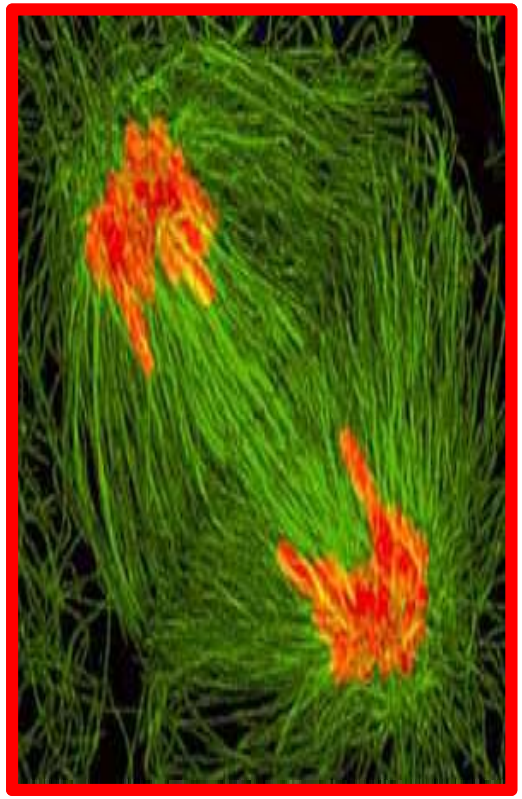
Möglichkeiten/Grenzen prädiktiver genetischer Diagnostik - Herzerkrankungen



