

# ***Etwas zur Genetik des Schlaganfalls***

8. Prophylaxe-Seminar des KNS  
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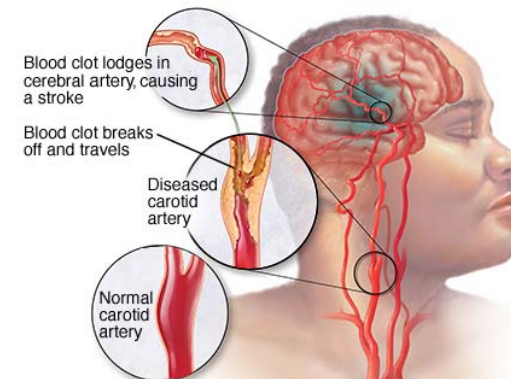
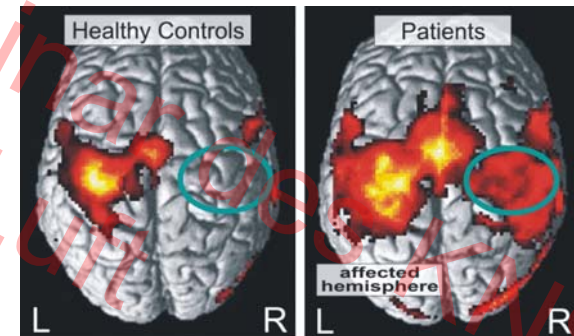
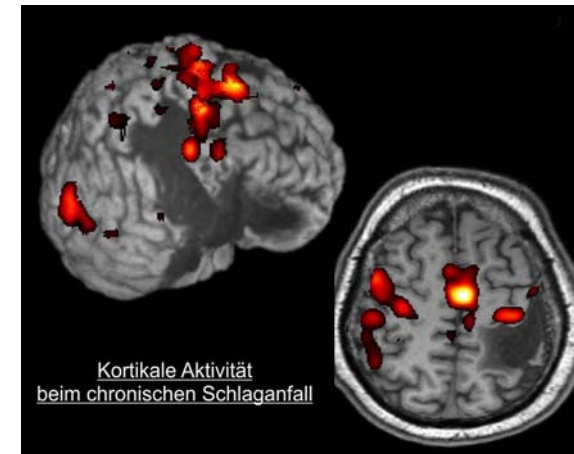
# Schlaganfall hat viele Ursachen

Ein Schlaganfall ist eine plötzlich („schlagartig“) auftretende **Erkrankung des Gehirns**, die oft zu einem länger anhaltenden Ausfall von Funktionen des Zentralnervensystems führt und durch kritische Störungen der Blutversorgung des Gehirns verursacht wird.

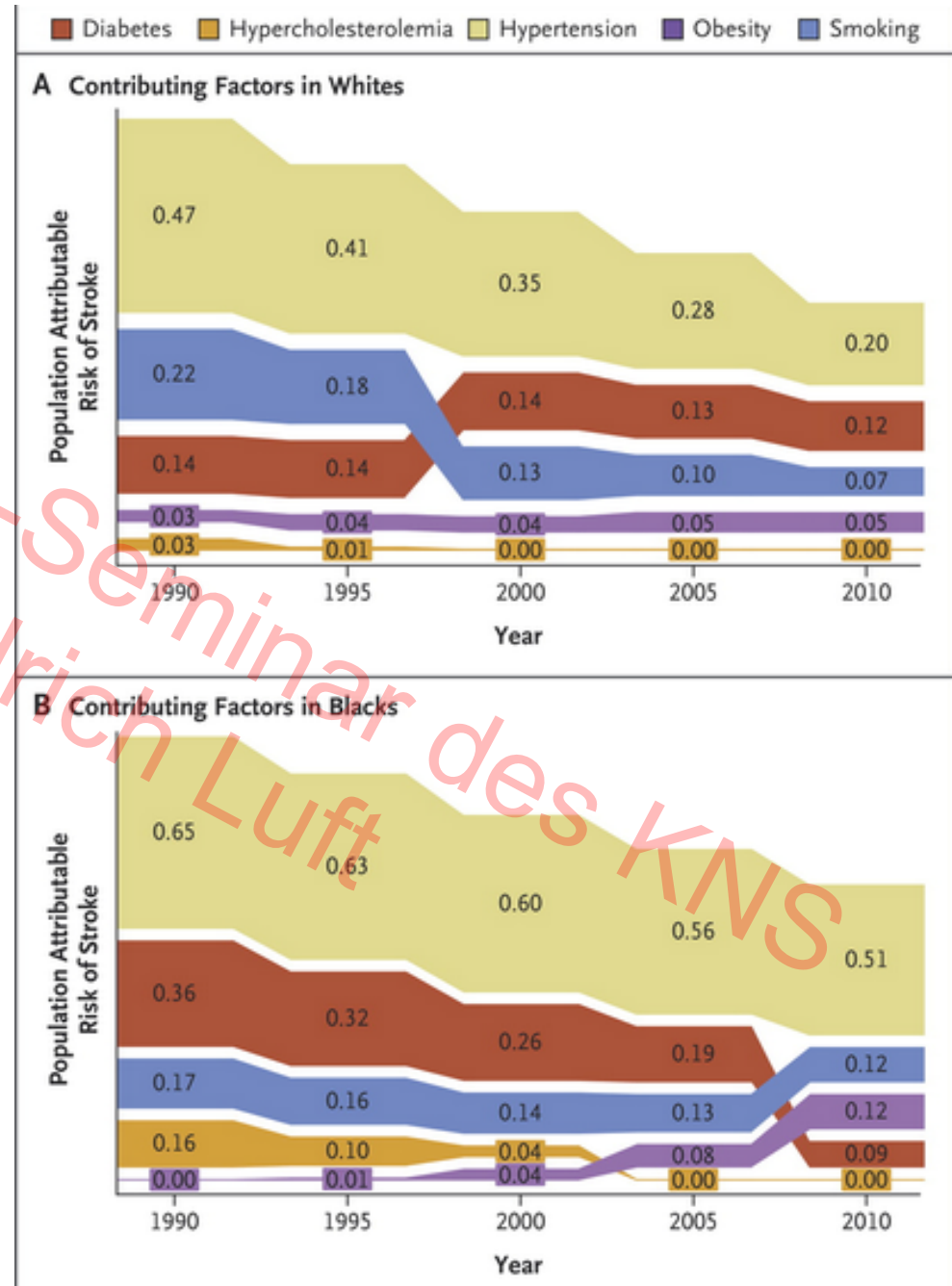
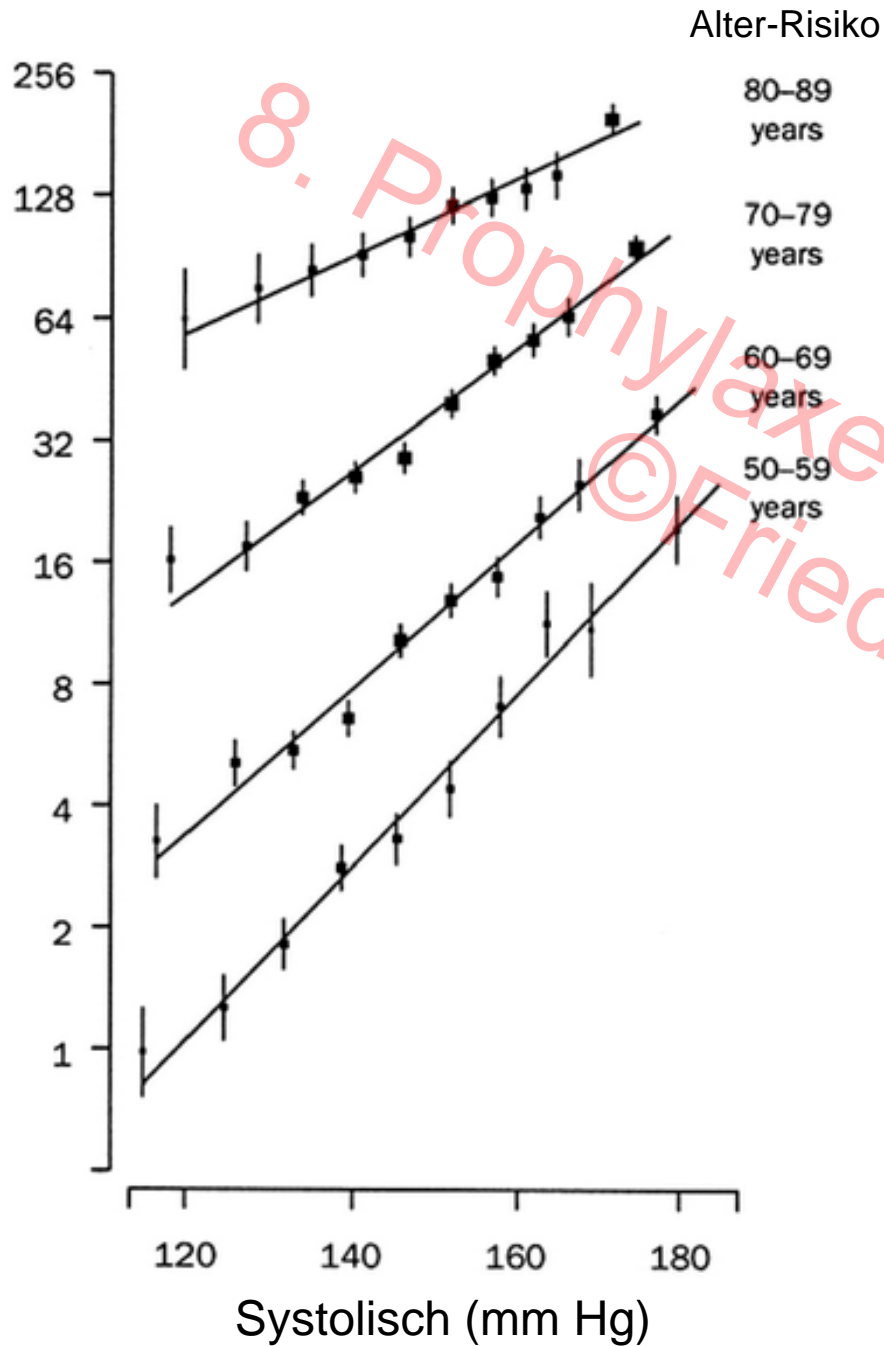
- durch Minderdurchblutung primär **ischämischer** Gehirnfarkte (Inzidenz 160–240 Ereignisse/100.000 Einwohner)
- Hirnblutungen** (24/100.000)
- Einblutungen in den das Gehirn umgebenden Liquor-raum, sogenannte Subarachnoidalblutungen (6/100.000)
- Schlaganfälle ungeklärter Ursache (8/100.000).

