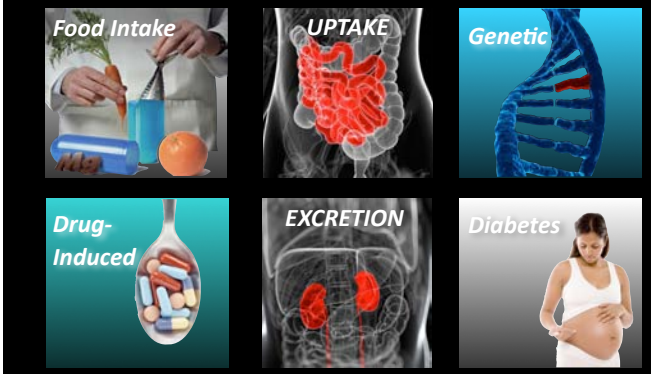
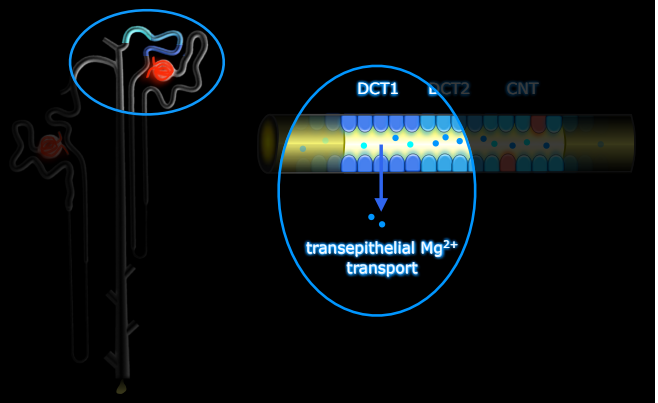
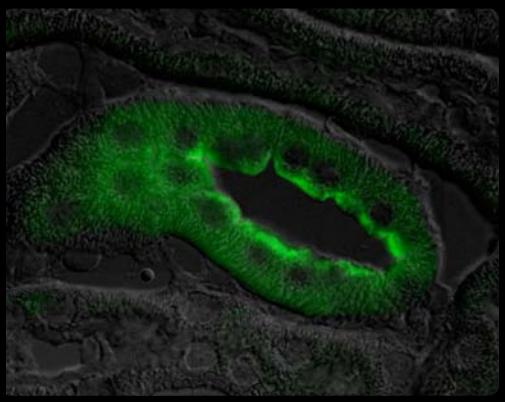
Understanding molecular regulation Mg^{2+} balance



Active Mg^{2+} reabsorption in the DCT



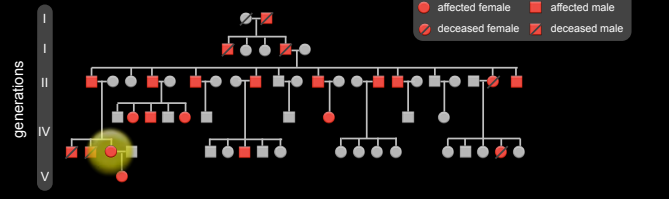
Active Mg^{2+} reabsorption in the DCT



Isolated dominant renal hypomagnesemia

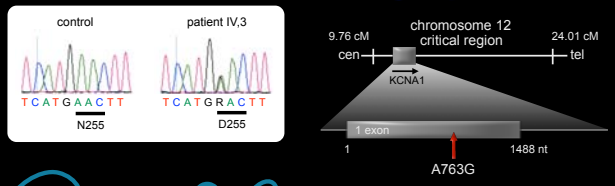
- Brazilian family
- hypomagnesemia due to renal Mg^{2+} wasting (plasma <0.4 mM Mg^{2+})
- normocalcemia and normocalciuria
- myokymia, seizures
- episodic ataxia

