Rare alleles with great effects

Mendelian hypertension

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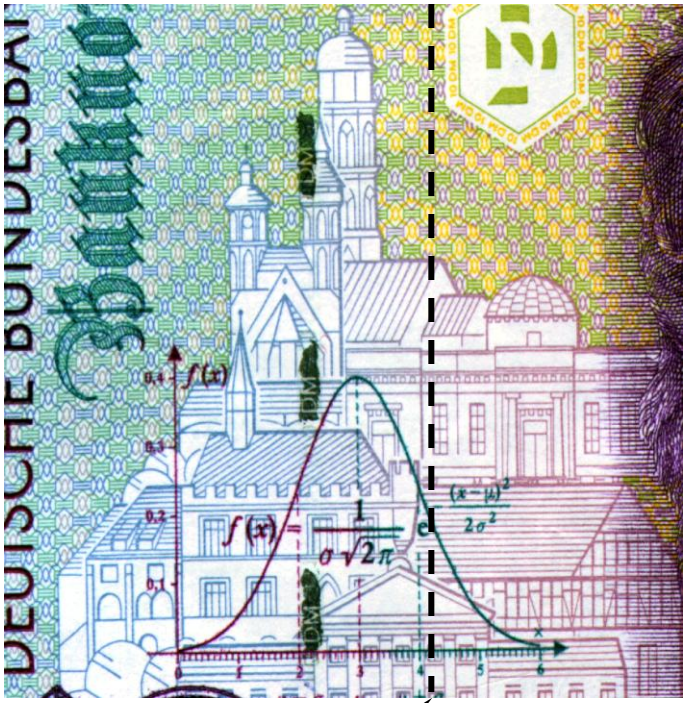
Finding genes that cause hypertension

- Wilhelm Weitz: Zur Ätiologie der genuinen Hypertonie. Tübingen, 1921. “Hypertension is a Mendelian, autosomal-dominant disease”

- Sir George Pickering: 1955. “Hypertension is not a disease; blood pressure is regulated as a complex genetic trait”

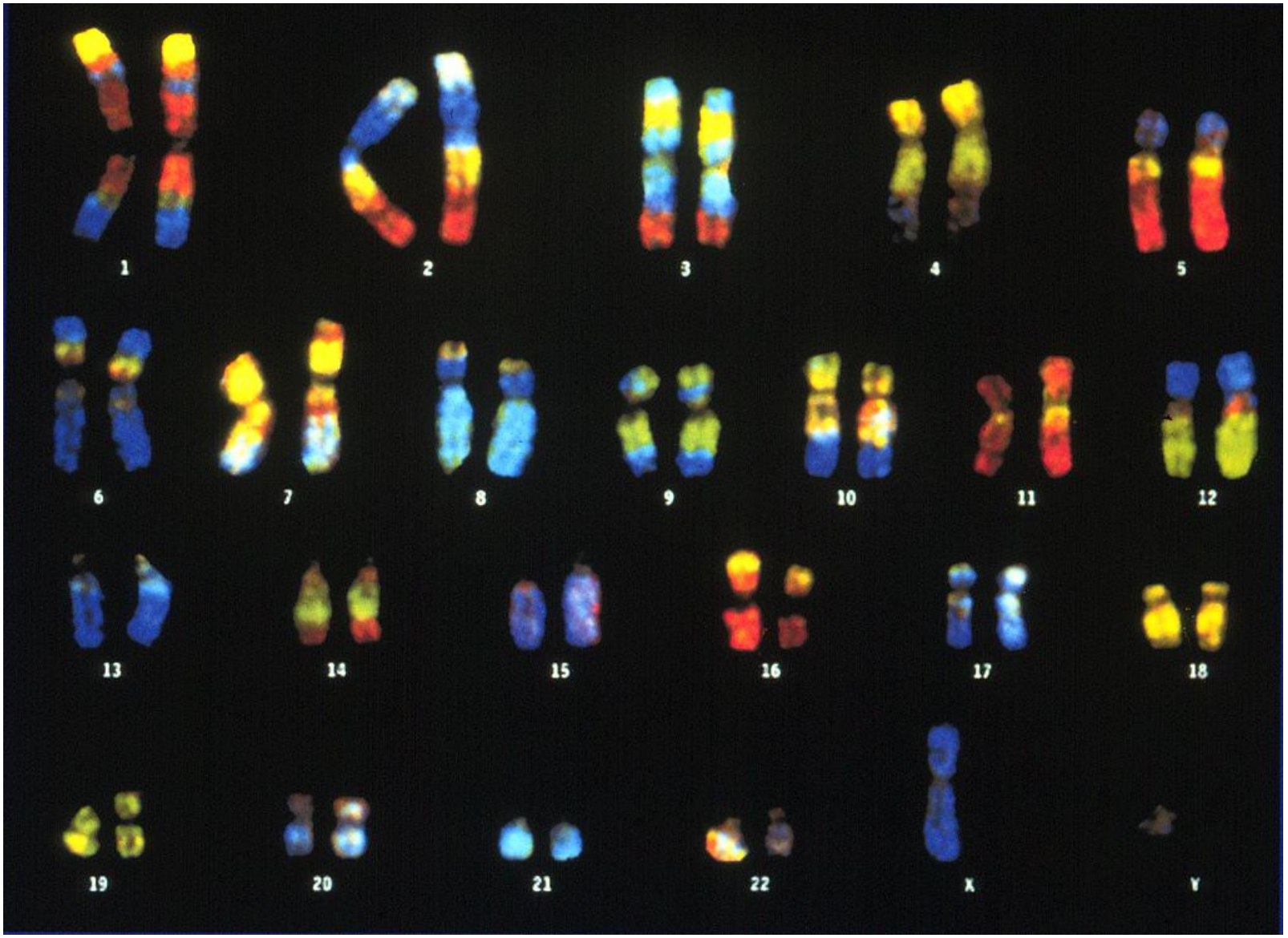
Back of a German 10 Mark note
when they still had money

Genetically affected hypertensive persons



Arbitrary definition of hypertension

First step is finding the gene locus (where is it?)



Satellites and microsatellites

D12S310

Possible alleles

C

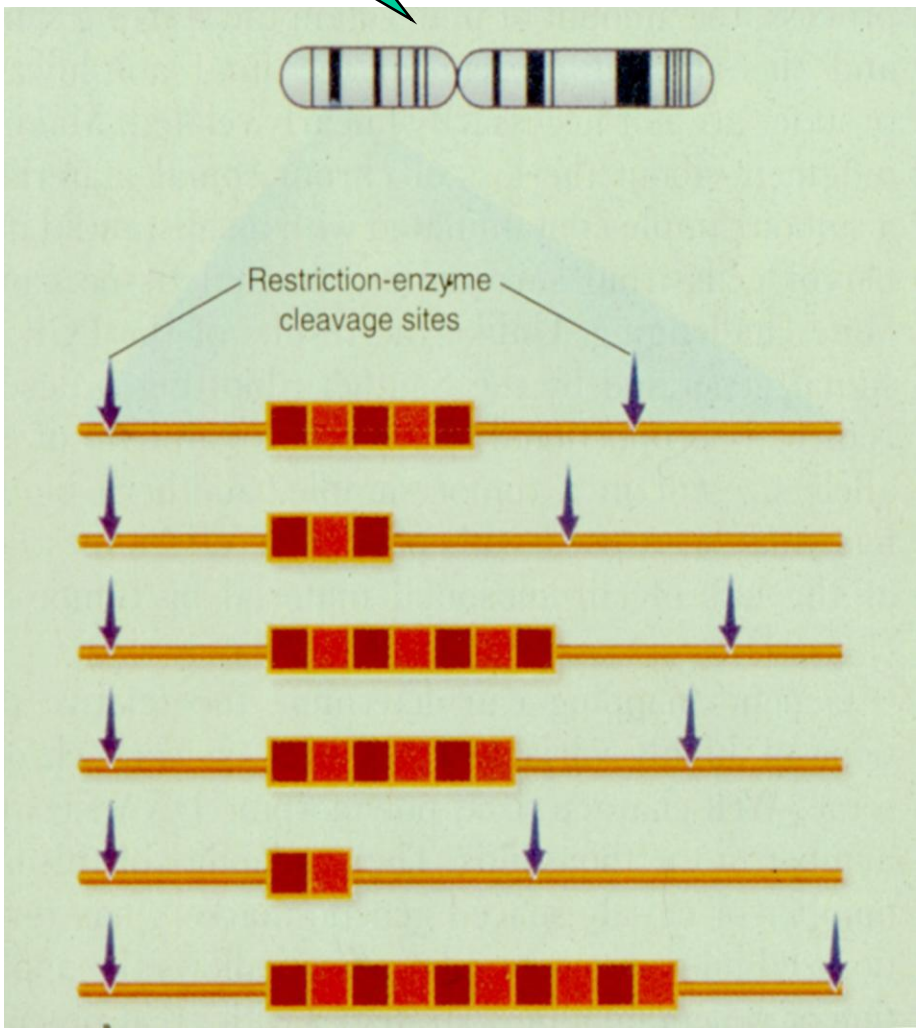
B

E

D

A

F



Linkage analysis, finding gene markers that are always inherited with the disease (we do not use RFLP anymore but the example is a good one)