Reversible Risikofaktoren:

**Hypertonie**, Rauchen, Diabetes, Diät, Bewegung, Arteriosklerose, Vorhofflimmern, Herzfehler, Sichelzellanämie



# Blutdruck ist Nummer 1

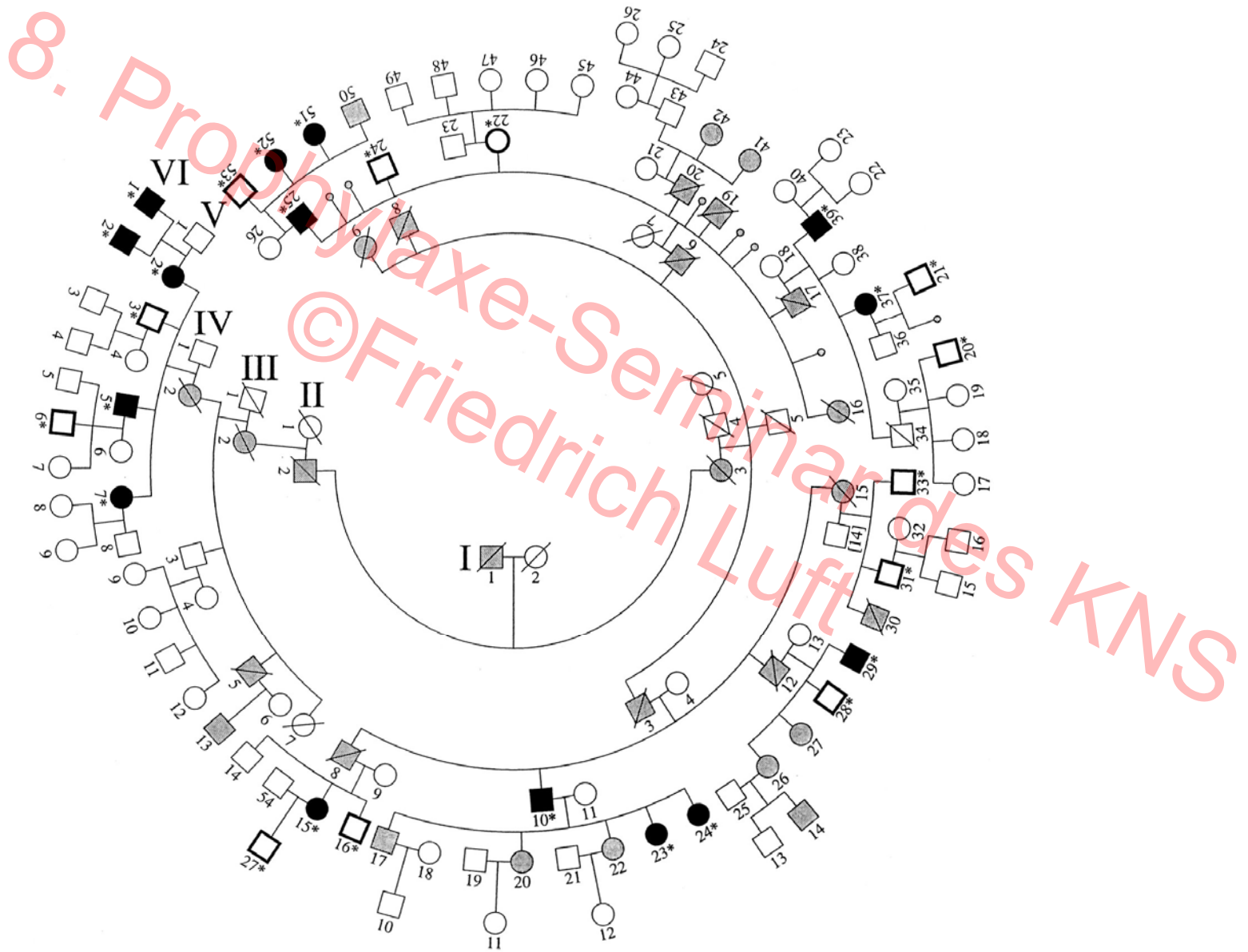


## ***Der klinische Fall***

1960. Kemal stand am Grab seines Onkels Mehmet und grübelte. Mehmet war noch keine 50 Jahre alt gewesen – zu jung zum Sterben. Viele in der Familie waren zu jung zum sterben.

- pH 7,40, PaCO<sub>2</sub> 40, PaO<sub>2</sub> 100 (mm Hg), Na 140, K 4,7, Cl 106, HCO<sub>3</sub> 24 (mmol/l)
- Krea 80 µmol/l, UpH 5,3, UNa 53, UK 34, UOsm 450
- Schilddrüse, PRA, PA, alle Hormone normal
- Stammbaum ergab 60 Leute, die Hälfte mit Hochdruck, Männer und Frauen betroffen, Vererbung von Vater auf Sohn
- Alle Betroffenen hatten kurze Finger

# Der Stammbaum 1994



# Trabson 1994



## Die erste Frage lautet: „Wo ist es?“

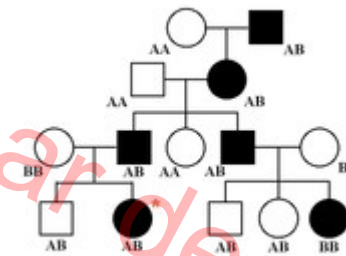
Unter einer Kopplungsanalyse versteht man ein Kartierungsverfahren für Gene. Dabei untersucht man von möglichst vielen genetischen Merkmalen eines Chromosoms, wie häufig sich diese bei Rekombinationsereignissen getrennt haben.

Gene auf verschiedenen Chromosomen trennen sich nach der dritten Mendelschen Regel zu 50 % Wahrscheinlichkeit. Trennen sich zwei Gene auf einem Chromosom jedoch seltener, so spricht man von Genkopplung. Je näher die Gene aneinander liegen, desto unwahrscheinlicher ist die Trennung bei einem Rekombinationsereignis.

Anhand vieler Kreuzungsexperimente über mehrere Generationen kann man die Wahrscheinlichkeit der Trennung ermitteln. Diese gibt den relativen Abstand zwischen Genen an, der in centiMorgan (cM) gemessen wird.

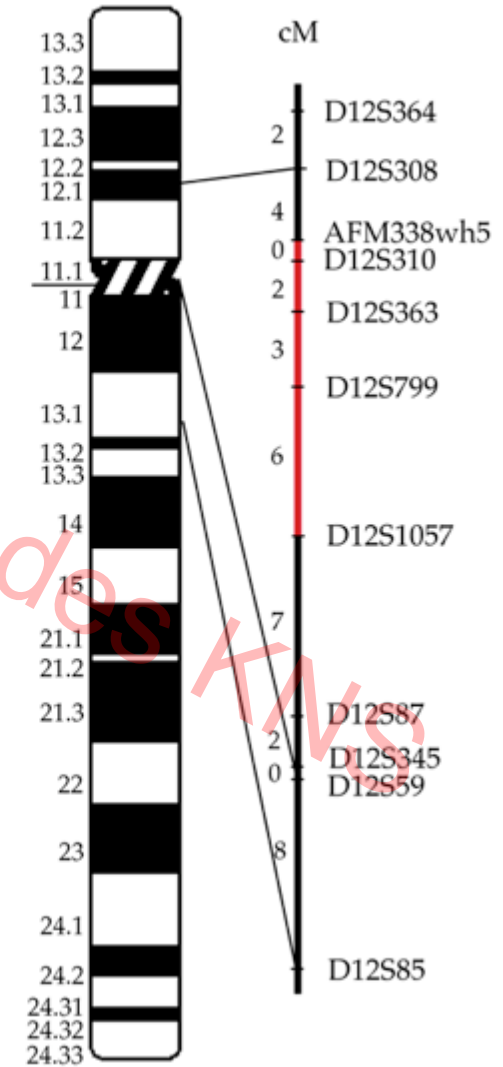
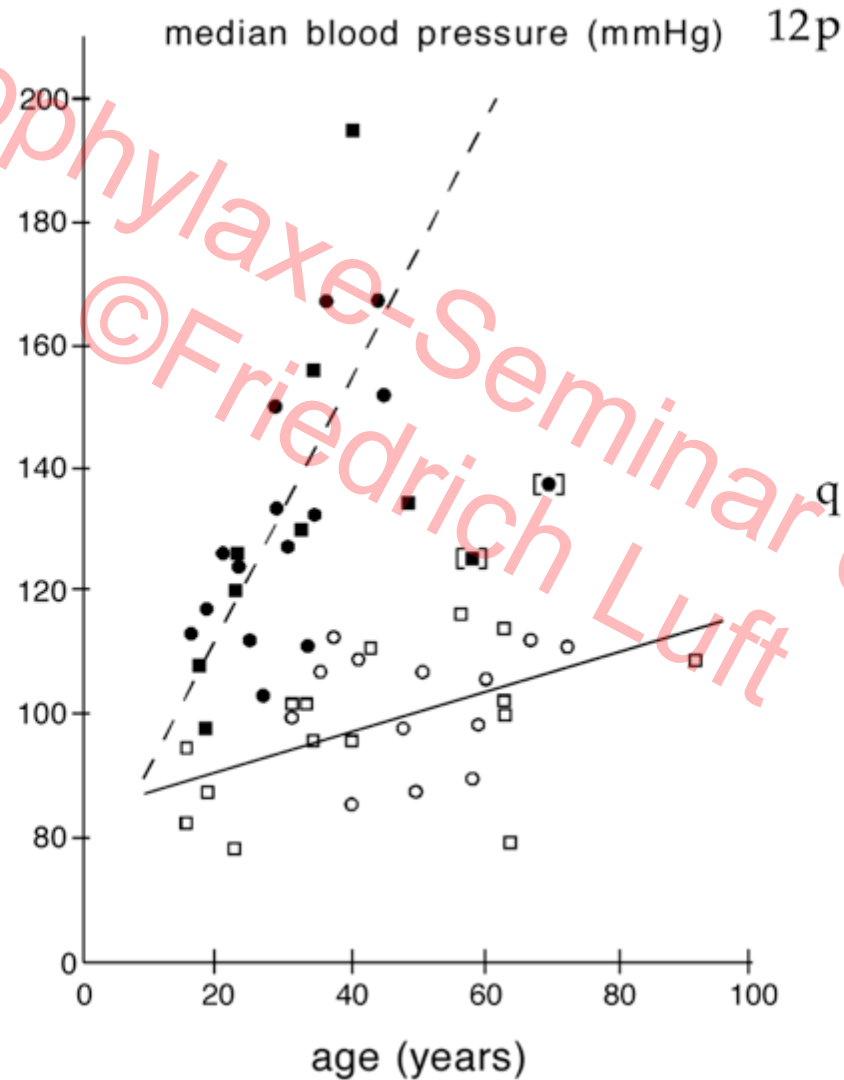
Da optisch auffällige Merkmale (Marker) nicht sehr häufig sind, nutzt man zur Kartierung molekulare Marker wie z. B. RFLPs, AFLPs, Mikrosatelliten und SNPs.

Hierzu braucht man Leute die mit einander verwandt sind.



Ich suche nach Kennzeichen, die immer mit der Krankheit vererbt sind.

# Phänotypisierung und Kartierung eines monogenen (nach Mendel vererbt) Schlaganfallsyndroms



Schuster et al. Nat Genet  
1996



## **Die zweite Frage lautet: „Was ist es?“ (monogene Krankheitsbilder)**

Syndrom	Gen	Mechanismus
CADASIL (autosomal dominant)	Notch3 receptor	Small vessel disease
CARASIL (autosomal recessive)	Notch3 receptor	Small vessel disease
Moya-moya disease (autosomal dominant)	Numerous	Internal carotid stenosis with new vessel formation
Fabry disease (X-linked recessive)	$\alpha$ -galactosidase A	Large and small vessel disease
Sickle-cell anaemia (autosomal recessive)	$\beta$ -haemoglobin	Large and small vessel disease, haemodynamic insufficiency
Homocystinuria (autosomal recessive)	Cystathione $\beta$ -synthase and others	Large and small vessel disease, cardioembolism, arterial dissection
MELAS (maternal)	Transfer RNA	Complex
Marfan syndrome (autosomal dominant)	Fibrillin 1	Cardioembolism and arterial dissection
Ehlers–Danlos syndrome (autosomal dominant)	Collagen type III	Arterial dissection

Gott-sei-Dank sind diese Krankheitsbilder relativ selten aber die Mechanismen sind einleuchtend

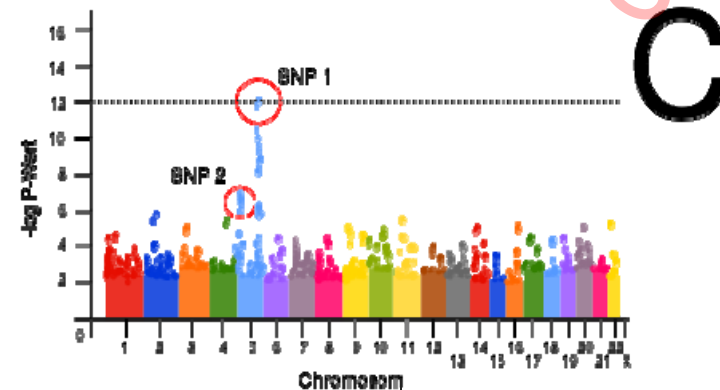
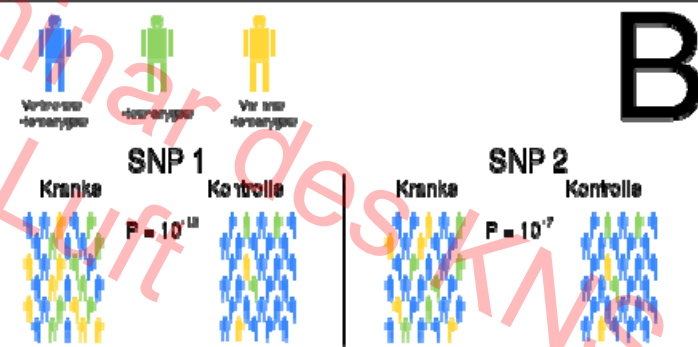
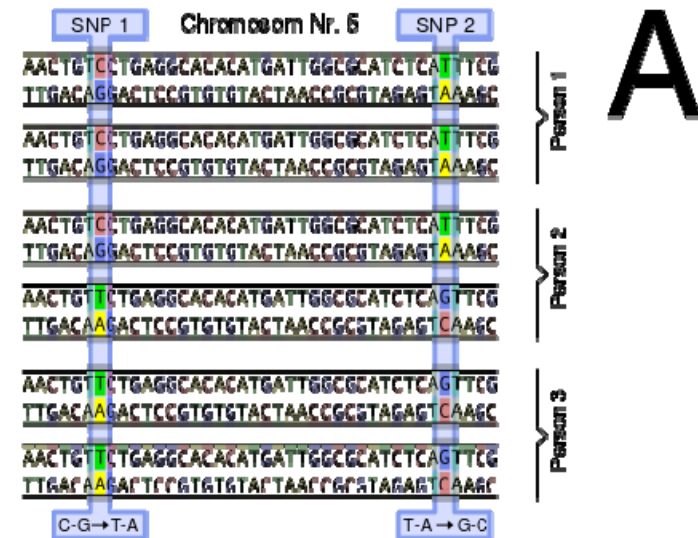
# Genomweite Assoziationsstudien

Eine genomweite Assoziationsstudie (GWAS) ist eine Untersuchung der genetischen Variation des Genoms eines Organismus – ausgelegt um einen bestimmten Phänotyp (zum Beispiel Schlaganfall) – mit bestimmten Haplotypen (bzw. Allelen) zu assoziieren.

