Viszeralmedizin 2015
16.-19. September
Leipzig

Genetische Grundlagen, neue Erkenntnisse der Forschung und Besonderheiten des Krankheitsverlaufs

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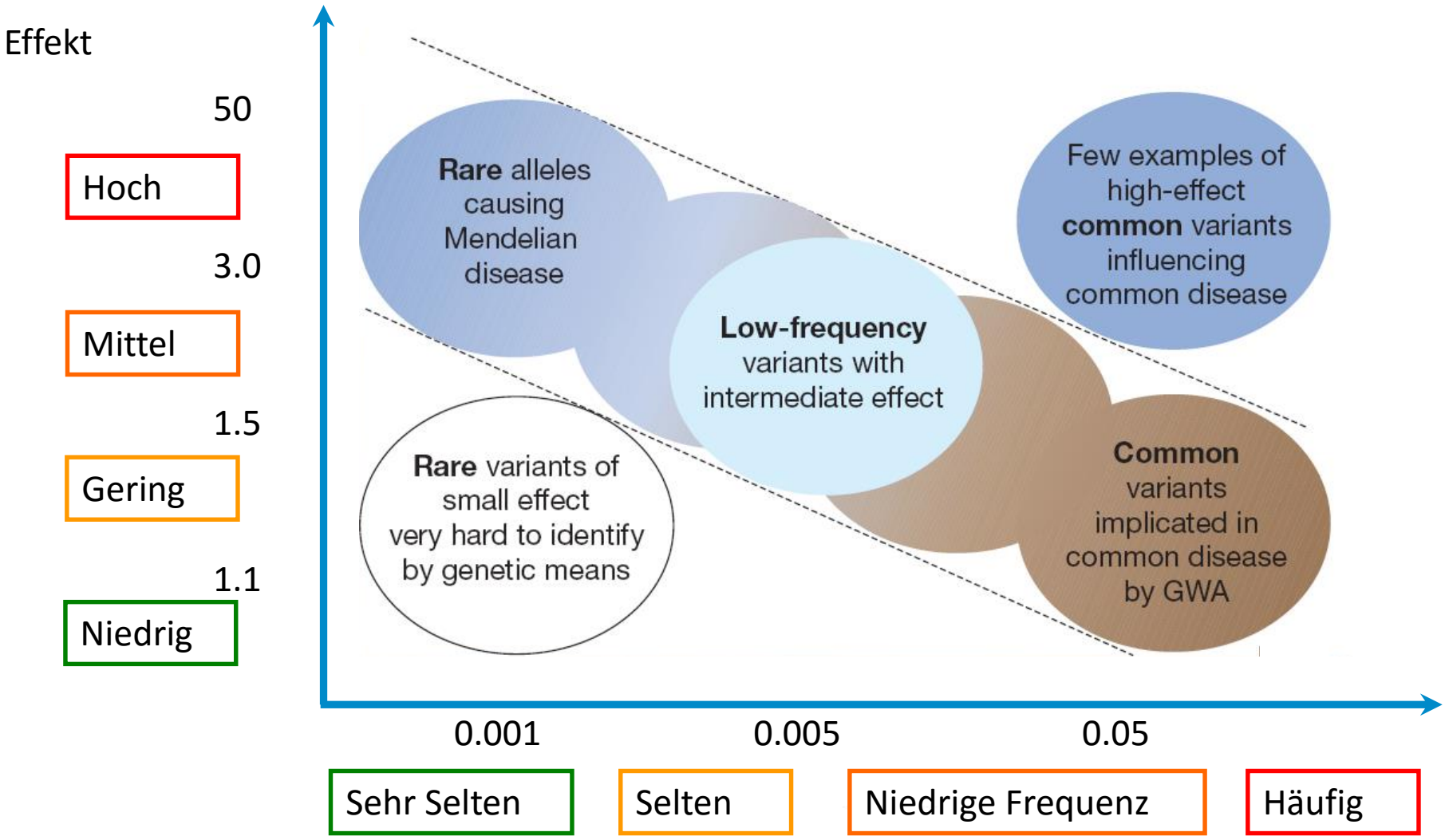
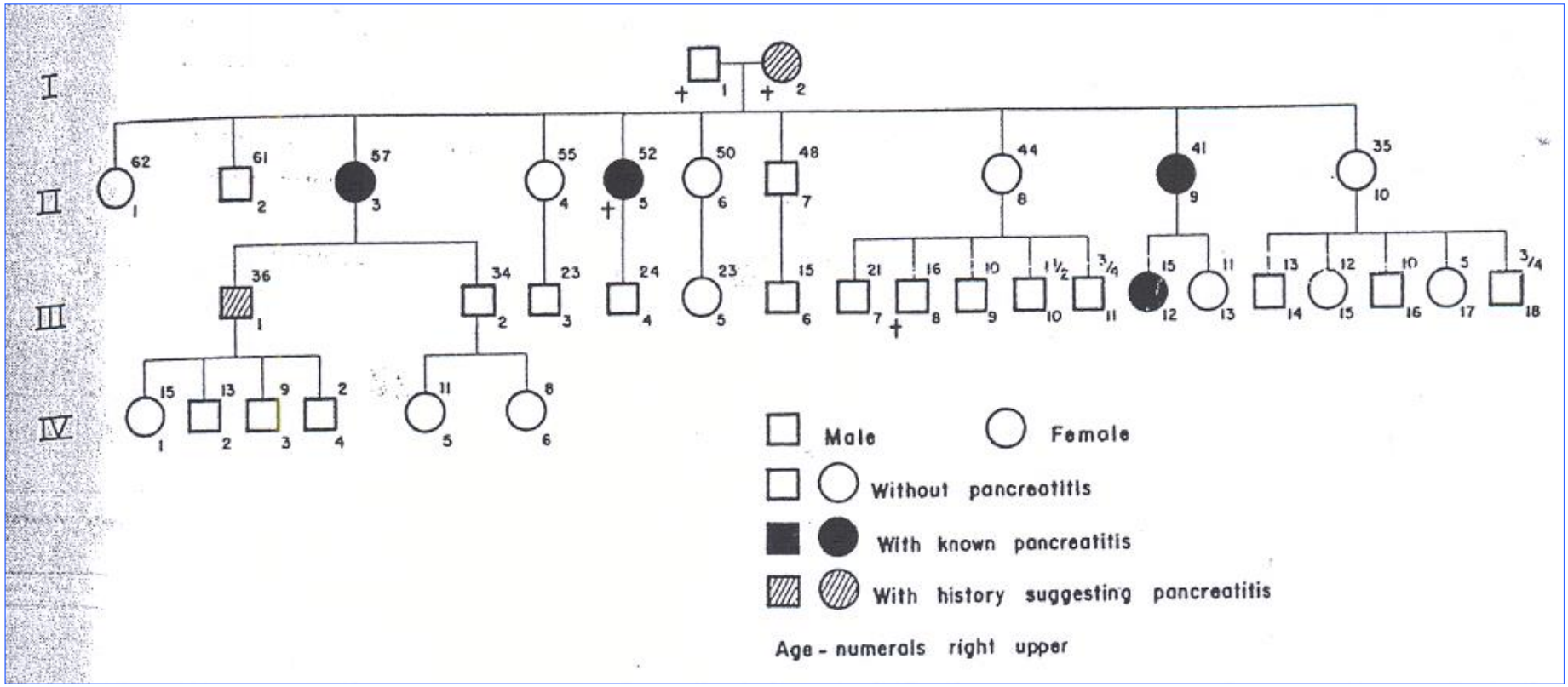
Genetische Studien



Manolio *et al.*, Nature 2009

Hereditäre Pankreatitis



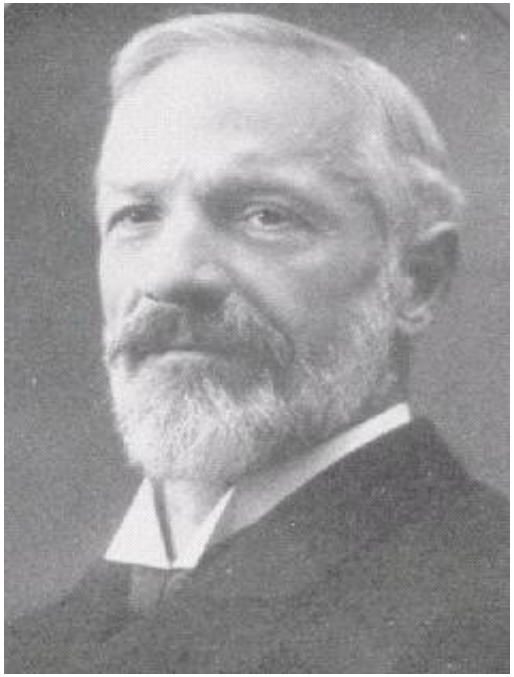
Comfort and Steinberg, Gastroenterology 1952

