

# SUBTOTAL RENAL ABLATION INDUCES TUBULOINTERSTITIAL EGR-2 OVEREXPRESSION IN MICE

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## BACKGROUND

The number of patients with chronic kidney disease and renal fibrosis is growing worldwide. Subtotal (5/6) renal ablation (SNX) is a commonly used model of progressive renal fibrosis, which induces glomerulosclerosis and tubulointerstitial fibrosis.

TGF- $\beta$ 1 plays a pivotal role in fibrosis by regulating profibrotic genes. Upon TGF- $\beta$ 1 stimulus, cultured fibroblasts increase the expression of EGR-2 (early growth response factor-2), an early transcription factor which induces collagen synthesis<sup>1</sup>.

We hypothesized that EGR-2 could also contribute to renal fibrosis in the mouse model of renal mass reduction.

## METHODS

### Animal model:

As C57Bl6 (B6) mice are less susceptible to renal mass reduction, we chose BalbCxB6 hybrid (F1) males at 8 weeks of age.

One week after removal of the right kidney, 66% of the left kidney was surgically excised (SNX, n=8).

Control mice underwent sham operation (n=8). Kidneys were removed 12 weeks after surgery, and analyzed for histology, immunohistochemistry and mRNA expression levels as follows.

### Performed analyses:

- Glomerulosclerosis index
- Tubular damage index
- TGF- $\beta$ 1 mRNA expression
- Collagen-1 mRNA expression
- EGR2 mRNA expression
- EGR2 immunostaining