Das Ziel von GWAS ist es also letztlich die Allele zu identifizieren, welche gemeinsam mit einem Merkmal auftreten. Dabei werden nicht die Gene direkt untersucht – v. a. aus ökonomischen Gründen nicht – sondern wohldefinierte Marker (SNP, Single Nucleotide Polymorphism).

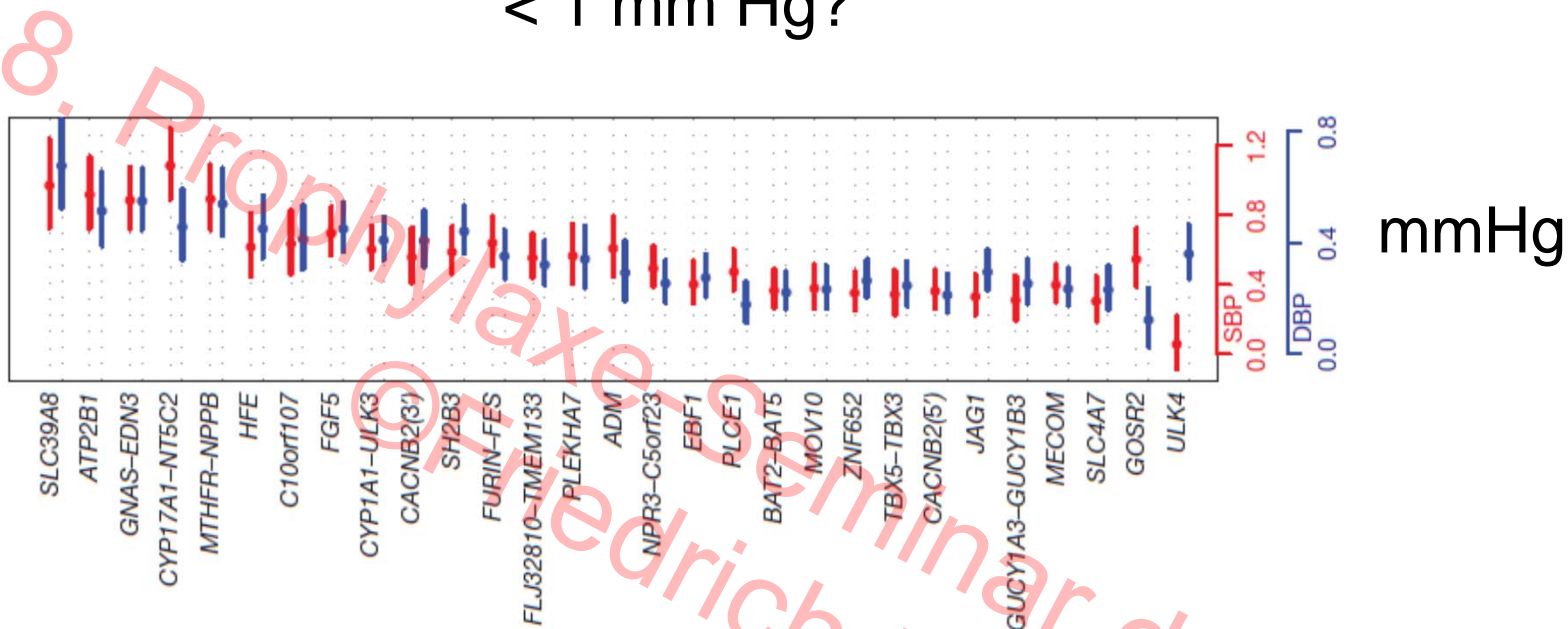
Um eine GWAS durchzuführen werden zwei Gruppen von Versuchsorganismen benötigt: Eine Vergleichsgruppe (also „normal“) und eine Gruppe, welche den Phänotyp von Interesse aufweist (also Schlaganfall). Dabei sagt GWAS aber nichts darüber aus, in welchem Zusammenhang das gefundene Allel nun konkret mit dem Phänotyp steht.

Der kausale Zusammenhang kann erst nach der Identifizierung solcher „Kandidaten-Genen“ mit molekularbiologischen und biochemischen Methoden erforscht werden.



# GWAS für Hypertonie

< 1 mm Hg?



Neue Metrik: Der genomische „Nutzlosigkeits-Index“ (GNI)

# der Autoren ÷ Effektgröße der besten Variante

$$400/1\text{mmHg} = 400$$

# GWAS für Schlaganfall gibt es viele

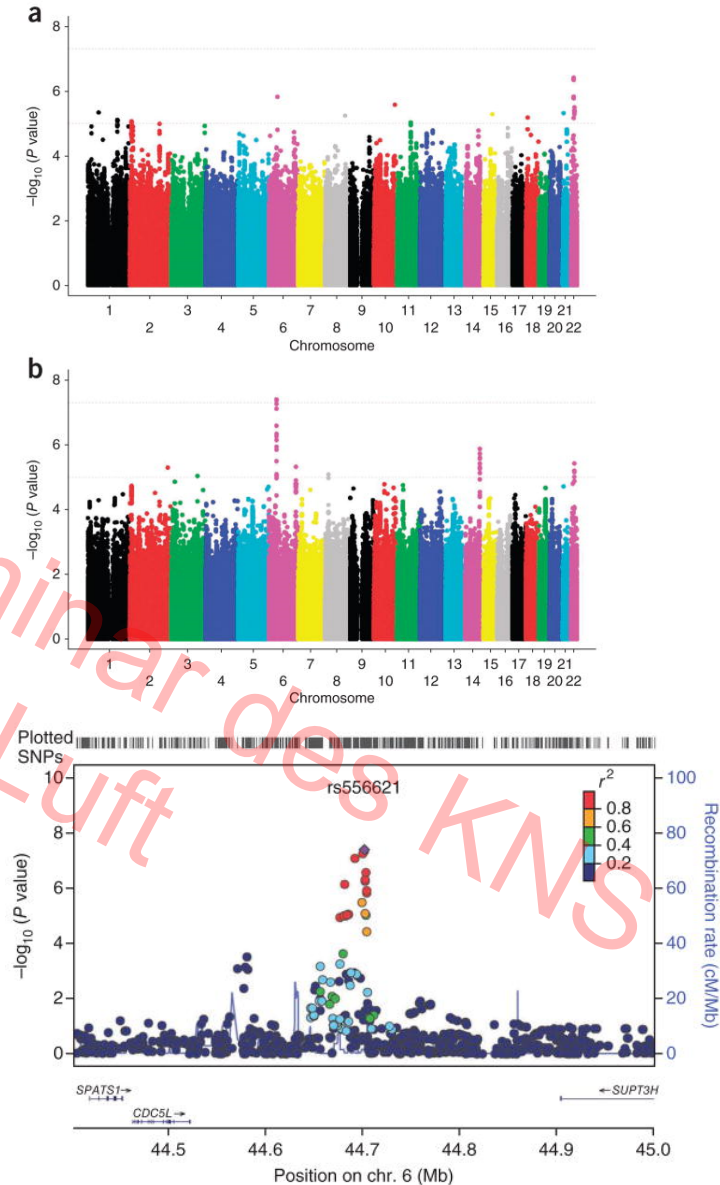
nature  
genetics

## Common variants at 6p21.1 are associated with large artery atherosclerotic stroke

Elizabeth G Holliday<sup>1,2</sup>, Jane M Maguire<sup>3-5</sup>, Tiffany-Jane Evans<sup>2,6</sup>, Simon A Koblar<sup>7,8</sup>, Jim Jannes<sup>7,8</sup>, Jonathan W Sturm<sup>5,9</sup>, Graeme J Hankey<sup>10,11</sup>, Ross Baker<sup>12,13</sup>, Jonathan Golledge<sup>14,15</sup>, Mark W Parsons<sup>4</sup>, Rainer Malik<sup>16</sup>, Mark McEvoy<sup>1,9,17</sup>, Erik Biros<sup>14</sup>, Martin D Lewis<sup>7,18</sup>, Lisa F Lincz<sup>4,6,19</sup>, Roseanne Peel<sup>1,9,17</sup>, Christopher Oldmeadow<sup>9,20</sup>, Wayne Smith<sup>9,17</sup>, Pablo Moscato<sup>2,21</sup>, Simona Barlera<sup>22</sup>, Steve Bevan<sup>23</sup>, Joshua C Bis<sup>24</sup>, Eric Boerwinkle<sup>25,26</sup>, Giorgio B Boncoraglio<sup>27</sup>, Thomas G Brott<sup>28</sup>, Robert D Brown Jr<sup>29</sup>, Yu-Ching Cheng<sup>30</sup>, John W Cole<sup>31,32</sup>, Ioana Cotlarciuc<sup>33</sup>, William J Devan<sup>34-36</sup>, Myriam Fornage<sup>25,26</sup>, Karen L Furie<sup>35,36</sup>, Sólveig Grétarsdóttir<sup>37</sup>, Andreas Gschwendtner<sup>16</sup>, M Arfan Ikram<sup>38-40</sup>, W T Longstreth Jr<sup>41-43</sup>, James F Meschia<sup>28</sup>, Braxton D Mitchell<sup>30</sup>, Thomas H Mosley<sup>44</sup>, Michael A Nalls<sup>45</sup>, Eugenio A Parati<sup>27</sup>, Bruce M Psaty<sup>24,41,46,47</sup>, Pankaj Sharma<sup>33</sup>, Kari Stefansson<sup>37,48</sup>, Gudmar Thorleifsson<sup>37</sup>, Unnur Thorsteinsdottir<sup>37,48</sup>, Matthew Traylor<sup>23</sup>, Benjamin F J Verhaaren<sup>38,40</sup>, Kerri L Wiggins<sup>24</sup>, Bradford B Worrall<sup>49</sup>, The Australian Stroke Genetics Collaborative<sup>50</sup>, The International Stroke Genetics Consortium<sup>50</sup>, The Wellcome Trust Case Control Consortium 2<sup>50</sup>, Cathie Sudlow<sup>51,52</sup>, Peter M Rothwell<sup>53</sup>, Martin Farrall<sup>54,55</sup>, Martin Dichgans<sup>16</sup>, Jonathan Rosand<sup>34-36</sup>, Hugh S Markus<sup>23</sup>, Rodney J Scott<sup>2,6,56,57</sup>, Christopher Levi<sup>4,57</sup> & John Attia<sup>1,2,57</sup>

# Assoziationen bestimmen nicht Ursachen

Genome-wide association studies (GWAS) have not consistently detected replicable genetic risk factors for ischemic stroke, potentially due to etiological heterogeneity of this trait. We performed GWAS of ischemic stroke and a major ischemic stroke subtype (large artery atherosclerosis, LAA) using 1,162 ischemic stroke cases (including 421 LAA cases) and 1,244 population controls from Australia. Evidence for a genetic influence on ischemic stroke risk was detected, but this influence was higher and more significant for the LAA subtype. We identified a new LAA susceptibility locus on chromosome 6p21.1 (rs556621: odds ratio (OR)=1.62,  $P=3.9 \times 10^{-8}$ ) and replicated this association in 1,715 LAA cases and 52,695 population controls from 10 independent population cohorts (meta-analysis replication OR=1.15,  $P=3.9 \times 10^{-4}$ ; discovery and replication combined OR=1.21,  $P=4.7 \times 10^{-8}$ ). This study identifies a genetic risk locus for LAA and shows how analyzing etiological subtypes may better identify genetic risk alleles for ischemic stroke.