Prof. Dr. H. Schunkert • Medizinische Klinik II • Universität zu Lübeck

- **Multifaktorielle Erkrankungen**

  Koronare Herzerkrankung

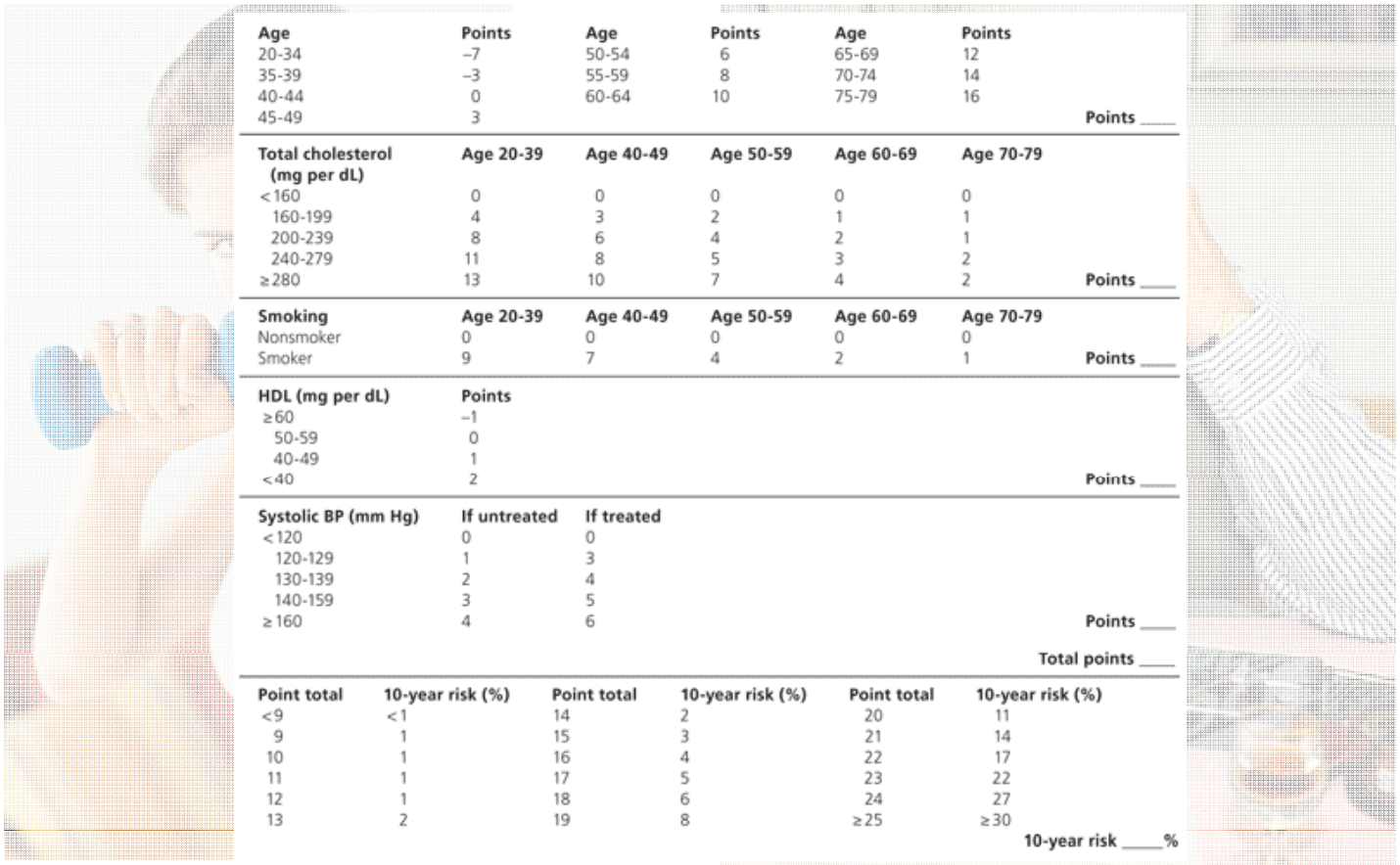
- **„Monogene“ Erkrankungen**

  Herzmuskelerkrankungen

  Rhythmusstörungen

Wer hat das höhere Risiko in den nächsten 10 Jahren einen Herzinfarkt zu erleiden ?

Unsere Antwort:



Age	Points	Age	Points	Age	Points
20-34	–7	50-54	6	65-69	12
35-39	–3	55-59	8	70-74	14
40-44	0	60-64	10	75-79	16
45-49	3				

Points ____

Total cholesterol (mg per dL)	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

Points ____

Smoking	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Points ____

HDL (mg per dL)	Points
≥60	–1
50-59	0
40-49	1
<40	2

Points ____

Systolic BP (mm Hg)	If untreated	If treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Points ____

Total points ____

Point total	10-year risk (%)	Point total	10-year risk (%)	Point total	10-year risk (%)
<9	<1	14	2	20	11
9	1	15	3	21	14
10	1	16	4	22	17
11	1	17	5	23	22
12	1	18	6	24	27
13	2	19	8	≥25	≥30

