Hairpatches *(Hpt)*: A Single Gene Mutation Characterized by Progressive Renal Disease and Alopecia

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L.D. Shultz *et al.* (1991) Lab. Invest. 65:588

Hairpatches (*Hpt* /+)

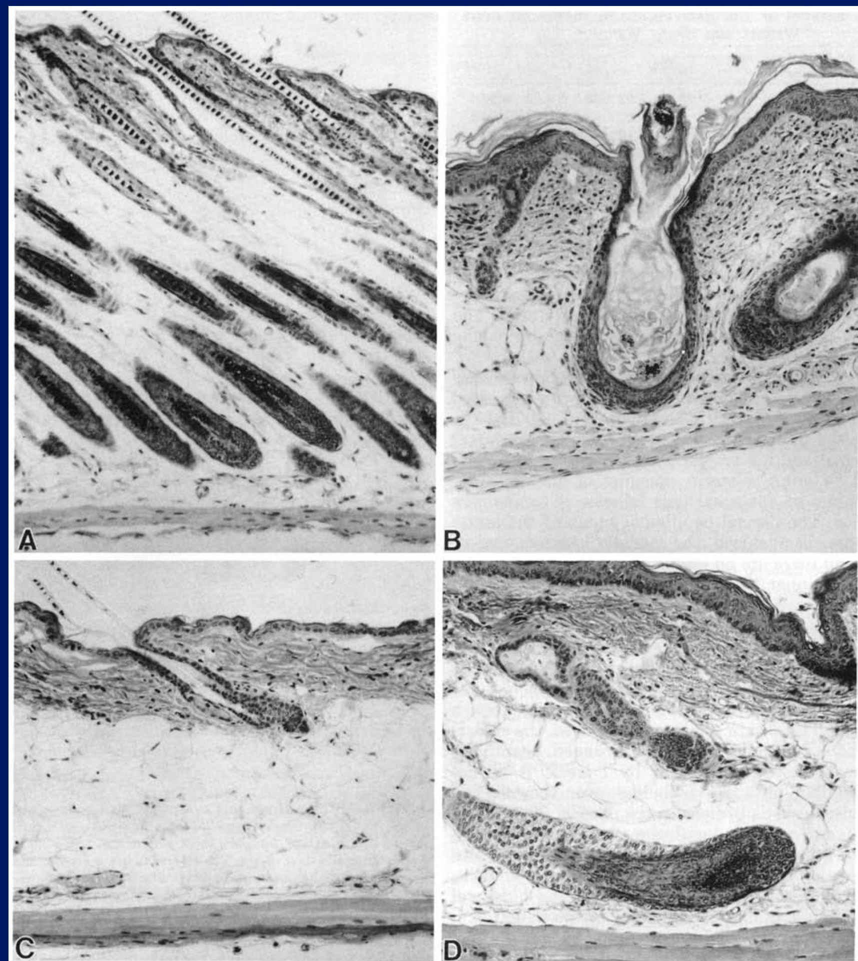
- Spontaneous autosomal dominant mutation at JAX in 1979
- Embryonic lethal (*Hpt*/*Hpt*)
- Originally on C57BL/6 x C3HFeB/FeJ-*a*/*a* hybrid background
- Currently on the HPT/Le inbred strain background
- Patchy absence of skin pigment at 3-4 days of age
- *Hpt*/+ mice are normoglycemic

Abnormalities in Skin and Hair in HPT/Le-*Hpt*/+ Mice

+/+ **_Hpt_/+**

2-weeks old

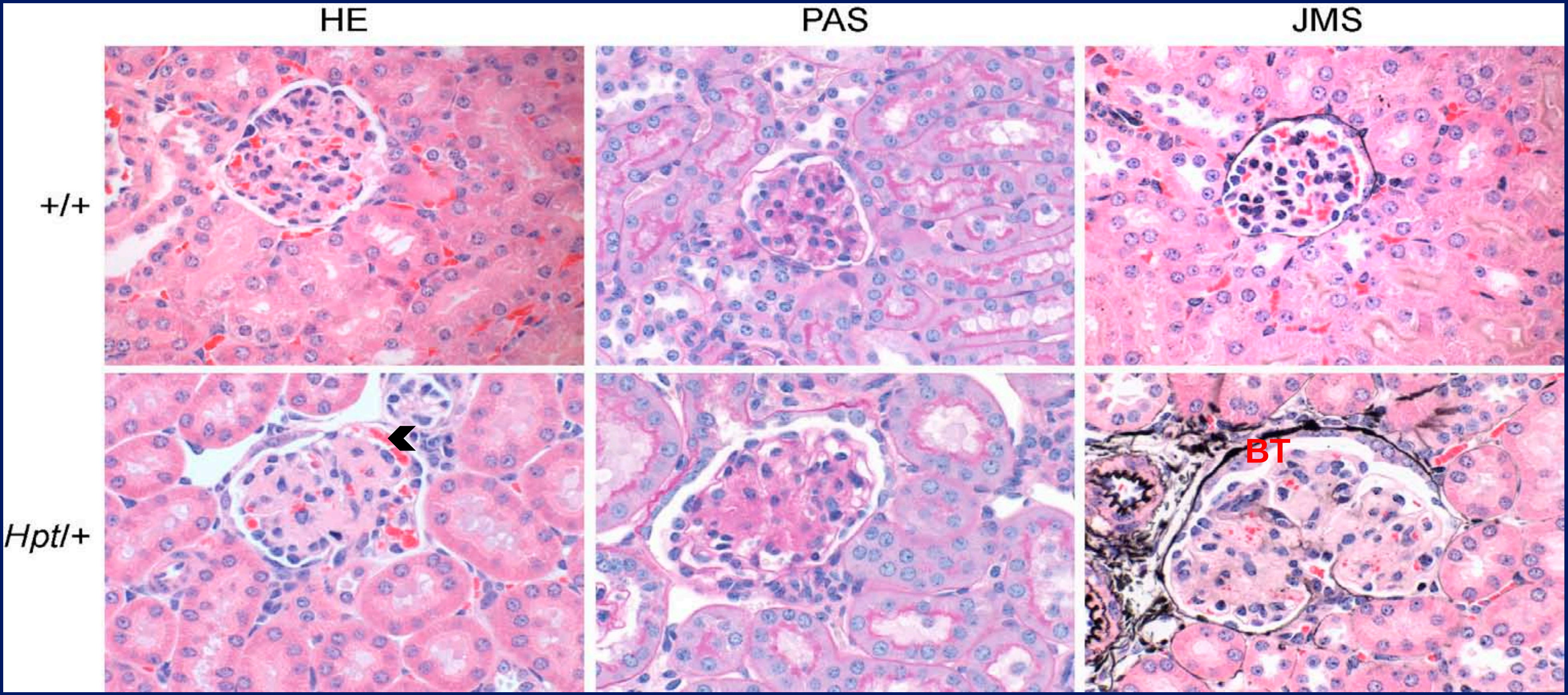
28-weeks old



Hpt/+ mice have decreased numbers of hair follicles. The follicles are enlarged and plugged with keratin. Abortive follicles are present.