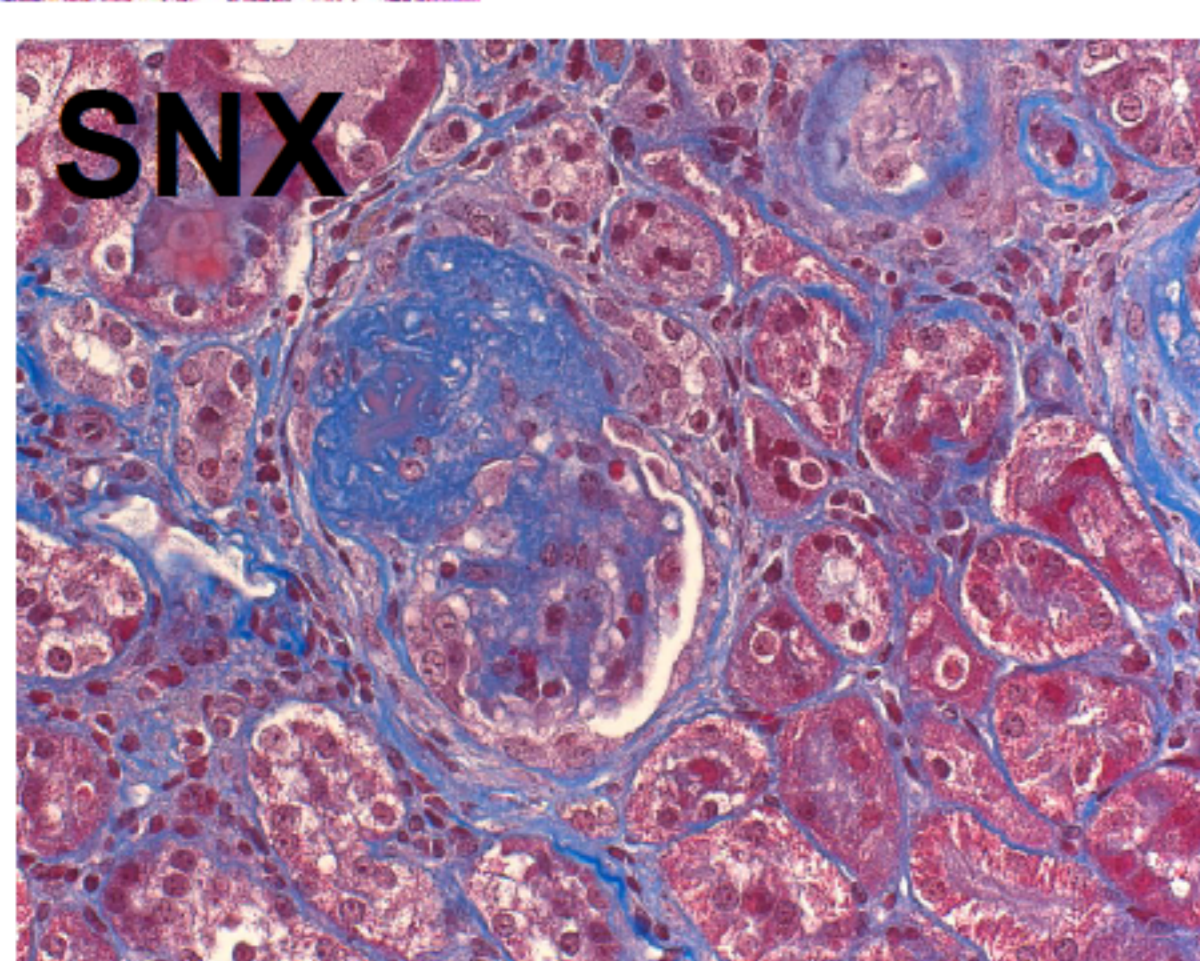
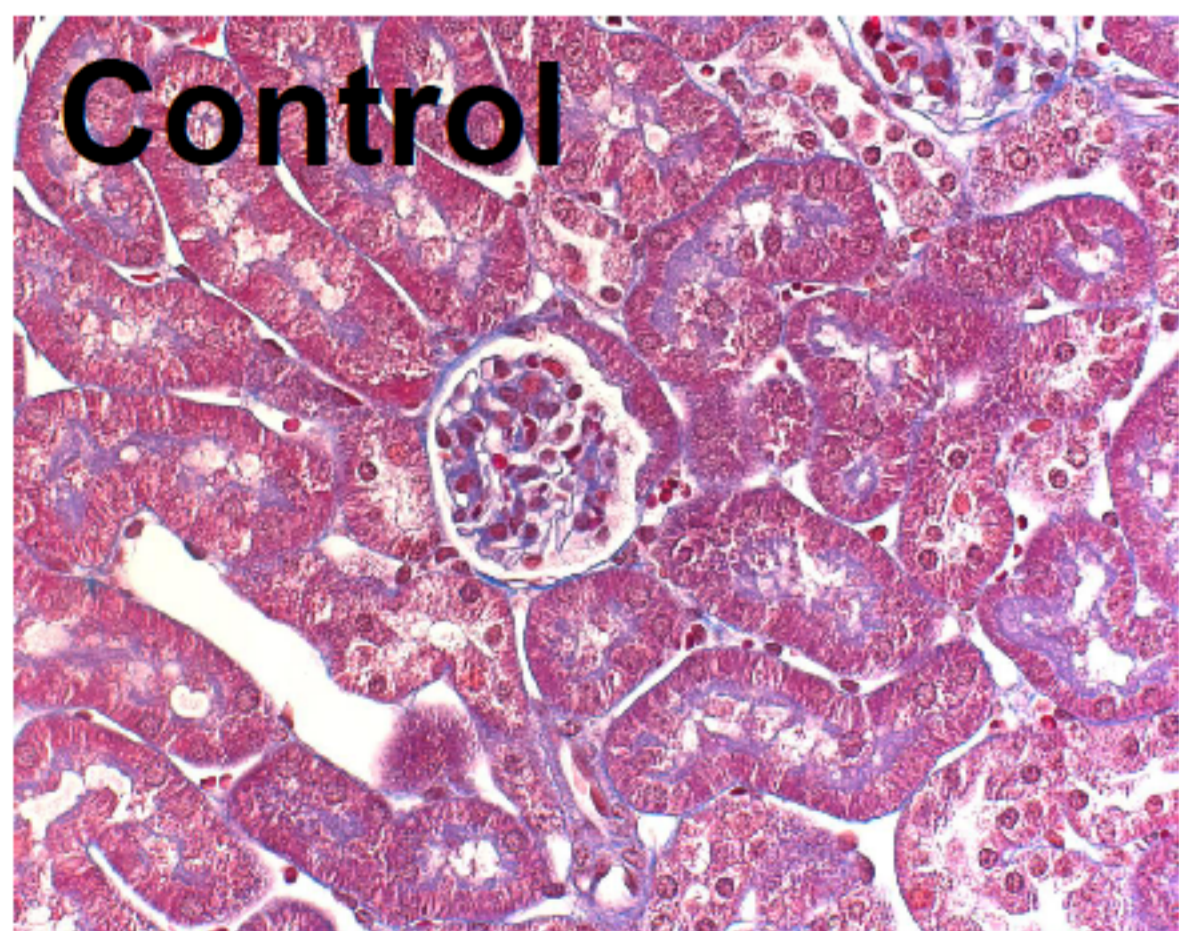
### Statistics:

Data are presented as mean+SD. Student's t-test and Mann-Whitney test were performed (SPSS 10).