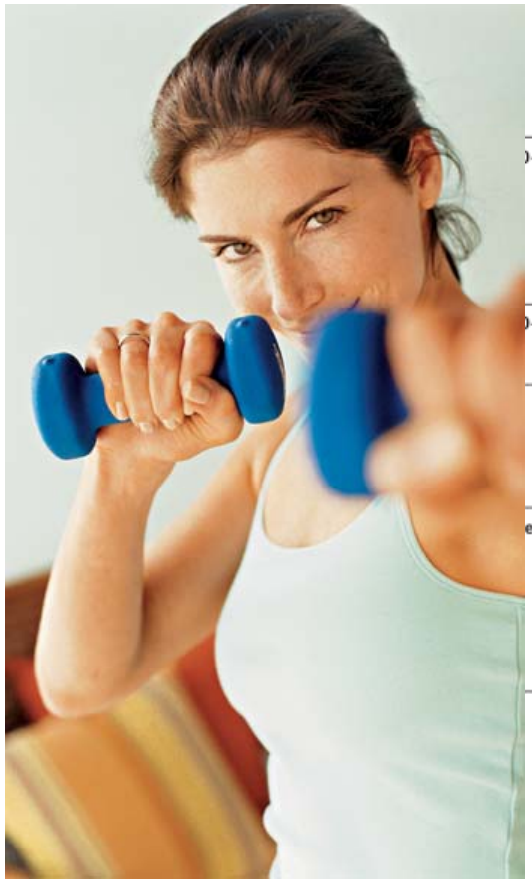
10-year risk ____%

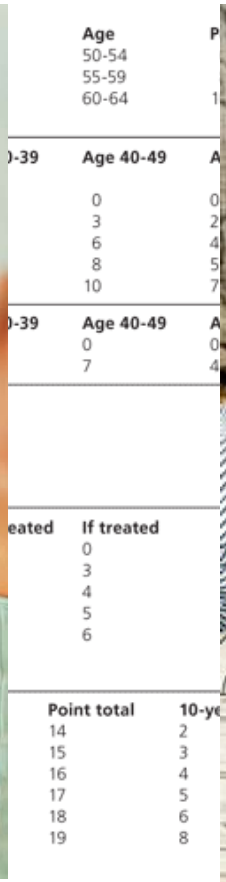
female, 32 years, non-smoker

male, 82 years, diabetic, hypertensive, smoker

Wer hat das höhere Risiko in den nächsten 10 Jahren einen Herzinfarkt zu erleiden ?

Unsere Antwort:





Age	P
50-54	
55-59	
60-64	1

-39	Age 40-49	A
	0	0
	3	2
	6	4
	8	5
	10	7

-39	Age 40-49	A
	0	0
	7	4

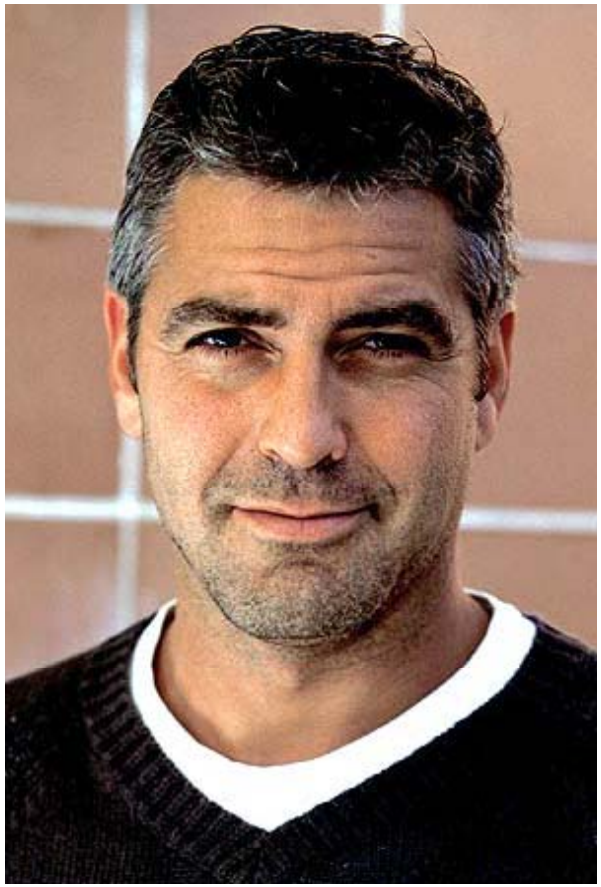
eated	If treated
	0
	3
	4
	5
	6

Point total	10-y
14	2
15	3
16	4
17	5
18	6
19	8

female, 32 years, non-smoker

male, 82 years, diabetic, hypertensive, smoker

Wer hat das höhere Risiko in den nächsten 10 Jahren einen Herzinfarkt zu erleiden ?