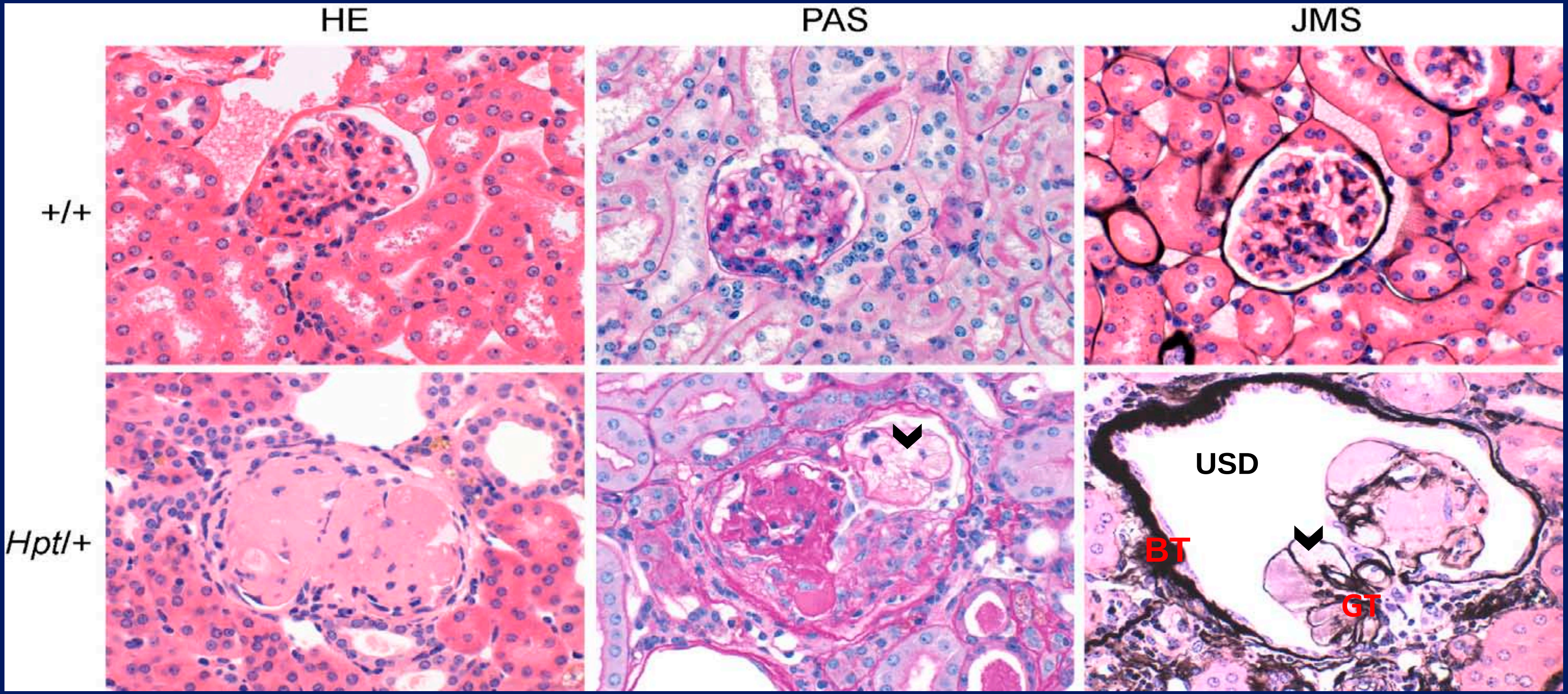
Skin shows hyperkeratosis and mild dermal inflammation

Glomerular changes at 4 weeks of age



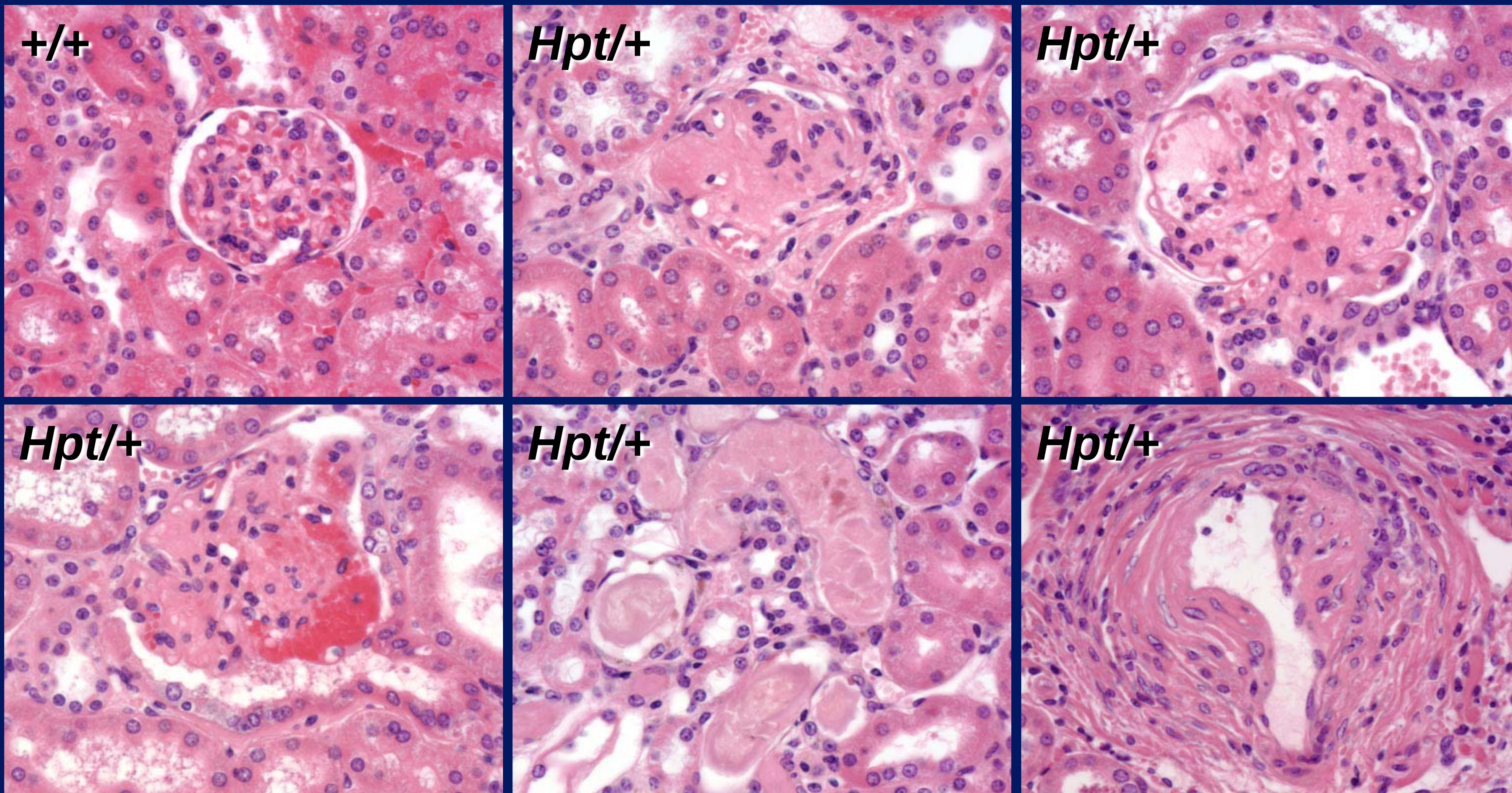
Enlargement of glomeruli
Glomerulosclerosis (diffuse increase in mesangial matrix)
Glomerular capillary dilation – arrowhead
BT – Early thickening of Bowman’s capsule basement membrane