## RESULTS

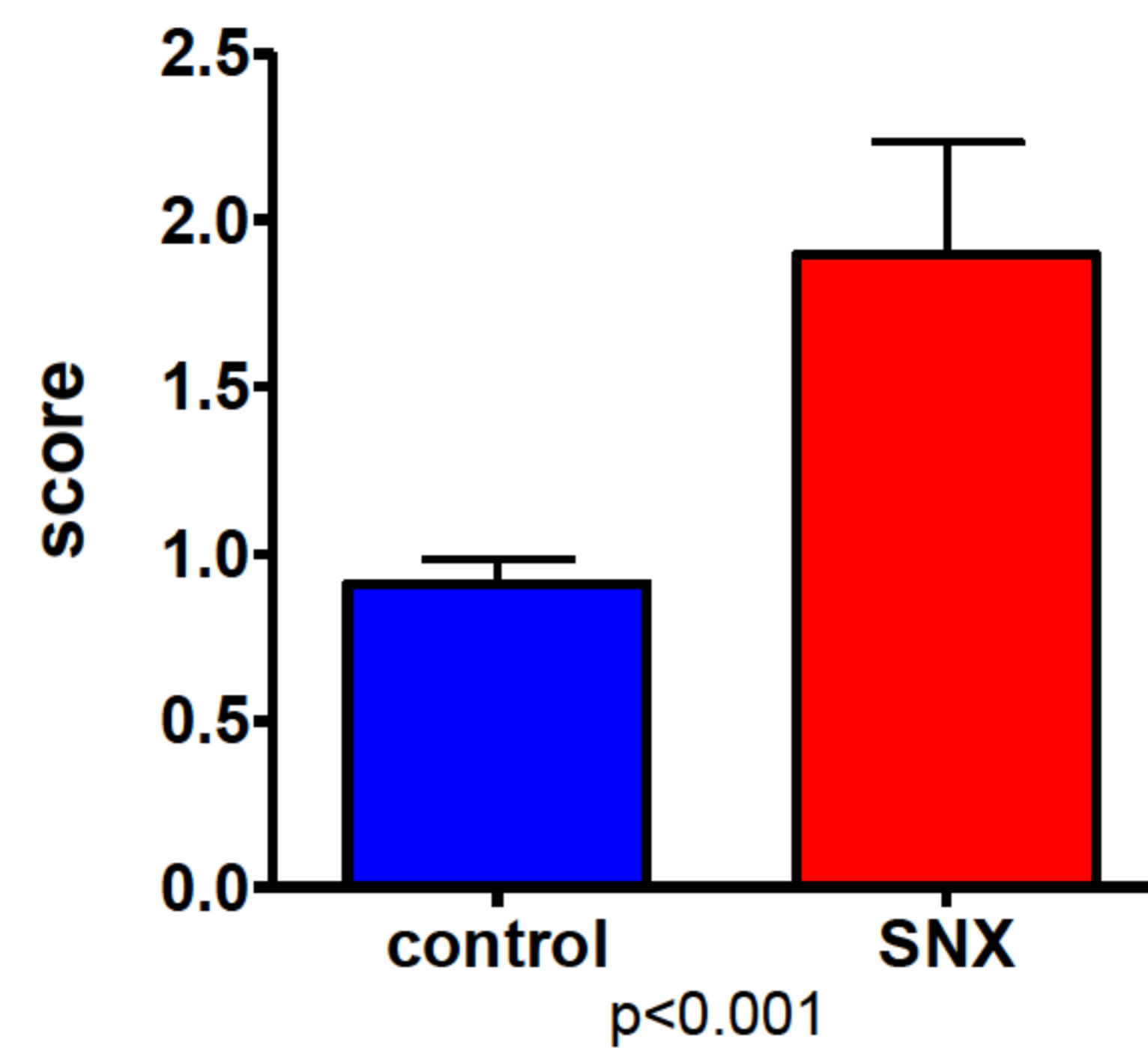
### Histology

SNX mice developed significant glomerulosclerosis (p<0.001) and tubulointerstitial damage (p<0.001).