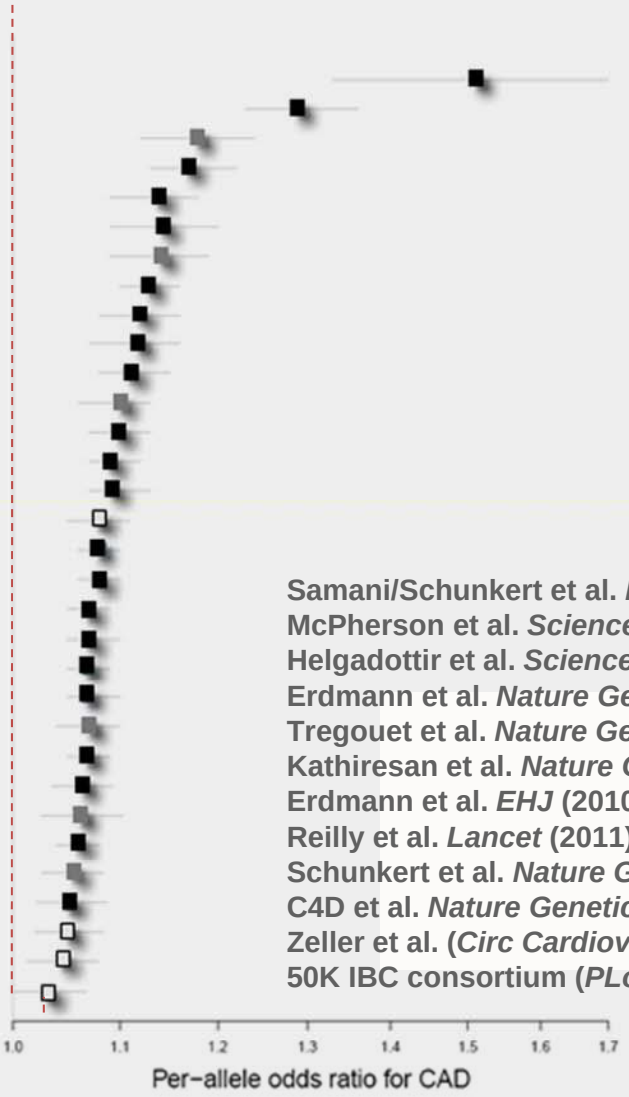


INTERNATIONAL
Herald Tribune
THE WORLD'S DAILY NEWSPAPER PUBLISHED BY THE NEW YORK TIMES EDITED IN PARIS AND PRINTED IN FRANKFURT
SATURDAY-SUNDAY, SEPTEMBER 11-12, 2004