Pathogenese

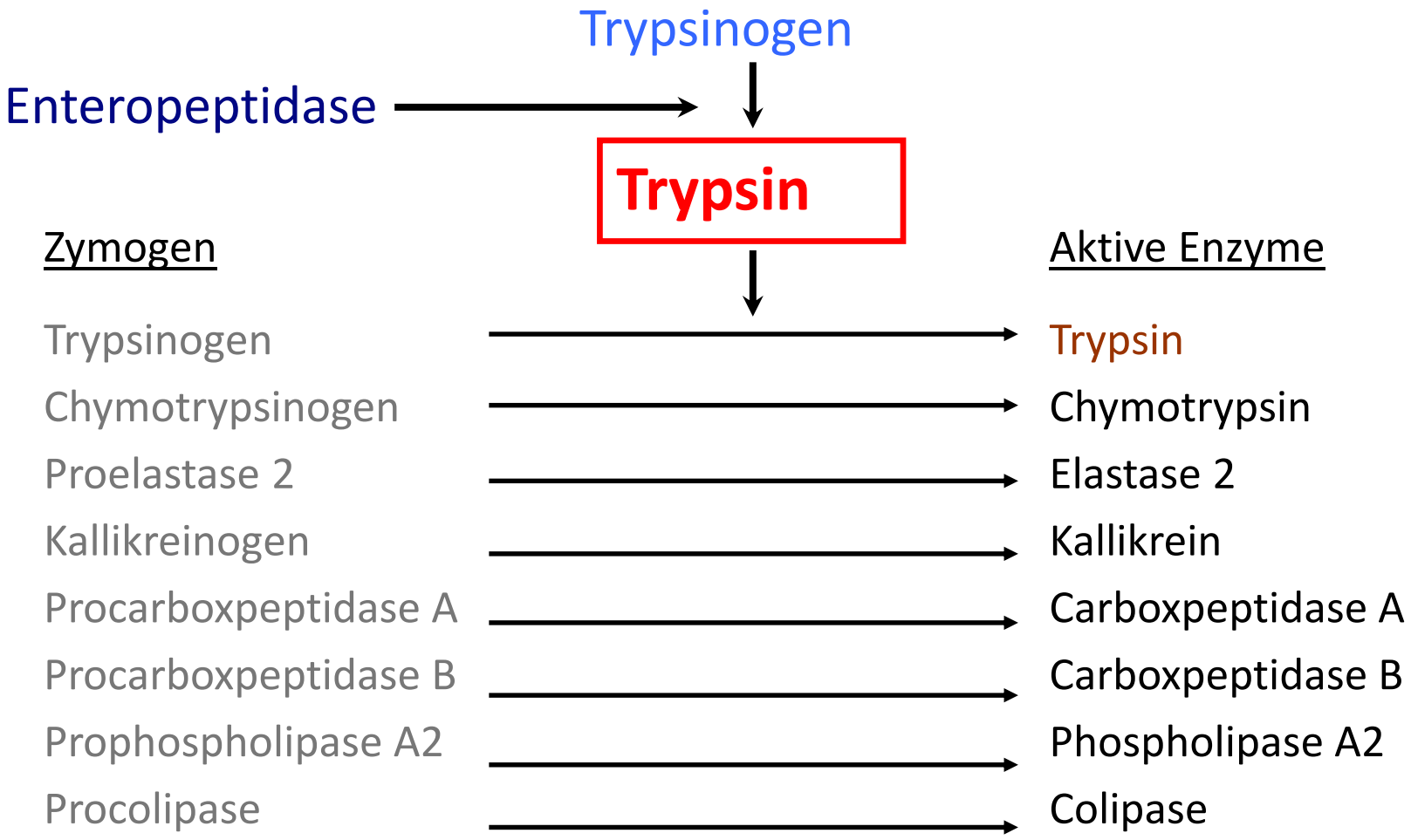
Hans Chiari (*1851-†1916)

"…eine herdweise Nekrose des Pankreas durch Autodigestion entstehen könne, an die sich eine reactive Pancreatitis interstitialis chronica anschliesst…"

Über Selbstverdauung des menschlichen Pankreas.
Hans Chiari, Zeitschrift für Heilkunde 1896;17:69-96



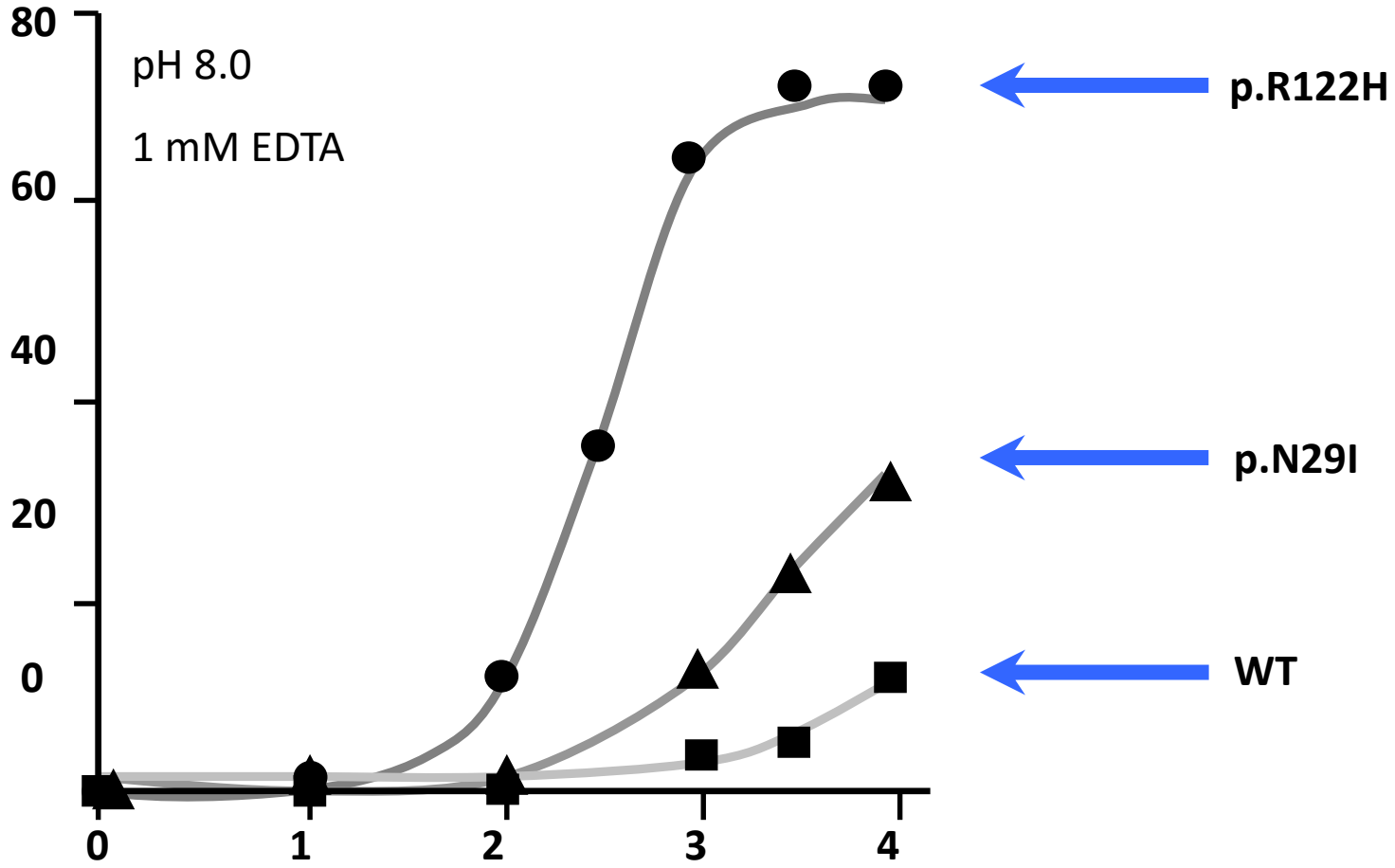
Verdauungsenzymkaskade



Kationisches Trypsinogen - PRSS1

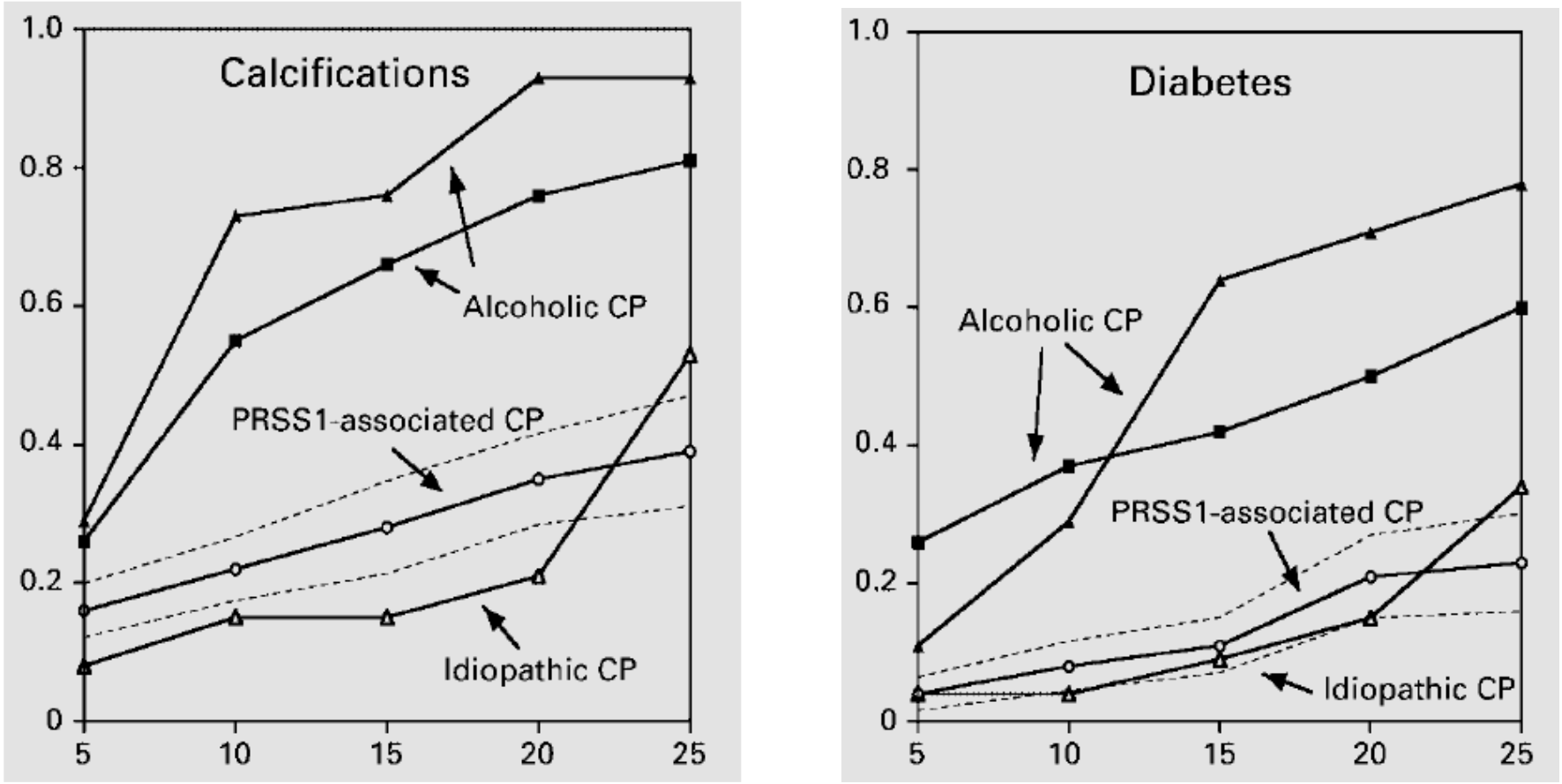
Modified from Whitcomb *et al.*, Nat Genet 1996

