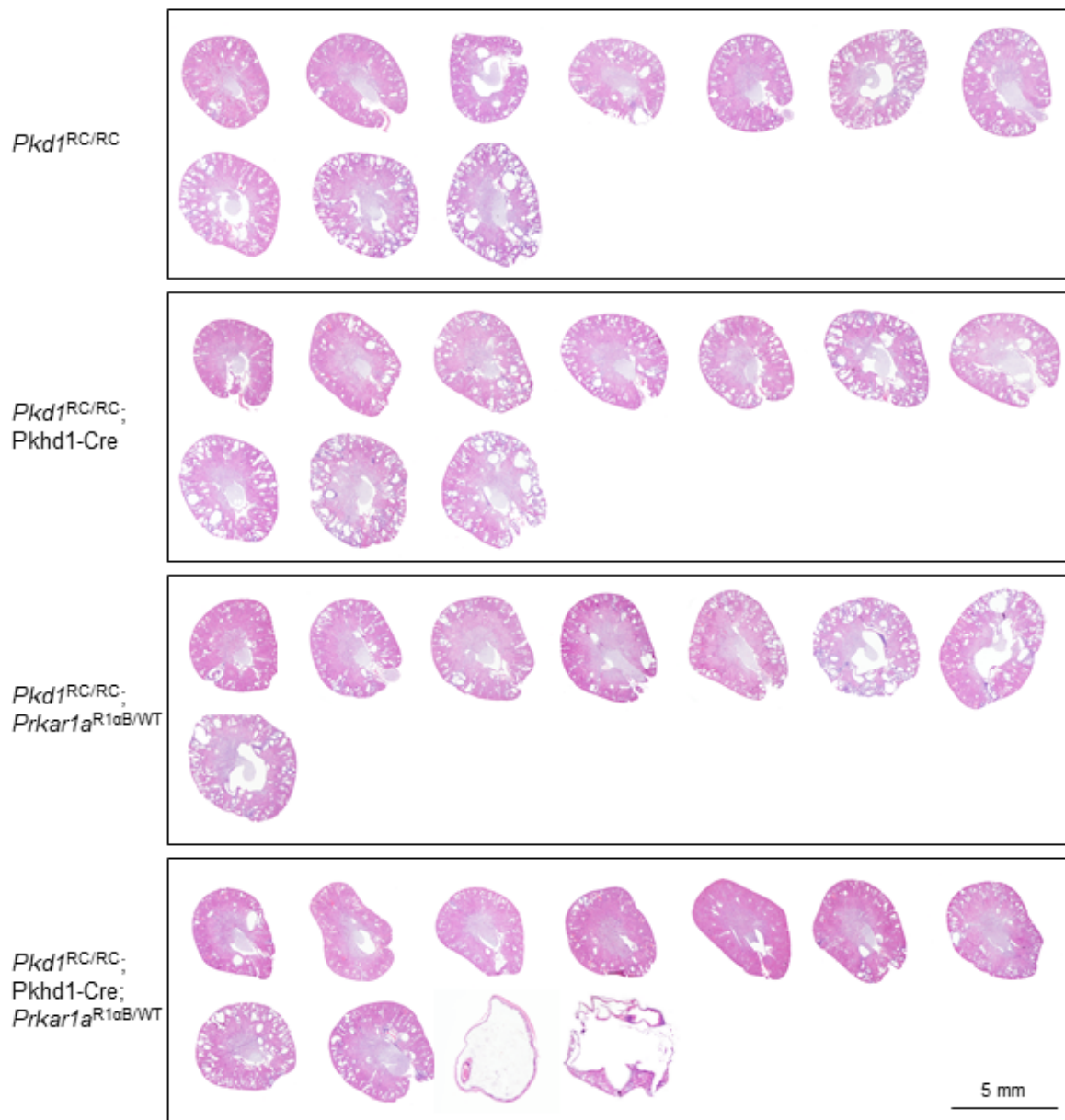


Supplemental Figure 1. Chemical structure of BLU2864.