Glomerular changes at 12 months of age



Diffuse and nodular glomerulosclerosis
Glomerular capillary aneurysm – arrowhead
USD – Urinary space dilation
BT – Bowman's capsule basement membrane thickening
GT – Glomerular capillary basement membrane thickening

Severe Pathological Changes in *Hpt*/+ Kidneys at 14 Months of Age(H+E)

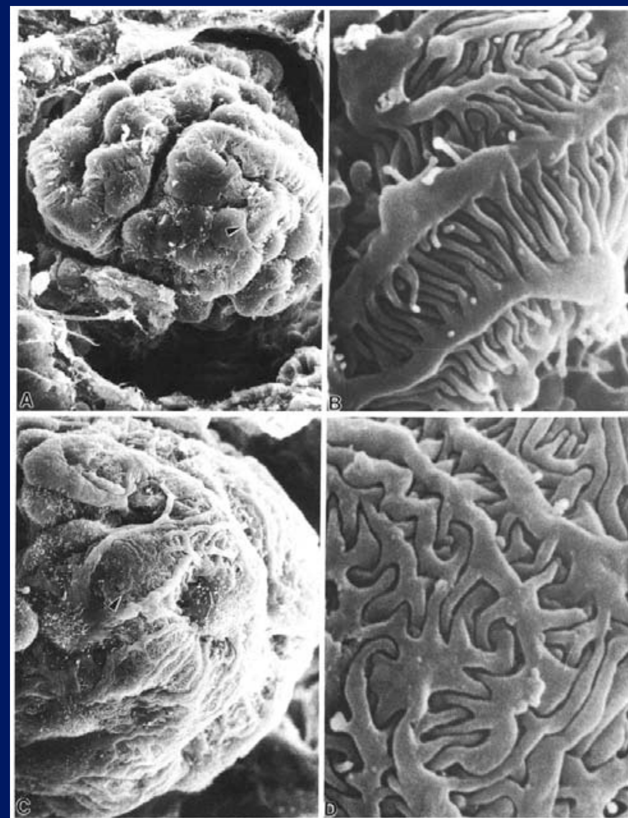


SEM of HPT/Le Kidneys (6 wk old)