Gesteigerte Autoaktivierung - PRSS1



Sahin-Tóth & Tóth, Biochem Biophys Res Commun 2000

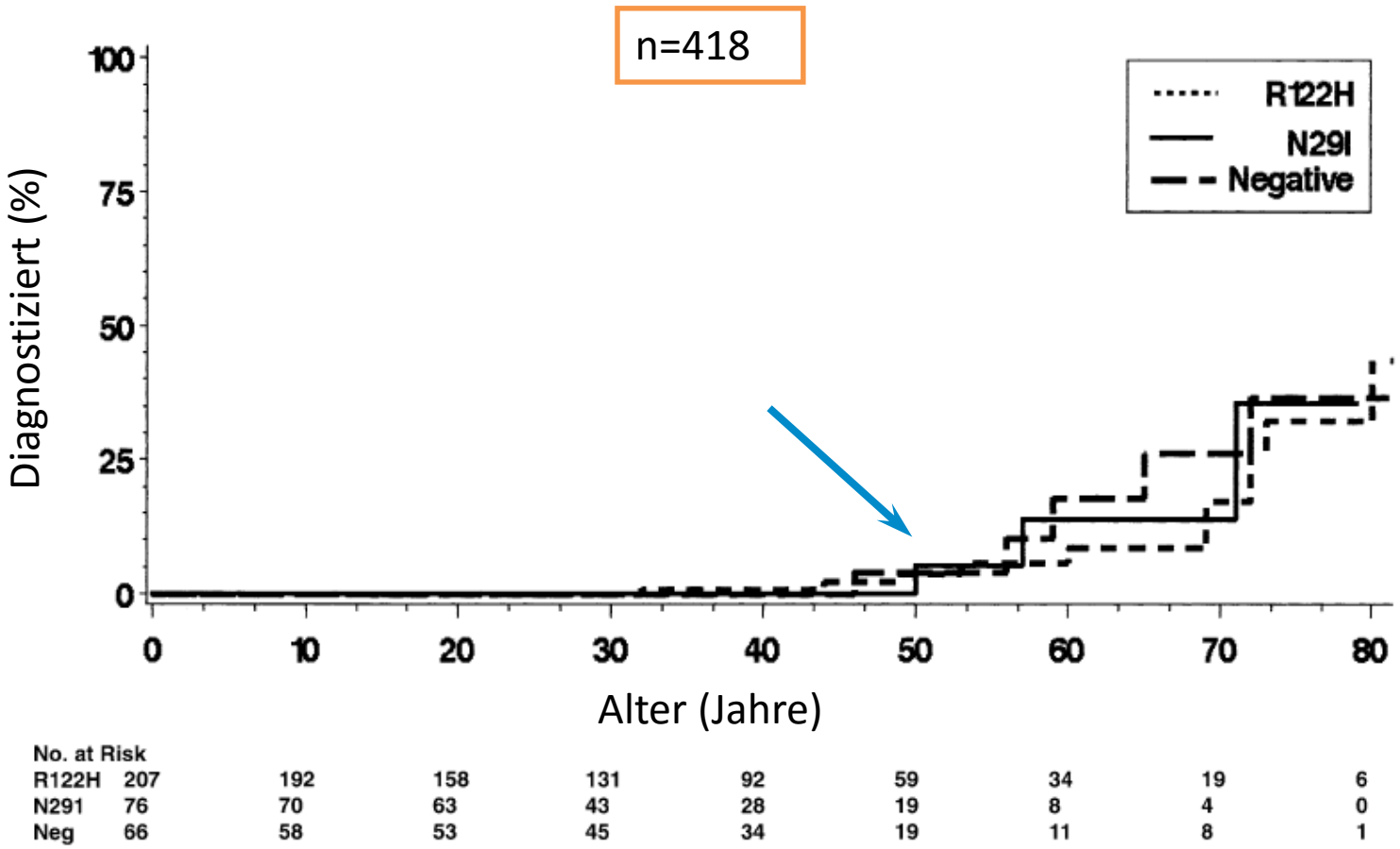
Verlauf der CP - Genetik vs. Alkohol



Keim *et al.*, Dig Dis 2003

Pankreaskarzinom bei HP - EUROPAC

n=418



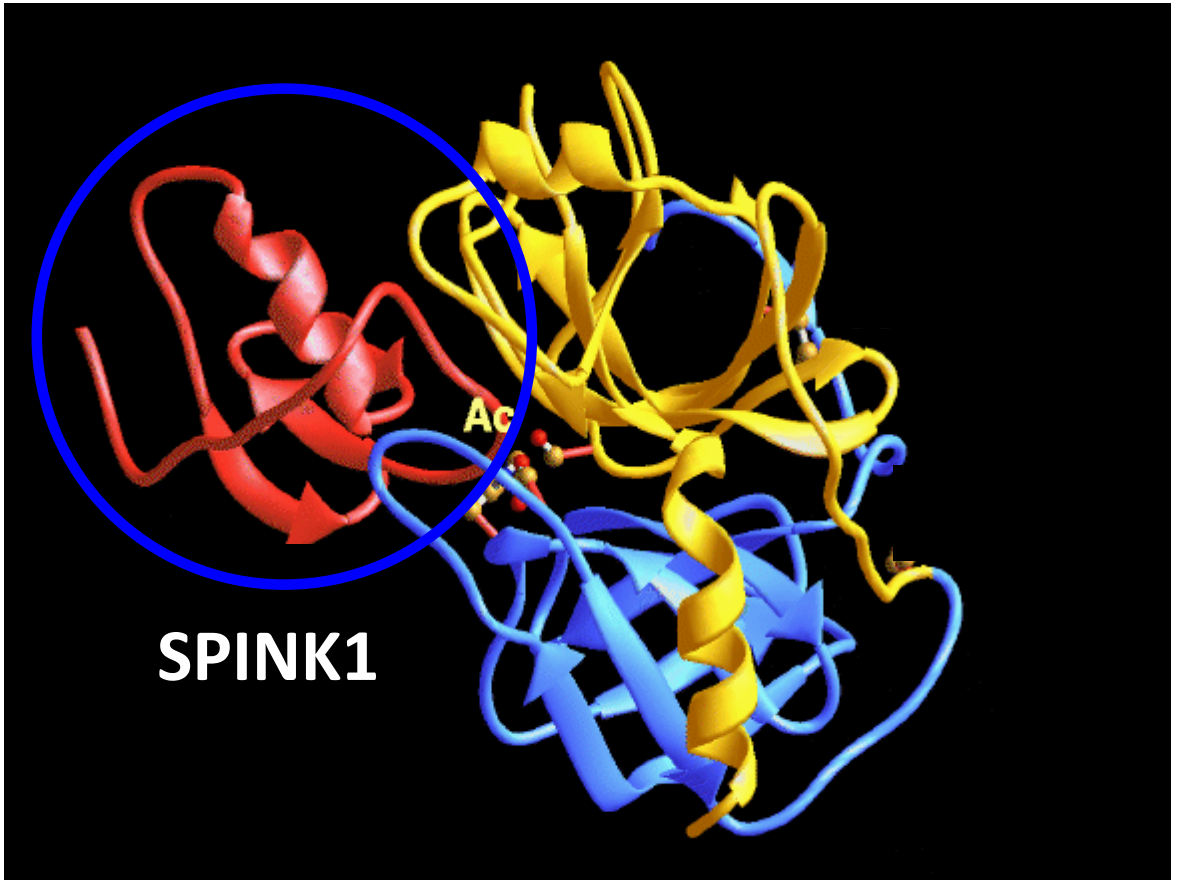
52%

21%

19%

Howes *et al.*, Clin Gastroenterol Hepatol 2004

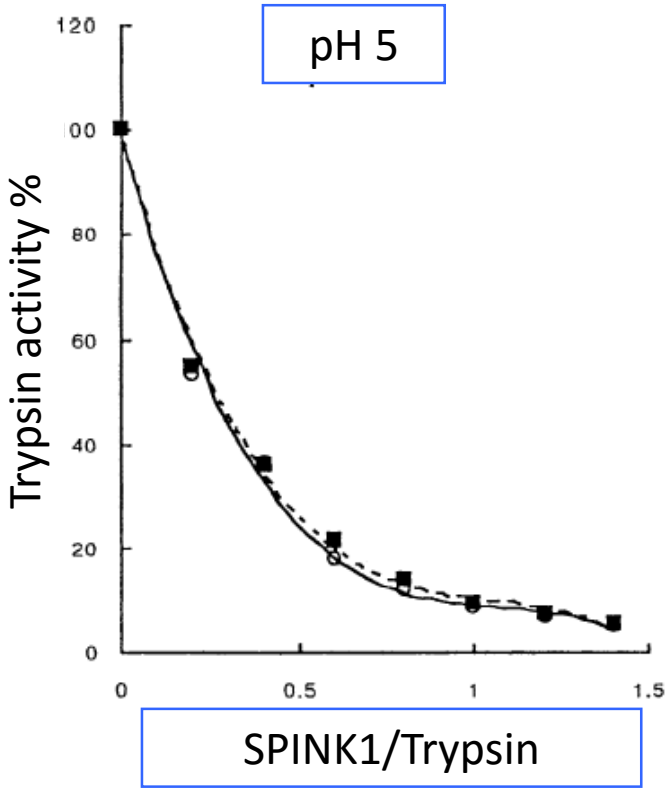
SPINK1

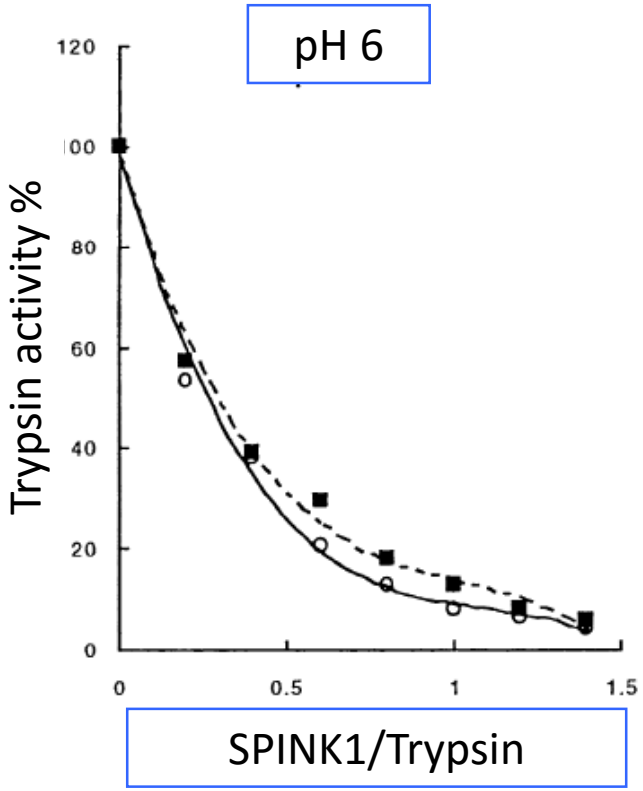


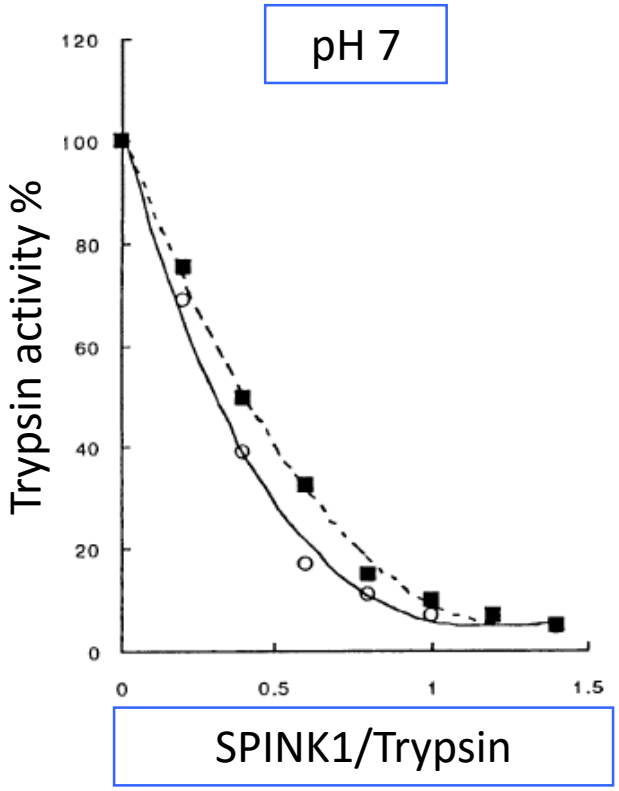
Modified from Whitcomb *et al.*, Nat Genet 1996