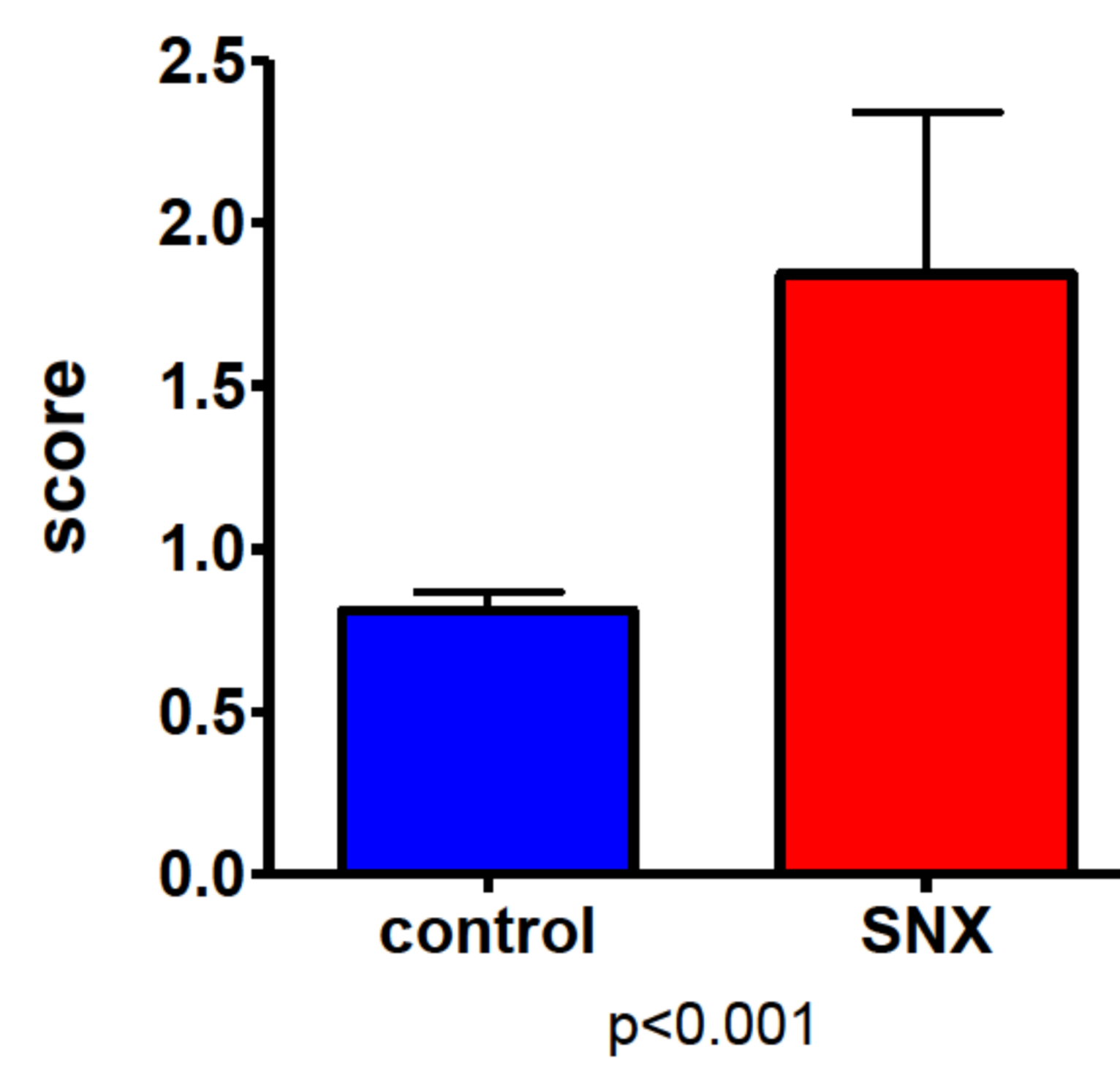


Masson's trichrome stain, 400x magnification (blue: connective tissue)