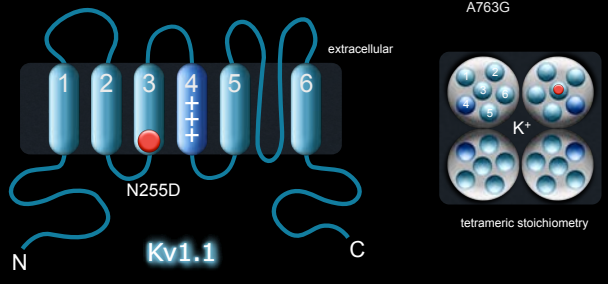
Pedigree Phenotype



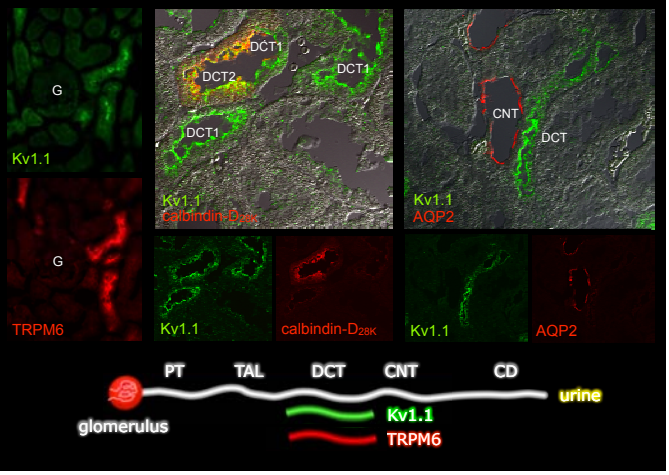
Isolated dominant renal hypomagnesemia

SNP linkage analysis

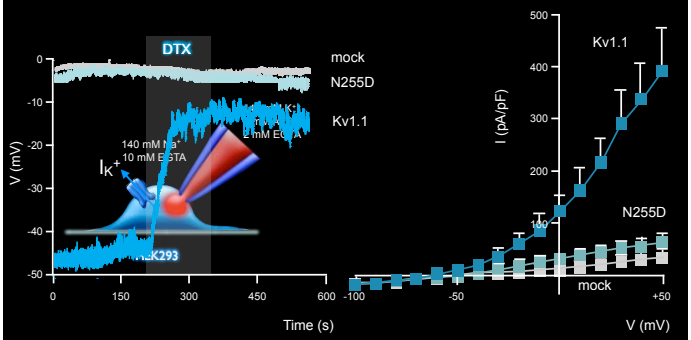




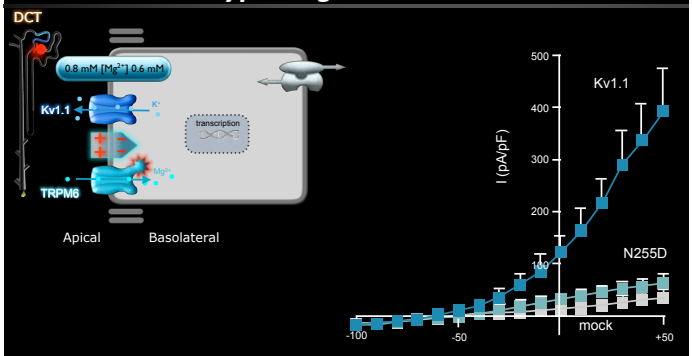
Localization of Kv1.1 in the kidney