Inhibitorische Kapazität

WT ——— p.N34S - - - - -

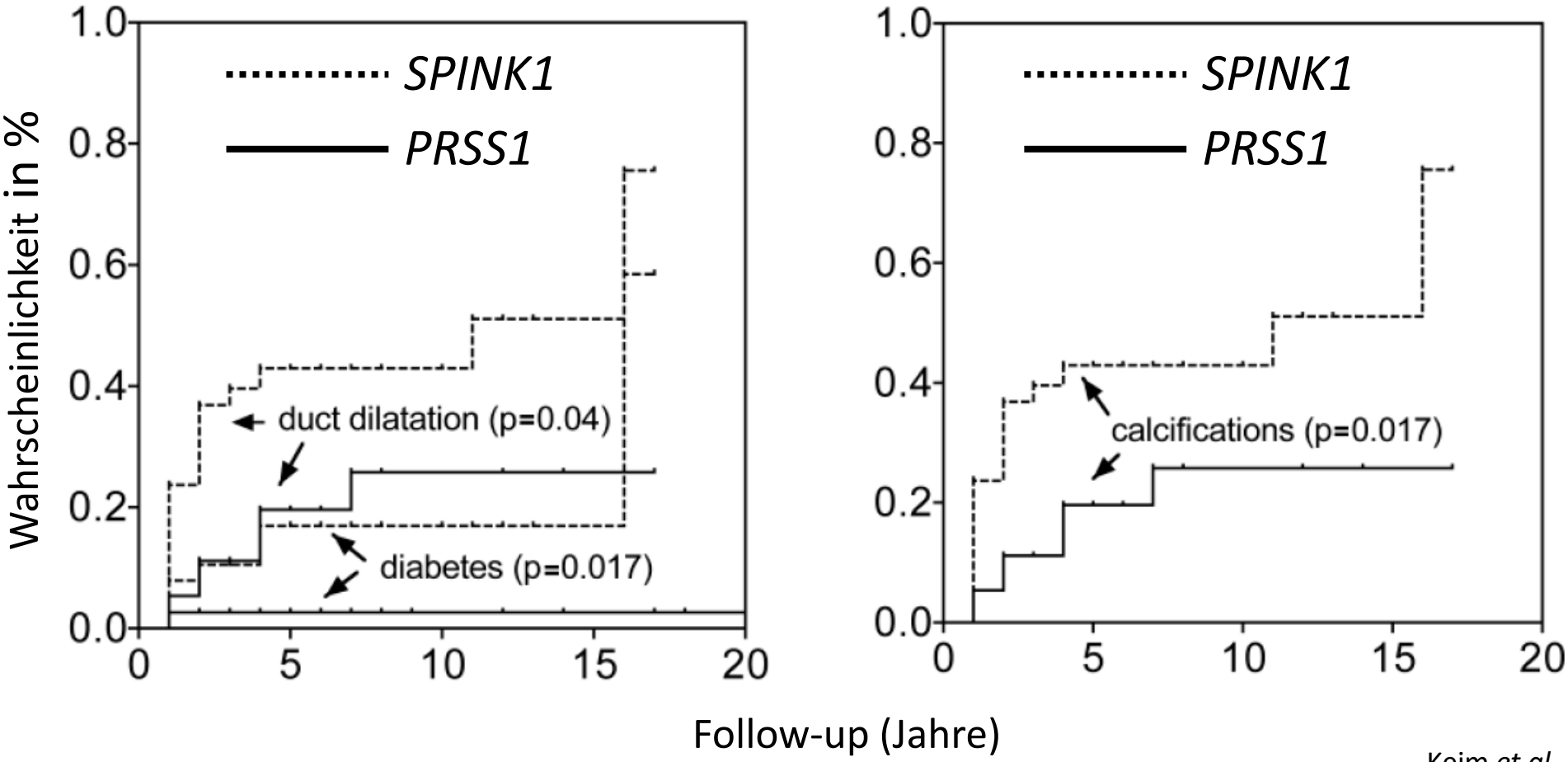






Modified from Kuwata *et al.*, J Gastroenterol 2002

Verlauf der CP- *PRSS1* - *SPINK1*



Keim *et al.*, JOP 2003

Chymotrypsinogen C - CTRC

CHYMOTRYPSIN C (CALDECRIN) STIMULATES AUTOACTIVATION OF HUMAN CATONIC TRYPSINOGEN

Zsófia Nemoda and Miklós Sahin-Tóth

Department of Molecular and Cell Biology, Boston University, Goldman School of Dental Medicine, Boston, MA, 02118

Running title: Chymotrypsin C stimulates trypsinogen autoactivation

Address correspondence to Miklós Sahin-Tóth, 715 Albany Street, Evans-433; Boston, MA 02118; Tel: (617) 414-1070; Fax: (617) 414-1041; E-mail: miklos@bu.edu

PNAS

Chymotrypsin C (caldecrin) promotes degradation of human cationic trypsin: Identity with Rinderknecht's enzyme Y

Richárd Szmola and Miklós Sahin-Tóth*

Department of Molecular and Cell Biology, Goldman School of Dental Medicine, Boston University, Boston, MA 02118

Communicated by Phillips W. Robbins, Boston Medical Center, Boston, MA, May 2, 2007 (received for review March 19, 2007)

Chymotrypsinogen C - CTRC

LETTERS

nature genetics

Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis

Jonas Rosendahl[1,23], Heiko Witt[2,23], Richárd Szmola[3,23], Eesh Bhatia[4], Béla Ózsvári[3,5], Olfert Landt[6], Hans-Ulrich Schulz[7], Thomas M Gress[8], Roland Pfützer[9], Matthias Löhr[10], Peter Kovacs[11], Matthias Blüher[12], Michael Stumvoll[12], Gourdas Choudhuri[13], Péter Hegyi[5], René HM te Morsche[14], Joost PH Drenth[14], Kaspar Truninger[15], Milan Macek Jr[16], Gero Puhl[17], Ulrike Witt[17], Hartmut Schmidt[18], Carsten Büning[19], Johann Ockenga[19], Andreas Kage[20], David Alexander Groneberg[21], Renate Nickel[22], Thomas Berg[2], Bertram Wiedenmann[2], Hans Bödeker[1], Volker Keim[1], Joachim Mössner[1], Niels Teich[1,23] & Miklós Sahin-Tóth[3,23]

Vorwiegend Varianten in Exon 7 (Europa)

Exon	Nucleotide-substitution	Variant	Patients	Controls	*P*-value	OR	95% CI
2	c.103G>C	p.D35H	0/901 (0%)	1/2689 (0.04%)	1.0	-	-
2	c.103G>A	p.D35N	0/901 (0%)	1/2689 (0.04%)	1.0	-	-
2	c.110G>A	p.R37Q	6/901 (0.7%)	10/2689 (0.4%)	0.25	-	-
3	c.143A>G	p.Y48C	2/901 (0.2%)	1/2689 (0.04%)	0.15	-	-
4	c.308delG	p.G103VfsX31	1/621 (0.2%)	0/614 (0%)	1.0	-	-
6	c.514A>G	p.K172E	0/621 (0%)	1/614 (0.2%)	0.5	-	-
7	c.649G>A	p.G217S	2/901 (0.2%)	1/2804 (0.04%)	0.15	-	-
7	c.652G>A	p.G218S	0/901 (0%)	1/2804 (0.04%)	1.0	-	-
7	c.659T>G	p.L220R	0/901 (0%)	1/2804 (0.04%)	1.0	-	-
7	c.674A>C	p.E225A	0/901 (0%)	1/2804 (0.04%)	1.0	-	-
7	c.703G>A	p.V235I	1/901 (0.1%)	1/2804 (0.04%)	0.43	-	-
7	c.760C>T	p.R254W	19/901 (2.1%)	18/2804 (0.6%)	0.0004*	3.3	1.7-6.4
7	c.738_761del24	p.K247_R254del	11/901 (1.2%)	3/2804 (0.1%)	0.00003*	11.5	3.2-41.5

p.R254W, p.K247_R254del

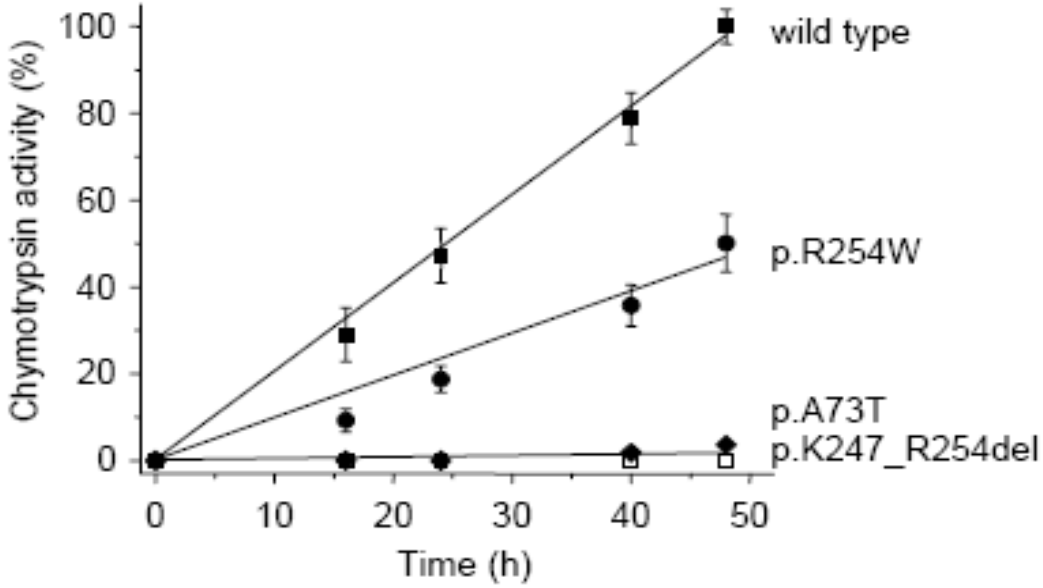
30/901 (3.3%) Patienten v.s. 21/2804 (0.7%) Kontrollen