1,500x 15,000x

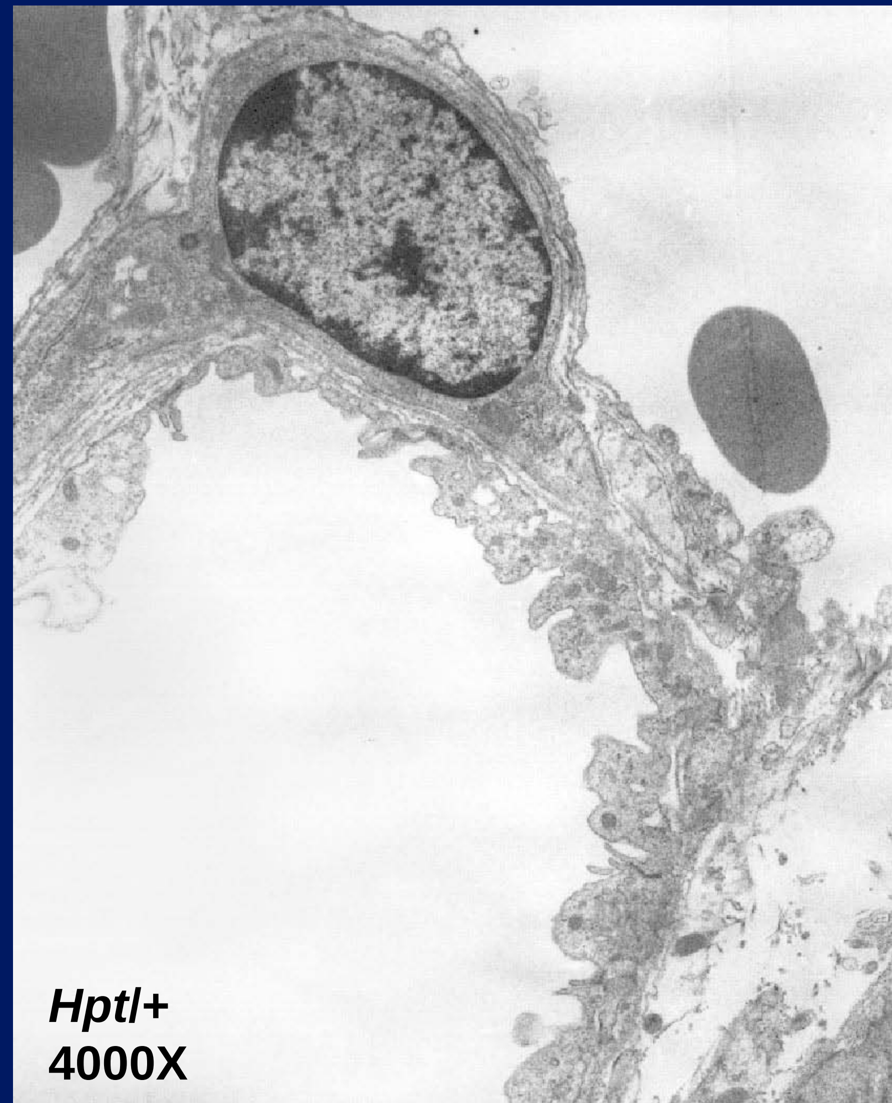
+/+

***Hpt*/+**

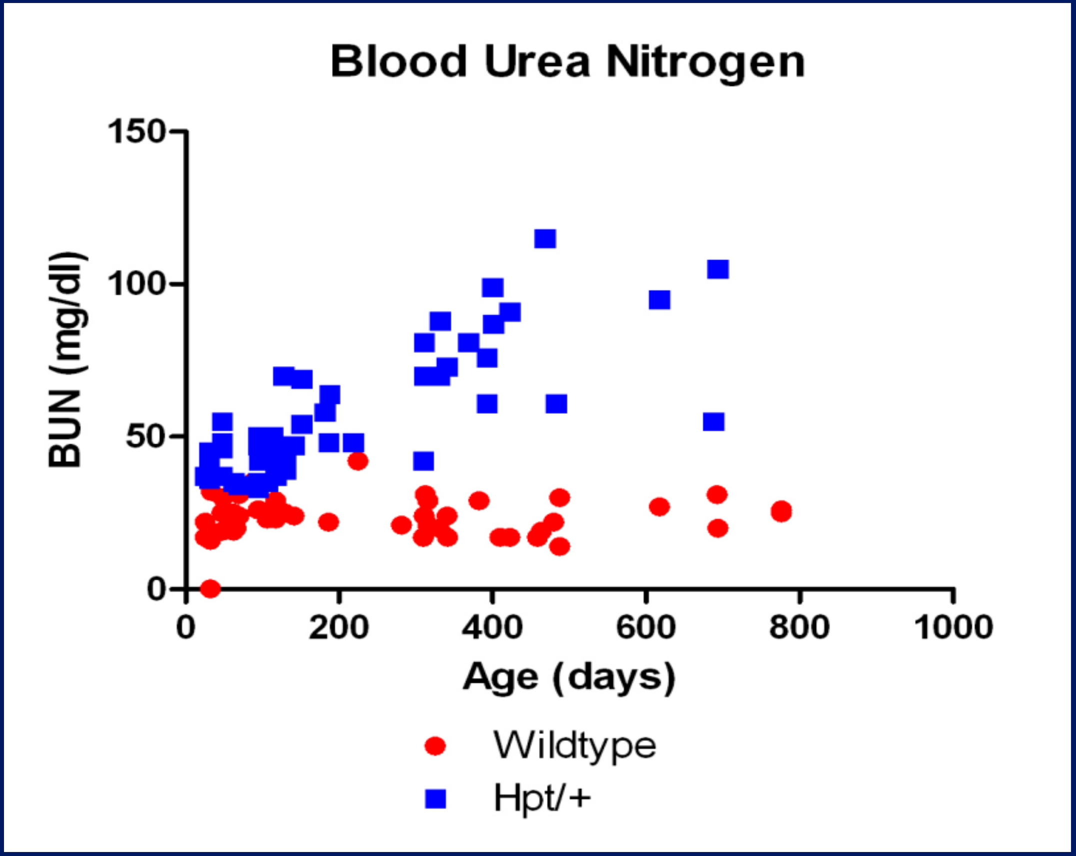


Hpt/+ glomeruli show swelling and blunting of foot processes and poorly-defined filtration slits.

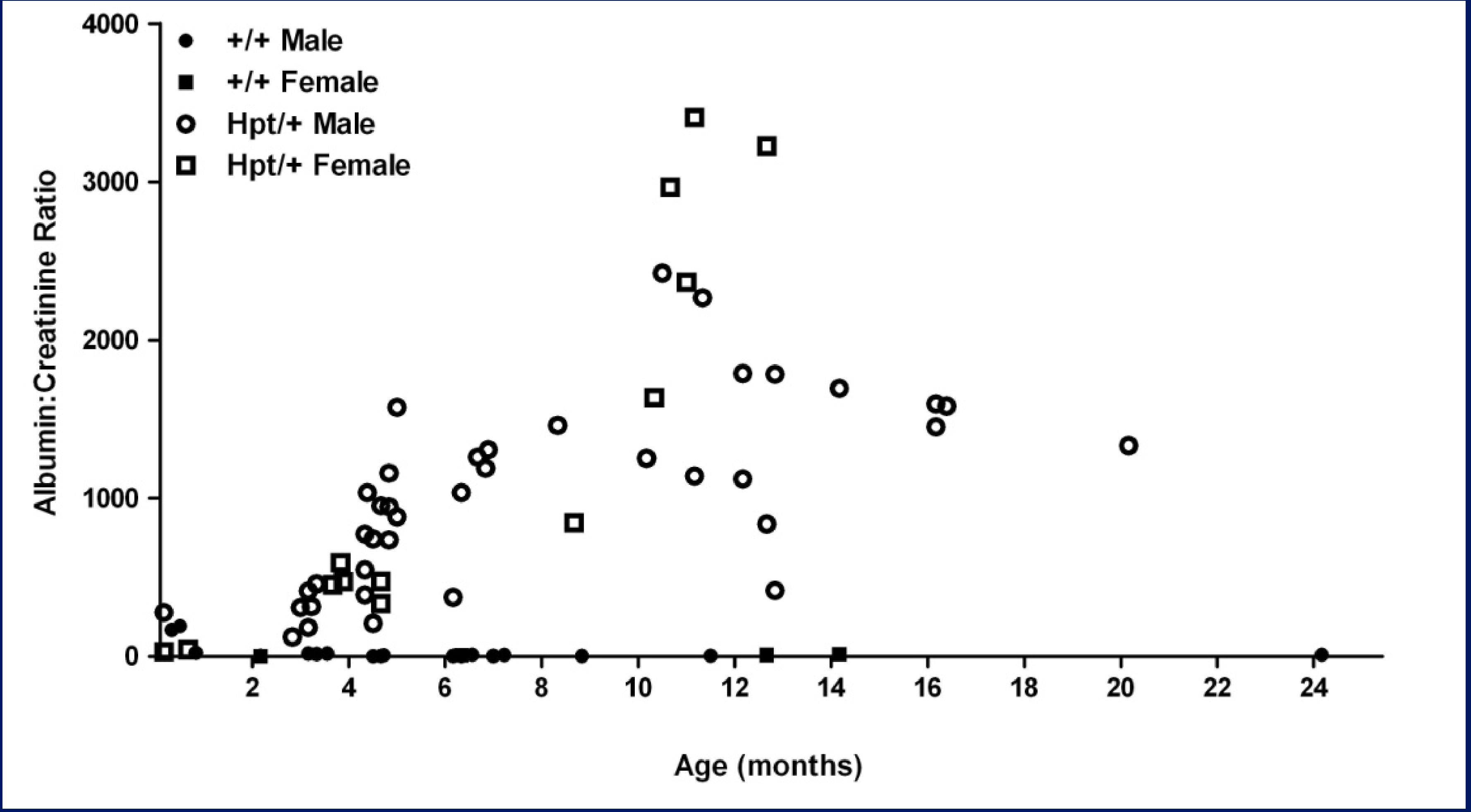
TEM of HPT-*Hpt*/+ Podocyte (10 wk males)