Female

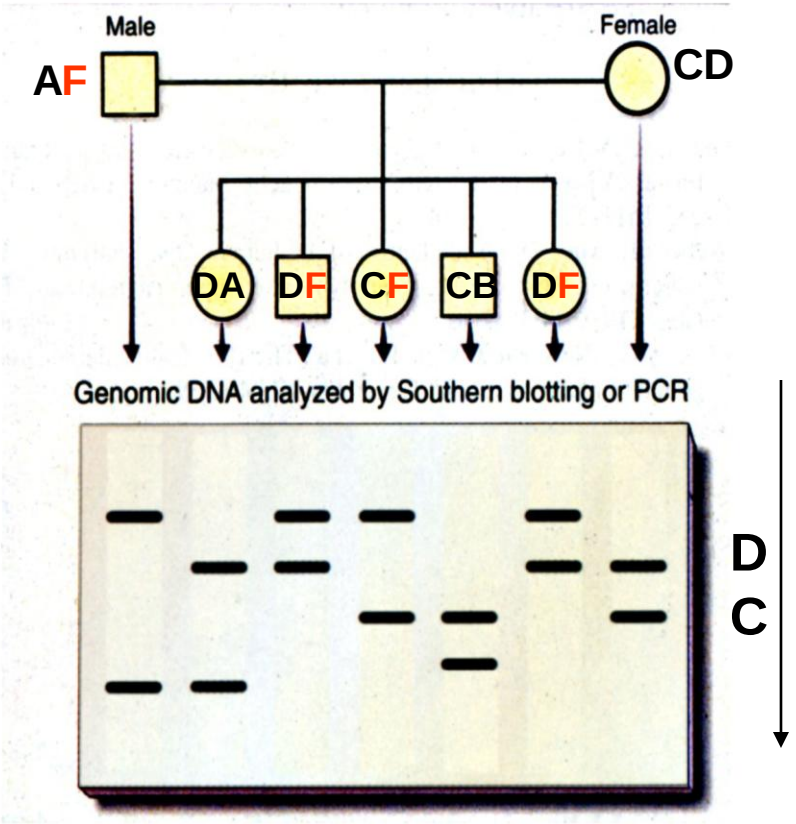
Male

Gel →

Slower { **F**

Faster { **A**

Disease gene is next to F

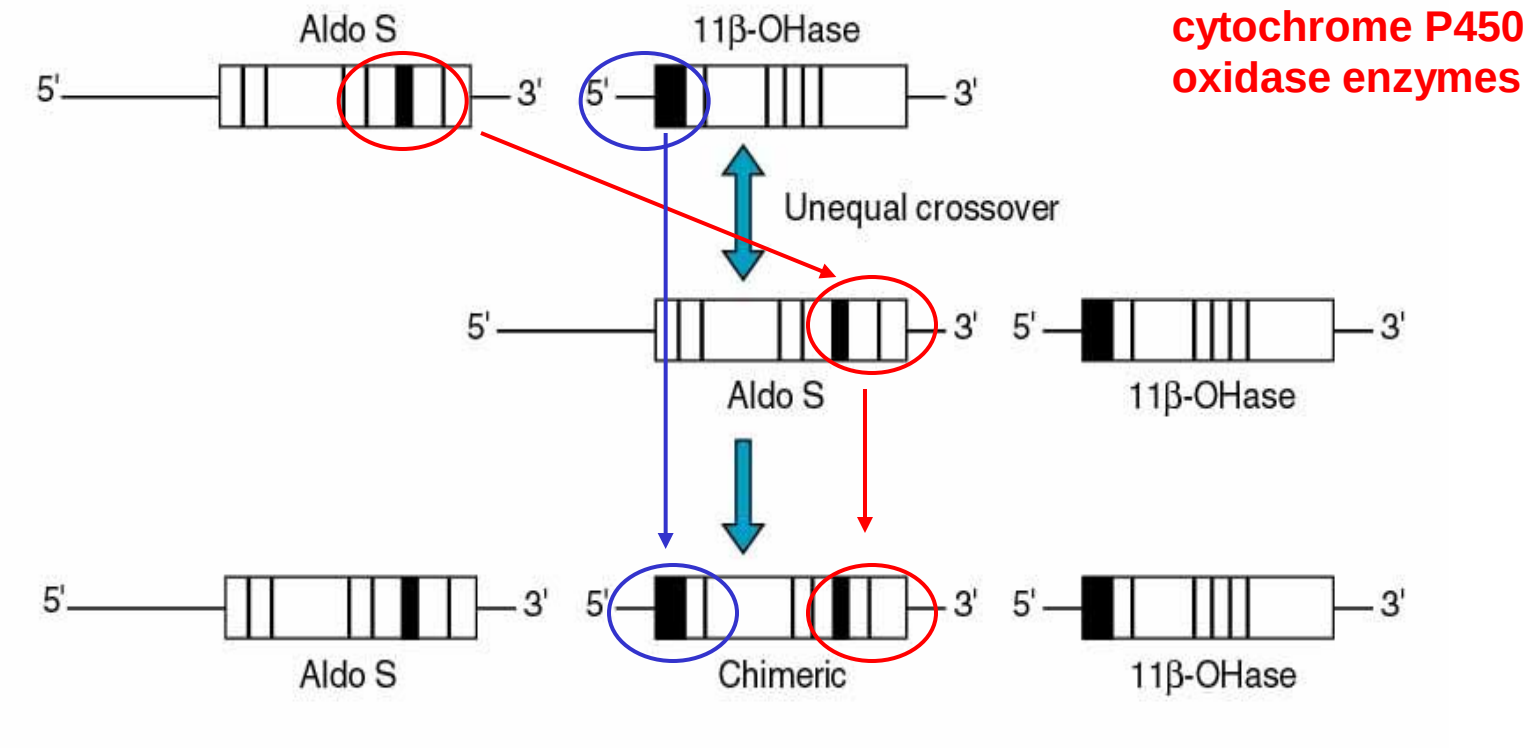


Glucocorticoid remediable aldosteronism

- Autosomal-dominant inheritance
- PRA is low; aldosterone is high
- Mistaken for Conn´s disease
- Blood pressure responds to spironolactone
- 5 mg prednisone “cures” the disease
- Chimera between aldo-synthase and 11ß OHase genes (Chromosome 8), exposing aldo synthesis to stimulation by ACTH

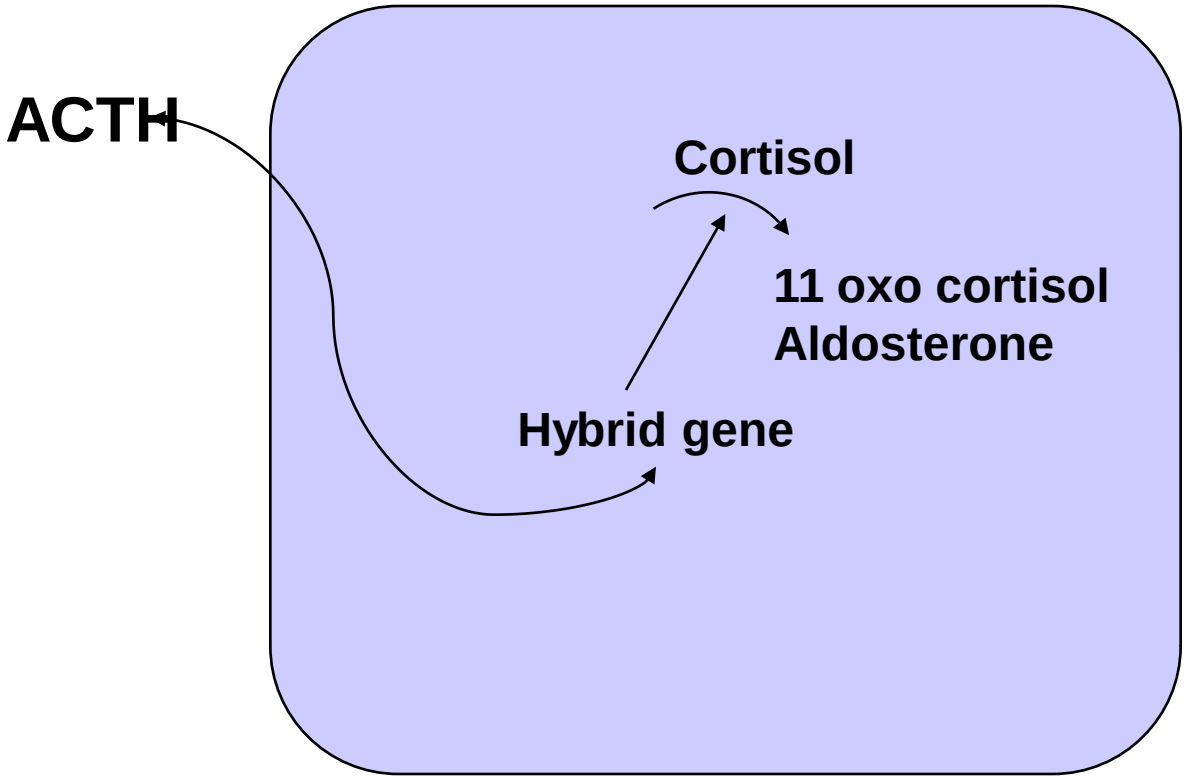
Lifton et al. Nature

Production of a hybrid gene by unequal crossing over in meiosis



cytochrome P450 oxidase enzymes

Zona fasciculata



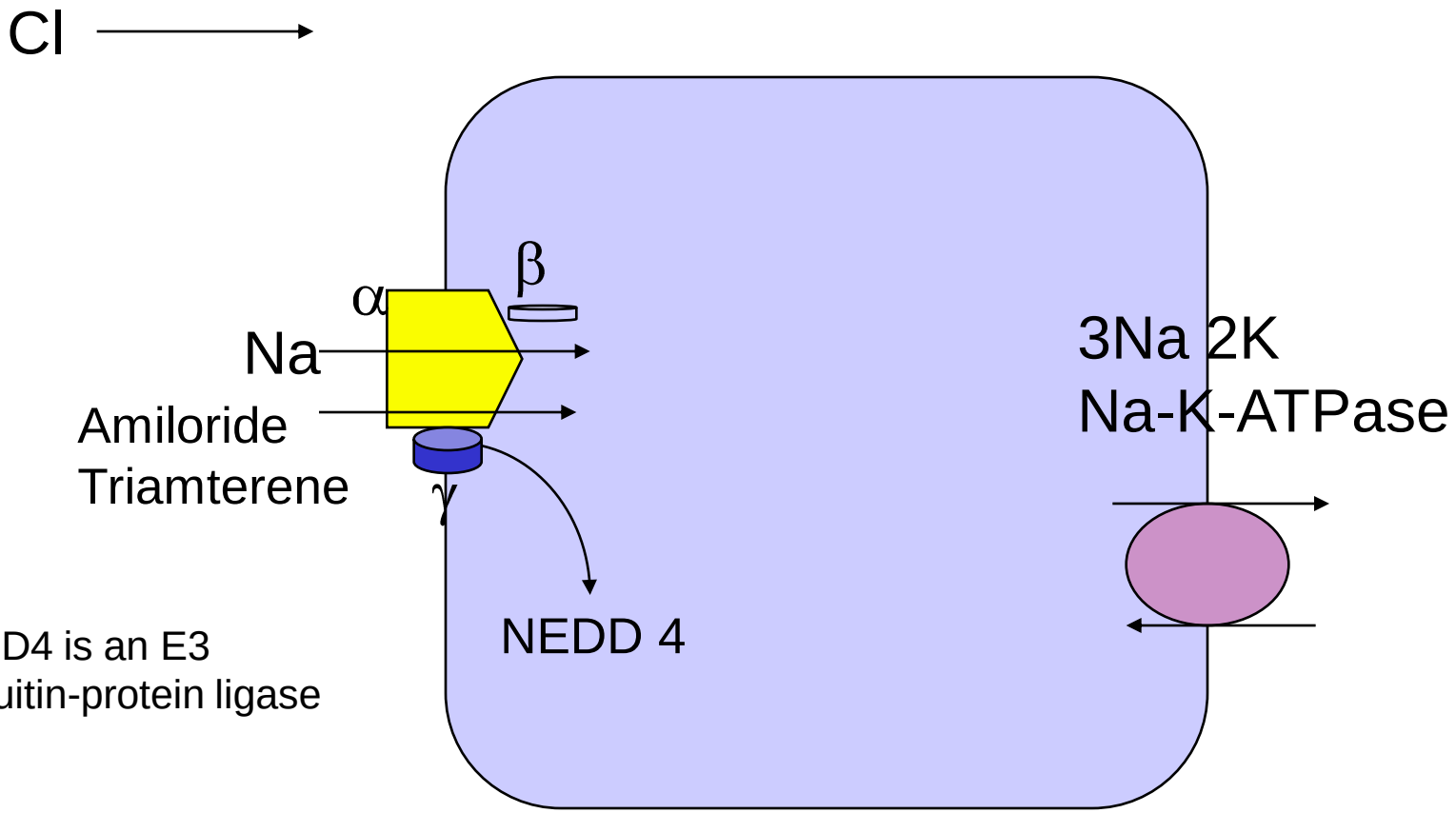
Grant Liddle was born on a farm in American Fork, Utah in 1921.
Professor of Medicine, Vanderbilt University 1956-1983.