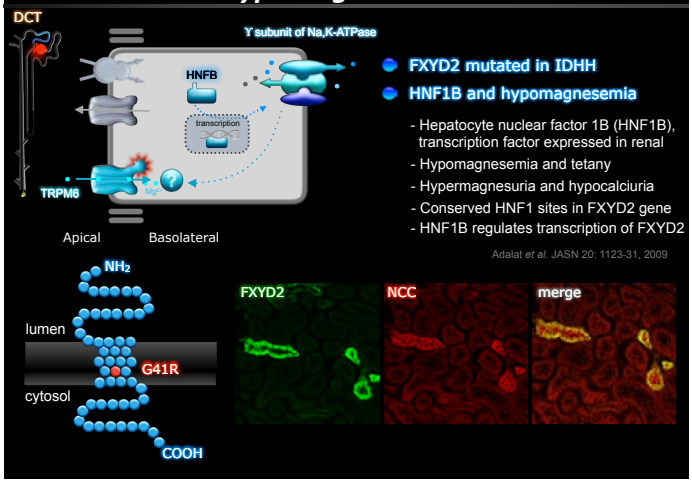
Functional analysis of Kv1.1-N255D



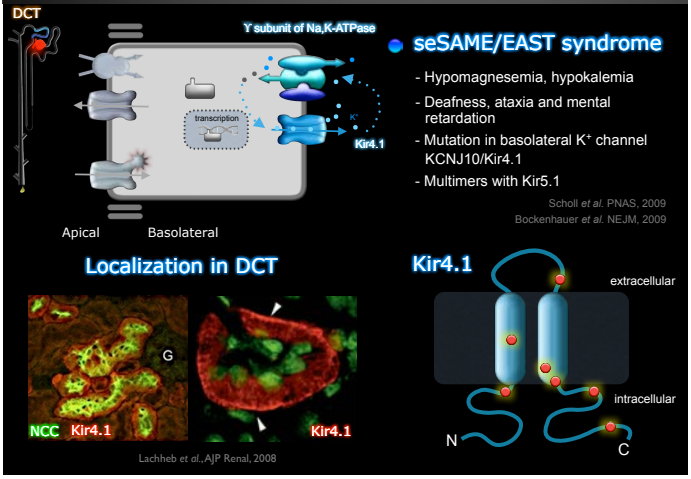
Kv1.1 and hypomagnesemia



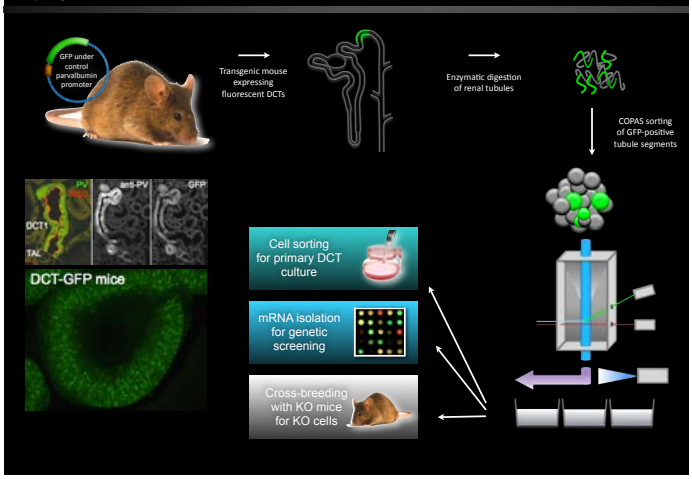
FXYD2 and hypomagnesemia



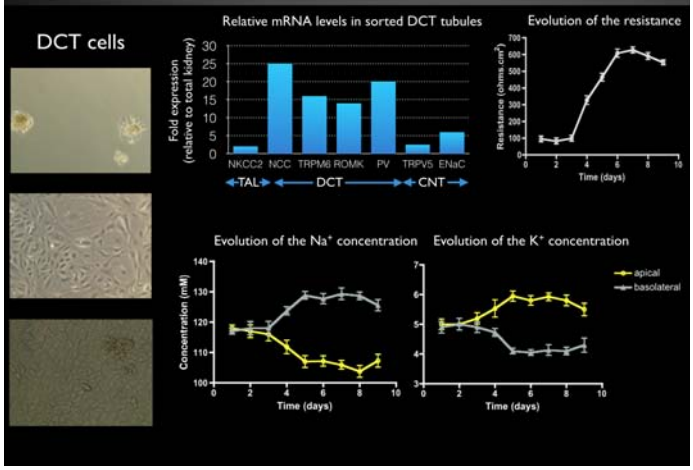
K+ recycling at the basolateral membrane