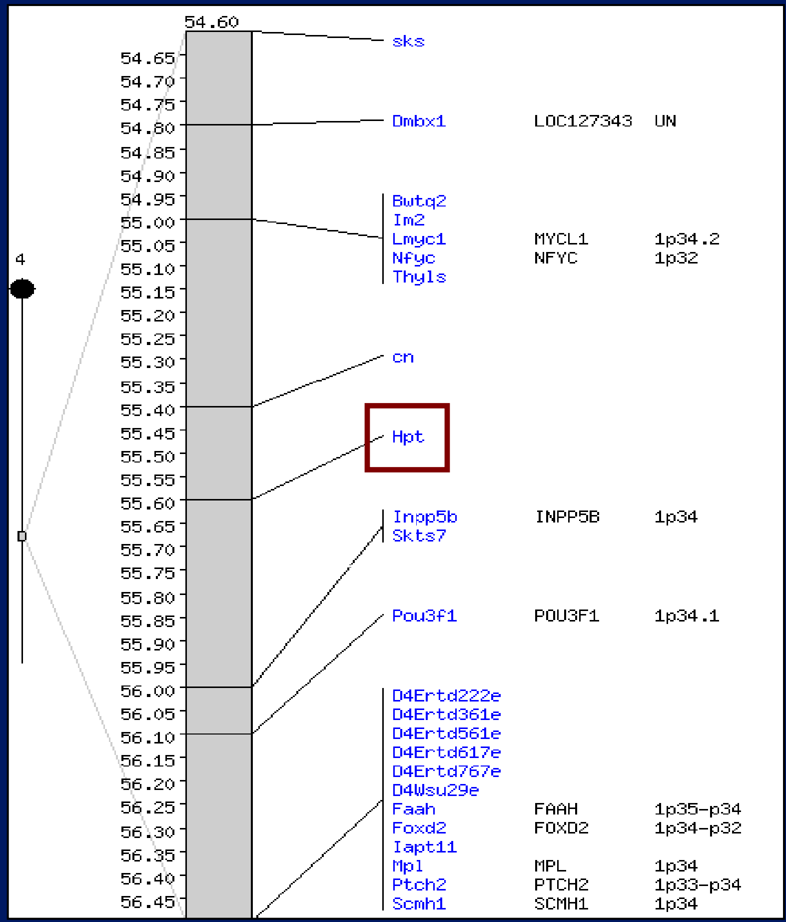
Increased Blood Urea Nitrogen Levels in *Hpt/+* Mice



Increased Urinary Albumin:Creatinine Ratios in *Hpt*/+Mice

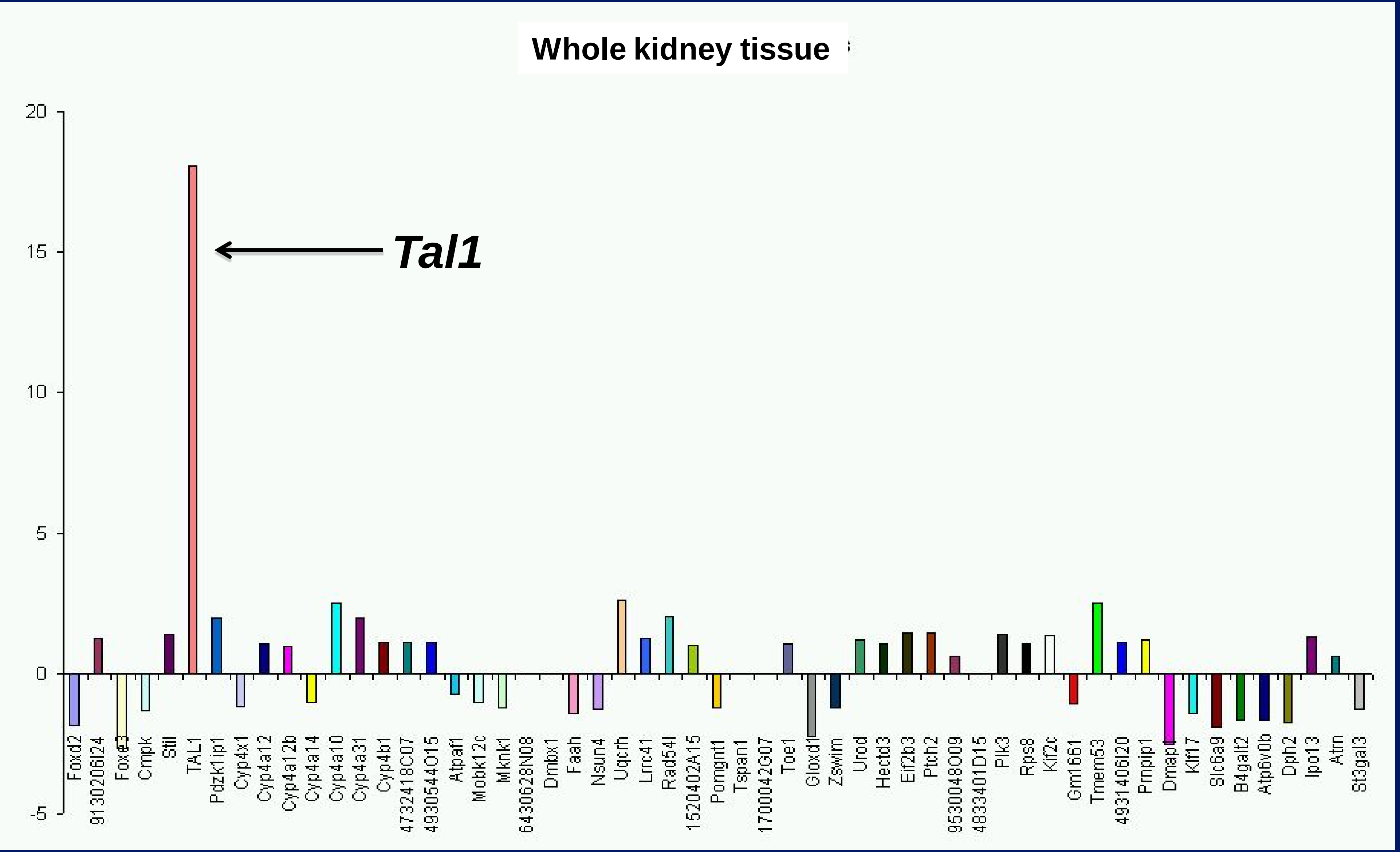


The *Hpt* Locus Maps to Mouse Chr. 4



Map position established 1989

Sybr Green qRT-PCR of ~60 genes in 5.7Mb candidate region of Chromosome 4



T-cell Acute Lymphocytic Leukemia (*Tal1*)

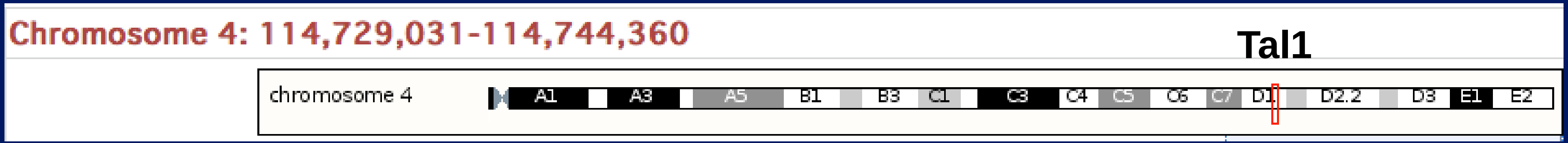
- A helix-loop-helix transcription factor critical for hematopoietic and endothelial lineage specification