Liddle‘s Disease

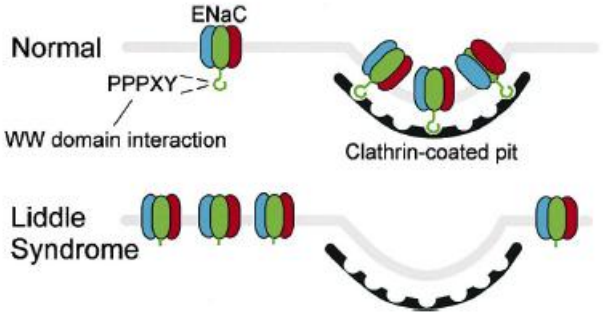
- Autosomal-dominant inheritance
- PRA is low, but aldosterone is low too
- Blood pressure improves with amiloride but not with spironolactone
- Gene mapped to chromosome 16
- Activating mutations in epithelial sodium channel
- gamma and beta subunits are mutated

Lifton et al. Nature

Defect in Liddle syndrome



NEDD4 is an E3 ubiquitin-protein ligase



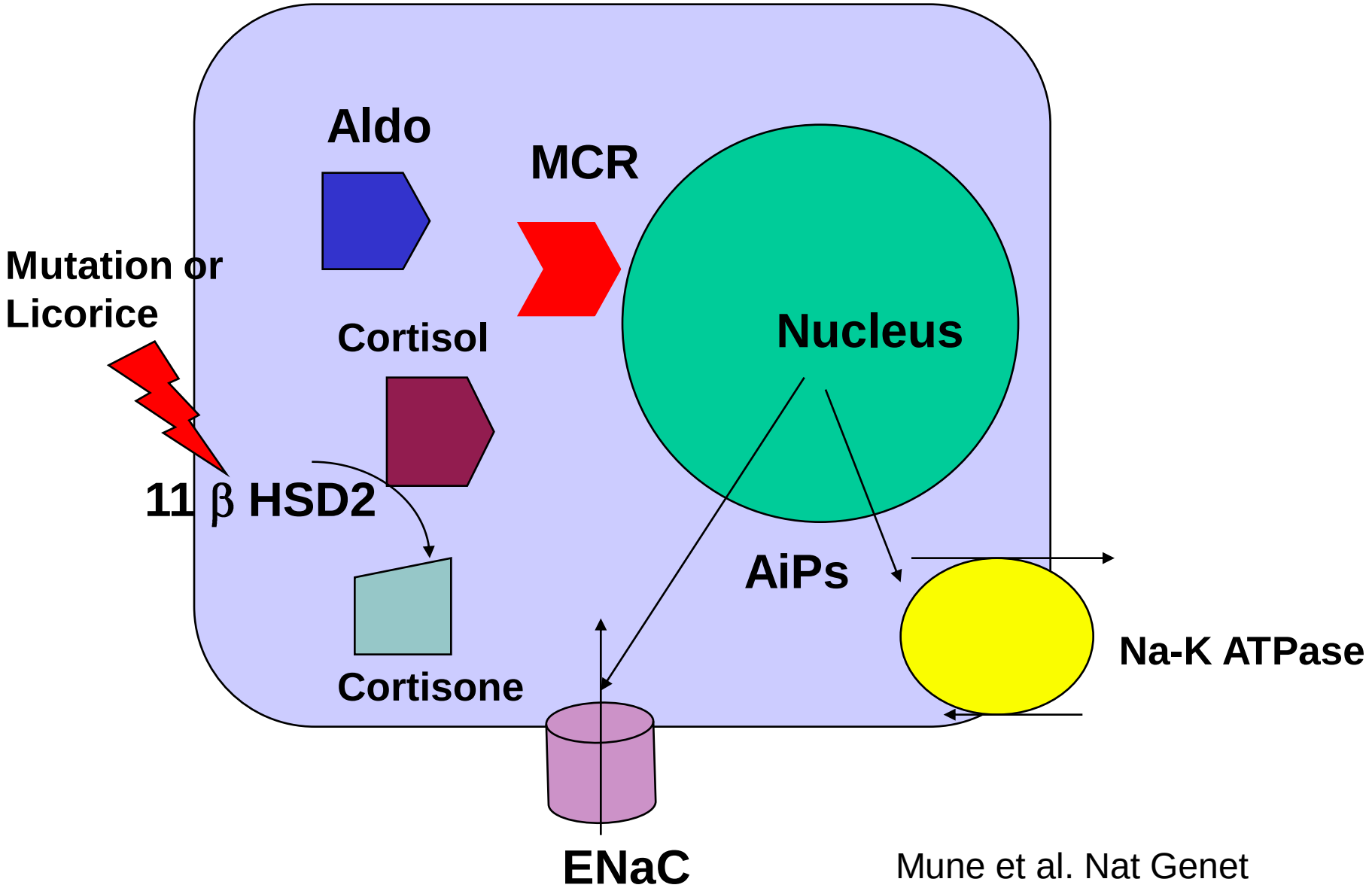
Loss of PPPXY motiv results in retention of ENaC in cell membrane and no clearance via clathrin-coated pits

Apparent mineralocorticoid excess

- Autosomal-recessive (pediatric) disease
- PRA and aldosterone are both low
- Blood pressure responds to thiazides and spironolactone
- Disease resembles licorice gluttony
- Inactivating mutations in 11ß hydroxysteroid dehydrogenase (11ßHSD2) gene, exposing the MR to cortisol

Mune et al. Nat Genet

11 β HSD, MCR, Aldosterone, and AiPs



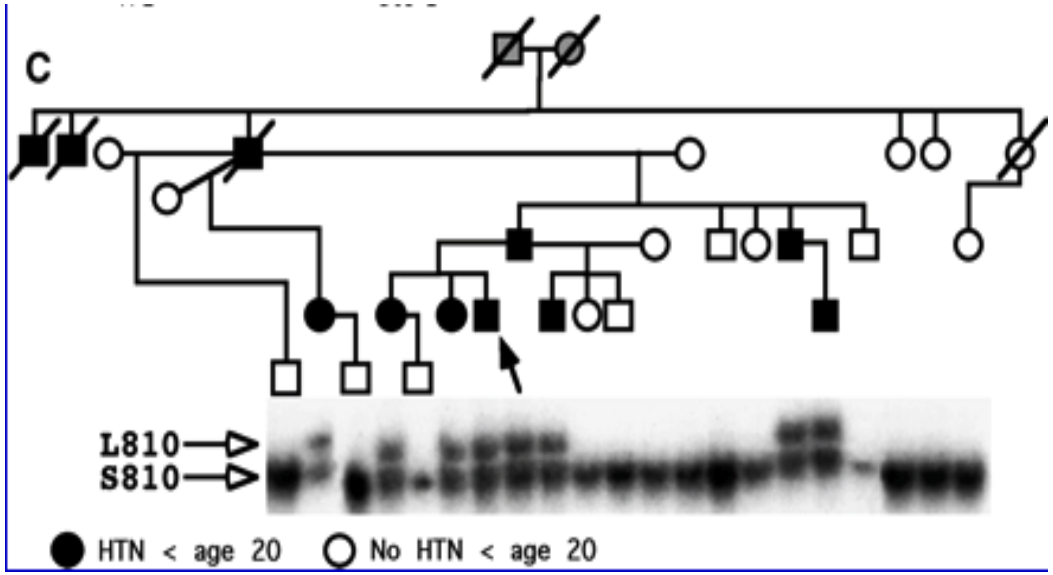
Mune et al. Nat Genet

Activating mutation in mineralocorticoid receptor (MR)

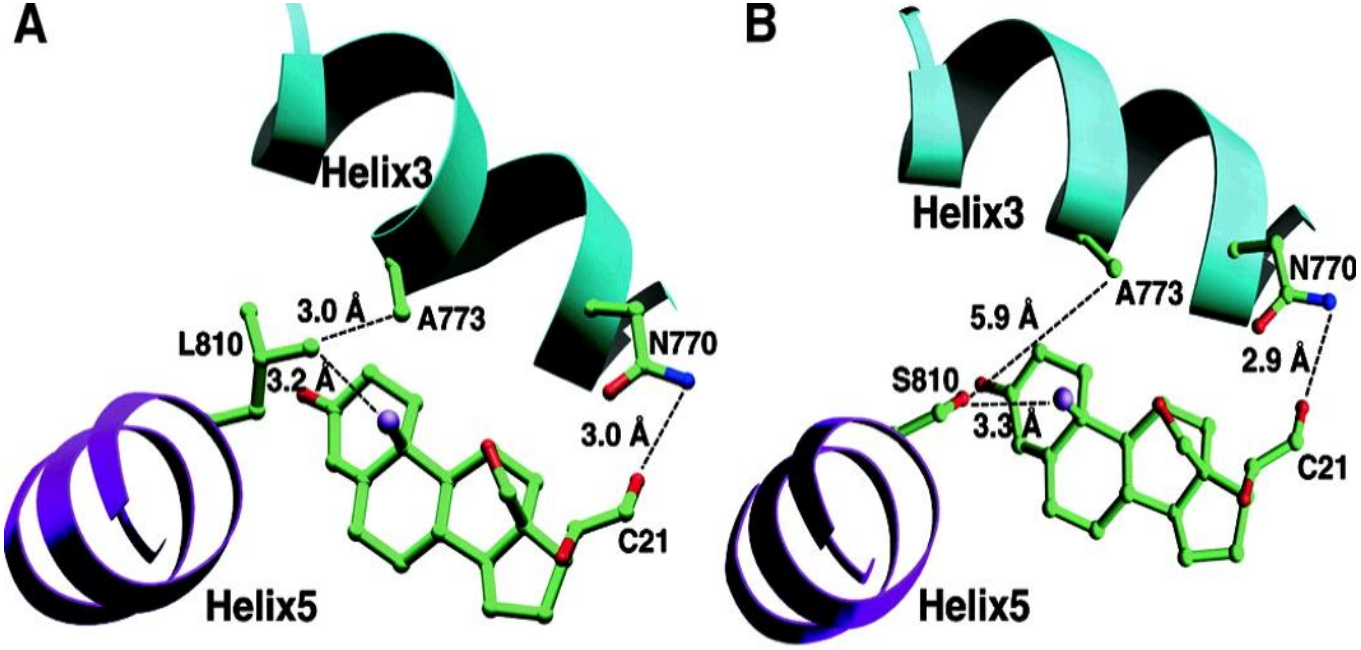
- Autosomal-dominant disease
- PRA is low; aldosterone is also low
- Spironolactone and pregnancy make the hypertension worse, not better

Geller et al. Science 2000

Family tree with the leucine>serine 810 MR activating mutation



Leucine vs. serine exchange at 810



C

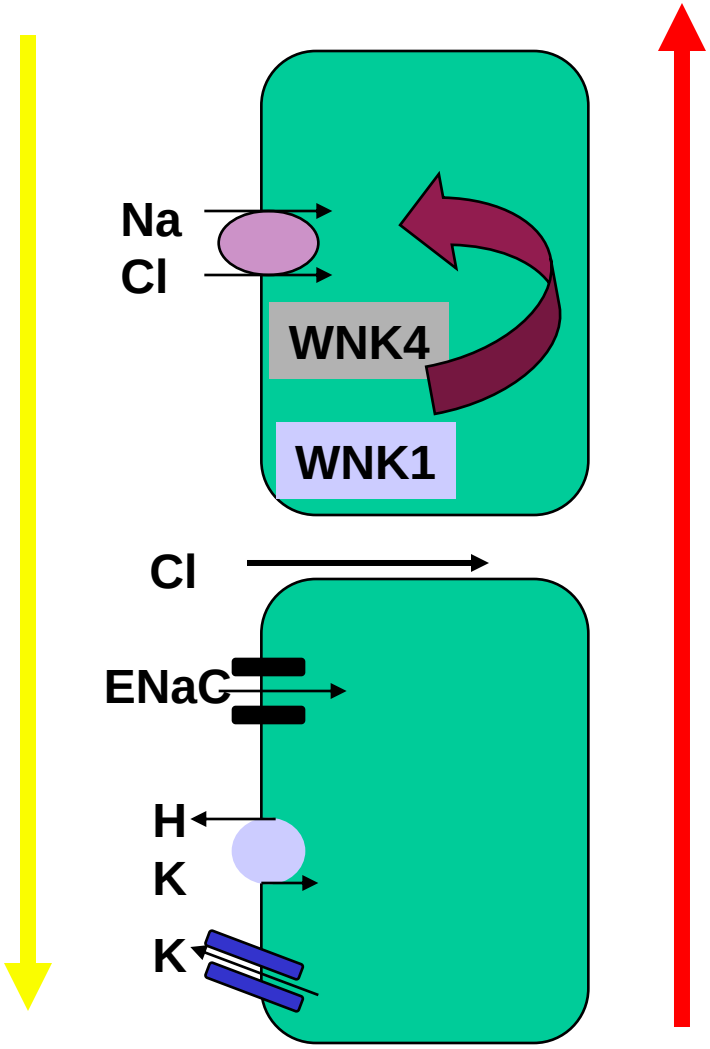
Helix 5		Helix 3		Aldosterone	19-NP
S	$-CH_2-OH$	CH_3-	A	100.0 ± 5.8	6.1 ± 1.2
M	$-CH_2-CH-S-CH_3$	CH_3-	A	120.3 ± 9.8	111.0 ± 5.5

A 24 year-old French lady with hypertension is referred because she became weak after starting her beta blocker. Her family history is strongly positive for hypertension. Half her family members have it.