It's probably the Clinton genes, not the diet

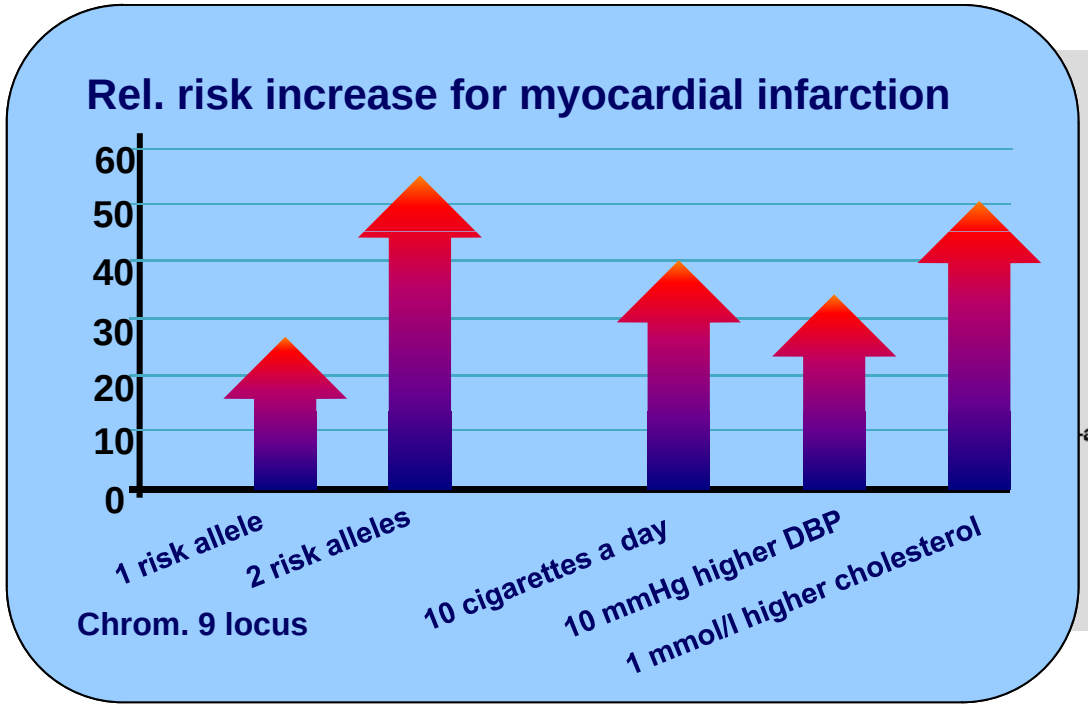
Goldrausch der KHK Genomforschung 2011

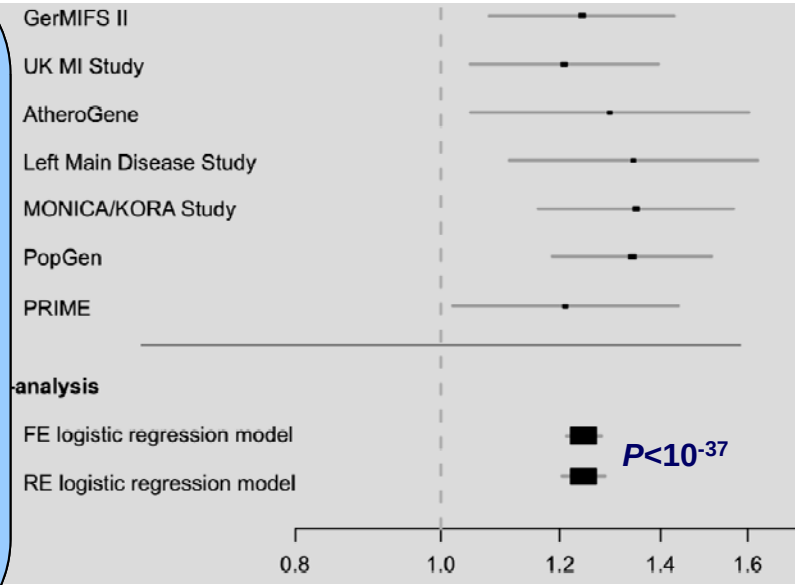
Band	Nearby gene(s)	SNP	Risk allele	Freq
6q25.3	LPA	rs3798220	C	2
9p21.3	CDKN2A,CDKN2B	rs4977574	G	46
21q22.11	MRPS6	rs9982601	T	15
1p32.2	PPAP2B	rs17114036	A	91
19p13.2	LDLR	rs1122608	G	77
1q41	MIA3	rs17465637	C	74
2q33.1	WDR12	rs6725887	C	15
11q23.3	ZNF259, APOA5−A4−C3−A1	rs964184	G	13
10q24.32	CYP17A1, CNNM2, NT5C2	rs12413409	G	89
3q22.3	MRAS	rs2306374	C	18
1p13.3	SORT1	rs599839	A	78
6p24.1	PHACTR1	rs12526453	C	67
9q34.2	ABO	rs579459	C	21
7q32.2	ZC3HC1	rs11556924	C	62
10q11.21	CXCL12	rs1746048	C	87
1p32.3	PCSK9	rs11206510	T	82
6q23.2	TCF21	rs12190287	C	62
15q25.1	ADAMTS7	rs3825807	A	57
17p11.2	RASD1, SMCR3, PEMT	rs12936587	G	56
6p21.31	ANKS1A	rs17609940	G	75
17p13.3	SMG6, SRR	rs216172	C	37
14q32.2	HHIPL1	rs2895811	C	43
12q24.12	SH2B3	rs3184504	T	44
13q34	COL4A1, COL4A2	rs4773144	G	44
10p11.23	KIAA1462	rs3739998	G	43
10q23.31	LIPA	rs1412444	T	35
17q21.32	UBE2Z, GIP, ATP5G1, SNF8	rs46522	T	53
8q24.13	TRIB1	rs17321515	A	52
2p21	ABCG8	rs4299376	G	29
11q22.3	PDGFD	rs974819	T	28
5q31.1	IL5	rs2706399	G	51
7q22	BCAP29	rs10953541	C	76



Samani/Schunkert et al. *NEJM* (2007)
McPherson et al. *Science* (2007)
Helgadottir et al. *Science* (2007)
Erdmann et al. *Nature Genetics* (2009)
Tregouet et al. *Nature Genetics* (2009)
Kathiresan et al. *Nature Genetics* (2009)
Erdmann et al. *EHJ* (2010)
Reilly et al. *Lancet* (2011)
Schunkert et al. *Nature Genetics* (2011)
C4D et al. *Nature Genetics* (2011)
Zeller et al. (*Circ Cardiovasc Genetics* 2011)
50K IBC consortium (*PLoSGenetics* 2011)