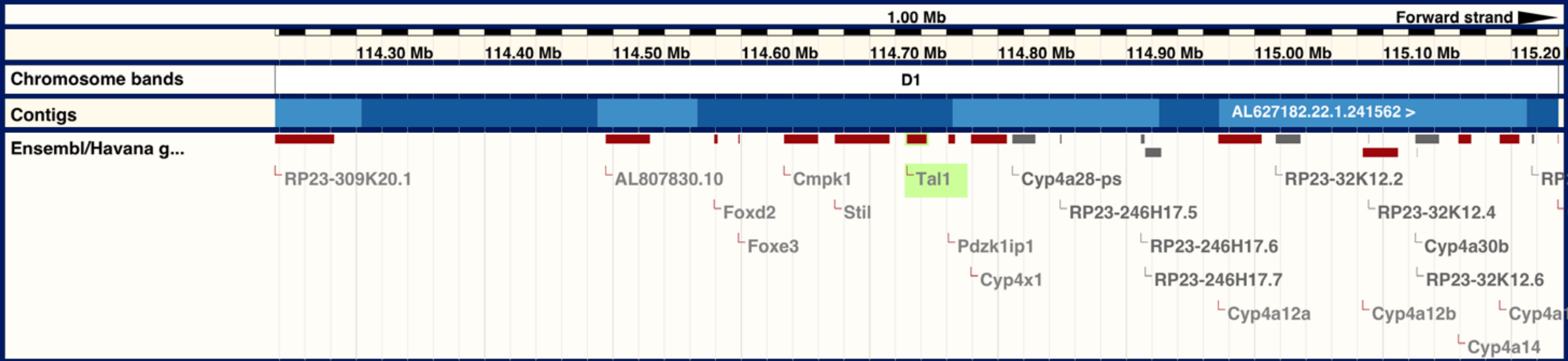
- Named for T-cell lymphocytic leukemia in humans

  Also known as Stem Cell Leukemia (*Scl*)

- Chromosomal translocation of *Tal1* and its upstream neighbor, Stil (SCL/TAL1 interrupting locus) from Chromosome 1 to 14 causes ectopic expression of *Tal1*

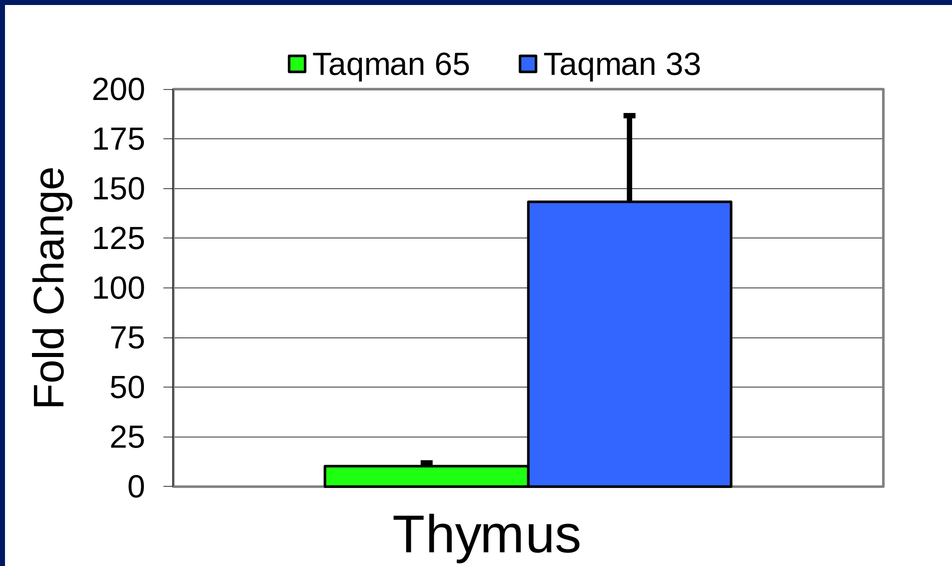
Chromosomal Location and Exon Structure for Mouse T cell Acute Leukemia 1 *(Tal1)* Gene