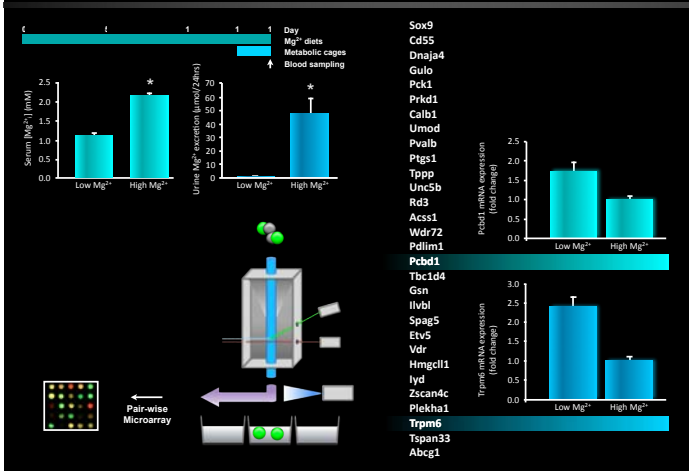
COPAS sorting of mouse DCT tubules



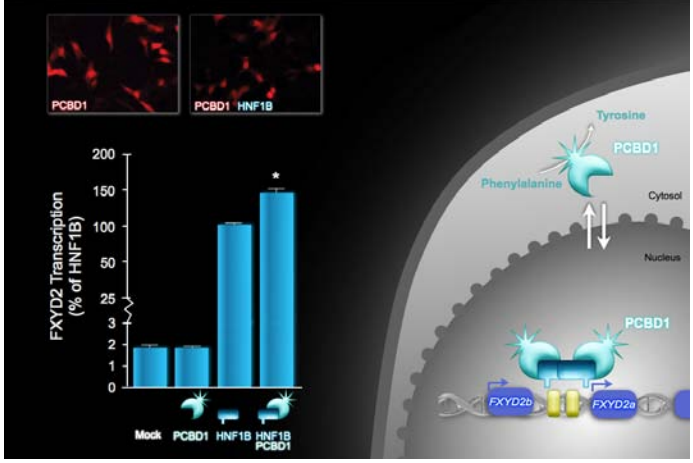
COPAS-sorted mouse DCT tubules



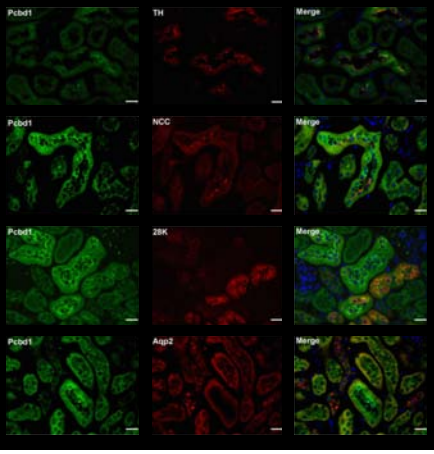
Mg²⁺-sensitive expression in the DCT



PCBD1 enhances HNF1B transcription



PCBD1 present in TAL & DCT



Patients with PCBD1 mutations show renal Mg²⁺ wasting

Symptoms at birth

- Hyperphenylalaninemia
- Elevated urine neopterin
- Decreased urine biopterin

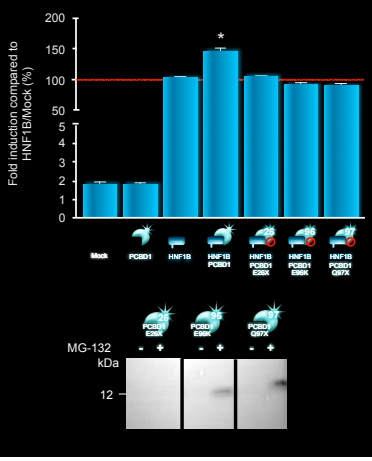
Symptoms at later age

- Hypomagnesemia
- Renal Mg²⁺ wasting
- MODY diabetes
- No cysts

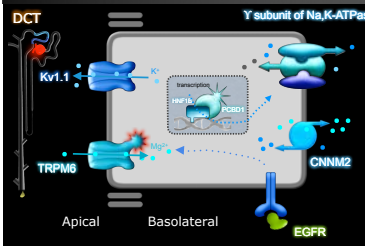
	P1	P2	P3	Ref
Na⁺ (mmol/L)	141	138	139	135-145
K⁺ (mmol/L)	4.0	4.5	4.0	3.5-5.0
Mg²⁺ (mmol/L)	0.64	0.65	0.74	0.7-1.1
Ca²⁺ (mmol/L)	2.41	2.25	2.43	2.2-2.65
FeMg (%)	6.6		3.5	<2.2
FeCa (%)	0.9		0.9	<1
HbA1c (%)	7.2	4.95	6.5	4.3-6.1

De Baaij et al., JASN 25:574, 2014

PCBD1 mutations cause hypomagnesemia



New family with dominant hypomagnesemia

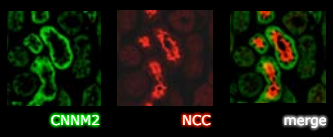


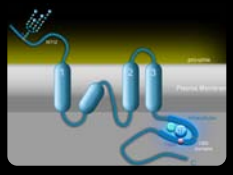
CNNM2 in DH

- Hypomagnesemia
- Fatique
- Muscle problems
- Epileptic seizures
- Cardiac arrhythmias

Stuiver *et al.* Am J Hum Genet 88: 333-43, 2011
de Baaij *et al.* J Biol Chem 287: 13644-55, 2012

