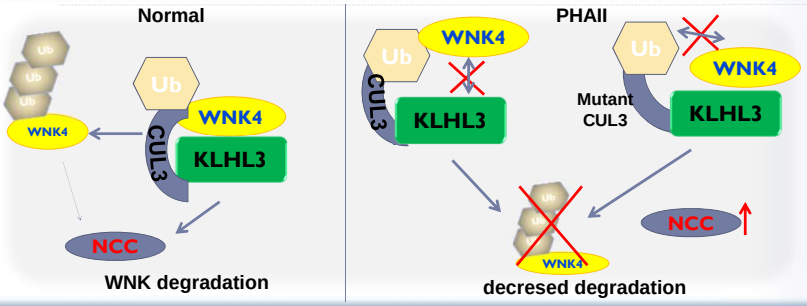
Bone Loss in KLHL3 Knock-In Mice Characterized by a Pseudohypoaldosteronism Type II-like Phenotype is Mediated by Renal PTH Resistance

Olena Andrukhova *, Jinwei Zhang †, Dario G Alessi †, Reinhold G Erben *.

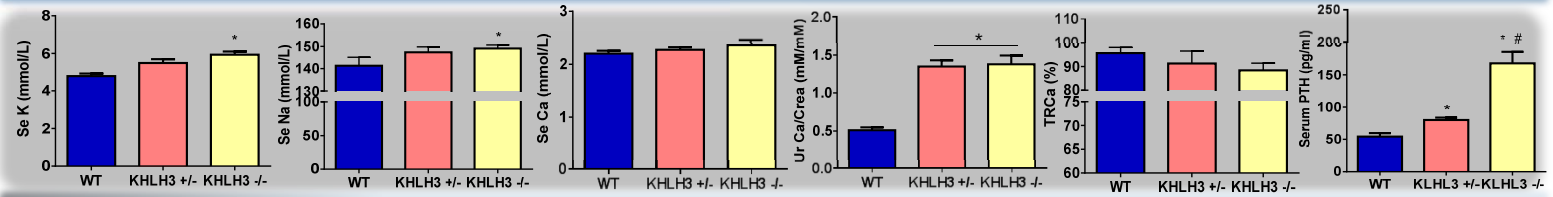
*Department of Biomedical Sciences, University of Veterinary Medicine, Vienna, Austria, and
† MRC Protein Phosphorylation and Ubiquitylation Unit, College of Life Sciences, University of Dundee, UK.