- **pH** **7.38**
- **$PaCO_2$** **35 mm Hg**
- **HCO_3** **21 mmol/l**
- **Na** **140**
- **K** **6.3**
- **Cl** **109**
- **PCr** **99 µmol/l**
- **UpH** **5.3**
- **UKV** **54 mmol/l**
- **UNaV** **53 mmol/l**
- **Uosm** **650 mosm/l**
- **PRA low, Aldo high**

- **Explain the acid-base disturbance**
- **What is the Ddx here?**
- **What do you think about the family history?**
- **TTKG???**
- **What is this called?**

Pseudohypoaldosteronism type II (Gordon syndrome)
Wilson et al. Science 2001;293:1107-1112



WNKs regulate NaCl cotransport

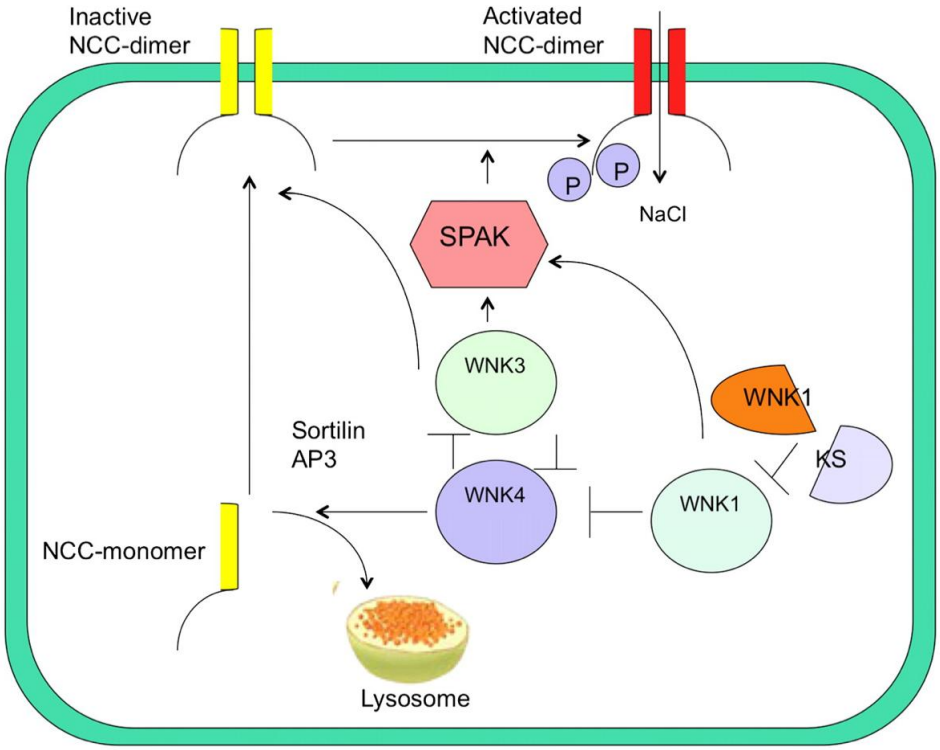
PHA type II is characterized by:

Salt-sensitive hypertension (increased NaCl reabsorption)

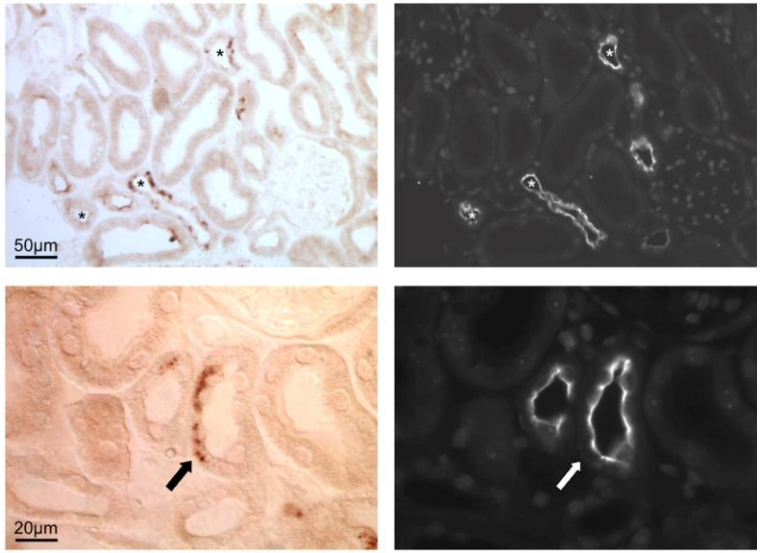
Mild hyperchloremic acidosis (decreased Na-H exchange)
Hyperkalemia (decreased ROMK in CCT)

Response to thiazide diuretics (supports increased NaCl cotransport)

WNK are serine-threonine kinases. **Function is now becoming clear**



Hoorn et al. Nat Med 2011;17:1304-1309.



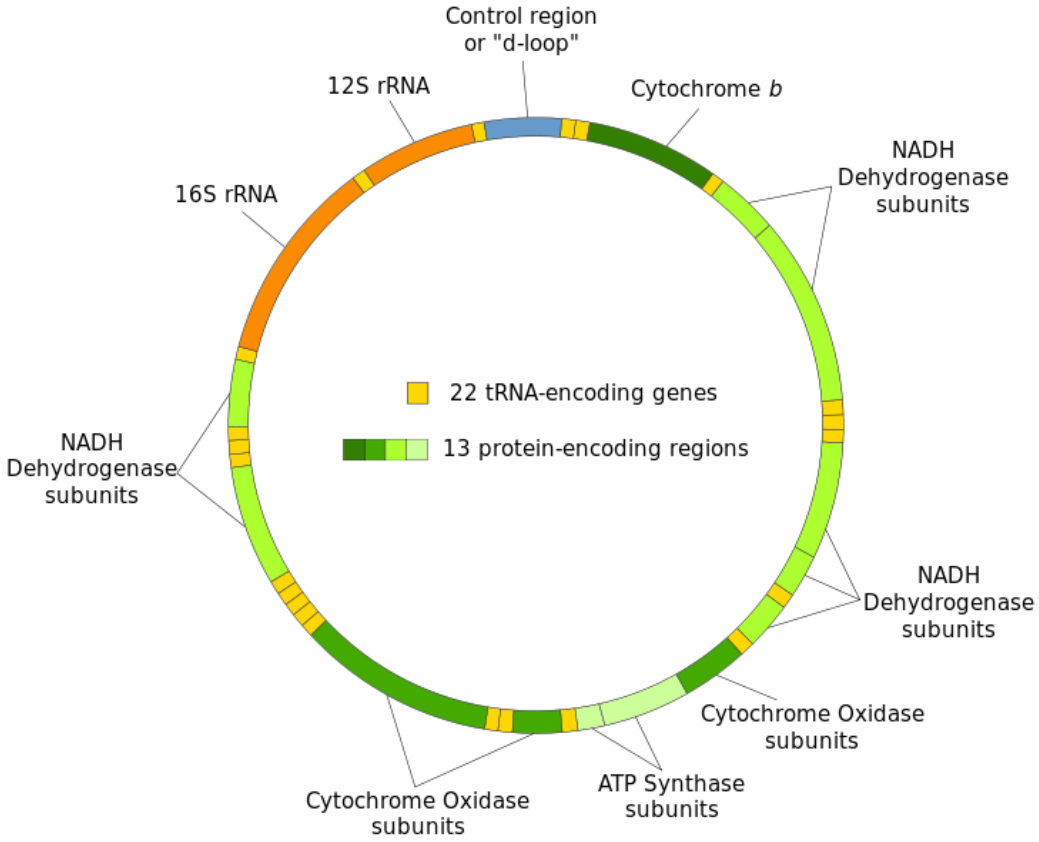
How do CNI cause high blood pressure?

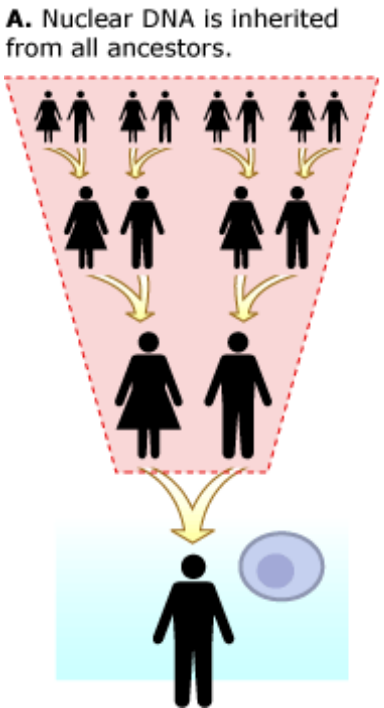
Calcineurin is co-expressed with NCC. WNK3, WNK4 and SPAK are activated by tacrolimus. Tacrolimus induces salt-sensitive Hypertension. NCC knock-out mice get no hypertensinon with tacrolimus. (Hoorn et al Nat Med 2011)

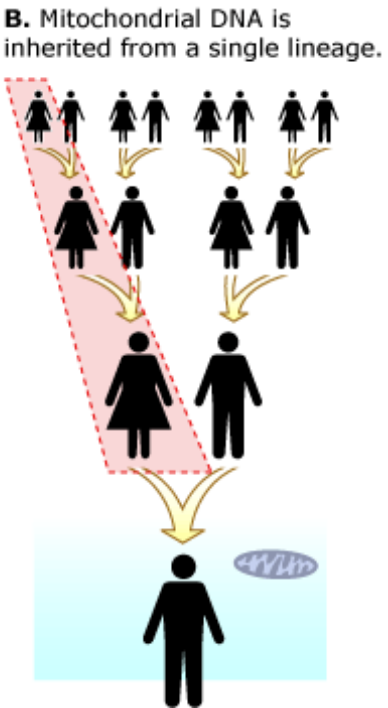
Metabolic defects caused by mitochondrial DNA