Supplemental Figure 2a-Male

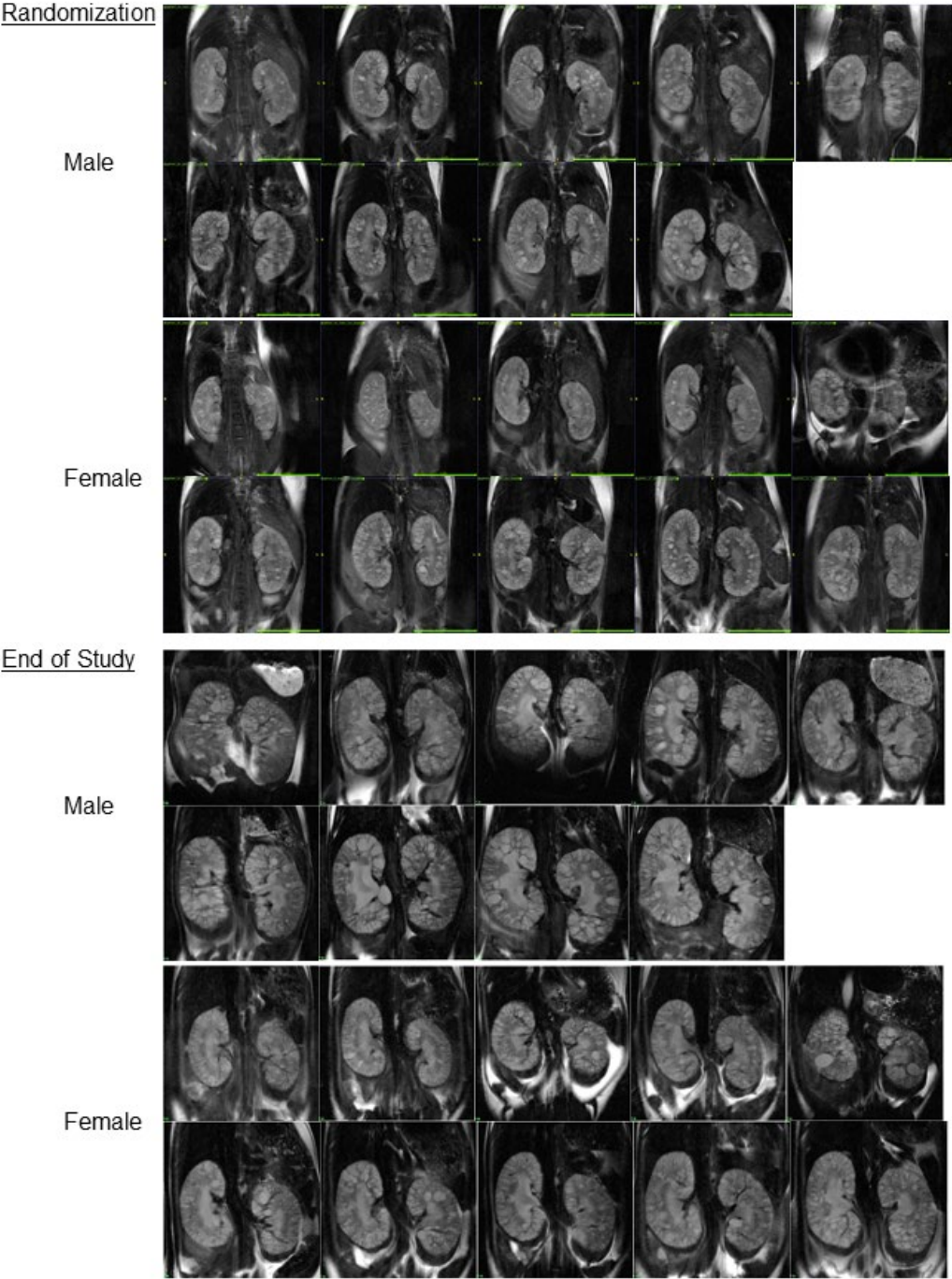


Supplemental Figure 2b-Female

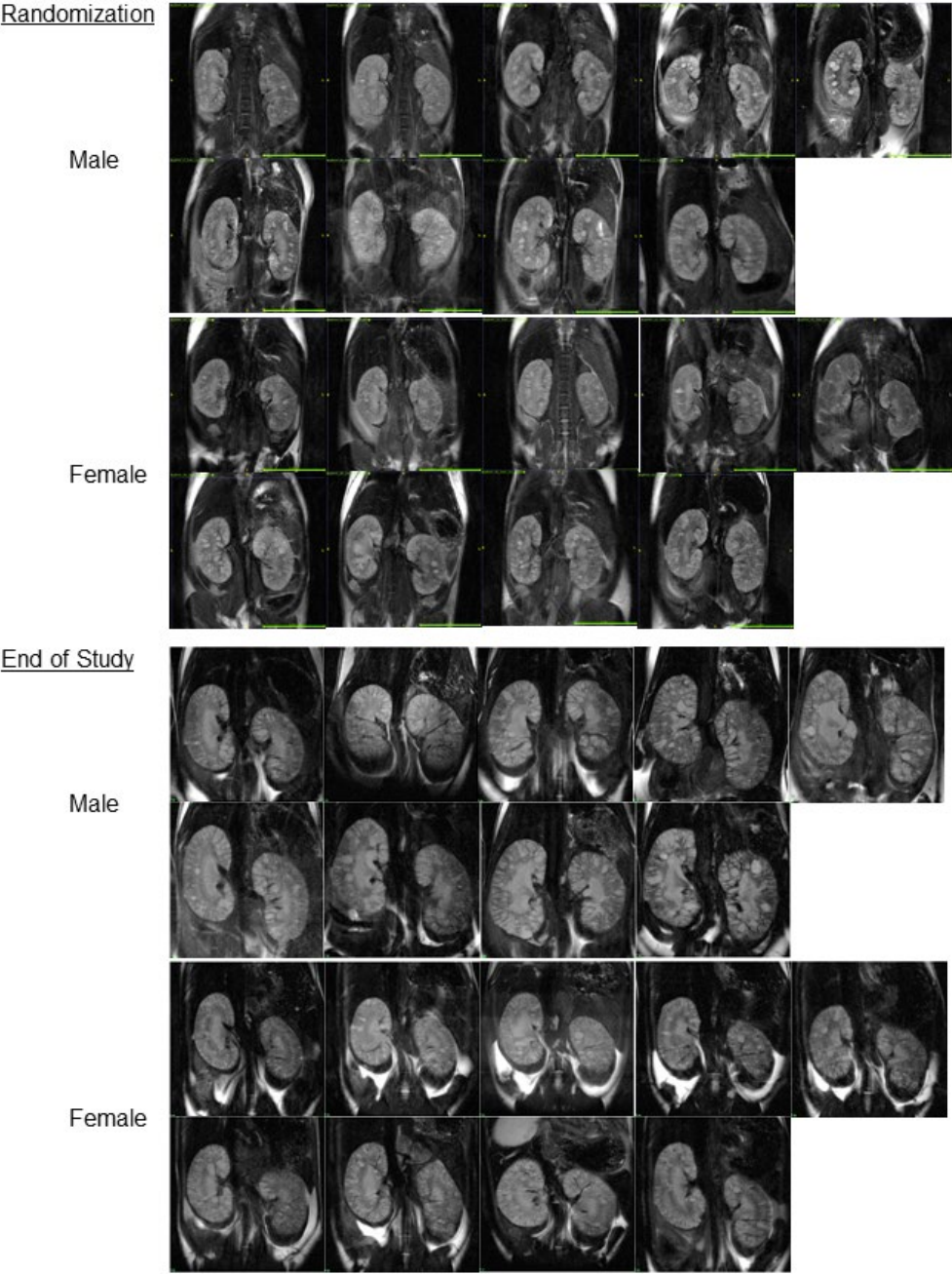


Supplemental Figure 2. Cross-sections of left kidneys stained with periodic hematoxylin and eosin from all control $Pkd1^{RC/RC}$ male (A) and female (B) mice ($Pkd1^{RC/RC}; Pkhd1-Cre; Prkar1\alpha^{WT/WT}$, $Pkd1^{RC/RC}; Prkar1\alpha^{WT/WT}$ and $Pkd1^{RC/RC}; Prkar1\alpha^{R1\alpha B/WT}$) and from all $Pkd1^{RC/RC}$ male (A) and female (B) mice expressing the R1 α B allele ($Pkd1^{RC/RC}; Pkhd1-Cre; Prkar1\alpha^{R1\alpha B/WT}$), ordered from least to most cystic.