### Glomerulosclerosis



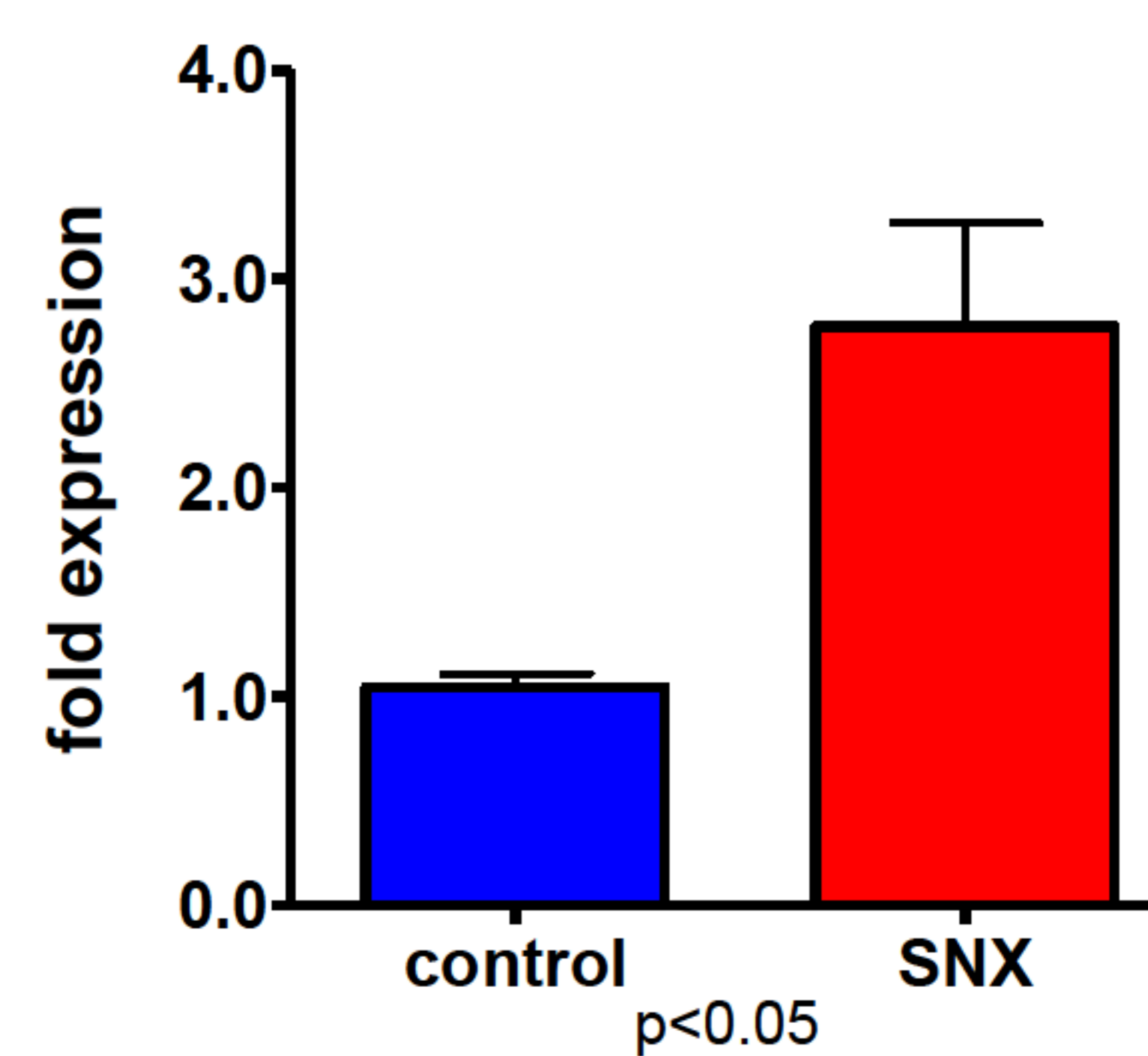
### Tubulointerstitial damage



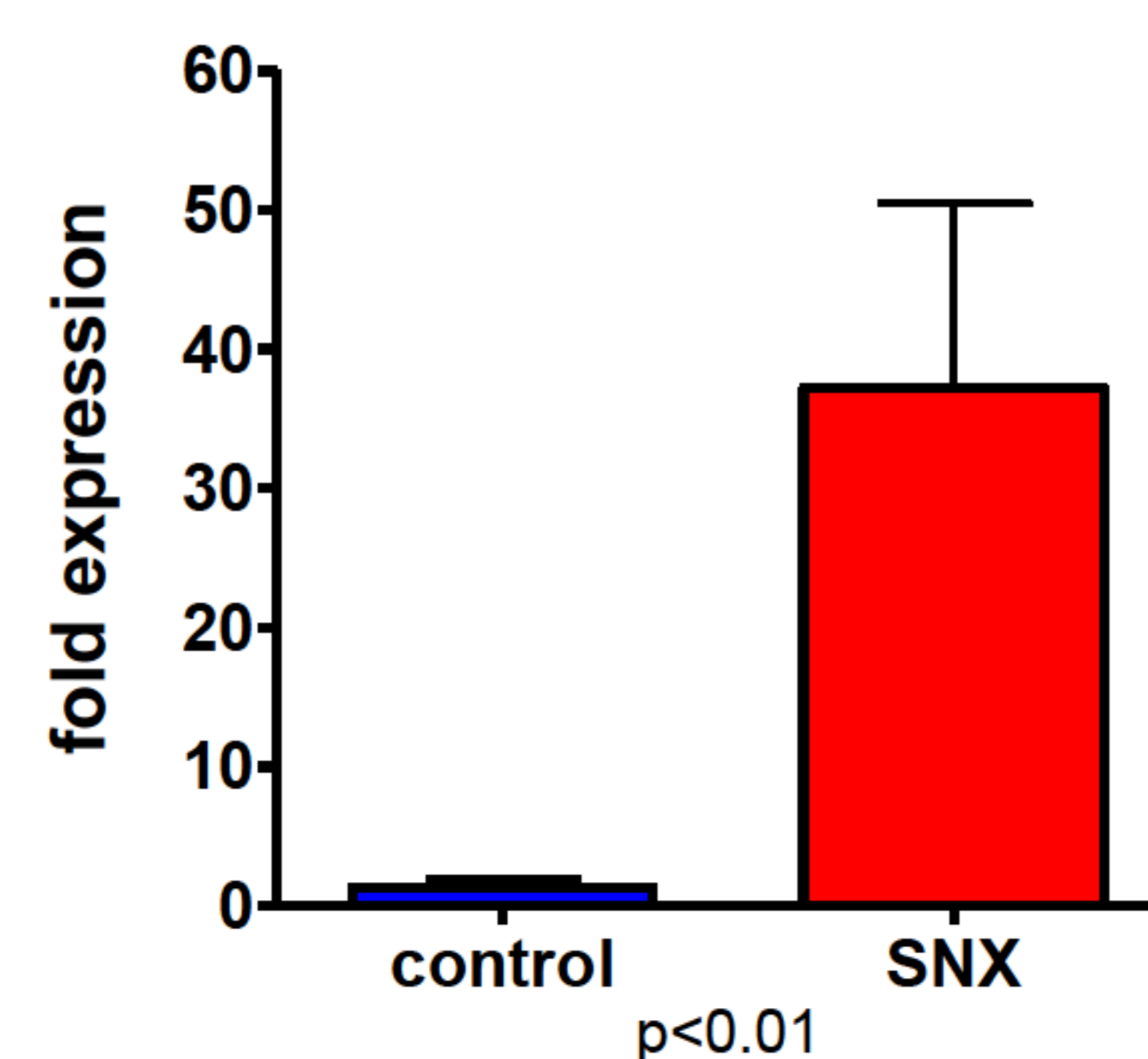
### TGF- $\beta$ 1 and collagen expression

SNX kidneys had increased mRNA expression of profibrotic TGF- $\beta$ 1 (p<0.05) and collagen-1 (p<0.01).