Aber, Effektgröße, Sensitivität, Spezifität, Vorhersagekraft, werden nie erwähnt.

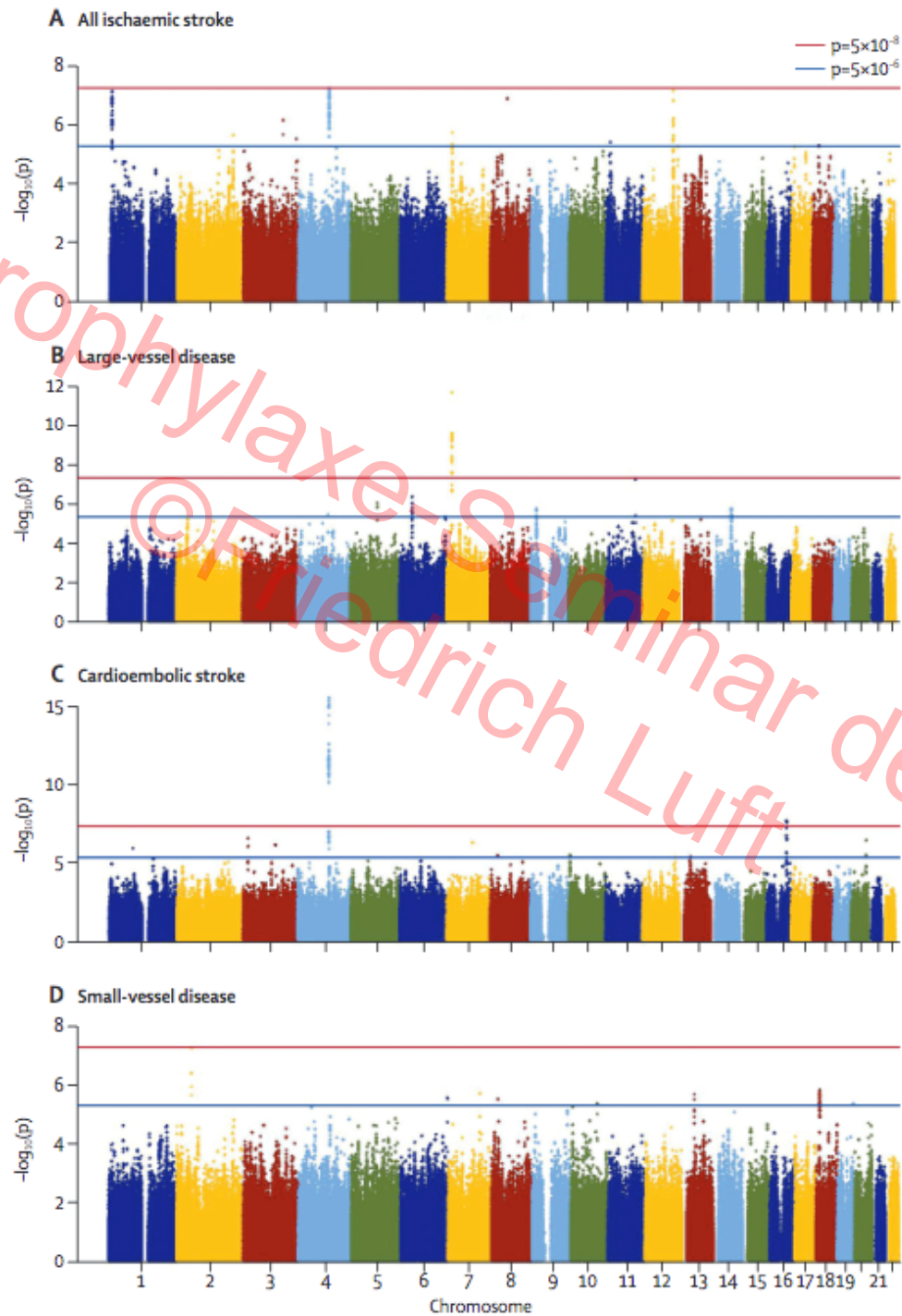
# Meta-Analysen sind die Metaphysik der Medizin



## Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE Collaboration): a meta-analysis of genome-wide association studies

Matthew Traylor, Martin Farrall, Elizabeth G Holliday, Cathie Sudlow, Jemma C Hopewell, Yu-Ching Cheng, Myriam Fornage, M Arfan Ikram, Rainer Malik, Steve Bevan, Unnur Thorsteinsdottir, Mike A Nalls, WT Longstreth, Kerri L Wiggins, Sunaina Yadav, Eugenio A Parati, Anita L DeStefano, Bradford B Worrall, Steven J Kittner, Muhammad Saleem Khan, Alex P Reiner, Anna Helgadottir, Sefanja Achterberg, Israel Fernandez-Cadenas, Sherine Abboud, Reinhold Schmidt, Matthew Walters, Wei-Min Chen, E Bernd Ringelstein, Martin O'Donnell, Weang Kee Ho, Joanna Pera, Robin Lemmens, Bo Norrving, Peter Higgins, Marianne Benn, Michele Sale, Gregor Kuhlenbäumer, Alexander S F Doney, Astrid M Vicente, Hossein Delavaran, Ale Algra, Gail Davies, Sofia A Oliveira, Colin N A Palmer, Ian Deary, Helena Schmidt, Massimo Pandolfo, Joan Montaner, Cara Carty, Paul I W de Bakker, Konstantinos Kostulas, Jose M Ferro, Natalie R van Zuydam, Einar Valdimarsson, Børge G Nordestgaard, Arne Lindgren, Vincent Thijs, Agnieszka Slowik, Danish Saleheen, Guillaume Paré, Klaus Berger, Gudmar Thorleifsson, The Australian Stroke Genetics Collaborative, Wellcome Trust Case Control Consortium 2 (WTCCC2), Albert Hofman, Thomas H Mosley, Braxton D Mitchell, Karen Furie, Robert Clarke, Christopher Levi, Sudha Seshadri, Andreas Gschwendtner, Giorgio B Boncoraglio, Pankaj Sharma, Joshua C Bis, Solveig Gretarsdottir, Bruce M Psaty, Peter M Rothwell, Jonathan Rosand, James F Meschia, Kari Stefansson, Martin Dichgans, Hugh S Markus, on behalf of the International Stroke Genetics Consortium

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# Phosphodiesterasen bauen cAMP und cGMP ab. Die bekannteste ist die PDE5A – Ziel von „Viagra“.



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journal homepage: [www.elsevier.com/locate/jns](http://www.elsevier.com/locate/jns)



Review article

## Phosphodiesterase4D (PDE4D) – A risk factor for atrial fibrillation and stroke?



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<sup>a</sup> Department of Neurology, Copenhagen University Hospital Glostrup, DK-2600 Glostrup, Denmark

<sup>b</sup> Acute Stroke Unit, Copenhagen University Hospital Glostrup, DK-2600 Glostrup, Denmark

<sup>c</sup> Lundbeck Foundation Center for Neurovascular Signaling, Glostrup Research Institute, Glostrup Hospital, Denmark

<sup>d</sup> Dept. Neurology, Neurovascular Research Unit, Copenhagen, University Hospital Herlev, Denmark

Gretarsdottir et al.  
Nat Genet 2003

### Highlights

- Mutations in PDE4D are associated with large artery and cardio-embolic stroke.
- PDE4 plays a role in development of atherosclerosis involved in large artery stroke.
- PDE4D mutations increase risk of atrial fibrillation.
- PDE4 modulators are potential drugs in large artery and cardio-embolic stroke.



## Phänotypische Arbeit über 20 Jahren

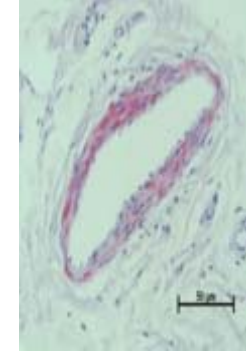
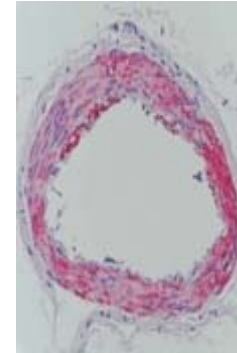
Aldo, Pheo, Cushing's, thyroid, PTH, Lipide,  
Nierenarterien etc. - Alles negative

Salzesensitivität nach akzeptierten Protokollen negativ

Wenig Zielorganschädigung

Baroreceptor Blutdruckpufferung war nicht normal

Fibroblasten wuchsen schneller.