***P*-Wert = 1.3 x 10^{-7}, OR = 4.6, 95% CI = 2.6-8.0**

Rosendahl *et al.*, Nat Genet 2008

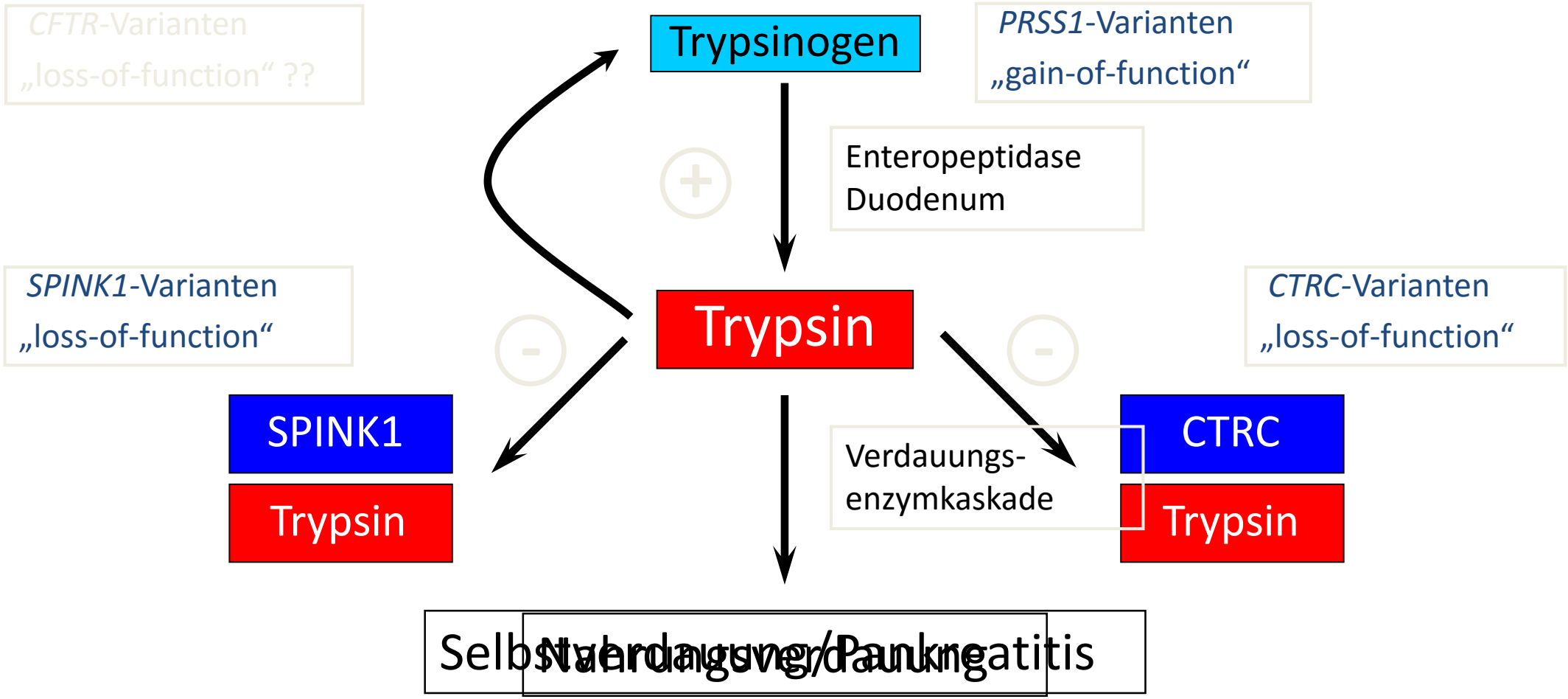
Verminderte Aktivität und Expression

CTRC Aktivität

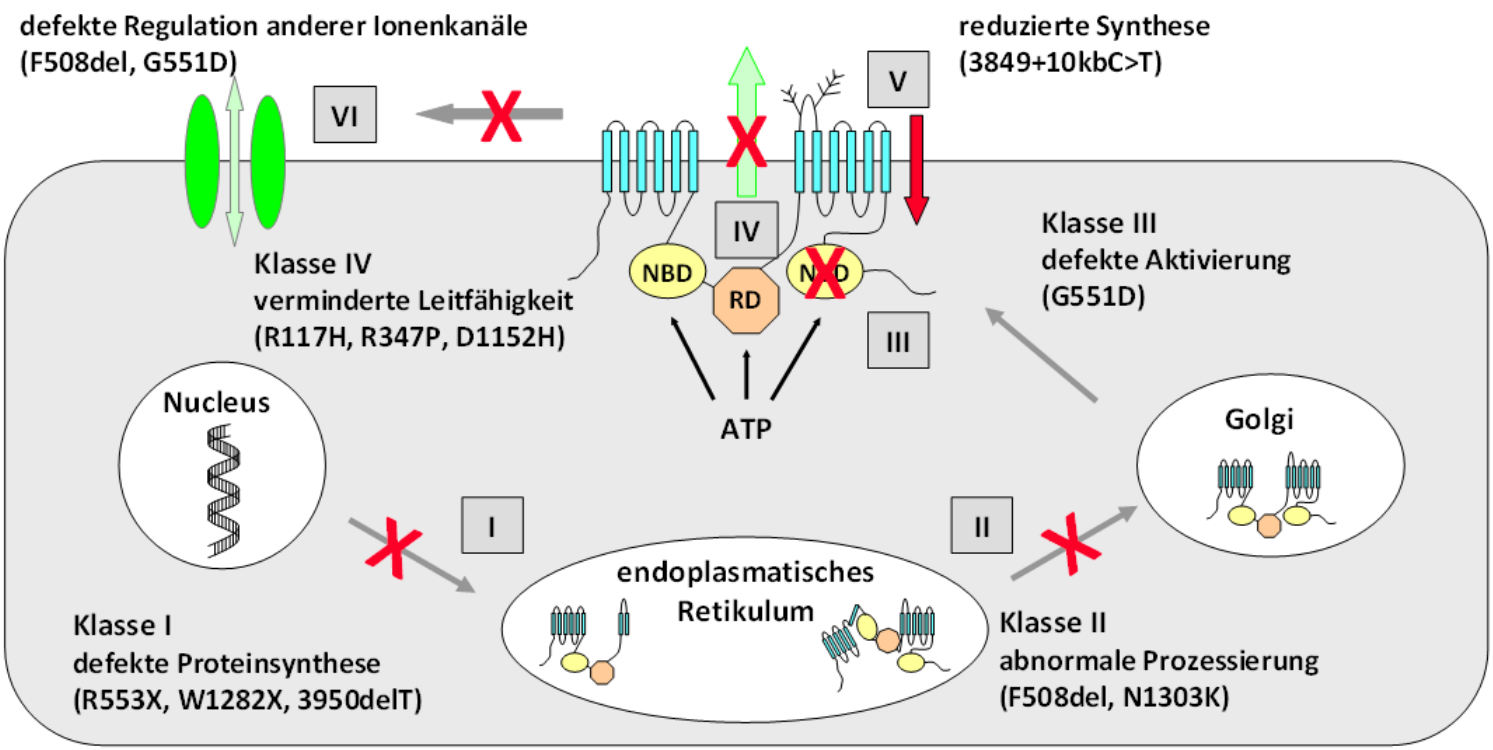


Rosendahl *et al*., Nat Genet 2008

Nahrungsverdauung - Physiologisch

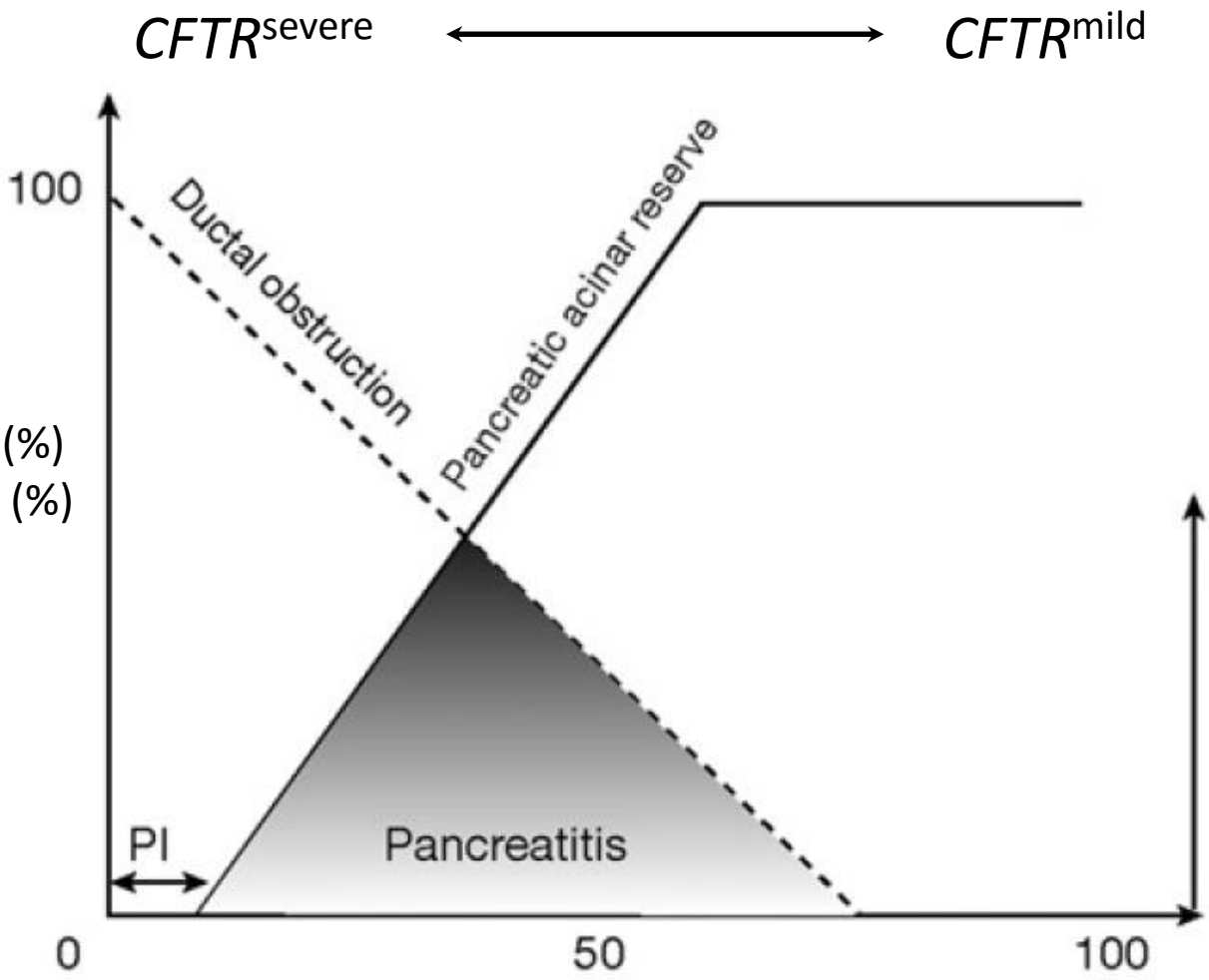


CFTR - Mutationsklassen



Witt *et al.*, Gut 2003

CFTR - Kompliziert?