Background

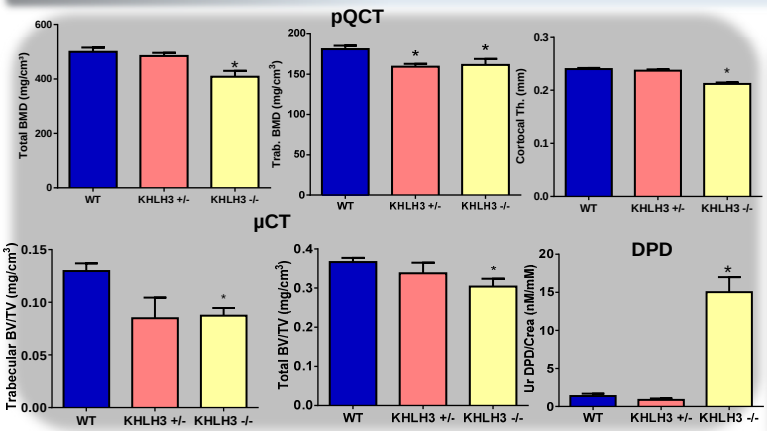


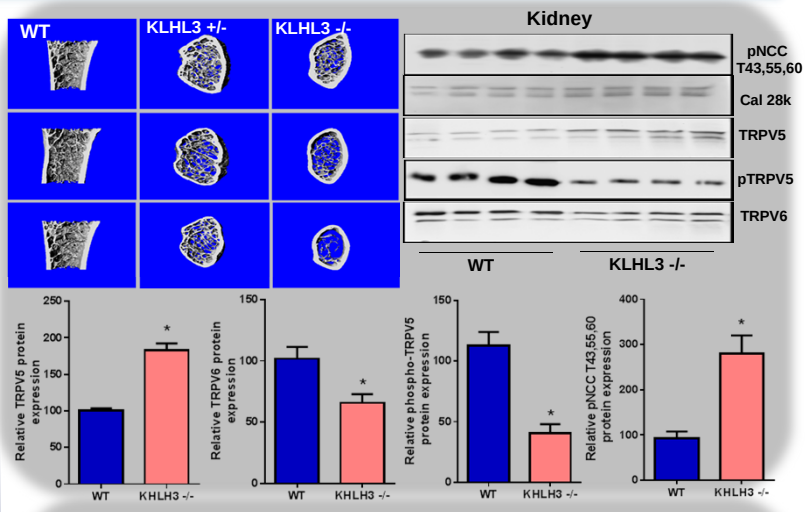
Pseudohypoaldosteronism type II (PHAII) is a hereditary disease characterized by hypertension, hypercalciuria and osteopenia. PHAII is caused by mutations in with-no-lysine kinase 1 (WNK1), WNK4, or the cullin RING ligase family members kelch-like 3 (**KLHL3**) or cullin 3 (CUL3). All mutations result in up-regulation of the WNK signalling pathway which activates thiazide-sensitive Na-Cl cotransporters (NCC) in renal distal tubules, leading to salt retention and hypertension in PHAII. The mechanism underlying hypercalciuria in PHAII is unknown. To better understand the mechanisms leading to osteopenia in PHAII, we used KLHL3R528H/+ knock-in mice carrying the same mutation as some PHAII patients.

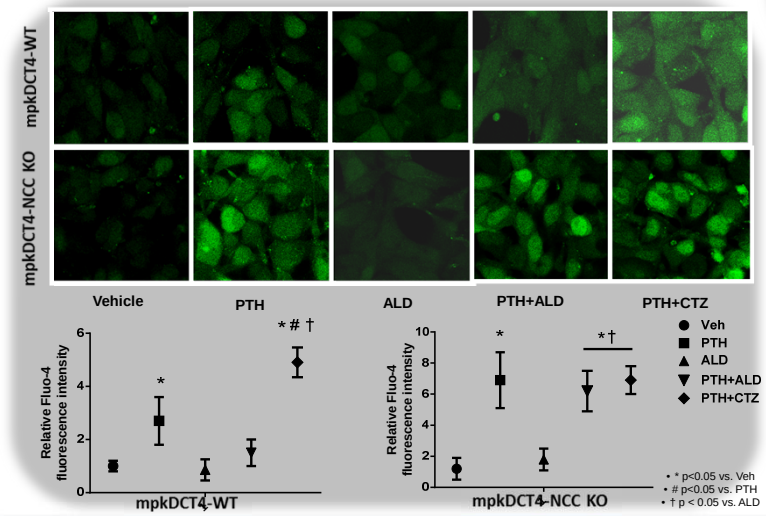
Results

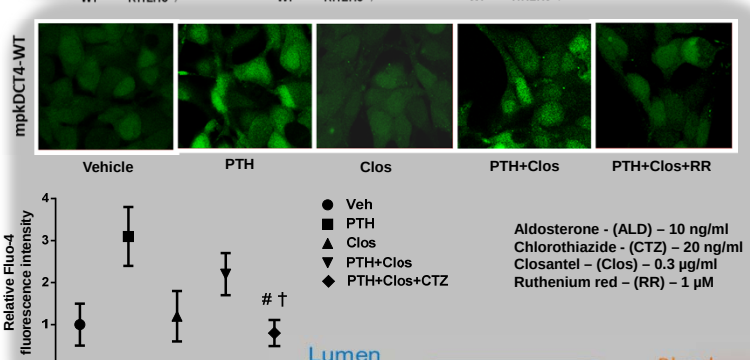


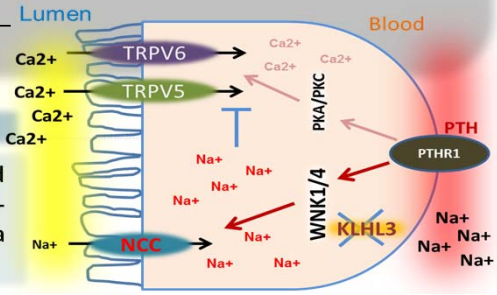
As expected, KLHL3R528H/+ mutants exhibited hyperkalemia, hypernatremia and renal calcium wasting. Furthermore, KLHL3R528H/+ mutants showed elevated serum parathyroid hormone (PTH), increased bone resorption as demonstrated by elevated urinary collagen crosslinks excretion and increased osteoclast numbers in femoral cancellous bone, and reduced distal femoral cancellous bone BMD and volume as evidenced by pQCT and µCT analysis.











Conclusion

Taken together, our study provides a mechanistic explanation for the hypercalciuria and bone loss found in PHAII patients: elevated WNK signaling increases NCC activity in KLHL3R528H/+ mice and blocks PTH-mediated TRPV5 activation, leading to renal PTH resistance with subsequent renal Ca wasting and a counter-regulatory PTH-induced bone loss.