Schuster et al. Hypertension 1996

Naraghi et al. Stroke 1997

Schuster et al. Kidney Int 1998

Hattenbach et al. Br J Ophthalmol 1998

Jordan et al. Circulation 2000

Bähring et al. Hypertension 2004

Bähring et al. Hypertension 2008

Toka et al. Hypertension 2010

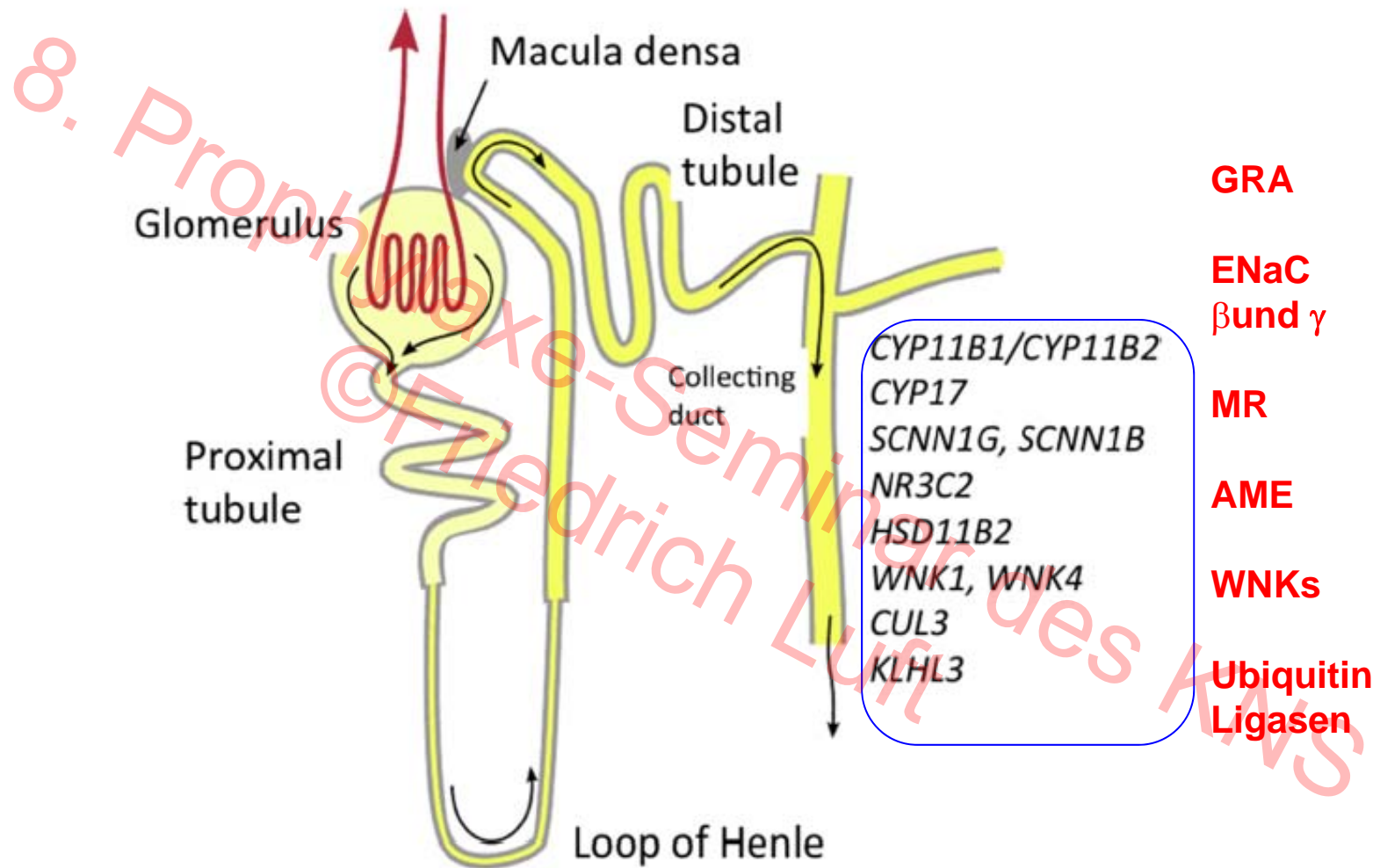
Toka et al. Hypertension 2015



Kopplungsintervall (10 MB)  
Chromosom 12P

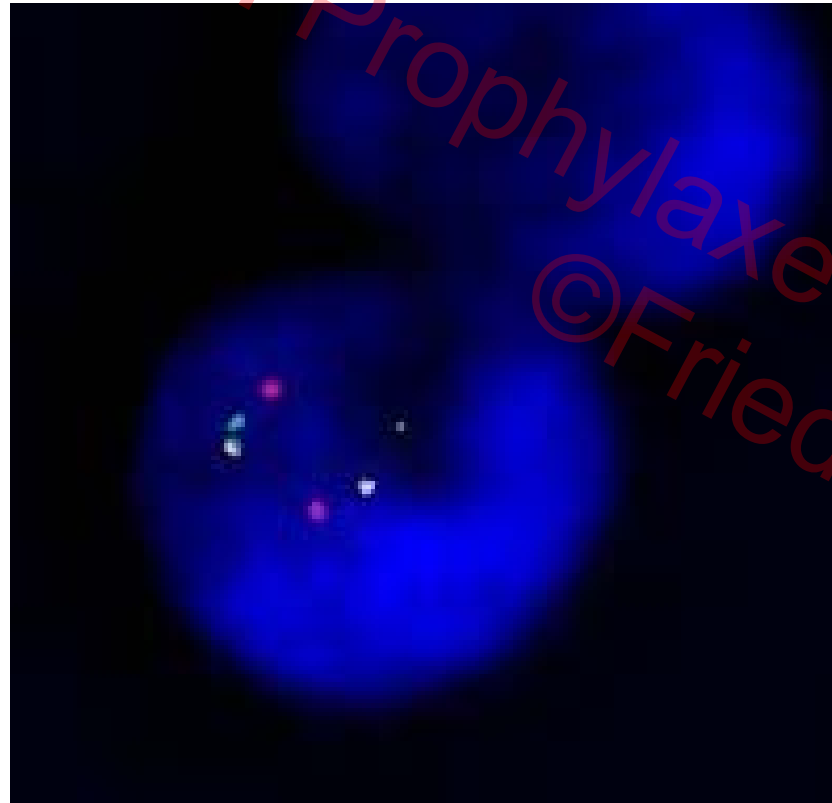
Alle Familien mit HTNB haben diese "Inversion"

# Die monogenen Hypertonieformen beruhen auf NaCl Transport



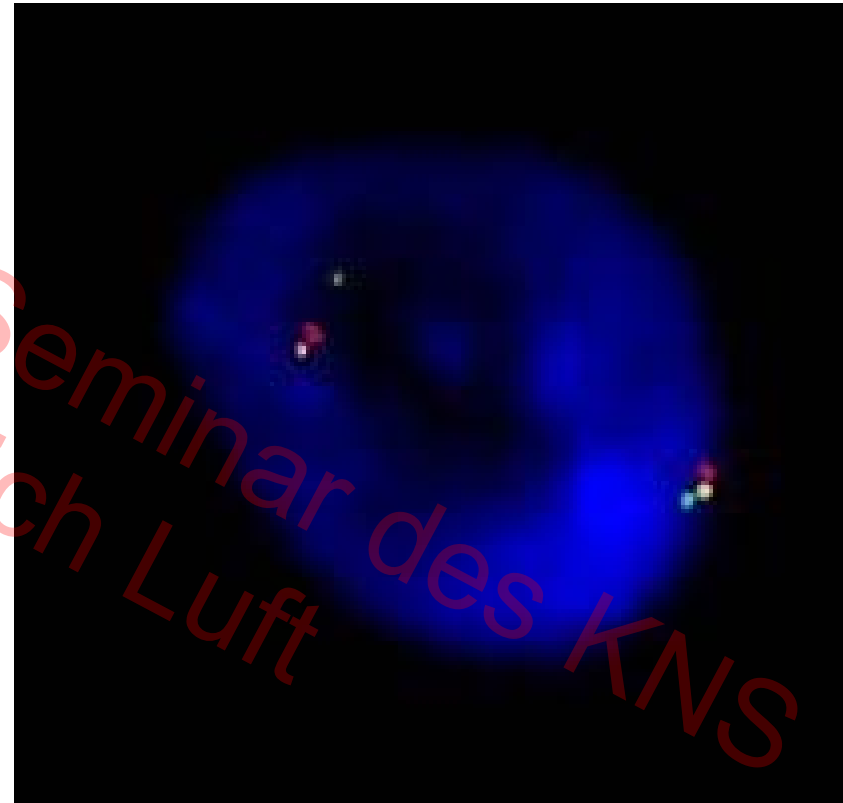
11-β Hydroxylase-Aldosteronsynthese chimerisches Gen Syndrom  
ENaC Untereinheiten, MR Rezeptor aktivierende Mutation, Lakritze-Syndrom,  
die “with-no-lysine” Kinasen, Cullin und Kelch Ubiquitinligasen die WNKs regulieren

# Interphase FISH innerhalb der INDEL Region



BAC clone order

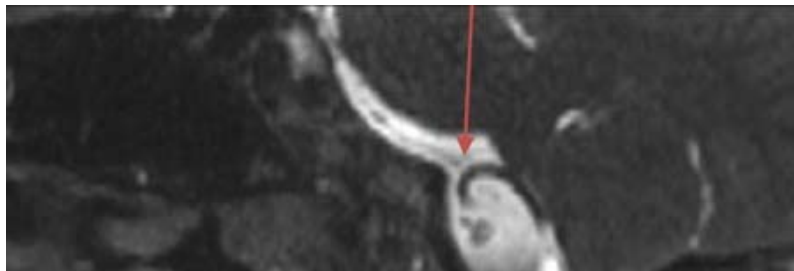
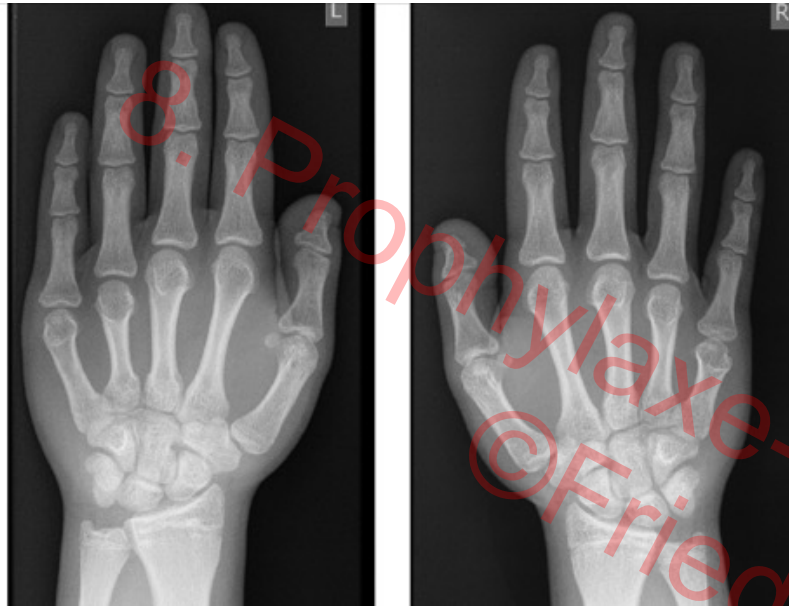
96K9 284C17 345P1



BAC clone order

184C8 96K9 284C17

# Geboren Stuttgart 1997

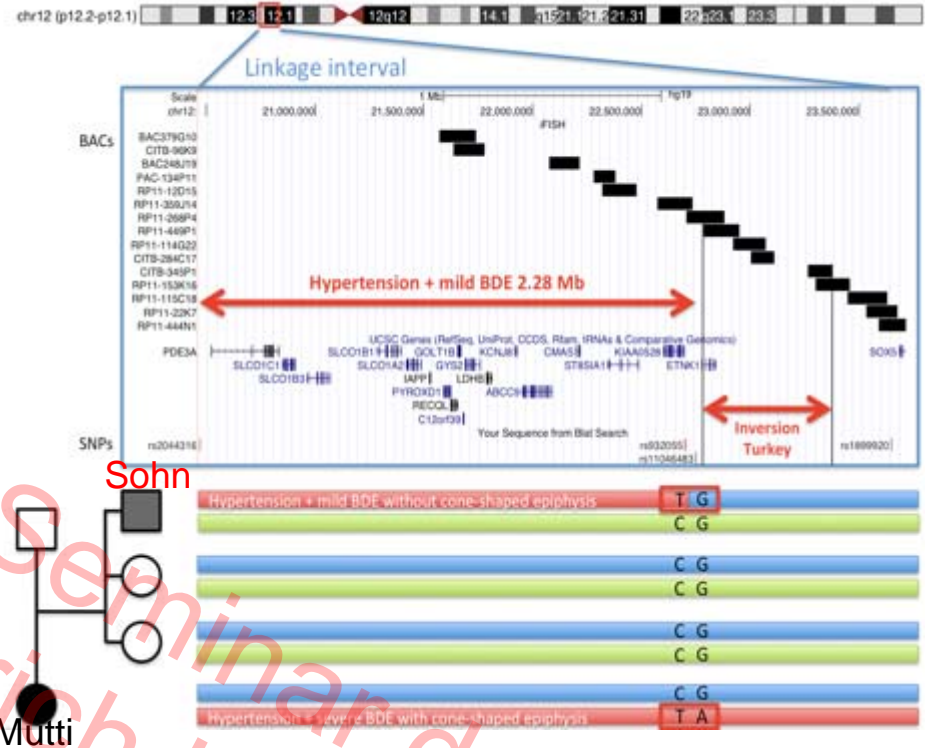


BP 150/90 mm Hg; Alter 15 Jahre

Er hat die Finger, er hat den Blutdruck  
aber die Inversion hat er nicht.

Also, wir fangen wieder von Vorne an.

Die DFG wird vertröstet.