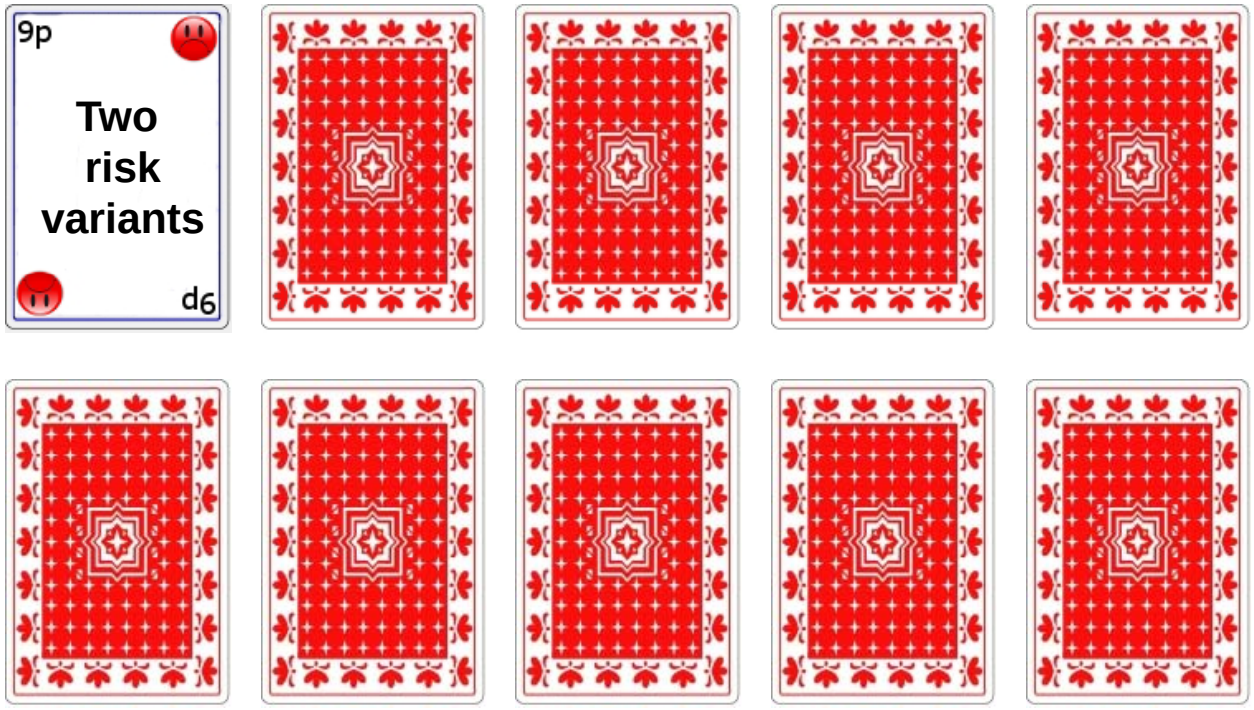
The currently most important CAD gene
chromosome 9p21.3