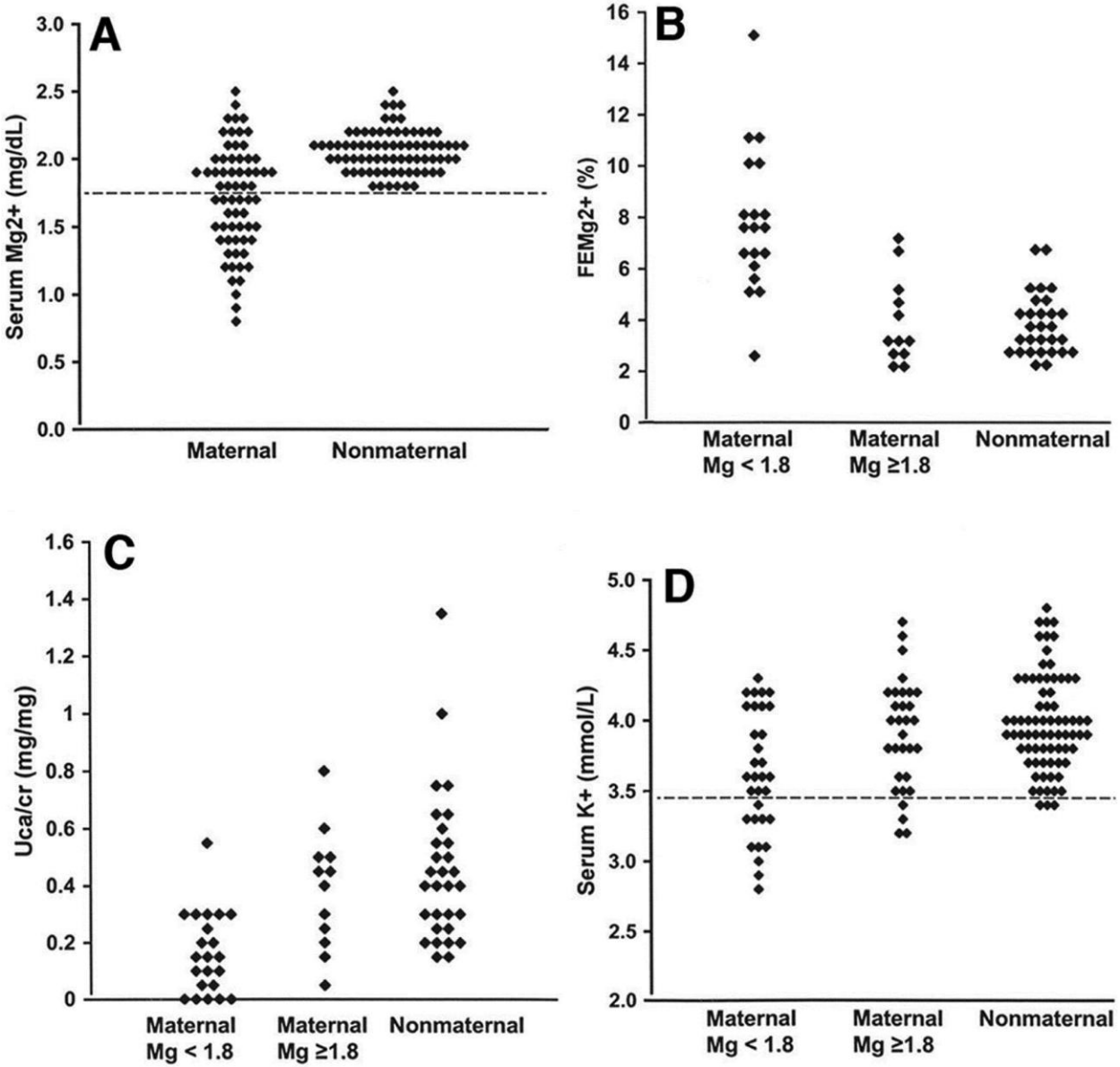
- Hypertension, lipid disturbances, hypokalemia, hypomagnesemia
- Inheritance is always from the mother to offspring
- Transfer RNA of the Ile anticodon

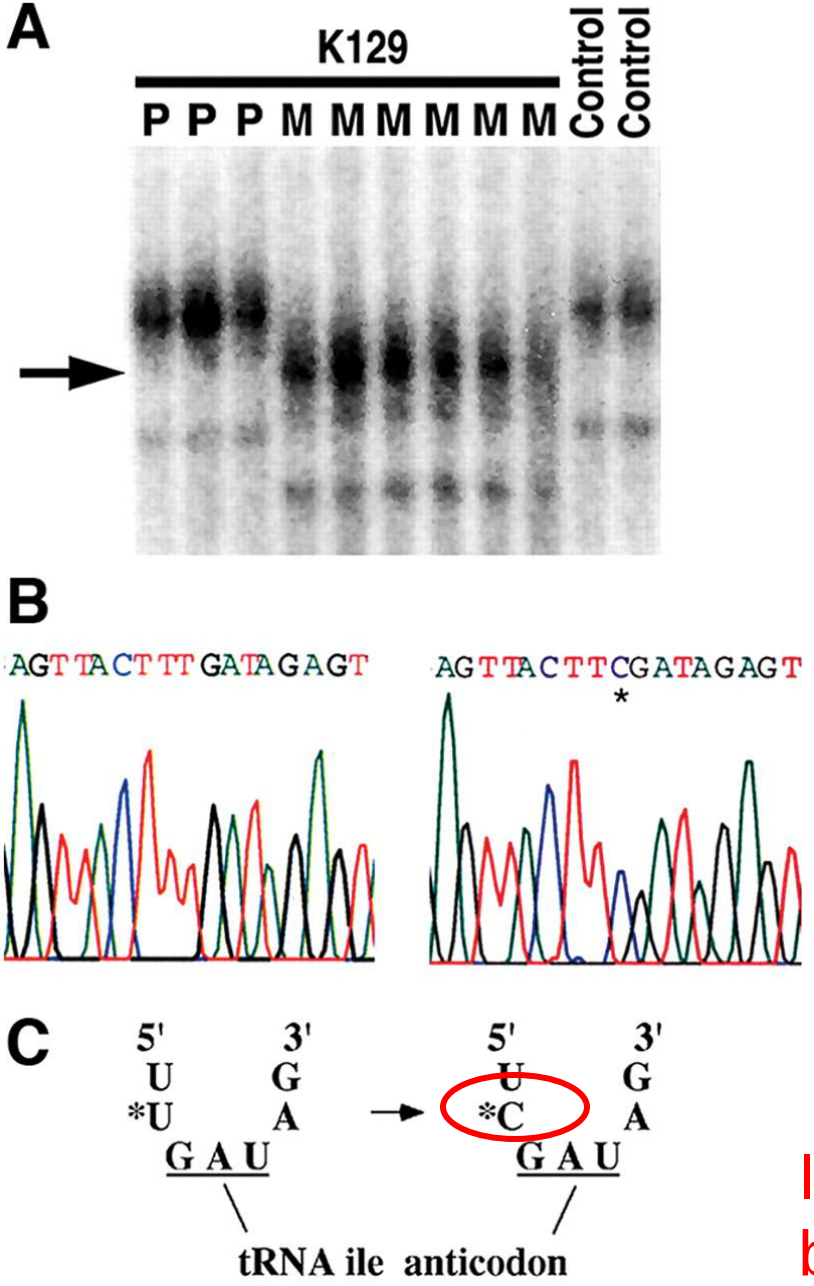
Wilson et al. Science 2004


Control region
or "d-loop"
12S rRNA
Cytochrome b
NADH
Dehydrogenase
subunits
16S rRNA
22 tRNA-encoding genes
13 protein-encoding regions
NADH
Dehydrogenase
subunits
NADH
Dehydrogenase
subunits
Cytochrome Oxidase
subunits
ATP Synthase
subunits
Cytochrome Oxidase
subunits


A. Nuclear DNA is inherited
from all ancestors.

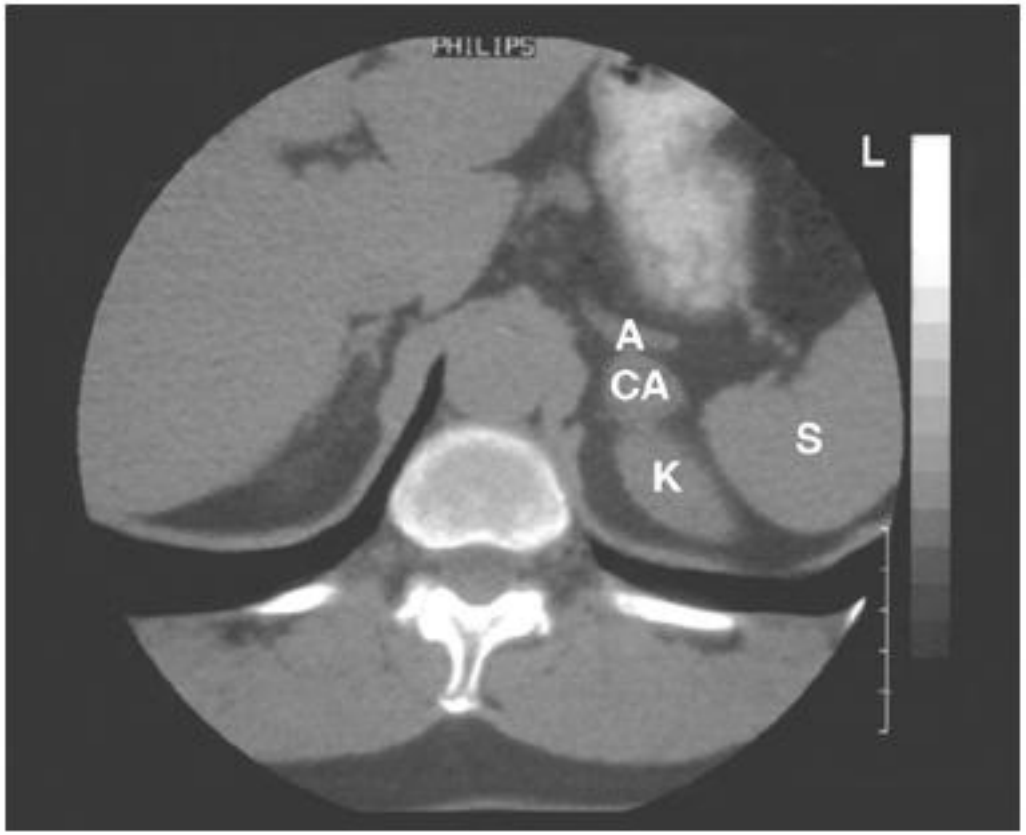

B. Mitochondrial DNA is
inherited from a single lineage.


A
Serum Mg2+ (mg/dL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Maternal
Nonmaternal
B
FEMg2+ (%)
16
14
12
10
8
6
4
2
0
Maternal Mg < 1.8
Maternal Mg ≥1.8
Nonmaternal
C
Uca/cr (mg/mg)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Maternal Mg < 1.8
Maternal Mg ≥1.8
Nonmaternal
D
Serum K+ (mmol/L)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Maternal Mg < 1.8
Maternal Mg ≥1.8
Nonmaternal

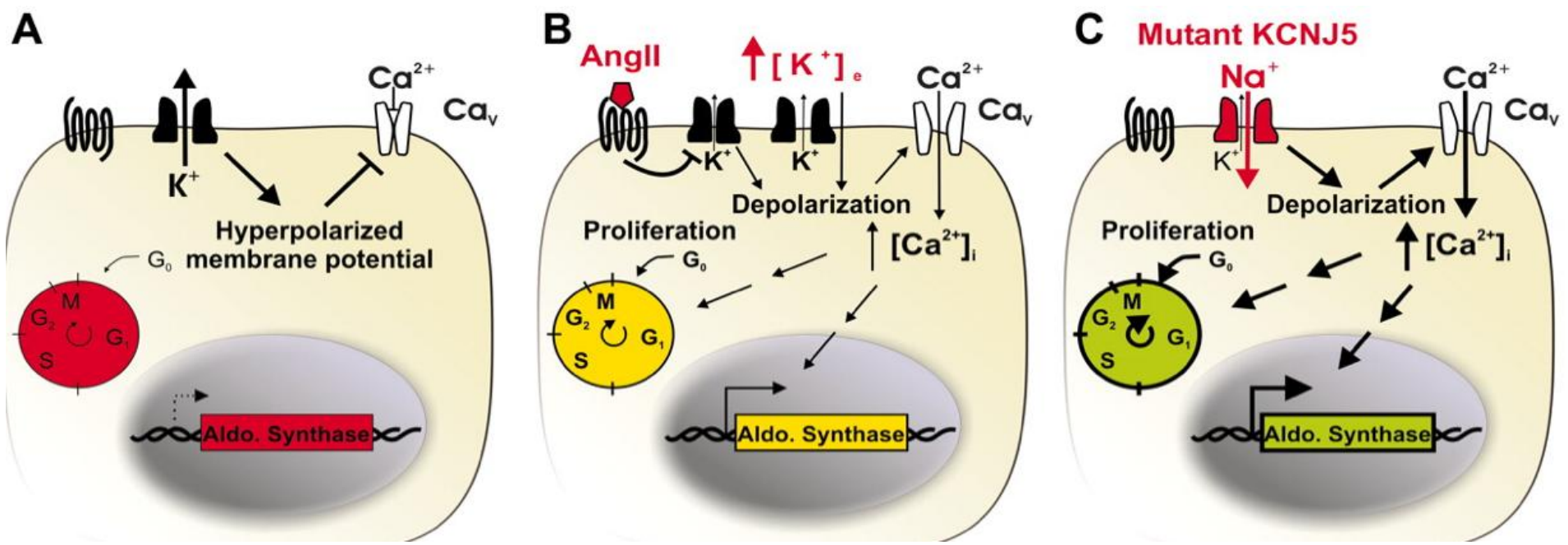


Impairs ribosomal binding

37 year-old woman with rather severe hypertension.
Plasma renin activity is low, aldosterone is high.