Supplemental Figure 3a.

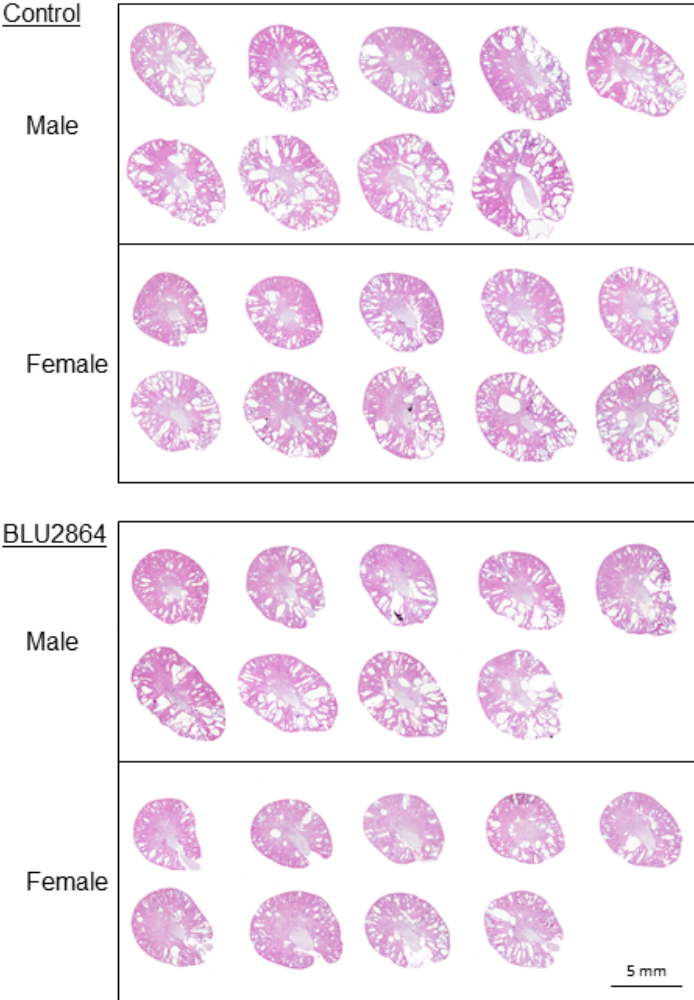


Supplemental Figure 3b.



Supplemental Figure 3. Coronal MR images of the kidneys from control (A) and BLU2864-treated *Pkd1^{RC/RC}* (B) mice at randomization and at the end of the study, ordered from least to most cystic at the end of the study.

Supplemental Figure 4.



Supplemental Figure 4. Cross-sections of left kidneys stained with periodic hematoxylin and eosin from control and BLU2864-treated *Pkd1*^{RC/RC} mice, ordered from least to most cystic.

Supplemental Table S1. Kinases with the highest binding affinity for BLU2864	
Target	Kd (nM)
PKAC-alpha	3.3
ROCK2	4.8
ROCK1	5.4
PKAC-beta	6.3
PRKX	16.5
SNARK	26
JAK2(JH1domain-catalytic)	27.5
MEK1	29
JAK3(JH1domain-catalytic)	50
MEK4	68.5
TYK2(JH1domain-catalytic)	99.5

Supplemental Table S2. Enzymatic inhibition of PRKACA and closely related kinases by BLU2864	
	IC50 at ATP Km
PRKACA	0.3 nM
PRKACB	0.7 nM
ROCK2	12.7 nM
AKT1	2120.0 nM
AKT2	4910.0 nM
AKT3	475.0 nM
PRKX	6.8 nM