Eine einzelne Rekombination

PDE3A

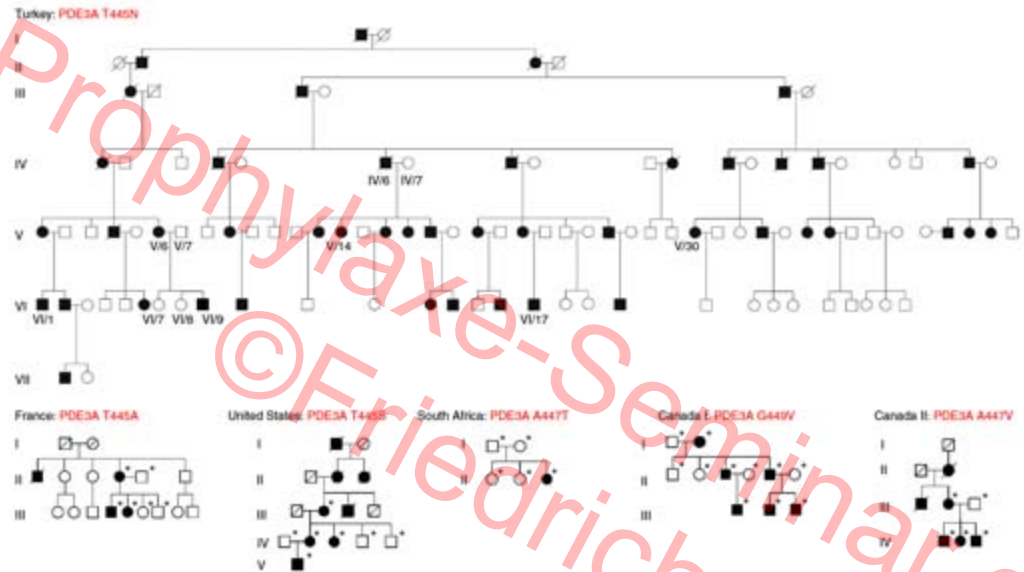
Viele "Indels"



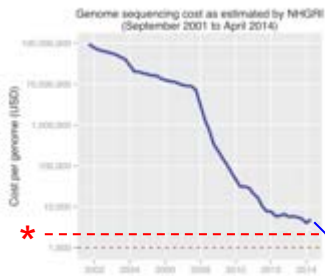
Kopplungsintervall (10 MB)  
Chromosom 12P

# Also machten wir Massensequenzierung an den 6 Familien

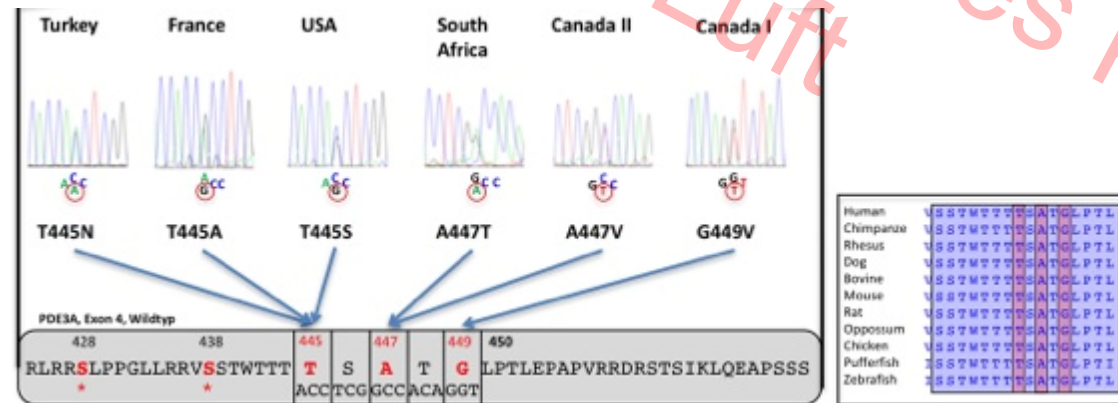
8. Prophylaxe-Seminar des KNS



Toka et al.  
Ann Intern Med 1998



Kosten sind gesunken  
auf Kolonspie Bereich

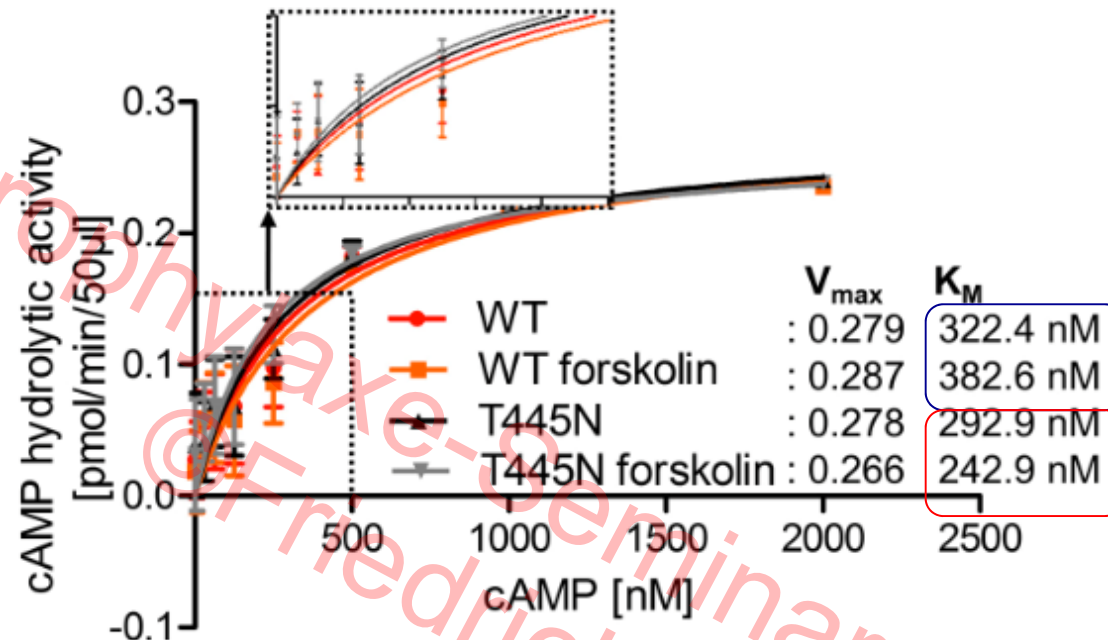


Phosphodiesterase 3A

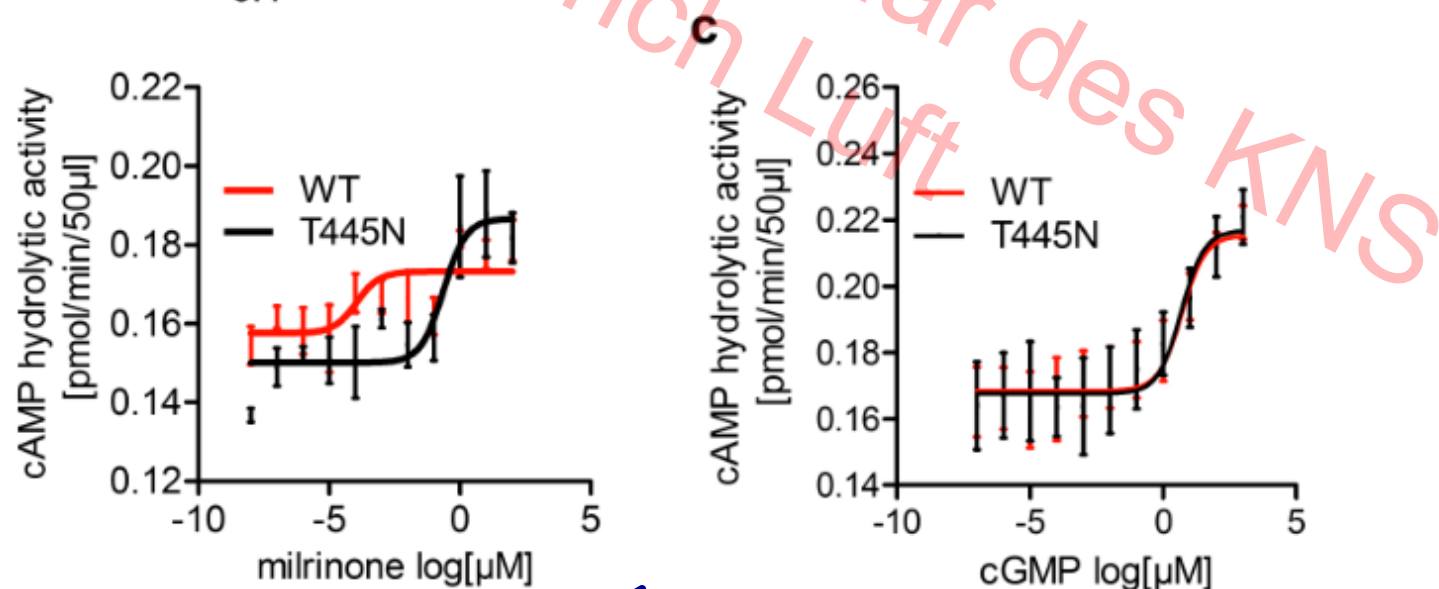
Maass et al. Nat Genet 2015

# Michaelis-Menten Kinetik und $IC_{50}$ Bestimmungen

Erhöhte Funktion  
(gain-of-function)

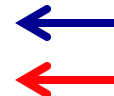


Increased affinity for cAMP



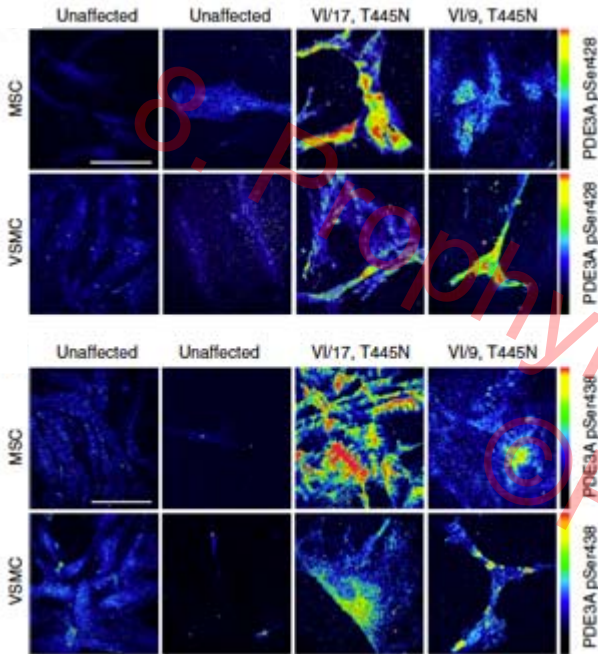
More milrinone necessary to inhibit

$IC_{50}$  WT :  $1.12 \times 10^{-4} \mu M$   
 $IC_{50}$  T445N:  $0.234 \mu M$

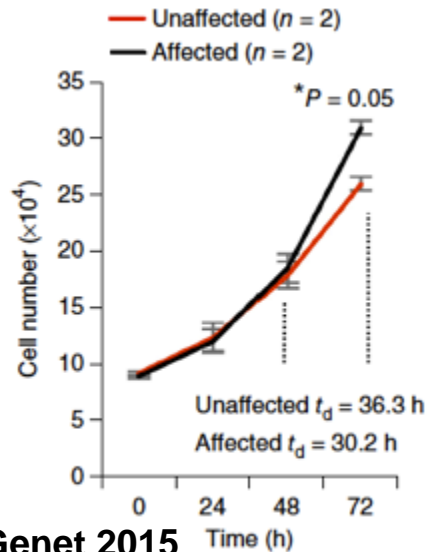


$IC_{50}$  WT :  $5.164 \mu M$   
 $IC_{50}$  T445N:  $4.780 \mu M$

# Woher die kurzen Finger?

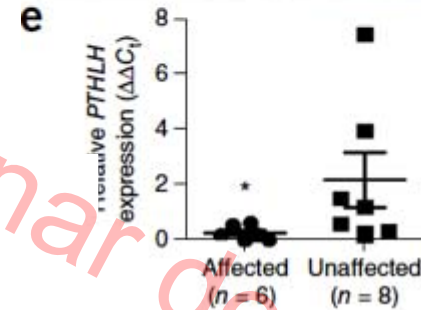
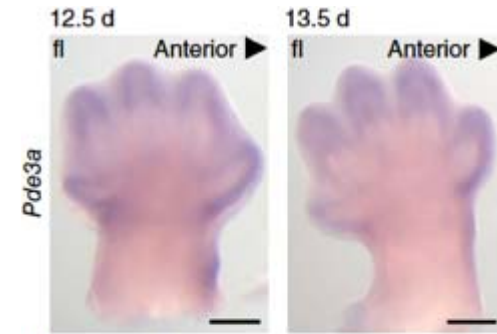


Phos. Unterschiede  
an 428 and 438?



VSMC  
Proliferation?