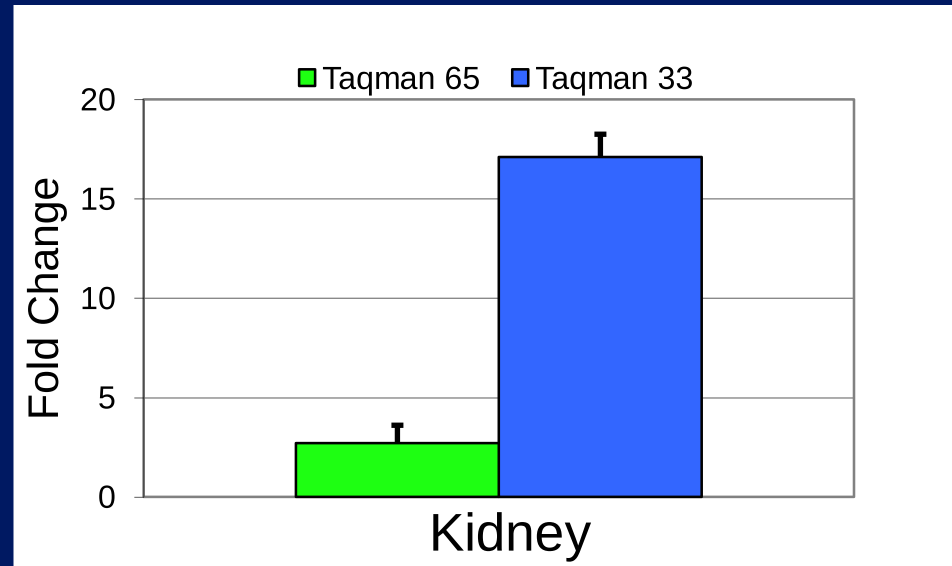


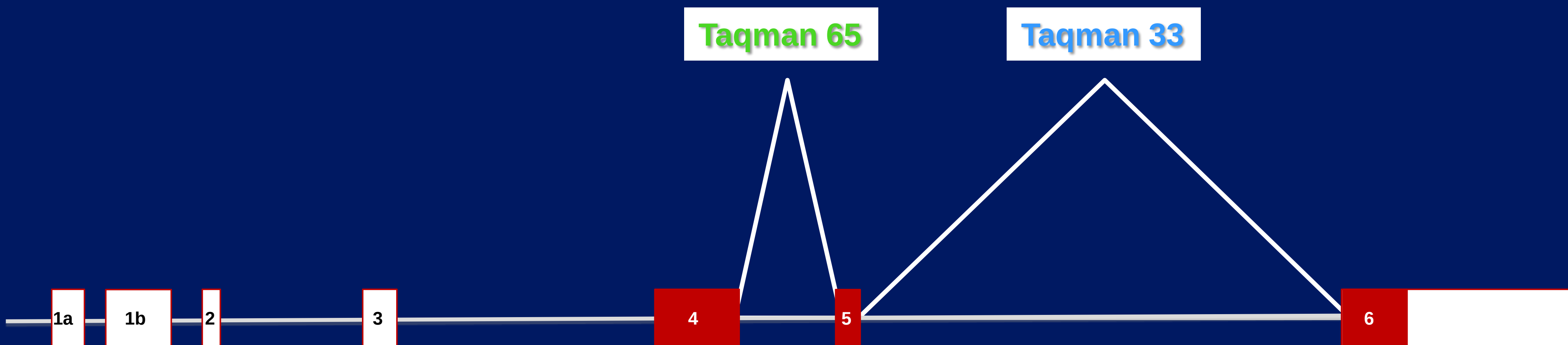


Tal1 exon structure

Tal1 Realtime RT-PCR

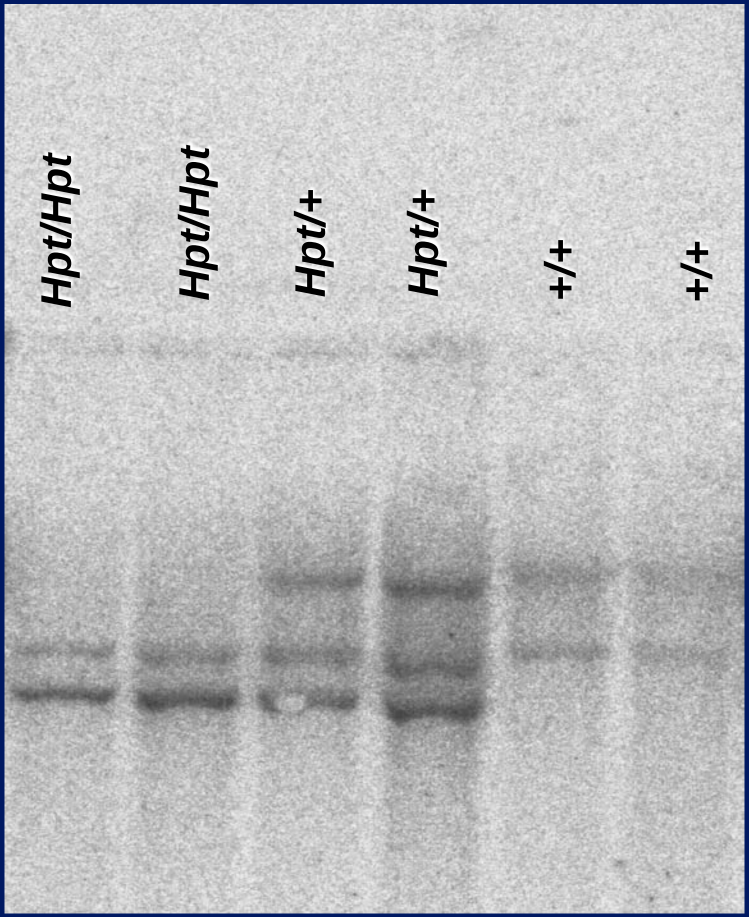






The *Hpt* Mutation creates a novel EcoR1 Restriction Site in the *Tal1* Gene

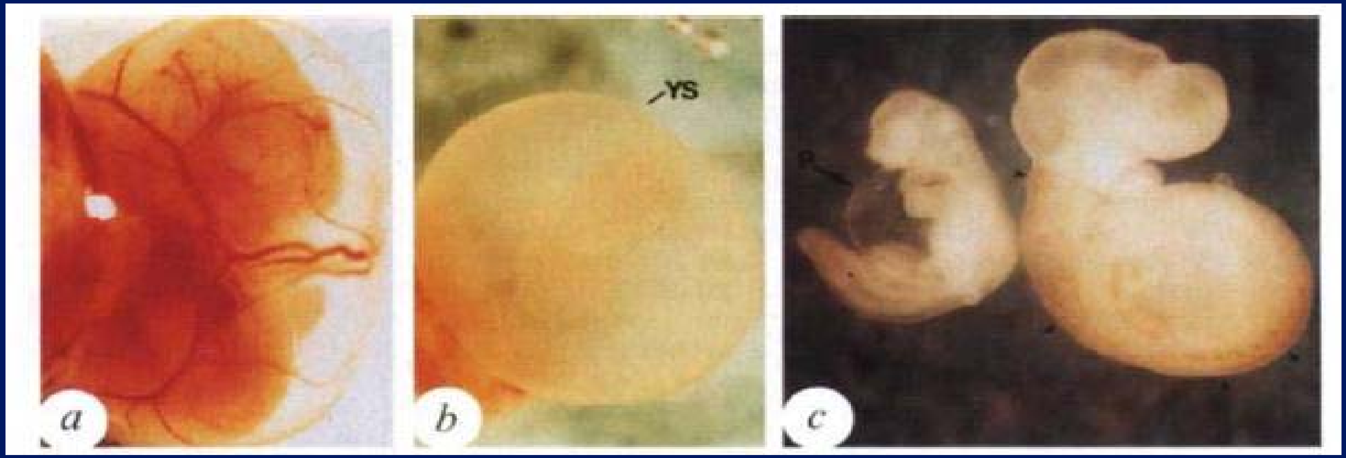
Mutant-specific EcoRI Site



Hpt/Hpt **homozygotes were obtained at ~ 12 days of gestation**

Tal1: Essential in Development

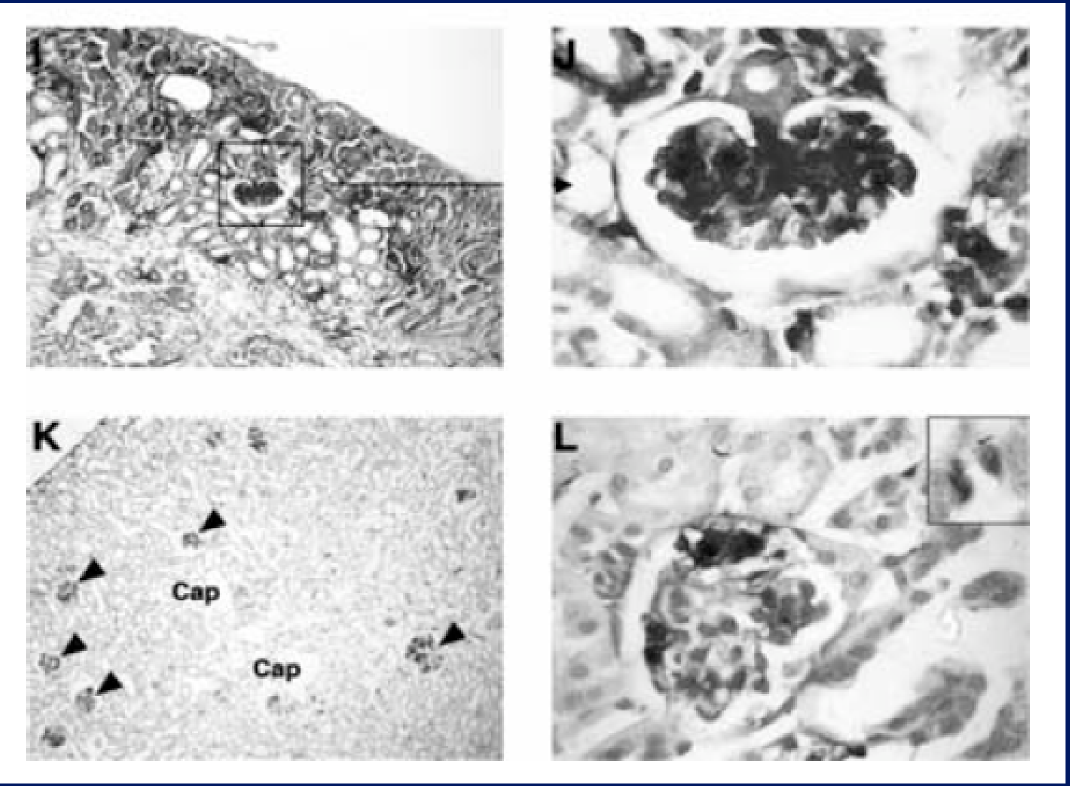
- Expressed in early posterior mesoderm during development
- Essential for the development of all hematopoietic lineages
- Also expressed in brain, kidney, and somitic tissues
- *Tal1* knockout mice die at implantation due to a complete lack of hematopoiesis in the yolk sac



Yolk sac: +/+ Yolk sac: KO KO and wt embryos, E9.5

Shivdasani *et al*., 1995

Expression of *Tal1* in Mouse Embryonic and Adult Kidneys



Tal1 **is highly expressed in day 16 embryonic kidney glomeruli**

Tal1 **shows less abundant expression in glomeruli, peritubular capillaries and scattered interstitial cells of adult kidneys**

Expression of *Tal1* in transgenic mice expressing *Tal1 LacZ* with its 3' hematopoietic and endothelial enhancer (SCL 3'En)