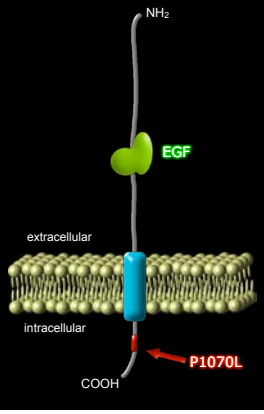
Localization in DCT

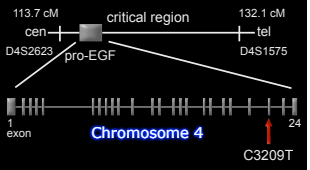




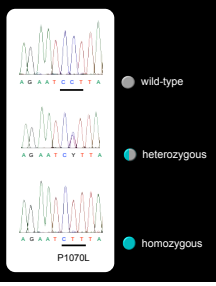
Isolated recessive renal hypomagnesemia

Structure of pro-EGF

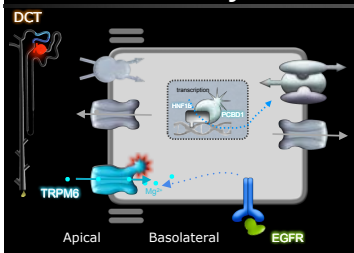




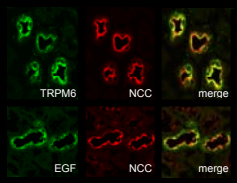
Genotype



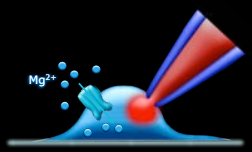
Activation of TRPM6 by EGF

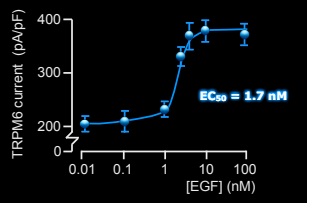


Localization in DCT

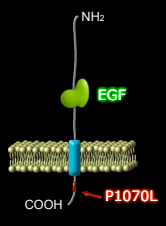


Patch clamp analysis

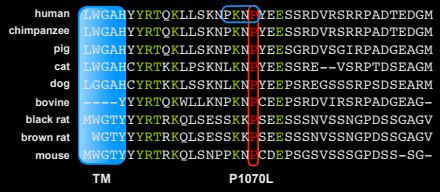




Conservation of P1070L in pro-EGF



Structure of pro-EGF

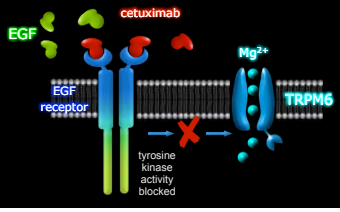


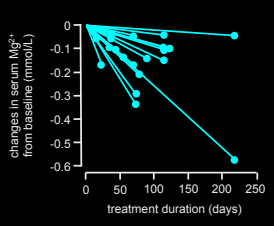
Potential functions of PXXP motif

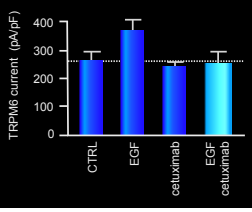
- basolateral sorting motif for the EGFR in epithelial cells
  Choowongkomon *et al.*, J Biol Chem, 2005
- motif in cathelicidins which enables insertion of carboxy-terminus in membrane
  Yang *et al.*, Biochemistry, 2006
- motif implicated in protein-protein interaction
  Hou *et al.*, PLOS, 2006; Kristenson *et al.*, EMBO J, 2006