### TGF- $\beta$ 1 mRNA expression



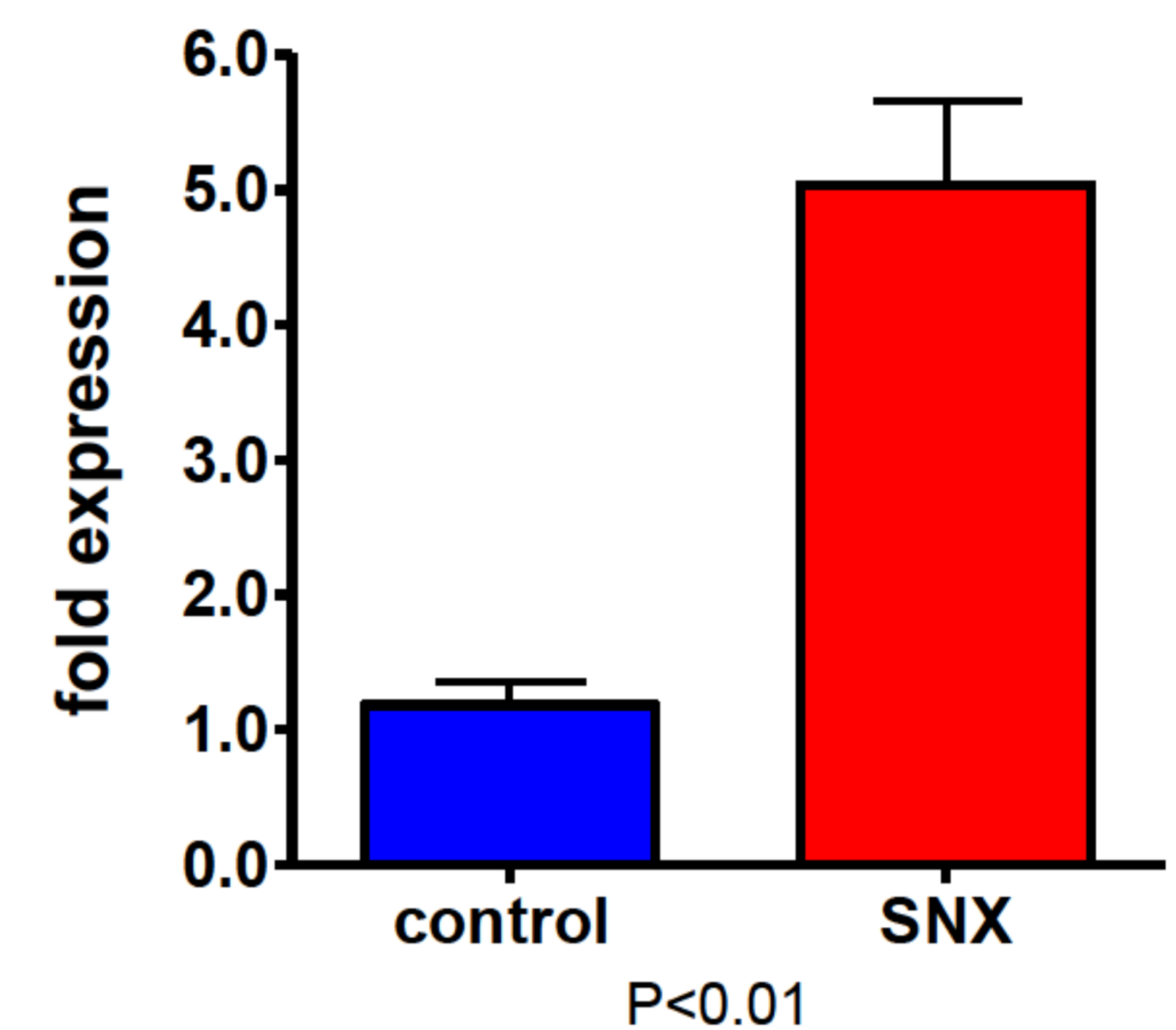
### Collagen-1 mRNA expression



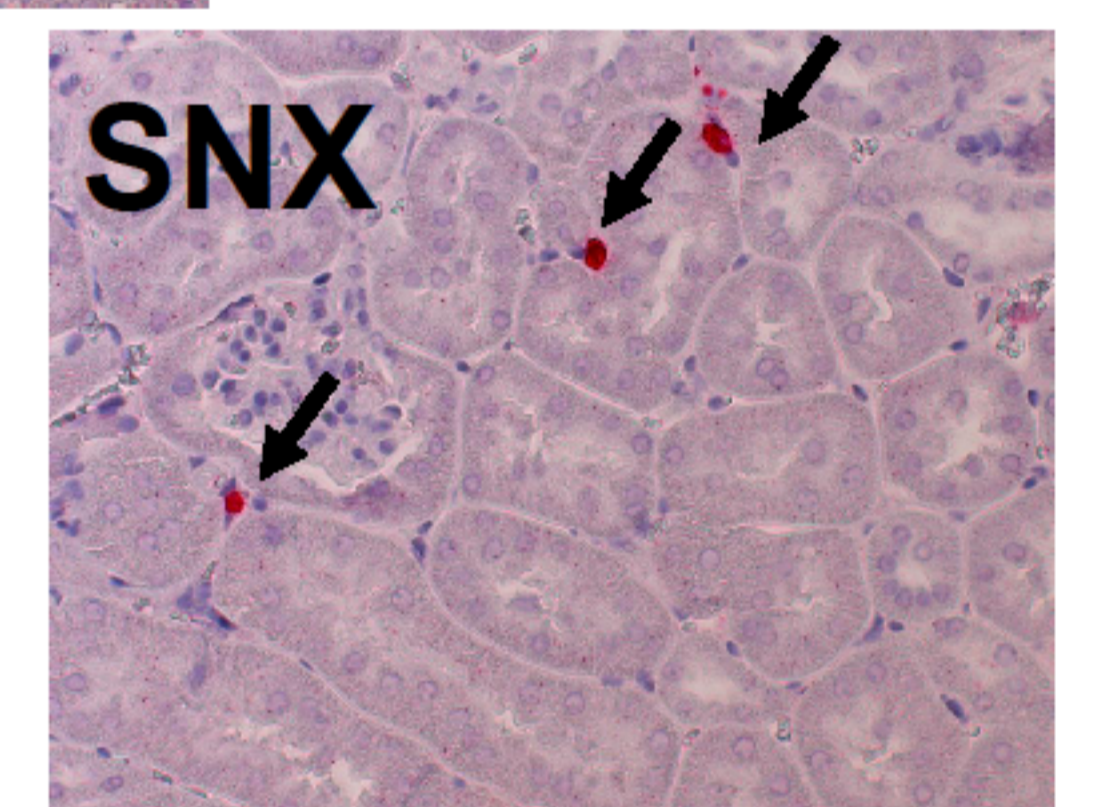