B. Dekel et al (2004) Kid. Internat. 65:1162

Human Syndrome: Glomerulonephritis With Sparse Hair And Telangiectases

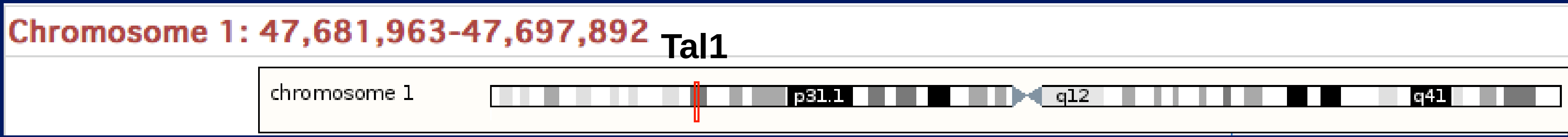
Sherwood et al., 1987

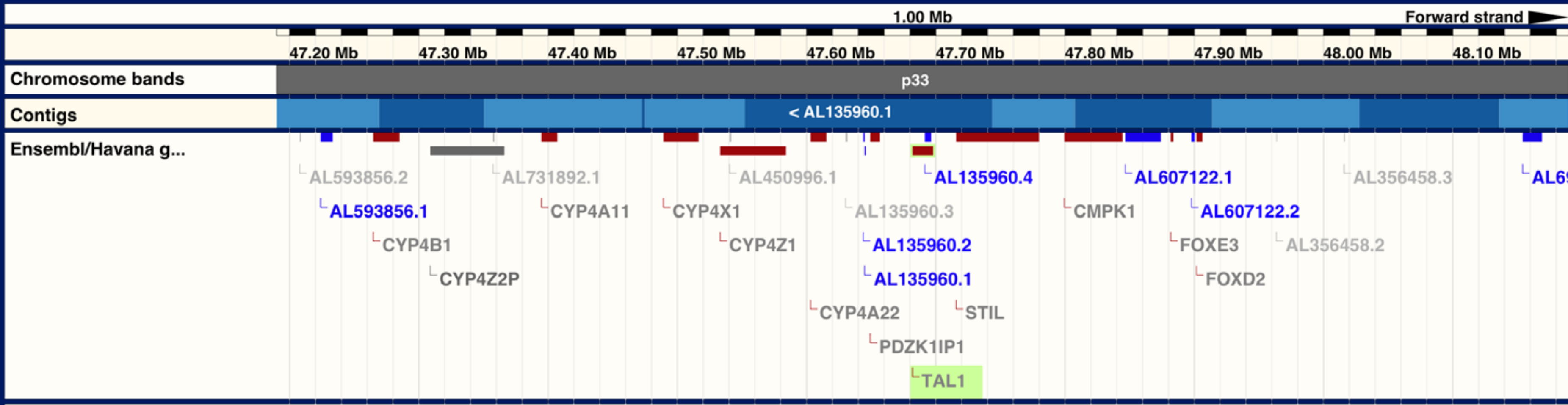
Proesmans et al., 1989

Gupta et al., 1999

Online Mendelian Inheritance in Man database # 137940

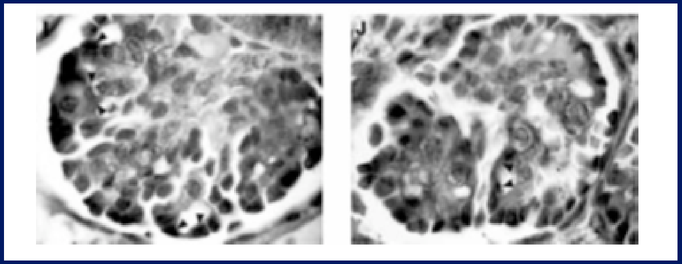
Chromosomal Location and Exon Structure for Human T cell Acute Leukemia 1 *(TAL1)* Gene





TAL1 exon structure

Immunolocalization of *TAL1* in Human Glomerular Endothelial Cells



Sections of human 14-20-week-old gestational kidney
TAL1 localizes to capillaries in developing glomeruli

B. Dekel et al (2004) Kid. Internat. 65:1162

Expression of *TAL-1* in Kidneys from Individuals with Diabetic Glomerulopathy

Hypothesis: Abnormal expression of *TAL1* plays a role in the pathogenesis of diabetic glomerulopathy in humans

Is *TAL-1* expression altered in glomeruli from diabetic individuals ?

If there is altered expression, does it play a role in renal disease progression ?

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