Ooi *et al.*, Gastroenterology 2011

CFTR - Überschätzter Einfluß?

1. ***CFTR* - CF-verursachend (hart)** - 8,3% Patienten (55/660) vs. 3% (53/1,758) Kontrollen

OR 2,9, 95% CI 2-4,3

2. ***CFTR* - CF-verursachend (mild)** - 3,5% Patienten (23/660) vs. 0,8% Kontrollen (14/1758)

OR 4,5, 95% CI 2,3-8,8

3. ***CFTR* - Nicht CF-verursachend** - 3,8% Patienten (25/660) vs. 2,6% Kontrollen (45/1758)

P-Wert nicht signifikant

Rosendahl *et al.*, Gut 2012

CFTR - Überschätzter Einfluß?

1. ***CFTR* - CF-verursachend (hart)** - 8,3% Patienten (55/662) vs. 3% (53/1,758) Kontrollen

OR 2.9, 95% CI 2-4,3

2. ***CFTR* - CF-verursachend (mild)** - 3,6% Patienten (24/662) vs. 0.8% Kontrollen (14/1758)

OR 4.7, 95% CI 2,4-9,1

3. ***CFTR* - Nicht CF-verursachend** - 4,1% Patienten (27/662) vs. 2,6% Kontrollen (45/1758)

P-Wert nicht signifikant

4. ***CFTR* - Alle** (ohne. p.R75Q, p.E528E) - 15,6% Pat. (103/660) vs. 6,4% Kon. (112/1758)

OR 2,7, 95% CI 2-3,6

Rosendahl *et al.*, Gut 2012

Carboxypeptidase A1

LETTERS

nature genetics

Variants in *CPA1* are strongly associated with early onset chronic pancreatitis

Heiko Witt[1–3], Sebastian Beer[4,44], Jonas Rosendahl[5,44], Jian-Min Chen[6,7,44], Giriraj Ratan Chandak[8,44], Atsushi Masamune[9,44], Melinda Bence[4,44], Richárd Szmola[4,10,44], Grzegorz Oracz[11], Milan Macek Jr[12], Eesh Bhatia[13], Sandra Steigenberger[1,2], Denise Lasher[1,2], Florence Bühler[1,2], Catherine Delaporte[1,2], Johanna Tebbing[1,2], Maren Ludwig[1,2], Claudia Pilsak[1,2], Karolin Saum[1,2], Peter Bugert[14], Emmanuelle Masson[6,7], Sumit Paliwal[8], Seema Bhaskar[8], Agnieszka Sobczynska-Tomaszewska[15,16], Daniel Bak[16], Ivan Balascak[17], Gourdas Choudhuri[18], D Nageshwar Reddy[19], G Venkat Rao[19], Varghese Thomas[20], Kiyoshi Kume[9], Eriko Nakano[9], Yoichi Kakuta[9], Tooru Shimosegawa[9], Lukasz Durko[21], András Szabó[4], Andrea Schnúr[4,22], Péter Hegyi[22], Zoltán Rakonczay Jr[22], Roland Pfützer[23], Alexander Schneider[24], David Alexander Groneberg[25], Markus Braun[25], Hartmut Schmidt[26], Ulrike Witt[27], Helmut Friess[27], Hana Algül[28], Olfert Landt[29], Markus Schuelke[30,31], Renate Krüger[32], Bertram Wiedenmann[33], Frank Schmidt[34], Klaus-Peter Zimmer[35], Peter Kovacs[36,37], Michael Stumvoll[36,37], Matthias Blüher[36,37], Thomas Müller[38], Andreas Janecke[38,39], Niels Teich[40], Robert Grützmann[41], Hans-Ulrich Schulz[42], Joachim Mössner[5], Volker Keim[5], Matthias Löhr[43], Claude Férec[6,7] & Miklós Sahin-Tóth[4]

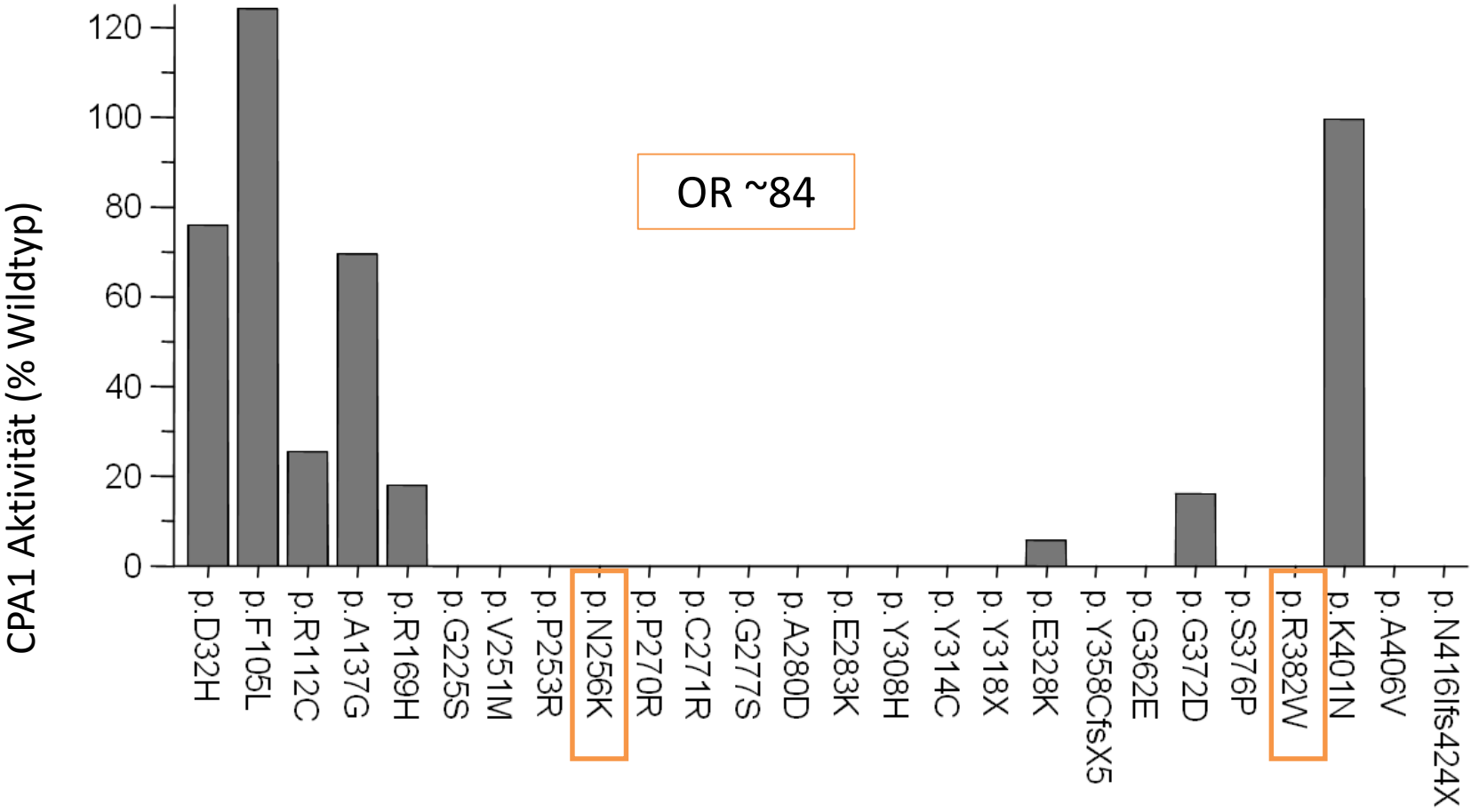
Witt *et al.*, Nat Genet 2013

Carboxypeptidase A1

Age of cases	Cases (%)	Controls (%)	*P*	OR	95% CI
All	29/944 (3.1)	5/3,938 (0.1)	1.5×10^{-16}	24.9	9.6–64.6
>20 years	2/358 (0.6)	5/3,938 (0.1)	0.2	–	–
≤20 years	27/586 (4.6)	5/3,938 (0.1)	6.8×10^{-20}	38.0	14.6–99.1
≤10 years	22/228 (9.7)	5/3,938 (0.1)	4.1×10^{-24}	84.0	31.5–224.1

Witt *et al.*, Nat Genet 2013

CPA1 Varianten - Funktionelle Untersuchung



Witt *et al.*, Nat Genet 2013

Erste GWAS bei CP

LETTERS

nature genetics

Common genetic variants in the *CLDN2* and *PRSS1-PRSS2* loci alter risk for alcohol-related and sporadic pancreatitis