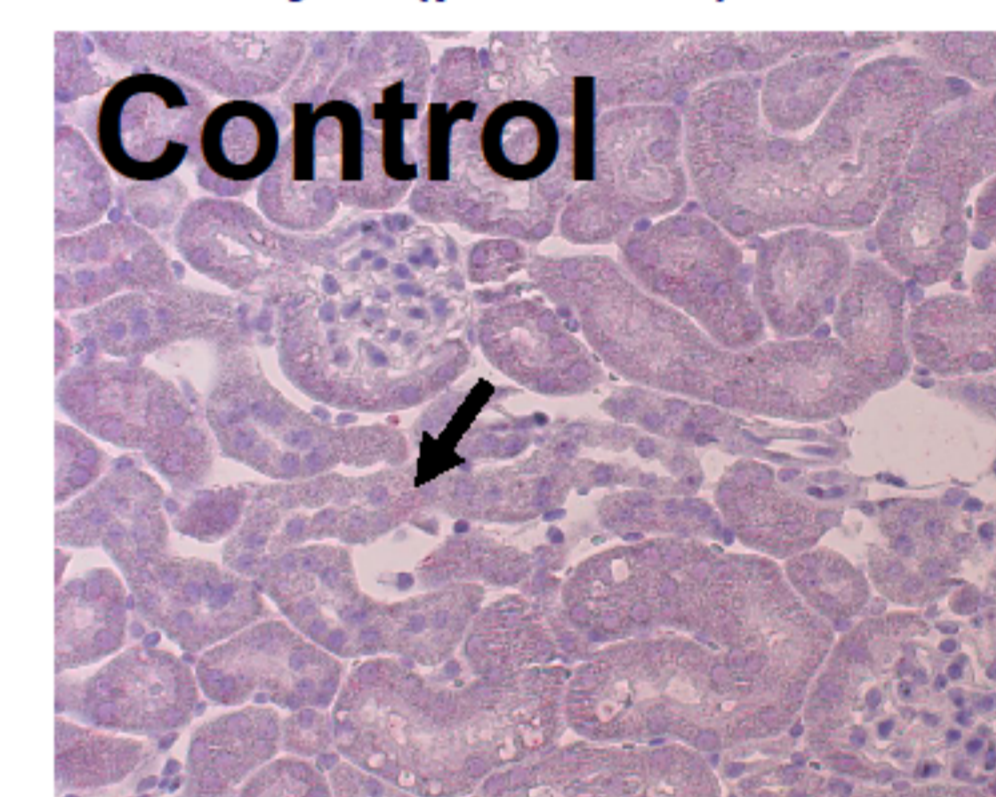
### Renal EGR-2 expression

In SNX mice, EGR-2 mRNA expression was 5-fold higher (p<0.01) than in control mice.