Drug-induced hypomagnesemia

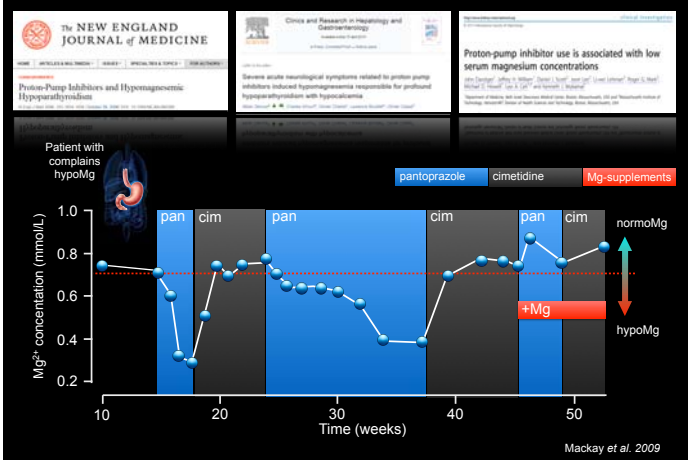
- Proton Pump Inhibitors (Omeprazol)
- Calcineurin inhibitors
- Cytostatics
- Diuretics
  Lameris *et al.*, Clin Sci. 123:1, 2012
- The EGFR antagonist cetuximab causes hypomagnesemia
- Colorectal cancer is third most common malignancy worldwide (12%)
- Renal Mg^{2+} wasting
  Tejpar *et al.*, Lancet Oncol. 8:387, 2007







Proton pump inhibitors and hypomagnesemia

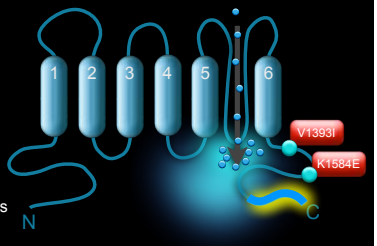


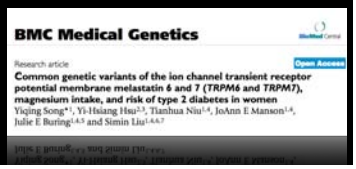
Mackay *et al. 2009*

Diabetes Mellitus and Mg^{2+} balance

Diabetes Mellitus: Type 2 & Gestational

- Clearly associated with Mg^{2+} loss
- Hypomagnesemia affects insulin resistance & increases risk for diabetes
- Treatment with additional Mg^{2+} reduces progression from prediabetes to diabetes



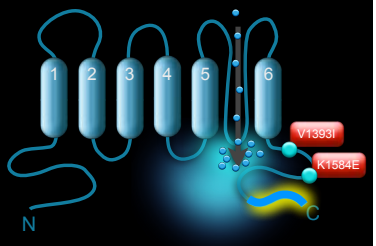

BMC Medical Genetics

Research article

Common genetic variants of the ion channel transient receptor potential membrane melastatin 6 and 7 (*TRPM6* and *TRPM7*), magnesium intake, and risk of type 2 diabetes in women