David C Whitcomb[1–3], Jessica LaRusch[1], Alyssa M Krasinskas[4], Lambertus Klei[5], Jill P Smith[6], Randall E Brand[1], John P Neoptolemos[7], Markus M Lerch[8], Matt Tector[9], Bimaljit S Sandhu[10], Nalini M Guda[9], Lidiya Orlichenko[1], Alzheimer's Disease Genetics Consortium[11], Samer Alkaade[12], Stephen T Amann[13], Michelle A Anderson[14], John Baillie[15], Peter A Banks[16], Darwin Conwell[16], Gregory A Coté[17], Peter B Cotton[18], James DiSario[19], Lindsay A Farrer[20,89,90,95], Chris E Forsmark[21], Marianne Johnstone[7], Timothy B Gardner[22], Andres Gelrud[1], William Greenhalf[7], Jonathan L Haines[23,24], Douglas J Hartman[4], Robert A Hawes[18], Christopher Lawrence[18], Michele Lewis[25], Julia Mayerle[8], Richard Mayeux[26,27], Nadine M Melhem[5], Mary E Money[28], Thiruvengadam Muniraj[29], Georgios I Papachristou[1], Margaret A Pericak-Vance[30,31], Joseph Romagnuolo[18], Gerard D Schellenberg[32], Stuart Sherman[17], Peter Simon[8], Vijay P Singh[1], Adam Slivka[1], Donna Stolz[2], Robert Sutton[7], Frank Ulrich Weiss[8], C Mel Wilcox[33], Narcis Octavian Zarnescu[1], Stephen R Wisniewski[34], Michael R O'Connell[1], Michelle L Kienholz[1], Kathryn Roeder[35], M Michael Barmada[3], Dhiraj Yadav[1] & Bernie Devlin[3,5]

GWAS - Ergebnisse

					CP + RAP		CP			CP + RAP			CP + RAP		
					Allele Frequency (A1)		Stage 1			Stage 2			Combined		
CHR	SNP	BP	A1*	A2	cases	controls	OR	se(OR)	P	OR	se(OR)	P	OR	se(OR)	P
7	rs10273639	142456928	T	C	0.350	0.424	0.712	0.044	3.0×10^{-8}	0.748	0.039	7.5×10^{-8}	0.734	0.029	2.0×10^{-14}
X	rs7057398	106144529	C	T	0.374	0.281	1.493	0.075	1.4×10^{-15}	1.210	0.066	1.8×10^{-5}	1.321	0.049	4.6×10^{-17}
X	rs12688220	106244767	T	C	0.367	0.261	1.612	0.081	2.4×10^{-21}	1.238	0.073	2.3×10^{-6}	1.385	0.054	2.3×10^{-22}

OR ~0,73-1,38

Whitcomb DC *et al.*, Nat Genet 2012

Carboxylesterlipase - CEL

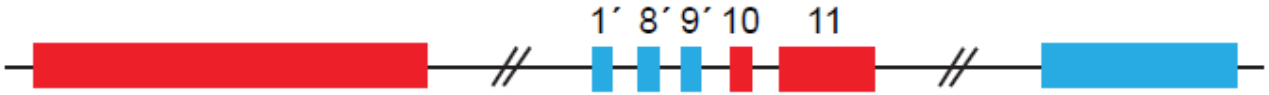
LETTERS

nature genetics

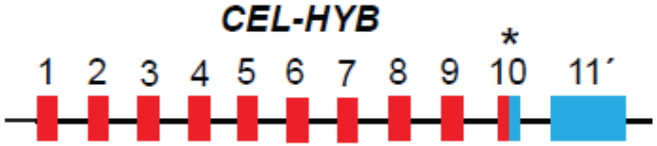
A recombined allele of the lipase gene *CEL* and its pseudogene *CELP* confers susceptibility to chronic pancreatitis

Karianne Fjeld[1,2], Frank Ulrich Weiss[3,25], Denise Lasher[4,5,25], Jonas Rosendahl[6,25], Jian-Min Chen[7–9,25], Bente B Johansson[1,2], Holger Kirsten[10–12], Claudia Ruffert[6,13,14], Emmanuelle Masson[7,15], Solrun J Steine[1,16], Peter Bugert[17], Miriam Cnop[18,19], Robert Grützmann[20], Julia Mayerle[3], Joachim Mössner[6], Monika Ringdal[1,2], Hans-Ulrich Schulz[21], Matthias Sendler[3], Peter Simon[3], Paweł Sztromwasser[1,2,22], Janniche Torsvik[1,2], Markus Scholz[11,12], Erling Tjora[1,23], Claude Férec[7–9,15], Heiko Witt[4,5], Markus M Lerch[3], Pål R Njølstad[1,23], Stefan Johansson[1,2] & Anders Molven[1,16,24]

CEL - Hybrid Allel



Duplicated hybrid allele



Deleted hybrid allele

Field *et al.*, Nat Genet 2015

CEL - Hyb Allel

Table 1 Carrier frequencies of the *CEL-HYB* variant in German and French subjects with chronic pancreatitis

Patient material	Cases		Controls				
	+/N	%	+/N	%	OR	CI	*P* value*
Discovery cohort a	10/71	14.1	5/478	1.0	15.5	5.1 – 46.9	1.3×10^{-6}
ICP/FCP cohort 1 b	22/474	4.6	16/2362	0.7	7.1	3.7 – 13.7	3.4×10^{-9}
ICP/FCP cohort 2 c	11/252	4.4	5/569	0.9	5.1	1.8 – 15.0	0.002
ICP/FCP cohort 3 d	9/339	2.7	9/1221	0.7	3.7	1.4 – 9.3	0.007
Meta-analysis**	-	-	-	-	**6.4**	**4.1 - 9.9**	**1.1×10^{-16}**
Alcoholic CP cohort*** e	15/853	1.8	26/3409	0.8	2.3	1.2 – 4.4	0.008

* Two-tailed Fisher´s exact test

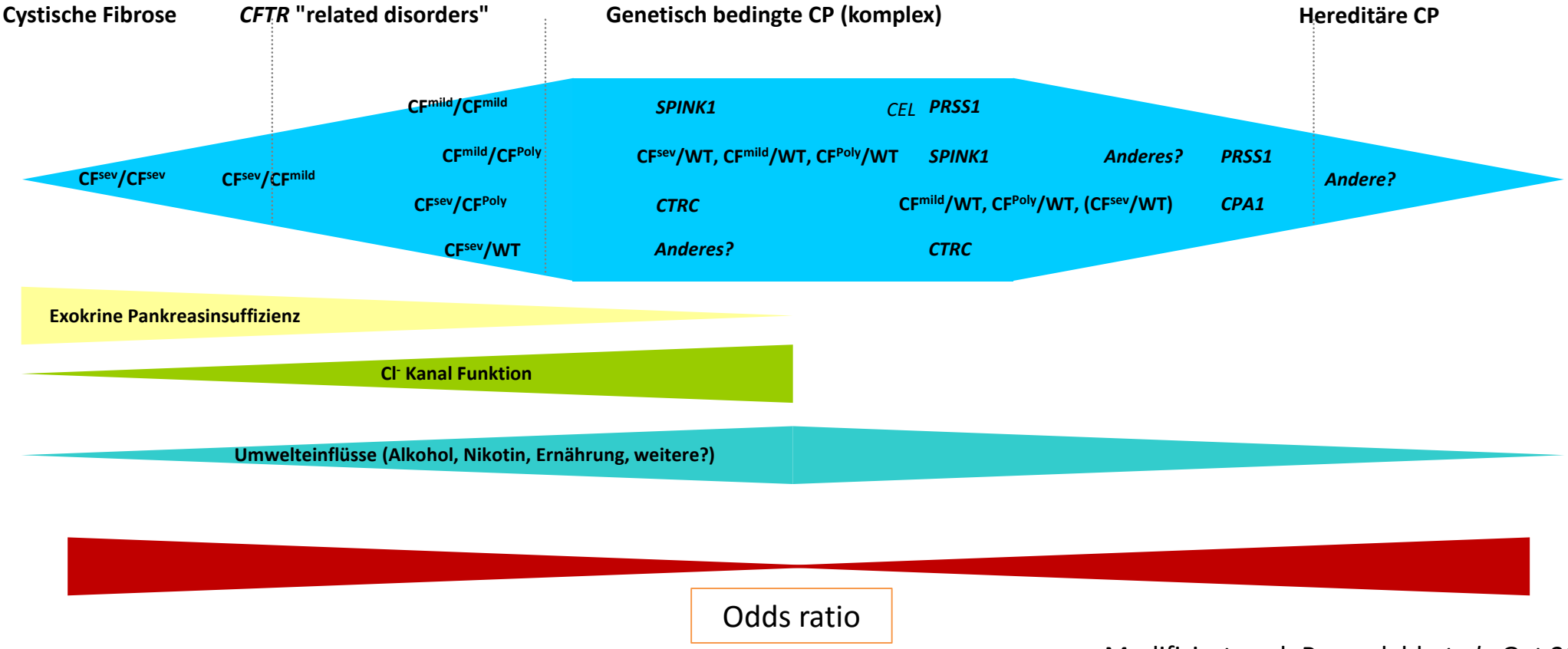
** Fixed effect model using the method of Mantel and Haenszel (Stata metan command)
Z= 8.29, Heterogeneity chi-squared = 4.09 (d.f. = 3), $p = 0.252$,
I-squared (variation in OR attributable to heterogeneity) = 26.7%

*** One-tailed Fisher´s exact test.

OR ~2,3-6,4

Field *et al.*, Nat Genet 2015

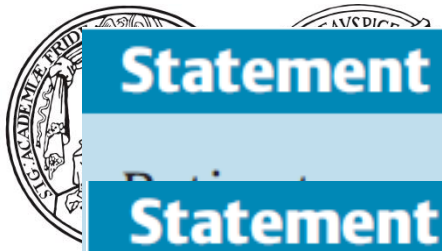
CP - Genetik und Umwelt



Modifiziert nach Rosendahl *et al.*, Gut 2012

UKH
Universitätsklinikum
Halle (Saale)

Vielen Dank!



sklinikum
)

Statement 2 – 1-6

Statement 2 – 2-1

Statement 2 – 2-3

Eine Mutationsanalyse auf Veränderungen im SPINK1-Gen, CFTR-Gen, CTRC-Gen oder einer anderen assoziierten Genveränderungen kann im Rahmen von Forschungsprojekten oder zur vertieften Ursachenabklärung erfolgen.
[*Evidenzgrad 3b, Empfehlungsgrad C, Konsens*]

[*Evidenzgrad 3b, Empfehlungsgrad B, Konsens*]

15 % in der gesunden Bevölkerung. Somit stellen CFTR-Mutationen einen Risikofaktor für die chronische idiopathische Pankreatitis dar.