### EGR2 mRNA expression

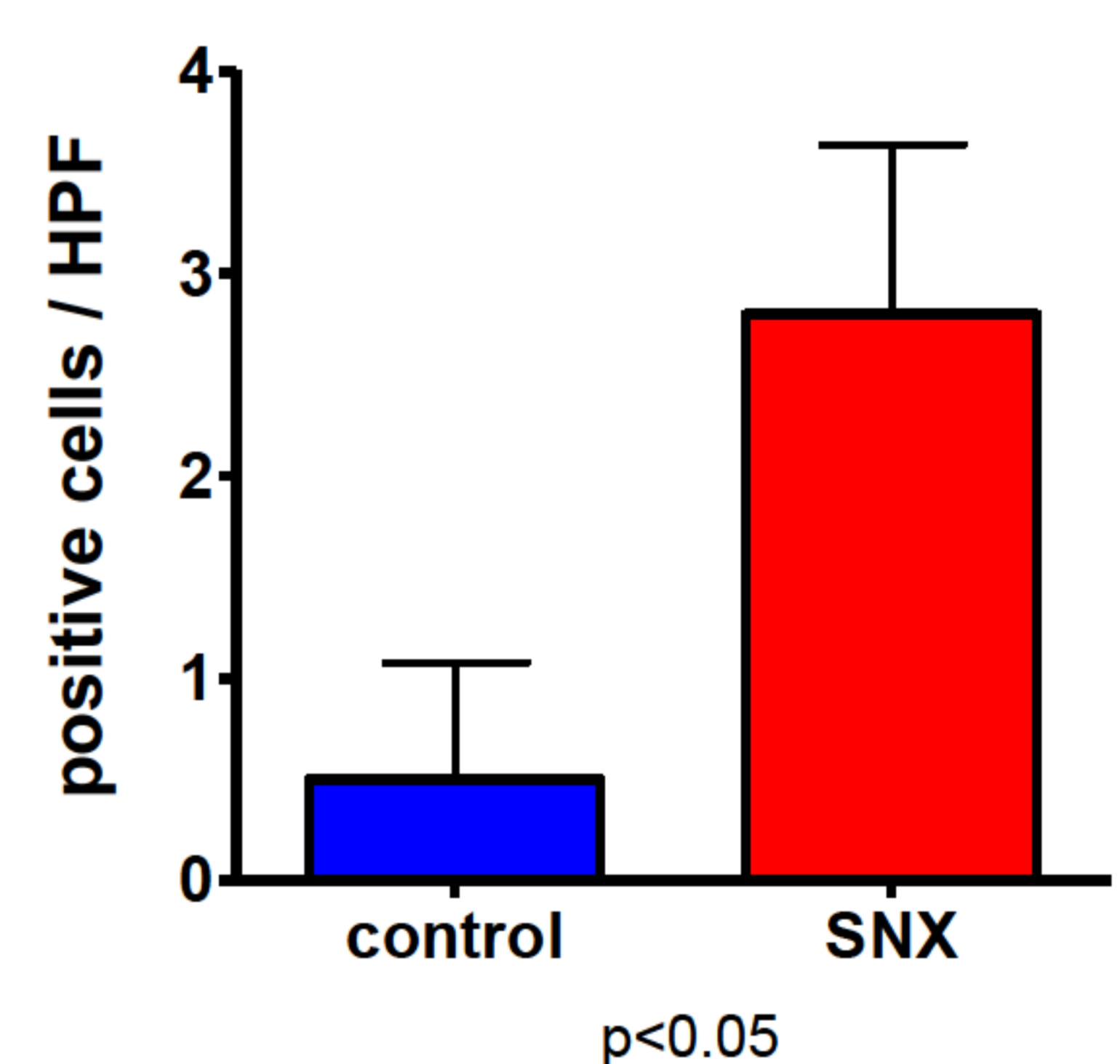


SNX kidneys depicted significantly more EGR-2 positive tubulointerstitial cells (see arrows below) as compared to control kidneys (p<0.05).



EGR-2 immunostaining (red), 400x magnification

### EGR-2 positive cell count



## CONCLUSION

Our results indicate that renal tubulointerstitial EGR-2 overexpression strongly correlates with matrix overproduction and might further exacerbate the profibrotic effects of TGF- $\beta$ 1. Thus, EGR-2 could serve as a novel target against fibrosis in the future.

## REFERENCES

- 1) Am J Pathol 2011, 178:2077–2090

## SUPPORT

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