Supplemental Table 3. Western blot quantification normalized to loading control						
Protein	<i>Pkd1</i> ^{RC/RC} <i>Prkar1α</i> ^{R1αB/WT} (N=3, M)	<i>Pkd1</i> ^{RC/RC} R1αB-ON (N=3, M)	P-value	Control (N=3, M)	BLU2864 (N=3, M)	P-value
PKA RIα	1.00±0.22	0.32±0.05	0.029	1.00±0.05	0.40±0.08	0.001
PKA RIβ	1.00±0.08	0.87±0.08	0.107	1.00±0.04	0.70±0.04	0.001
PKA RIIα	1.00±0.10	1.03±0.04	0.697	1.00±0.04	1.18±0.15	0.158
PKA RIIβ	1.00±0.21	0.90±0.12	0.504	1.00±0.07	0.93±0.03	0.214
PKA Cα	1.00±0.04	1.10±0.16	0.396	1.00±0.04	1.08±0.12	0.386
Glycosylated AQP2	1.00±0.07	0.16±0.07	<0.001	1.00±0.20	0.54±0.05	0.049
Unglycosylated AQP2	1.00±0.18	0.26±0.09	0.009	1.00±0.08	0.43±0.05	0.001
Total AQP2	1.00±0.07	0.17±0.07	<0.001	1.00±0.18	0.54±0.03	0.047
Glycosylated p-AQP2	1.00±0.01	0.12±0.03	<0.001	1.00±0.09	0.65±0.01	0.019
Unglycosylated p-AQP2	1.00±0.05	0.10±0.01	<0.001	1.00±0.10	0.66±0.05	0.015
Total p-AQP2	1.00±0.02	0.12±0.03	<0.001	1.00±0.09	0.65±0.01	0.020
PCNA	1.00±0.03	0.43±0.02	<0.001	1.00±0.05	0.66±0.08	0.005
Src	1.00±0.10	1.29±0.70	0.547	1.00±0.18	1.01±0.06	0.957
P-Src	1.00±0.09	0.63±0.06	0.007	1.00±0.18	0.40±0.03	0.028
ERK1/2	1.00±0.04	0.93±0.07	0.206	1.00±0.05	0.72±0.03	0.003
P-ERK1/2	1.00±0.07	0.46±0.05	<0.001	1.00±0.05	0.76±0.01	0.009
S6K	1.00±0.08	0.79±0.10	0.049	1.00±0.04	1.08±0.04	0.072
P-S6K	1.00±0.04	0.44±0.03	<0.001	1.00±0.12	0.53±0.05	0.011
4E-BP1	1.00±0.17	0.62±0.06	0.046	1.00±0.14	0.52±0.02	0.023
P-4E-BP1	1.00±0.19	0.53±0.04	0.049	1.00±0.10	0.59±0.03	0.011
GSK3β	1.00±0.12	0.92±0.06	0.370	1.00±0.14	0.84±0.04	0.190
P-GSK3β	1.00±0.10	0.45±0.05	0.004	1.00±0.09	0.40±0.01	0.007

Akt	1.00±0.05	0.93±0.03	0.114		1.00±0.10	1.15±0.11	0.155
PS473-Akt	1.00±0.06	0.40±0.05	<0.001		1.00±0.05	0.52±0.16	0.026
PT308-Akt	1.00±0.04	0.48±0.07	0.001		1.00±0.13	0.56±0.16	0.024
CREB	1.00±0.13	0.31±0.11	0.003		1.00±0.09	0.41±0.004	0.007
P-CREB	1.00±0.03	0.43±0.12	0.012		1.00±0.08	0.32±0.02	0.003
STAT3	1.00±0.09	0.67±0.07	0.007		1.00±0.02	0.75±0.03	0.001
P-STAT3	1.00±0.11	0.49±0.02	0.012		1.00±0.14	0.55±0.05	0.021
PAX2	1.00±0.10	0.37±0.11	0.002		1.00±0.10	0.60±0.09	0.008
Gli1	1.00±0.09	1.54±0.23	0.041		1.00±0.07	1.60±0.18	0.018
Gli2	1.00±0.05	1.33±0.15	0.048		1.00±0.01	1.24±0.05	0.015
Gli3-A	1.00±0.15	0.65±0.12	0.038		1.00±0.15	0.50±0.07	0.016
Gli3-R	1.00±0.14	1.07±0.22	0.677		1.00±0.05	1.11±0.04	0.049