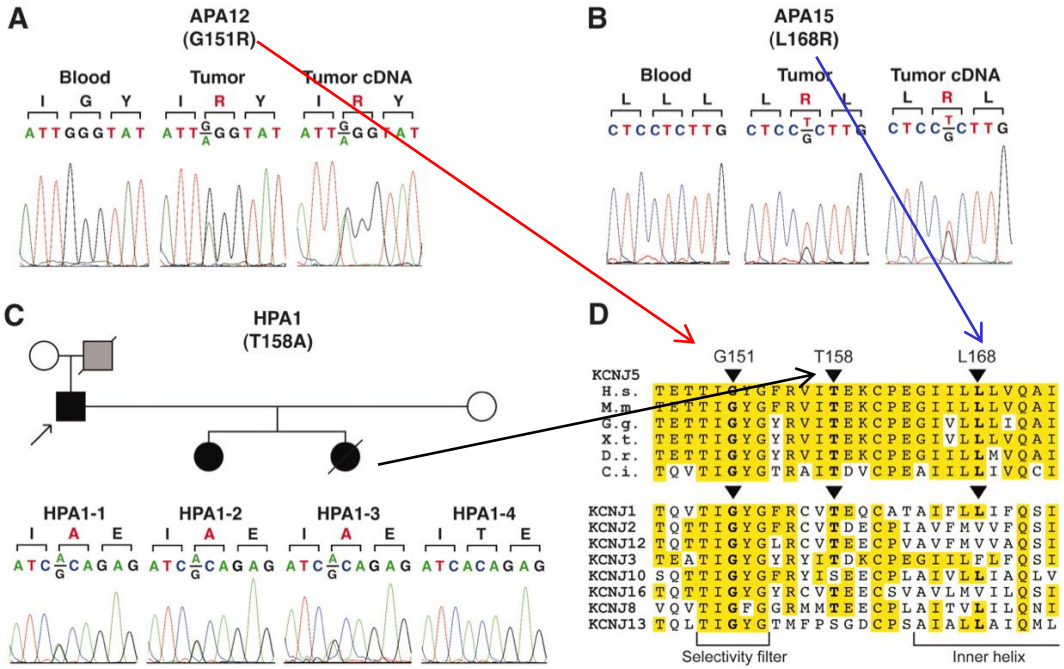
G protein-activated inward rectifier potassium channel 4 is a protein that in humans is encoded by the KCNJ5 gene and is a type of G protein-gated ion channel.



(A) Adrenal glomerulosa cells have a high resting K+ conductance, which produces a highly negative membrane potential. (B) Membrane depolarization by either elevation of extracellular K+ or closure of K+ channels by angiotensin II activates voltage-gated Ca2+ channels, increasing intracellular Ca2+ levels. This provides signals for increased expression of enzymes required for aldosterone biosynthesis, such as aldosterone synthase, and for increased cell proliferation. (C) Channels containing KCNJ5 with G151R, T158A, or L168R mutations conduct Na+, resulting in Na+ entry, chronic depolarization, constitutive aldosterone production, and cell proliferation.

K+ channel mutations in adrenal aldosterone-producing adenomas (APA) and hereditary hypertension.

Endocrine tumors such as aldosterone-producing adrenal adenomas (APAs), a cause of severe hypertension, feature constitutive hormone production and unrestrained cell proliferation; the mechanisms linking these events are unknown. We identify two recurrent somatic mutations in and near the selectivity filter of the potassium (K+) channel KCNJ5 that are present in 8 of 22 human APAs studied. ^These findings explain pathogenesis in a subset of patients with severe hypertension and implicate loss of K^+ channel selectivity in constitutive cell proliferation and hormone production.

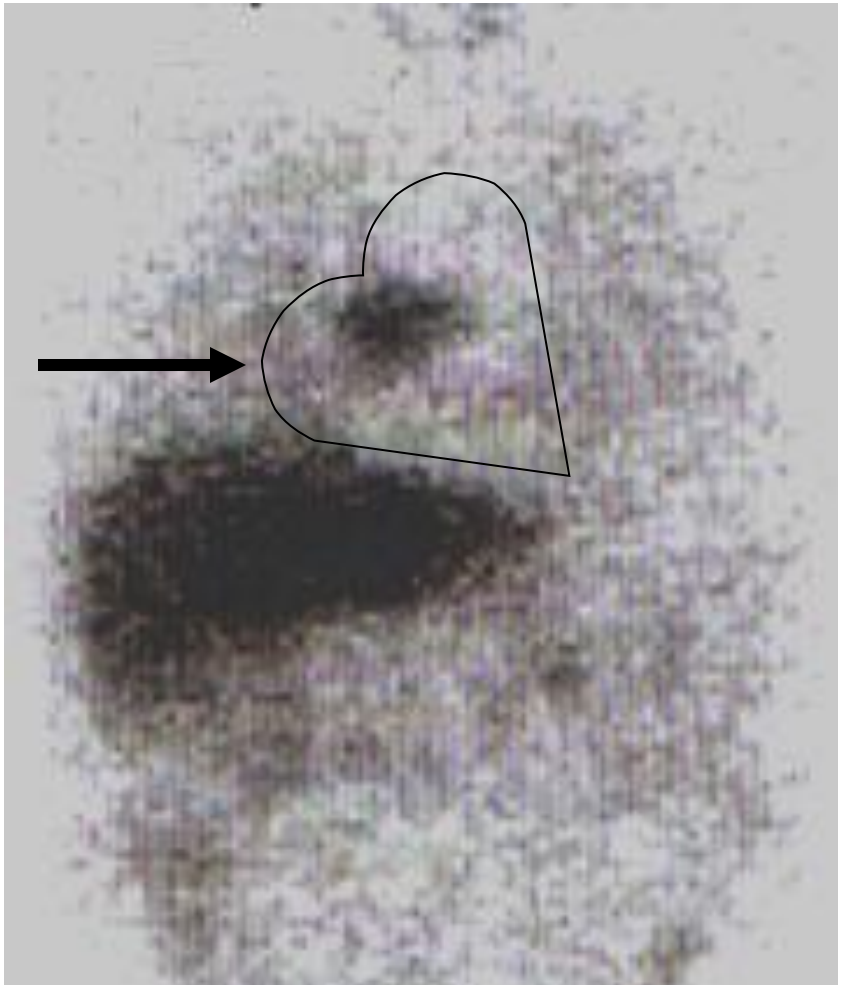


Choi et al. Science 2011

(A) Sequences of blood and tumor genomic DNA and tumor cDNA of KCNJ5 codons 150 to 152 in APA12. (B) Sequences of KCNJ5 codons 167 to 169 in APA. (C) KCNJ5 mutation in kindred HPA1. At top, kindred structure is shown; affected members are shown as filled symbols; gray symbol represents a subject who died at age 36 with severe hypertension, suspected to be affected. KCNJ5 sequences of codons 157 to 159 are shown. Reverse strand traces for (A) to (C) are shown in fig. S4. (D) Conservation of G151, T158, and L168 in orthologs and paralogs.

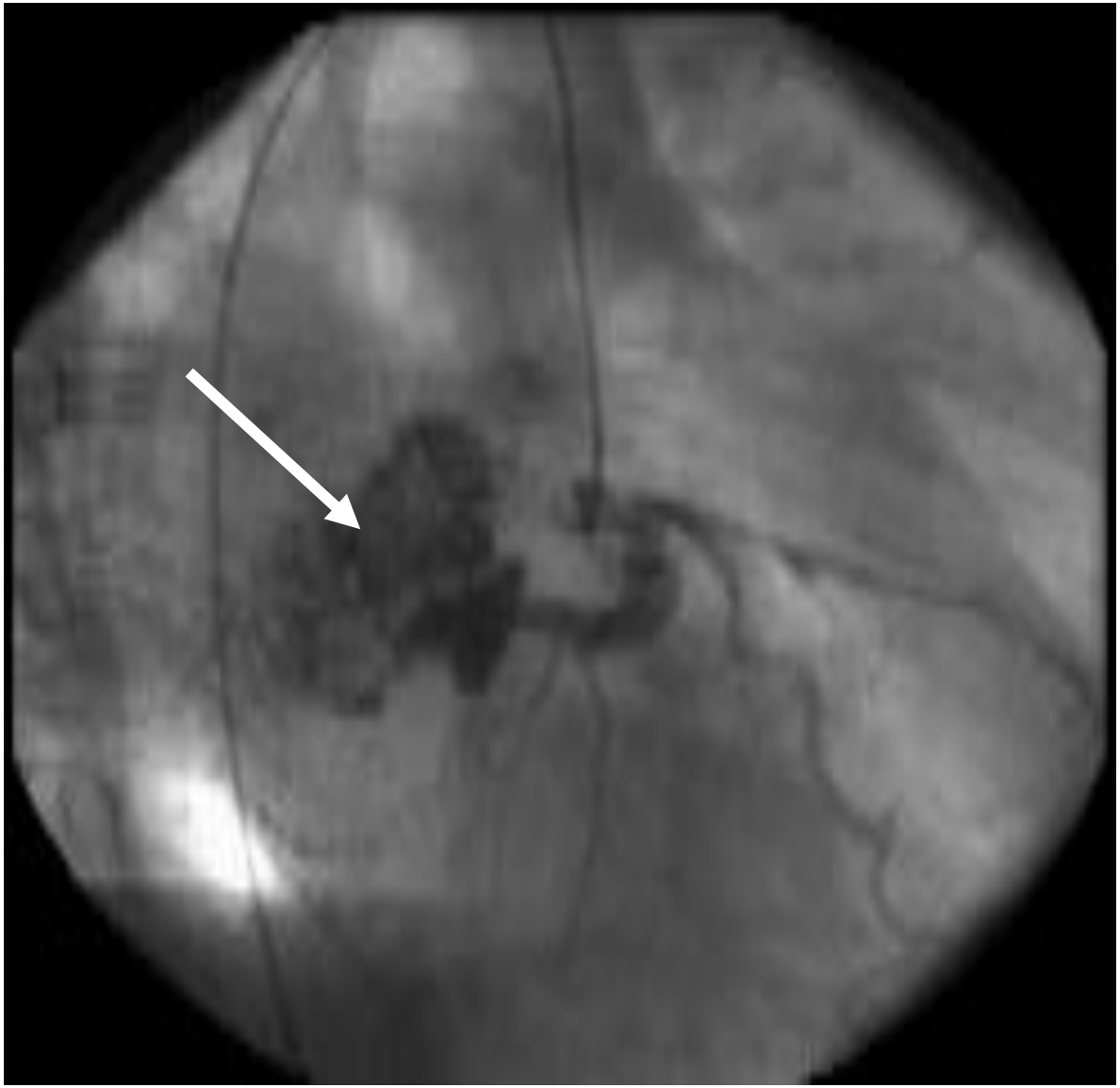
A 52 year-old man presented because of episodic headaches, sweating, and tachycardia. He had been hypertensive for 10 years. VMA w/u negative.