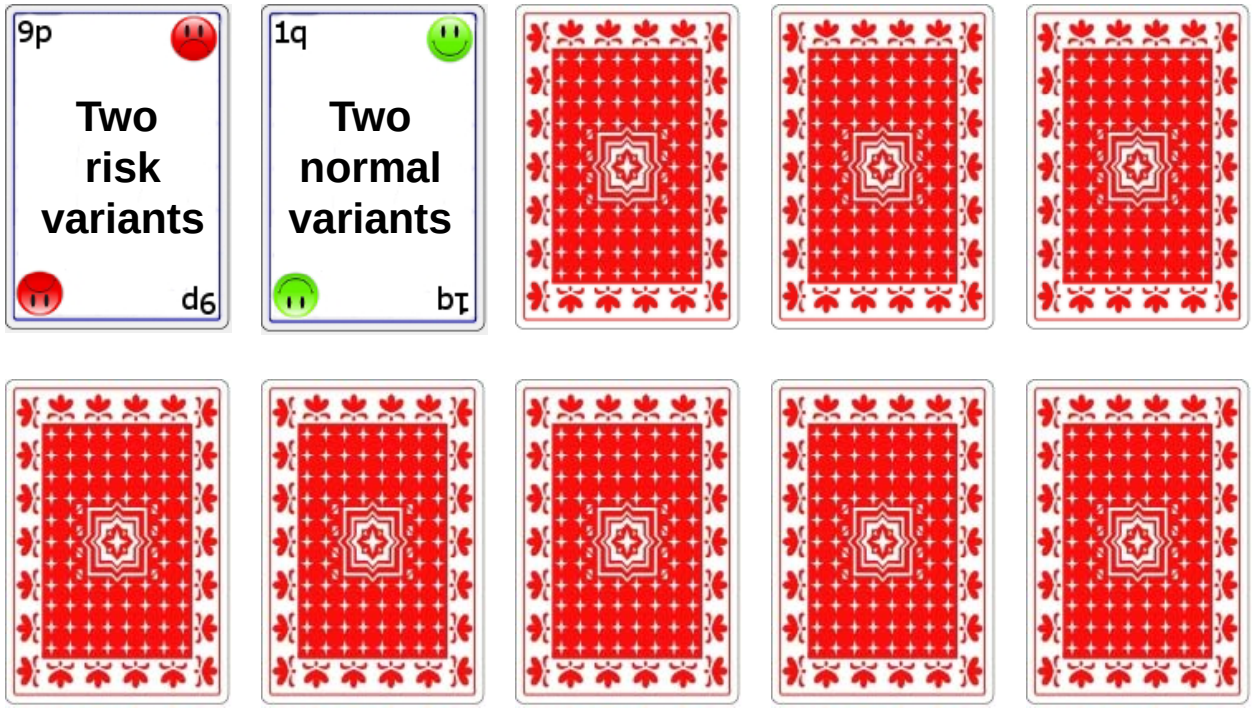


Schunkert et al. *Circulation* 2008;117:1675-84

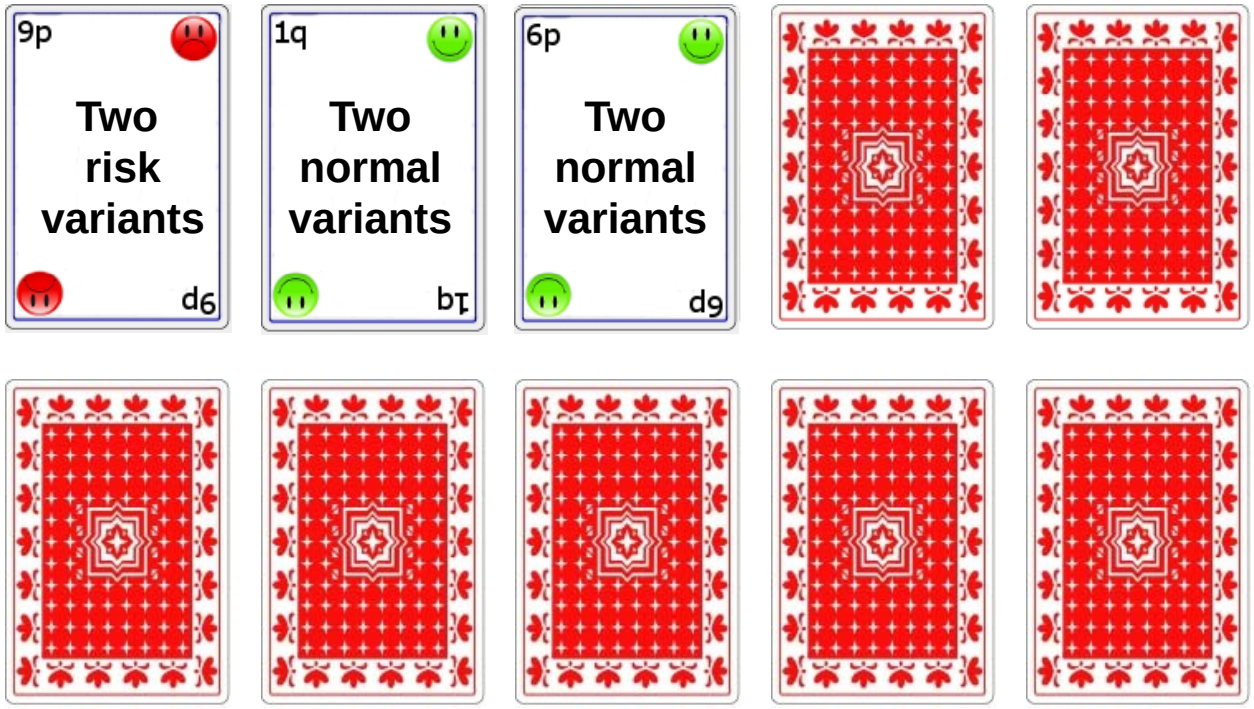