Maass et al. Nat Genet 2015

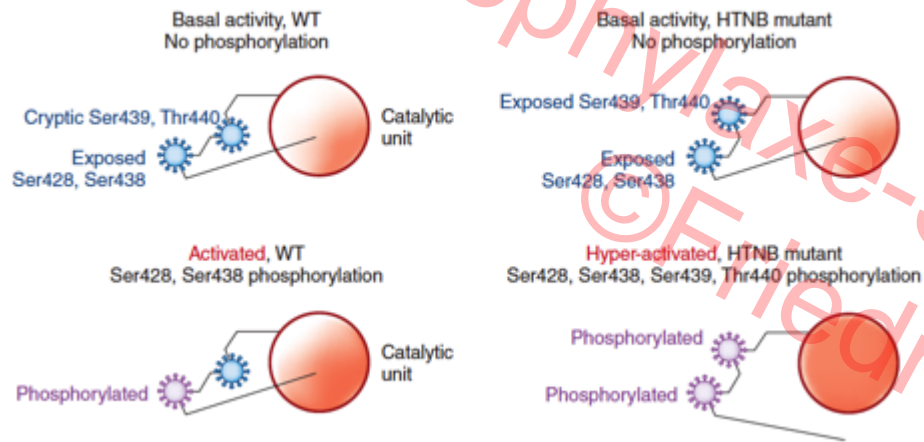


Maass et al. Hum Mol Genet 2009  
Maass et al. J Clin Invest 2012  
Maass et al. EMBO J 2017

*PTHLH* enkodiert Parathormone-  
related Peptide (PTHrP)

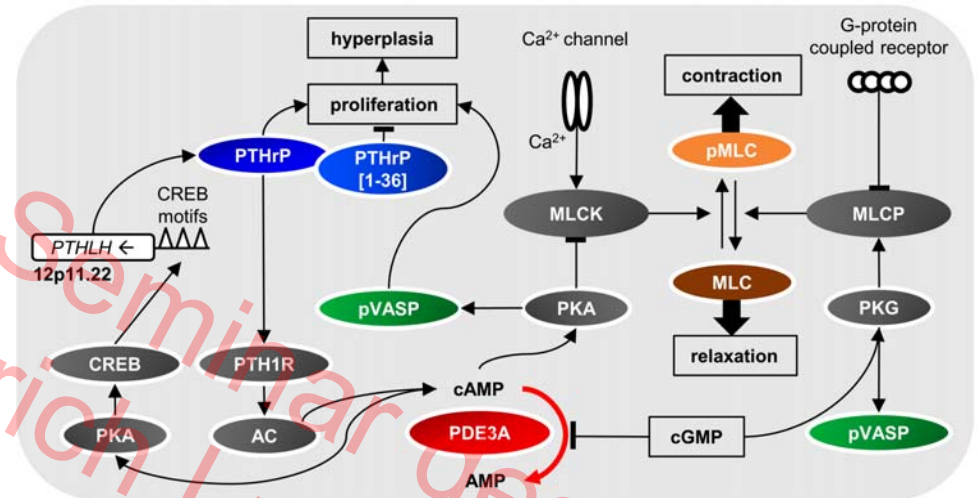
Mutiertes *PTHLH*  
verursacht Brachydaktylie Typ E

# Wie könnte dies alles Funktionieren?



HTNB-associated mutations alter PDE3A activity. (a) The PDE3A ORF encodes a 1,141-residue protein. Three distinct isoforms are generated by use of alternate translation initiation sites (note that even PDE3A1 is truncated). PDE3A3 is unaffected by HTNB-associated mutations and phosphorylation. Only PDE3A1 is phosphorylated by AKT-PKB. (b) Schematic illustrating hyper-activation of HTNB mutants by PKA and PKC. WT, wild type.

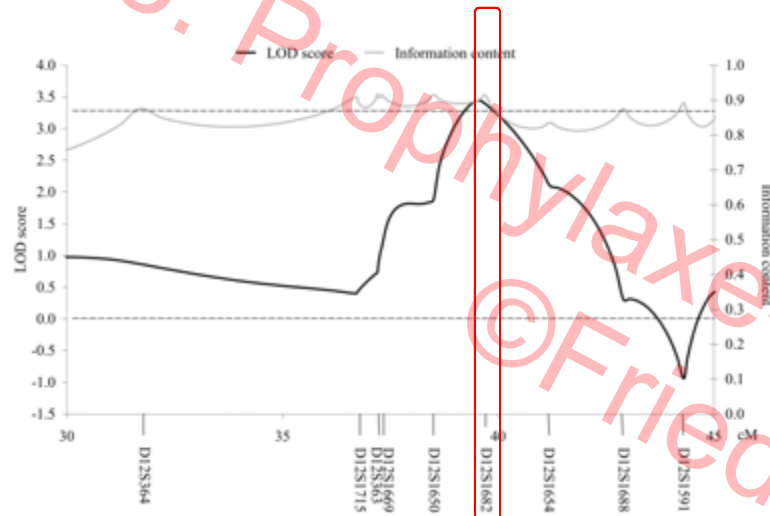
cAMP responsive element binding protein



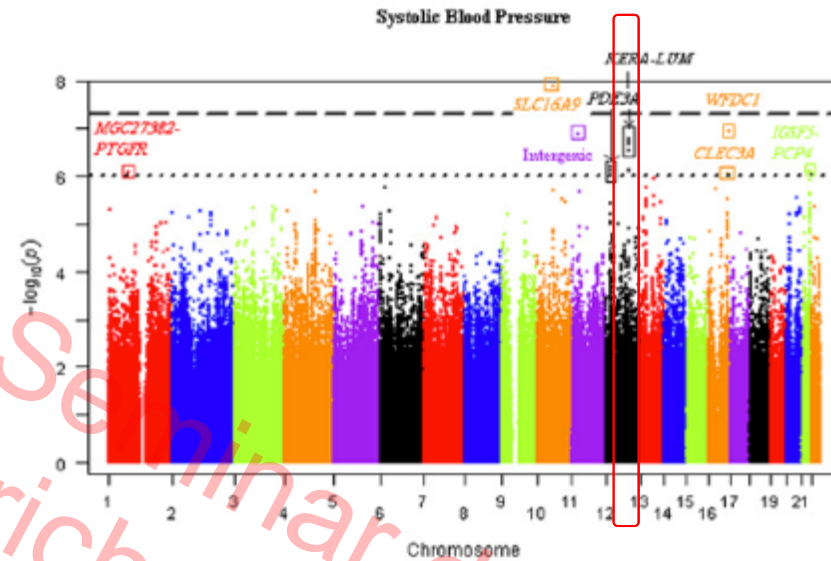


# Relevanz zu Hypertonie und Schlaganfall?

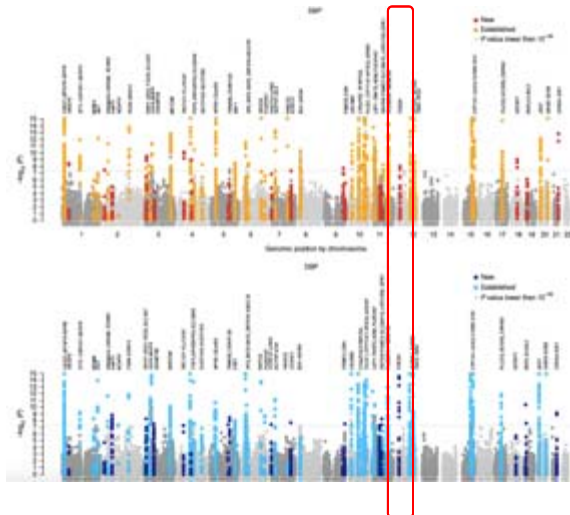
Gong et al. Hum Mol Genet 2003



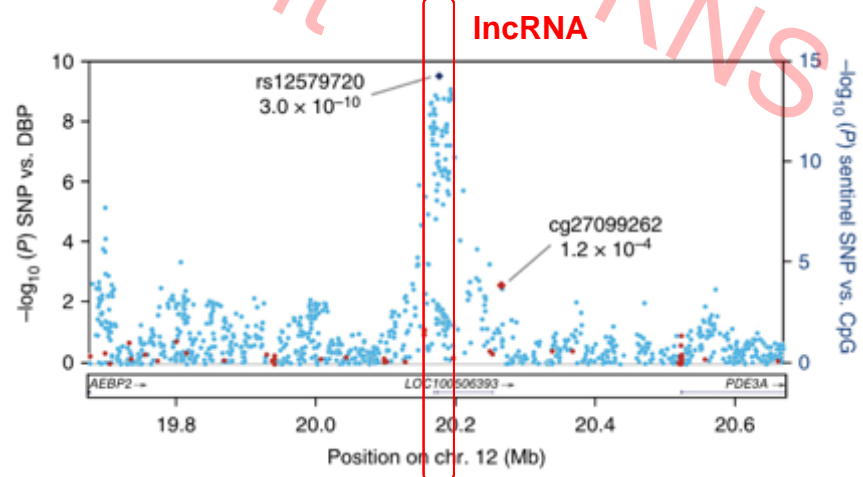
Simino et al. Front Genet 2013



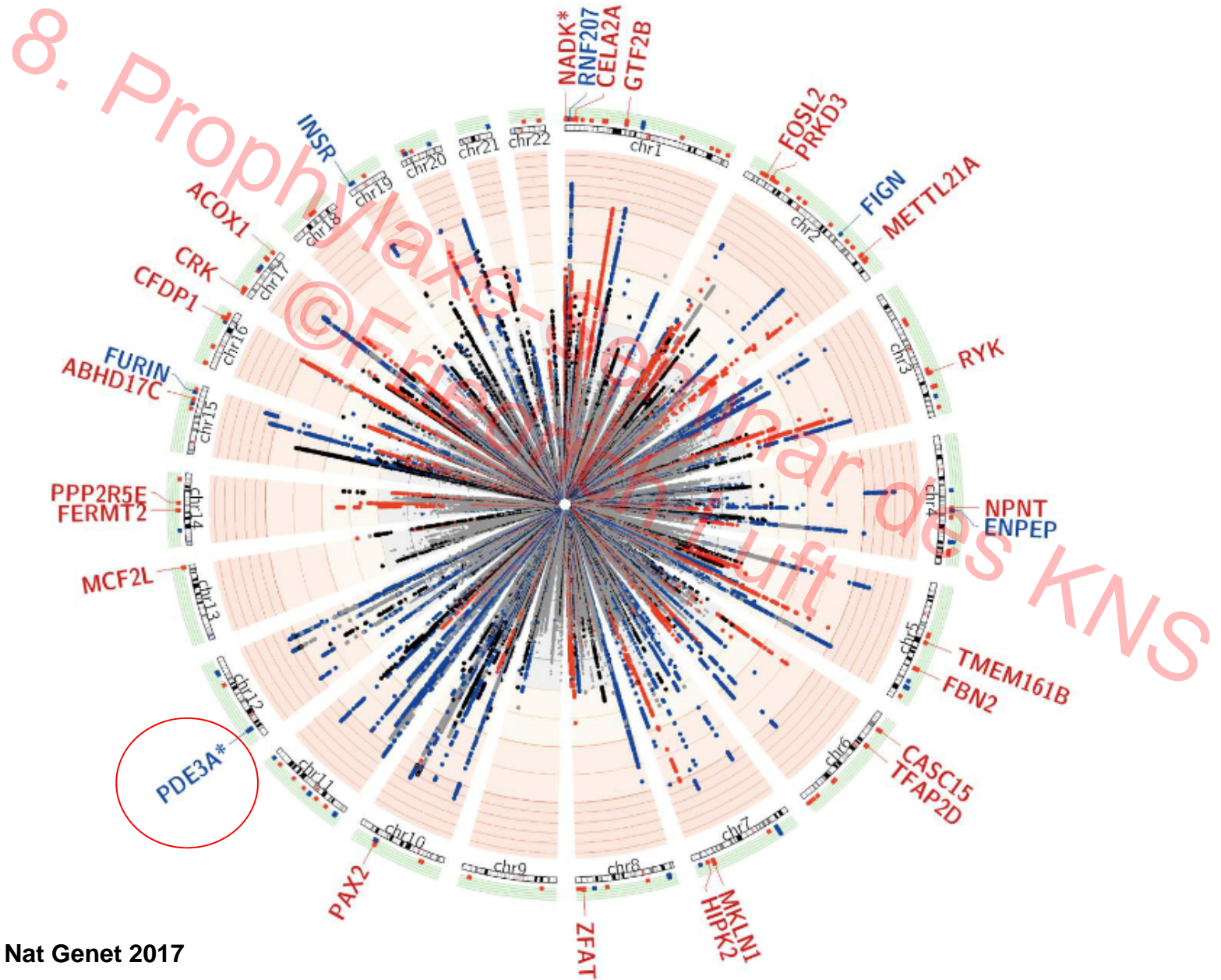
Ehret et al. Nat Genet 2016



Kato et al. Nat Genet 2015



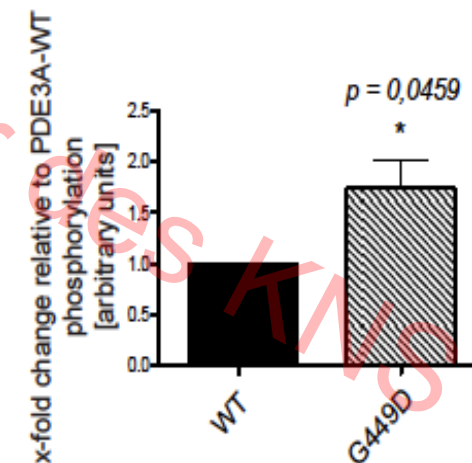
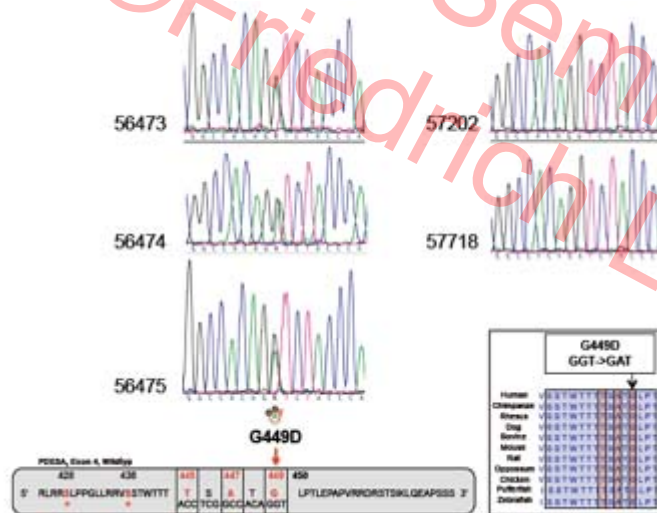
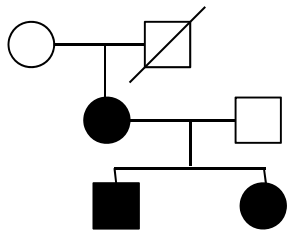
GWAS #4