- **BP 140/90 but 24 h showed values up to 212/114**
- **Tilt-test caused fainting**
- **Urine norepinephrine and normetanephrine elevated**
- **Plasma NE elevated**
- **Epinephrine not elevated**
- **Abd MRI negative**



^{123}I-Meta-iodobenzylguanidine (MIBG)

Left circumflex coronary artery



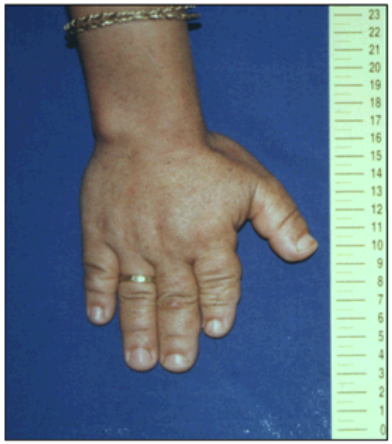
Pheochromocytoma

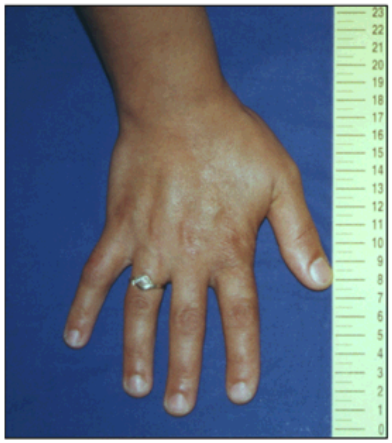
Neumann et al. NEJM 2002;346:1459

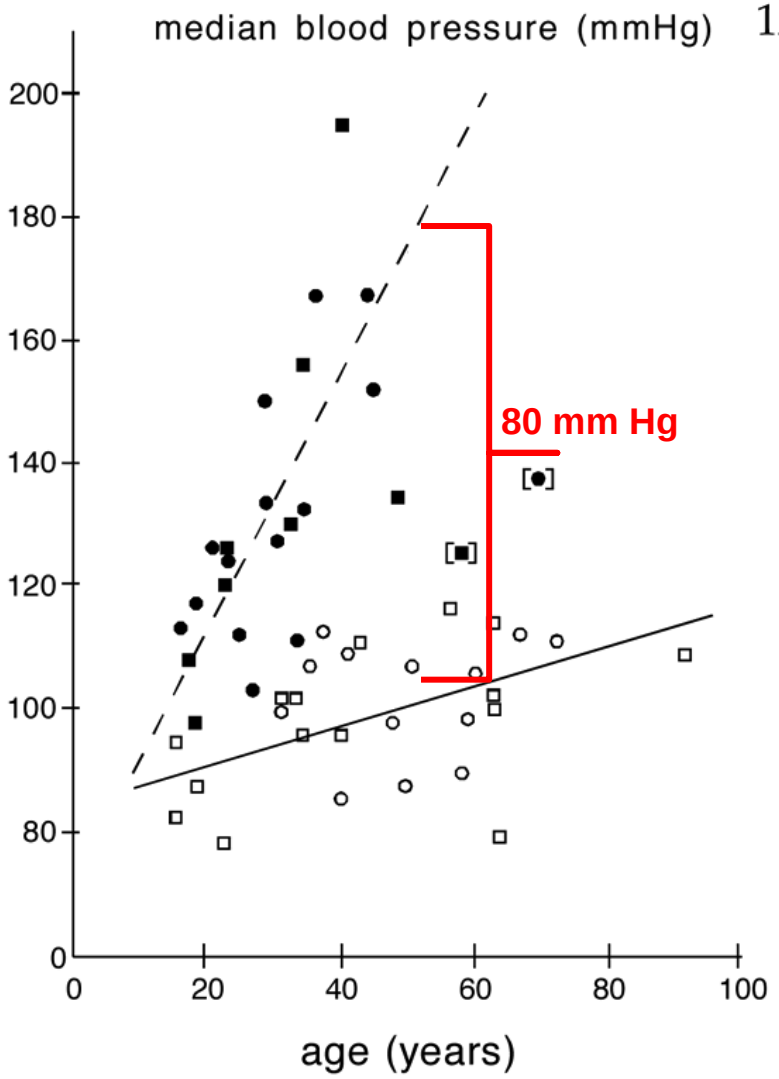
Syndrome	Phenotype	Incidence	Gene
MEN2B	ibid+neuromata	50%	*RET*
Neurofibr I	café au lait	1	*NF1*
VHL	eye-kidney-cns	10-20%	*VHL*
Paraganglioma	carotid body	20%	*SDHD**
Paraganglioma	& Zuckerkandl		*SDHB**

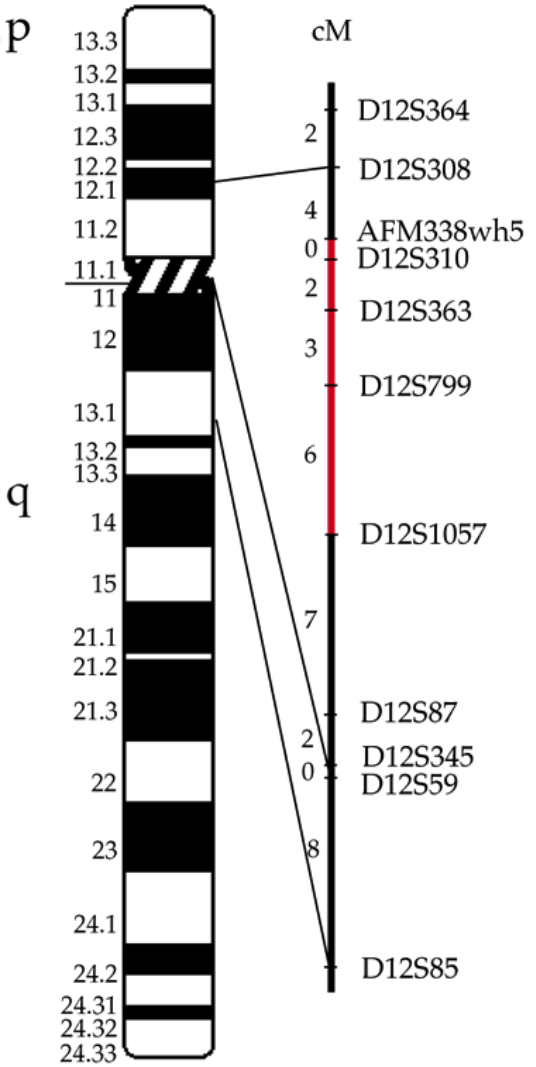
*Succinate dehydrogenase pathway mutations now involves 5 genes

Autosomal-dominant hypertension with brachydactyly type E



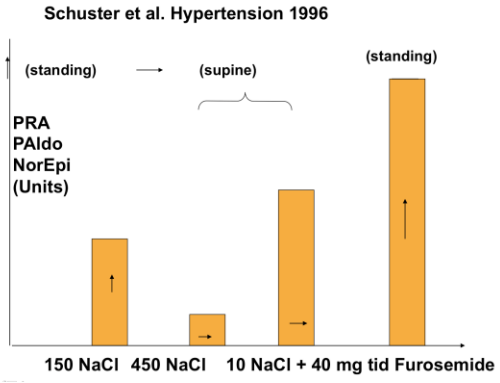


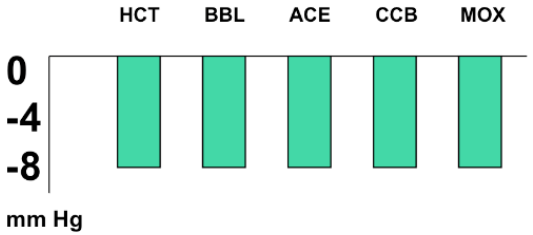




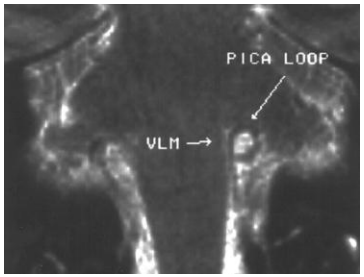
Schuster et al. Nat Genet 1996

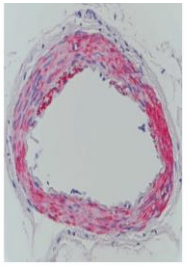
Autosomal-dominant HBP with BDE

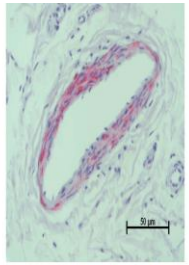




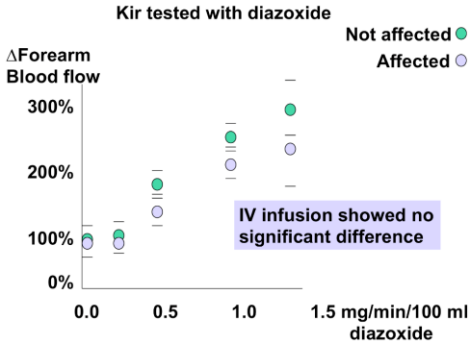
BP fall with 5 drugs compared to placebo (cross-over)

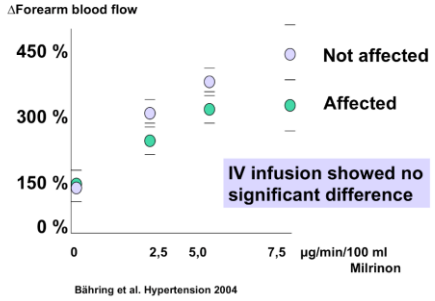




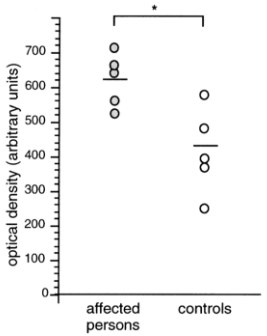


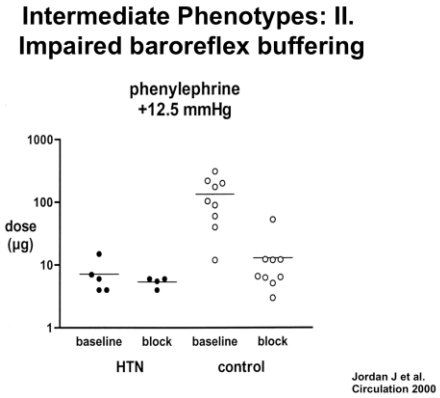
Affected Non-Affected

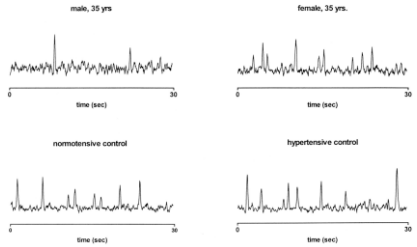


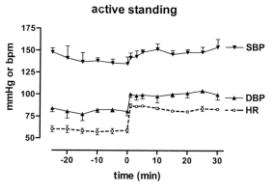


Bähring et al. Hypertension 2004







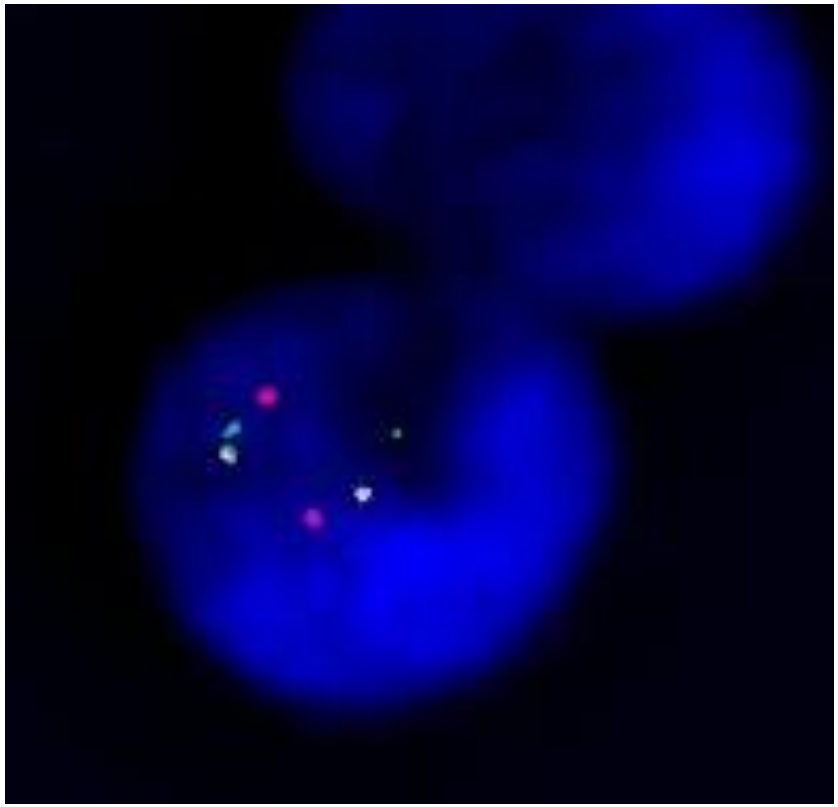


Am J Hum Genet 1997, Stroke 1997
Hypertension 1996, 2004, 2008, 2010
Kidney Int 1998, Ann Intern Med 1998
Circulation 2000

What causes the hypertension?