Yiqing Song[*1], Yi-Hsiang Hsu[2,3], Tianhua Niu[1,4], JoAnn E Manson[1,5], Julie E Buring[1,4,5] and Simin Liu[1,4,6,7]

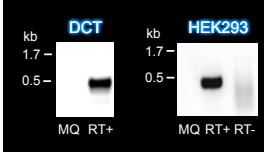
Berlin Birth Cohort



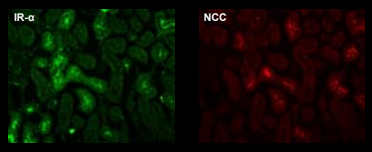
- 997 women
- 3% pregnant women develop GDM
- Women carrying TRPM6 V1393I and/or K1584E increased total glycosylated hemoglobin (TGH) insuline resistance

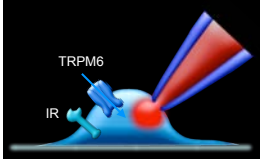
TRPM6 is stimulated by insulin

Insulin receptor (IR)

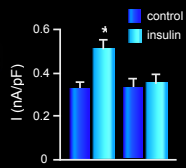


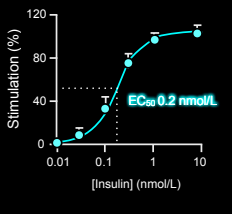
Co-localization of IR and NCC in DCT





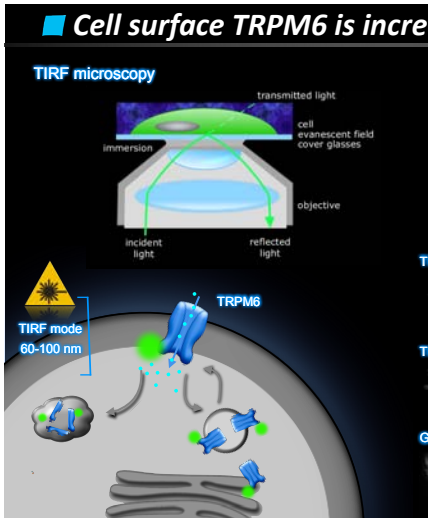
HEK293

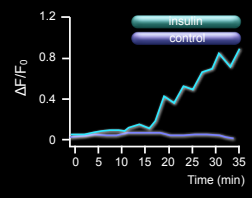


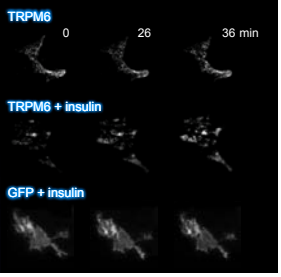


Cell surface TRPM6 is increased by insulin

TIRF microscopy







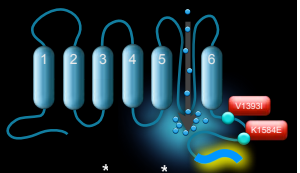
SNPs in TRPM6 and insulin action

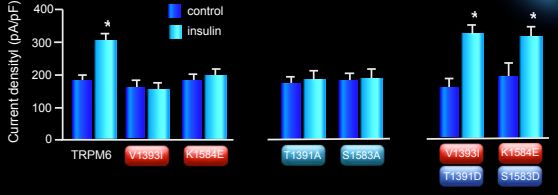
Implications of SNPs in TRPM6

Common genetic variants of the ion channel transient receptor potential membrane melastatin 6 and 7 (*TRPM6* and *TRPM7*), magnesium intake, and risk of type 2 diabetes in women

Yiqing Song[*1], Yi-Hsiang Hsu[2,3], Tianhua Niu[1,4], JoAnn E Manson[1,5], Julie E Buring[1,4,5] and Simin Liu[1,4,6,7]

BMC Medical Genetics, 2009





SNPs in close vicinity to putative phosphorylation sites

Human TRPM6 VLVHLTGQTPVSDWASVDE.....KMLTKDRRLSKKKNTQGLQ....

1391 1393 1583 1584

identified SNPs

putative phospho-site (cdk5 kinase)