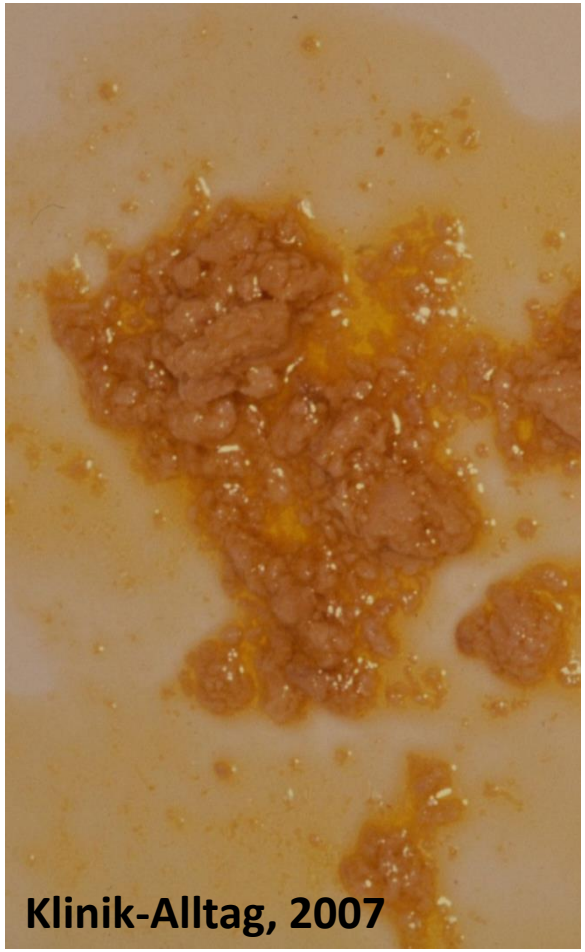
Patientencharakteristika

	Alcohol-related pancreatitis[a]	CP	RAP	CP + RAP
Stage 1	All cases	676	–	676
	Yes	264	–	264
	No	411	–	411
	Unknown	1	–	1
Stage 2	All cases	331	579	910
	Yes	70	113	183
	No	256	462	718
	Unknown	5	4	9
Combined	All cases	930	579	1,506
	Yes	334	113	447
	No	667	462	1,129
	Unknown	6	4	10

Whitcomb DC *et al.*, Nat Genet 2012

CFTR - Chronische Pankreatitis

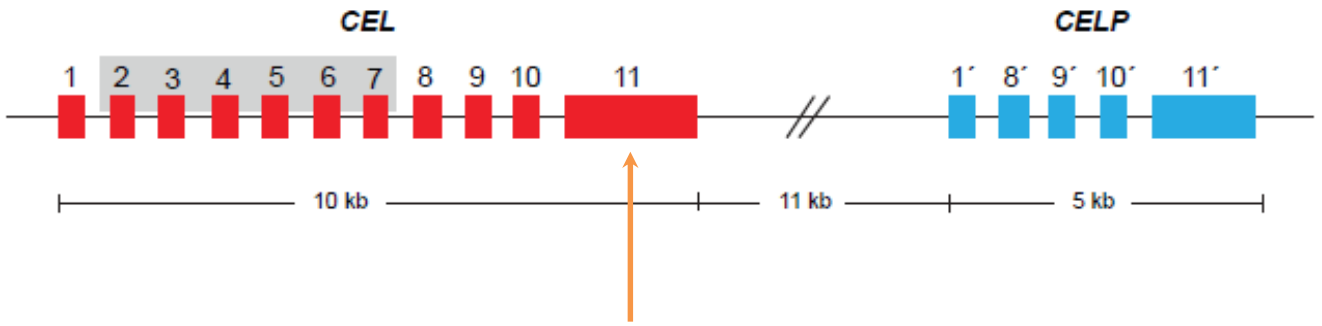
Joseph Beuys, 1964



Klinik-Alltag, 2007

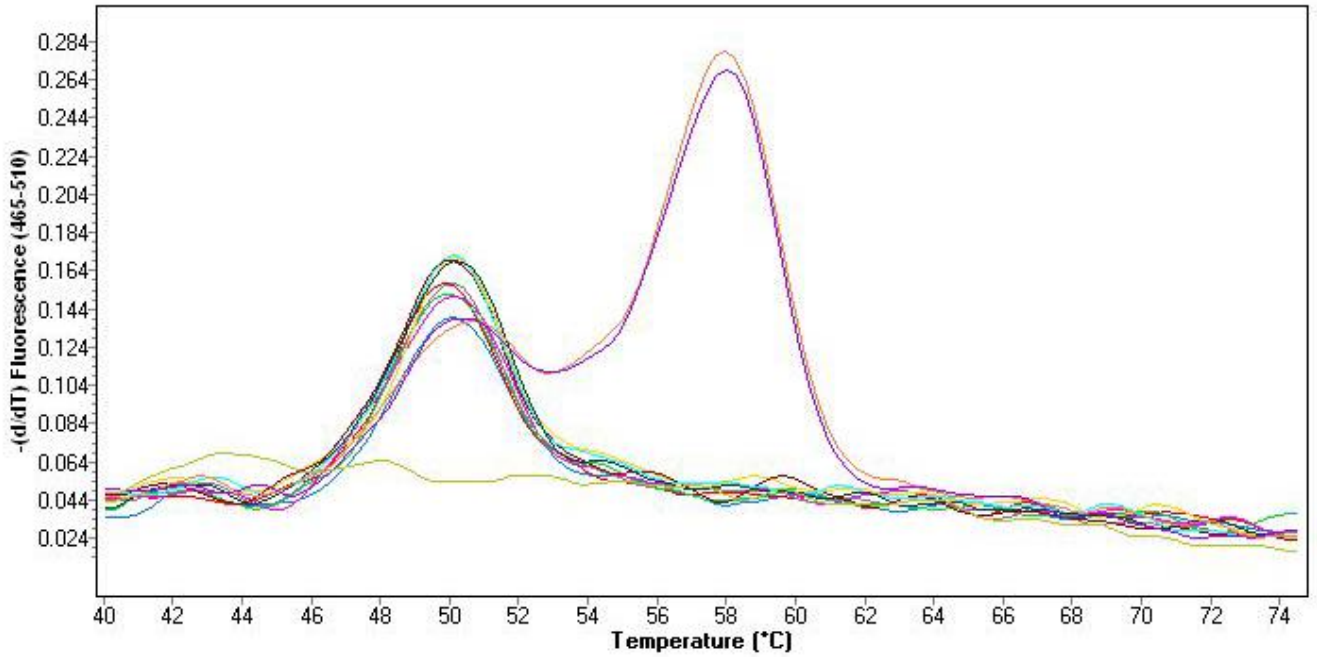
CEL - Carboxylesterlipase

- Carboxylesterlipase "wesentlicher" Bestandteil des Pankreassekrets
- verantwortlich für die Hydrolyse von Cholesterol und anderen Estern der Nahrung
- CEL-MODY (MODY8); ein monogenes Syndrom mit exokriner und endokriner Fehlfunktion



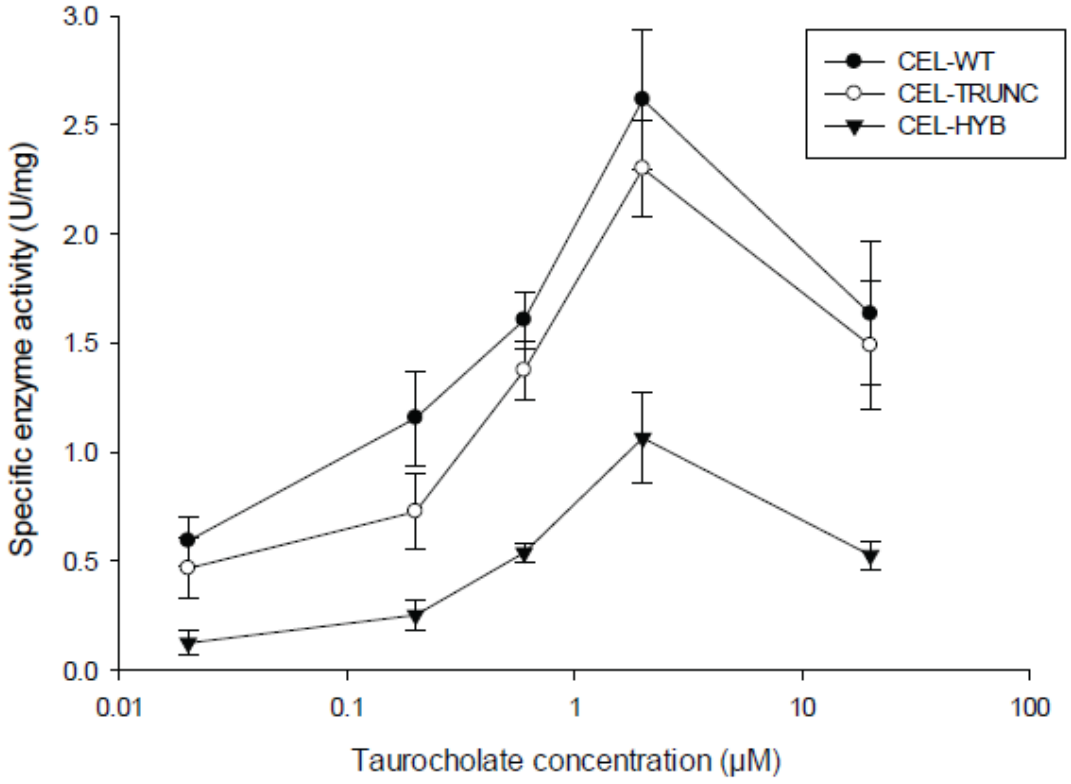
Exon 11: VNTR, 33bp; häufigste Variante 16 VNTR repeats

CEL - Hybrid Allel - LC



Field *et al.*, Nat Genet 2015

CEL Hyb - Verminderte Aktivität

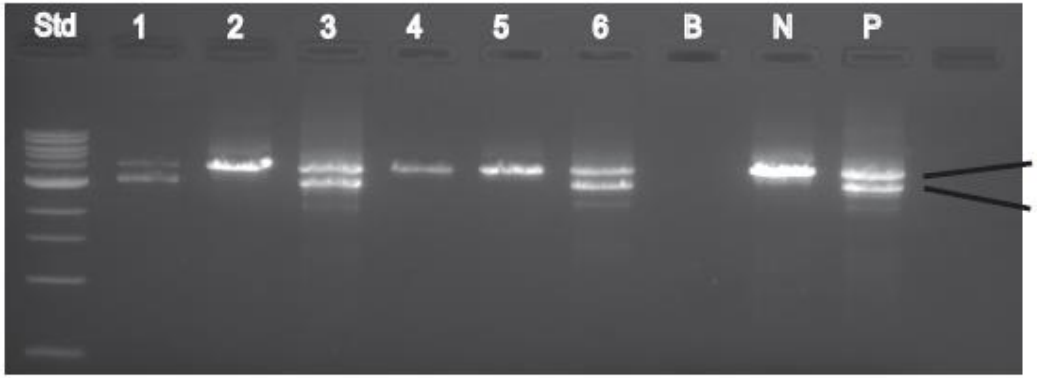


Field *et al.*, Nat Genet 2015

CEL - Hyb

CEL-HYB

CEL-WT (normal allele)



Field *et al.*, Nat Genet 2015