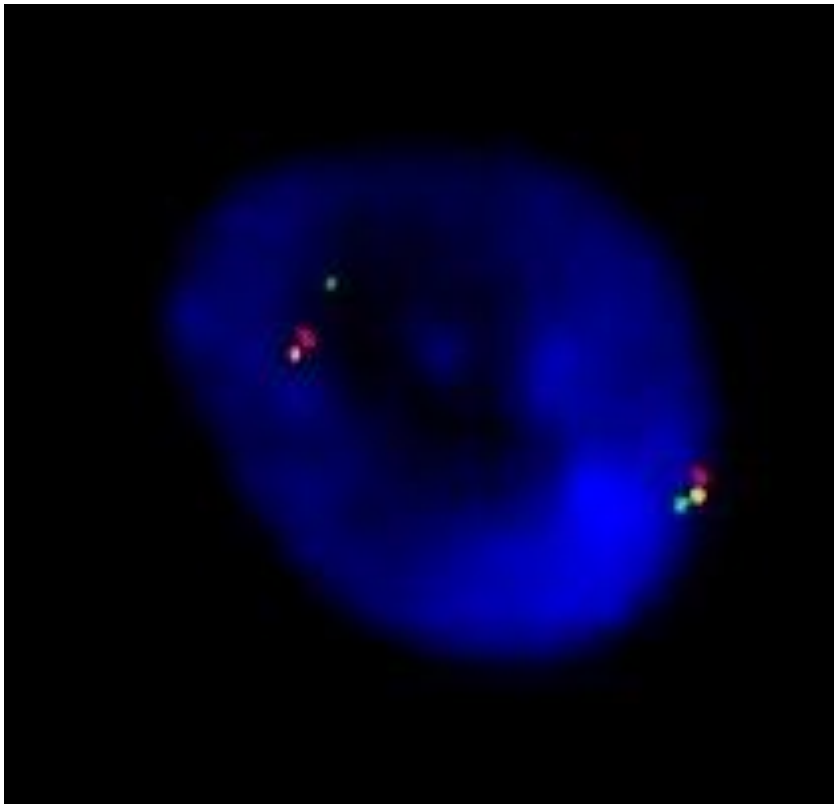
We do not know!

Affected person with Mendelian brachydactyly and hypertension



28komb1

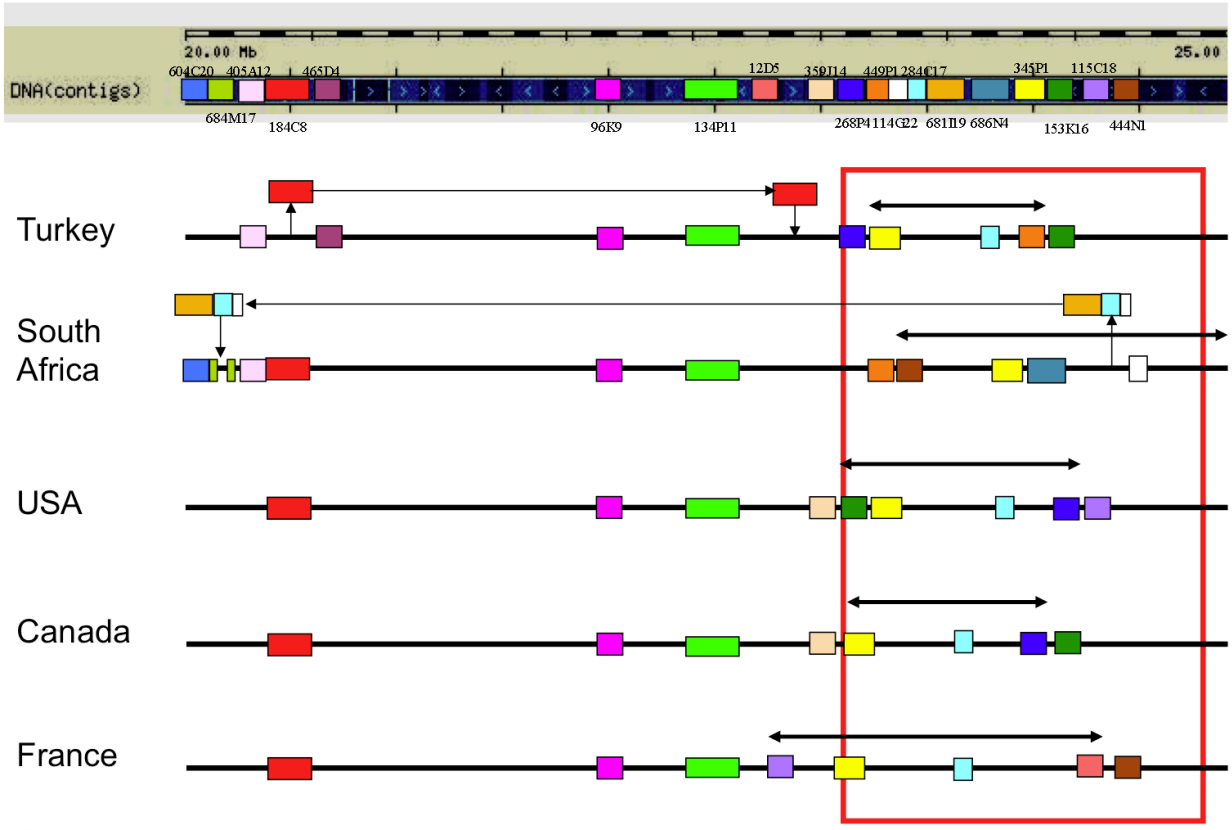
96K9 284C17 345P1



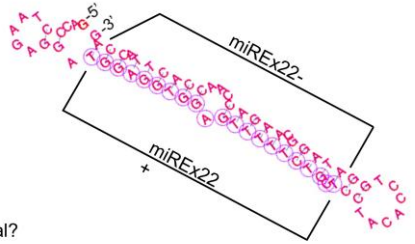
28komb4

184C8 96K9 284C17

Extended i-FISH study with 20 BACs



Predicted pre-microRNA structure of Exon22



Real?

Genomic sequence is present in man and monkey but not yet (mapped) in mouse.

(Hypertension 2008)

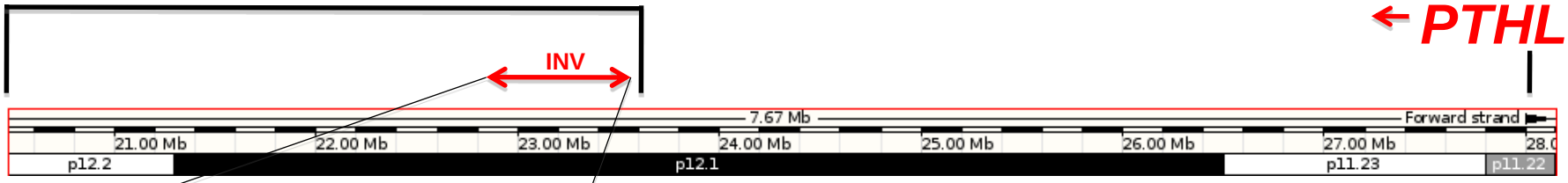
Bähring et al. Hypertension 2008

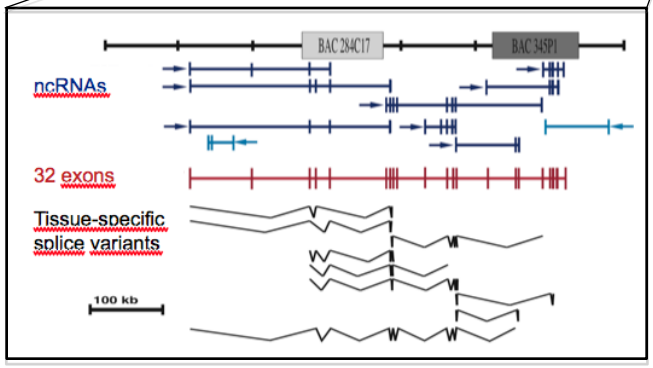
What about *PTHLH* in HBP with BDE?

This is a complex rearrangement syndrome and when I figure it out, I will let you know!

HBP with BDE

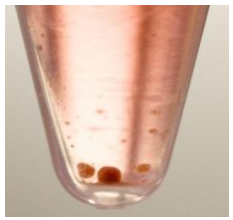
← ***PTHLH***

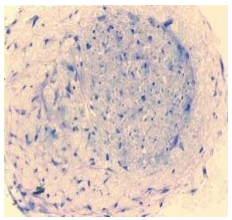


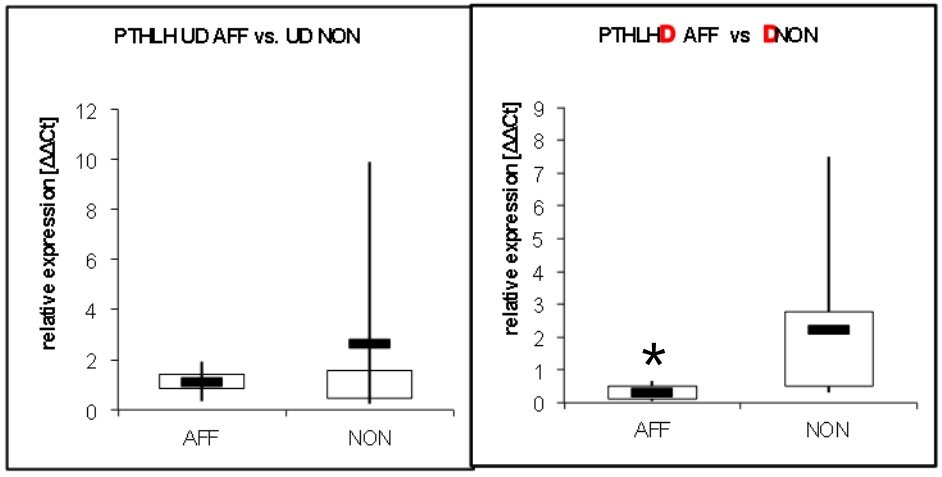


micromass culture

toluidin blue







* P <0,05 6 AFF vs. 8 NON

Chondrogenically differentiated fibroblasts

Mass et al. Hum Mol Genet 2009

Mendelian hypertension

- All are salt-sensitive except one
- PRA is low in all except one
- ALD is low in Liddle, AME, MR, high in GRA and Gordon‘s
- If it only comes from mom, then mitochondria
- KCNJ5 explains a lot of primary aldosteronism
- All pheos are a genetic syndrome until proven otherwise
- You might look at the fingers