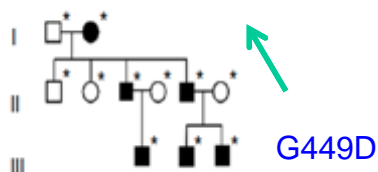
# Nun kontaktieren uns Patienten!

Sept. 11, 2015. 42-year old Dutch male teacher with hypertension. Short stature (height 1.53 m), brachydactyly, hands and feet. Patient tells doctor: "I have autosomal-dominant hypertension with brachydactyly (HTNB OMIM 112410)"; my sister (32 year-old dancer) has this too.

Has type E brachydactyly, PICA loop, and his sister has the same.

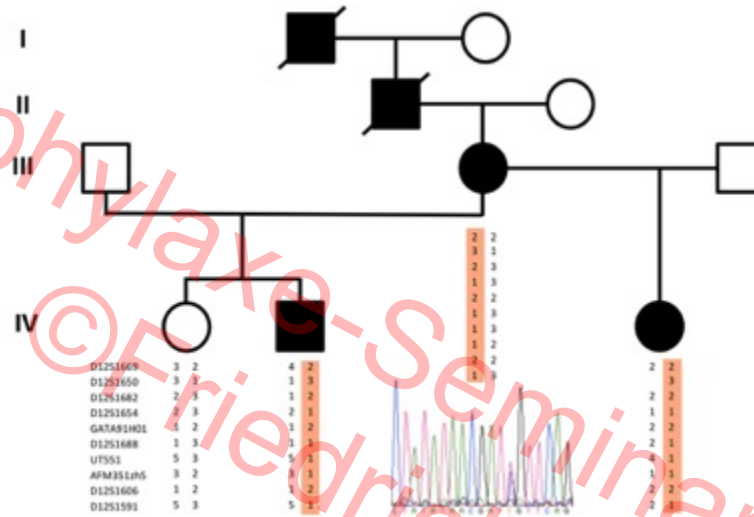


Canada I: PDE3A G449V



# Neuer Fall aus New Zealand

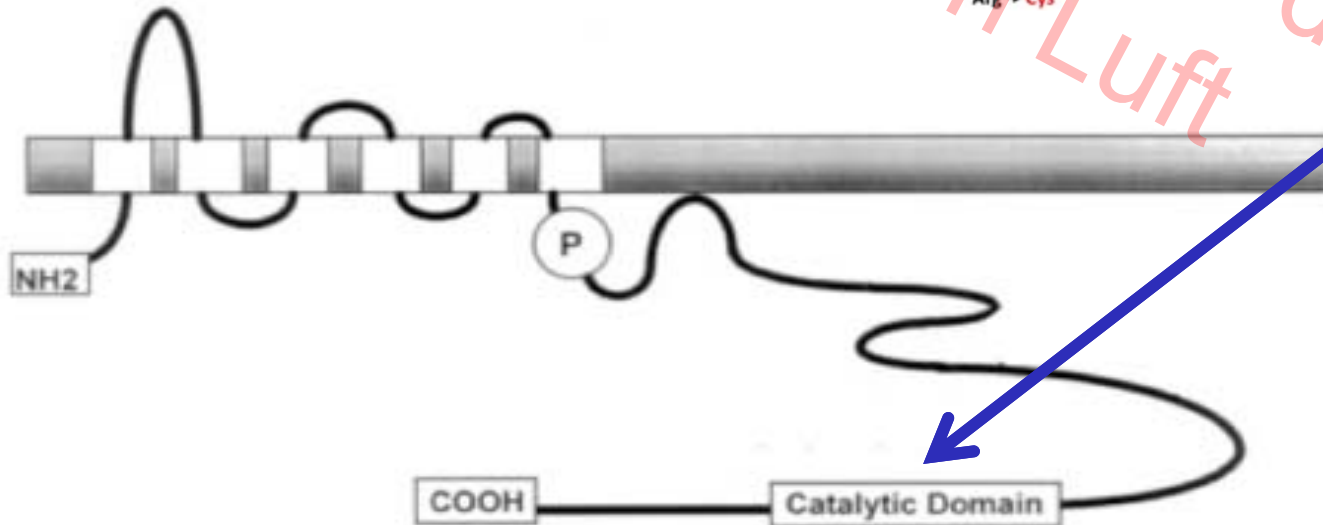
8. Prophylaxe-Seminar des Friedrich Luft



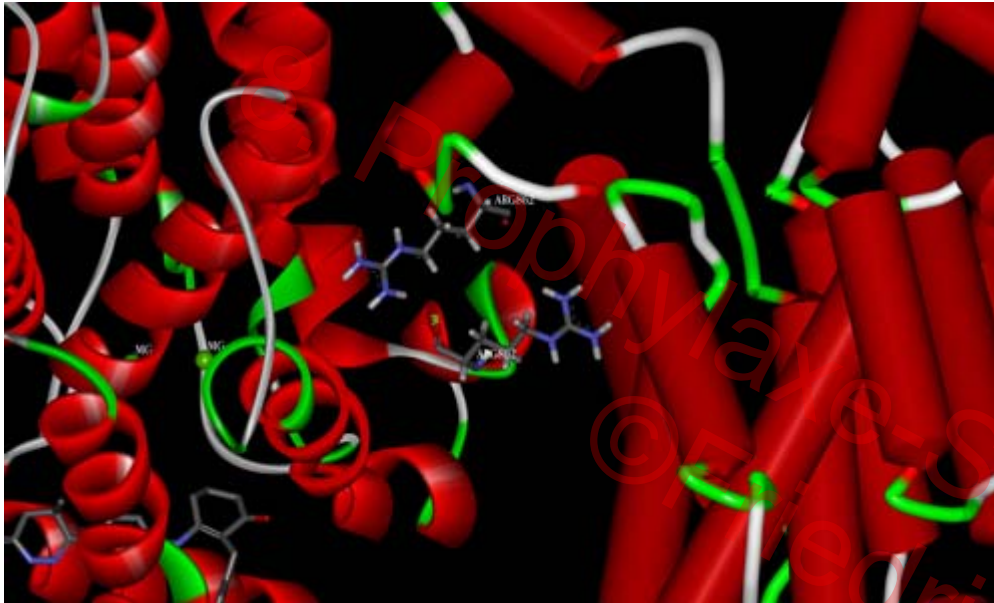
Family from NZ



BP 202/130



# Dimerisierung bestimmt Aktivität



Wild-typ katalytische Domäne mit zwei Arginine

Mutatierte katalytische Domäne mit zwei Cysteine, die disulfid Brücken bilden können.



Effekt bewegt Kette A näher an Kette B.

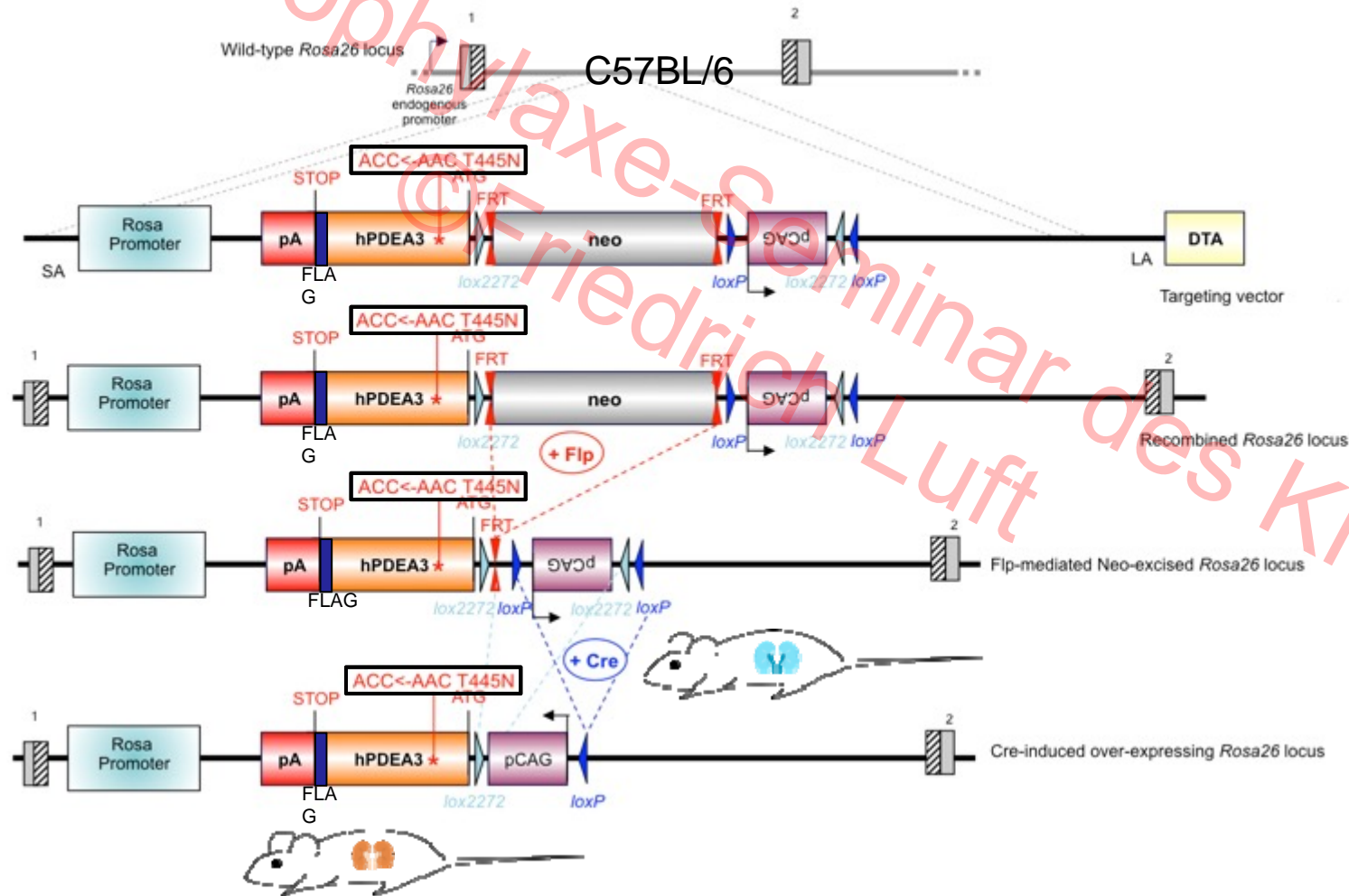
# ***Durch Blutdrucksenkung ist der Schlaganfall verschwunden***

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# Mäuse sind nicht immer gehorsam

8. Prophylaxe-Seminar Luft des KNS  
Mouse model: 1st quarter 2018



**Klussmann Labor, Luft Labor, Bader Labor,  
Hübner Labor und alle sind willkommen**

**8. (Unten unseren PKA-cAMP-cGMP Club)**