Computing individual probability



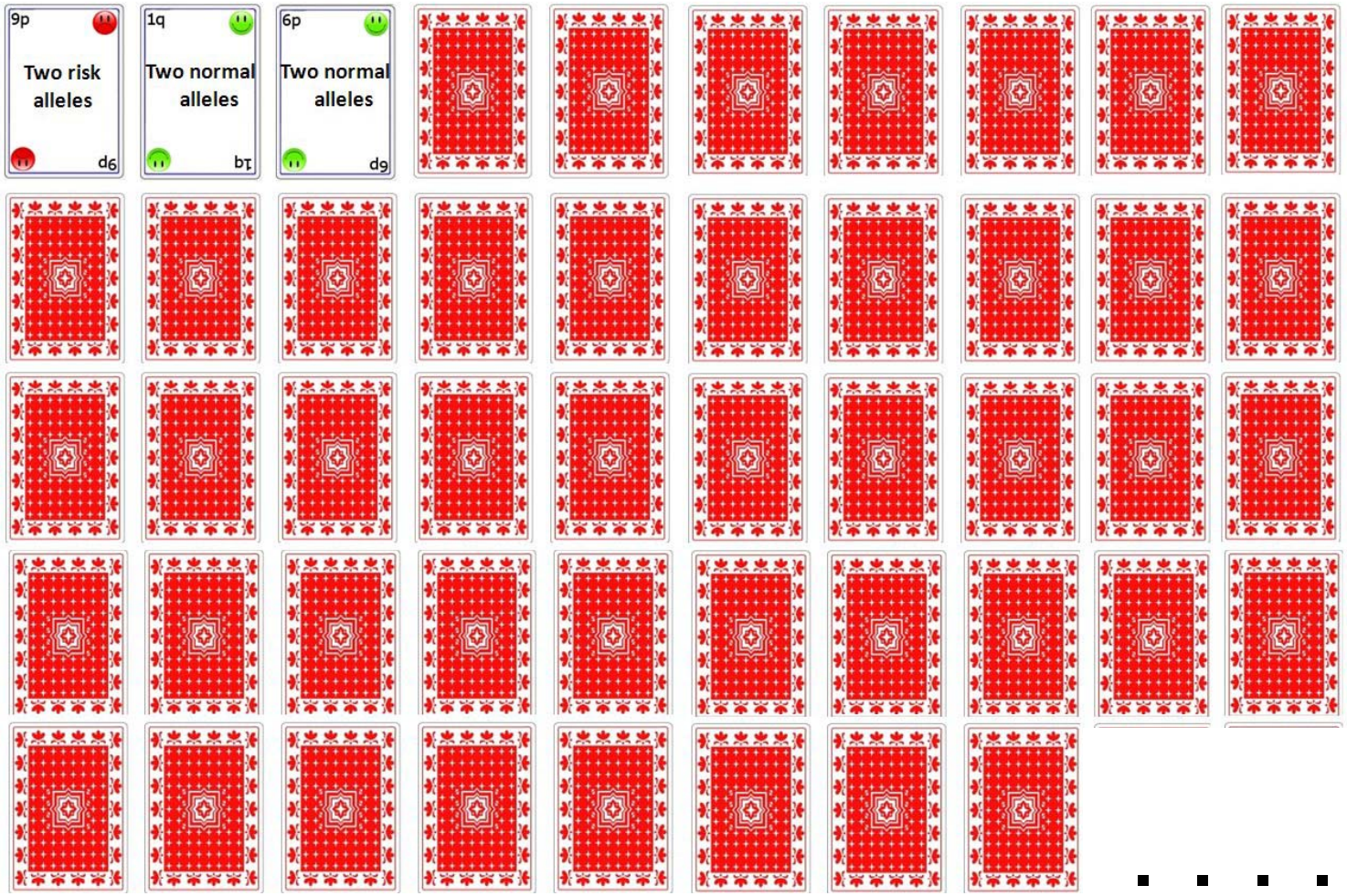
Computing individual probability



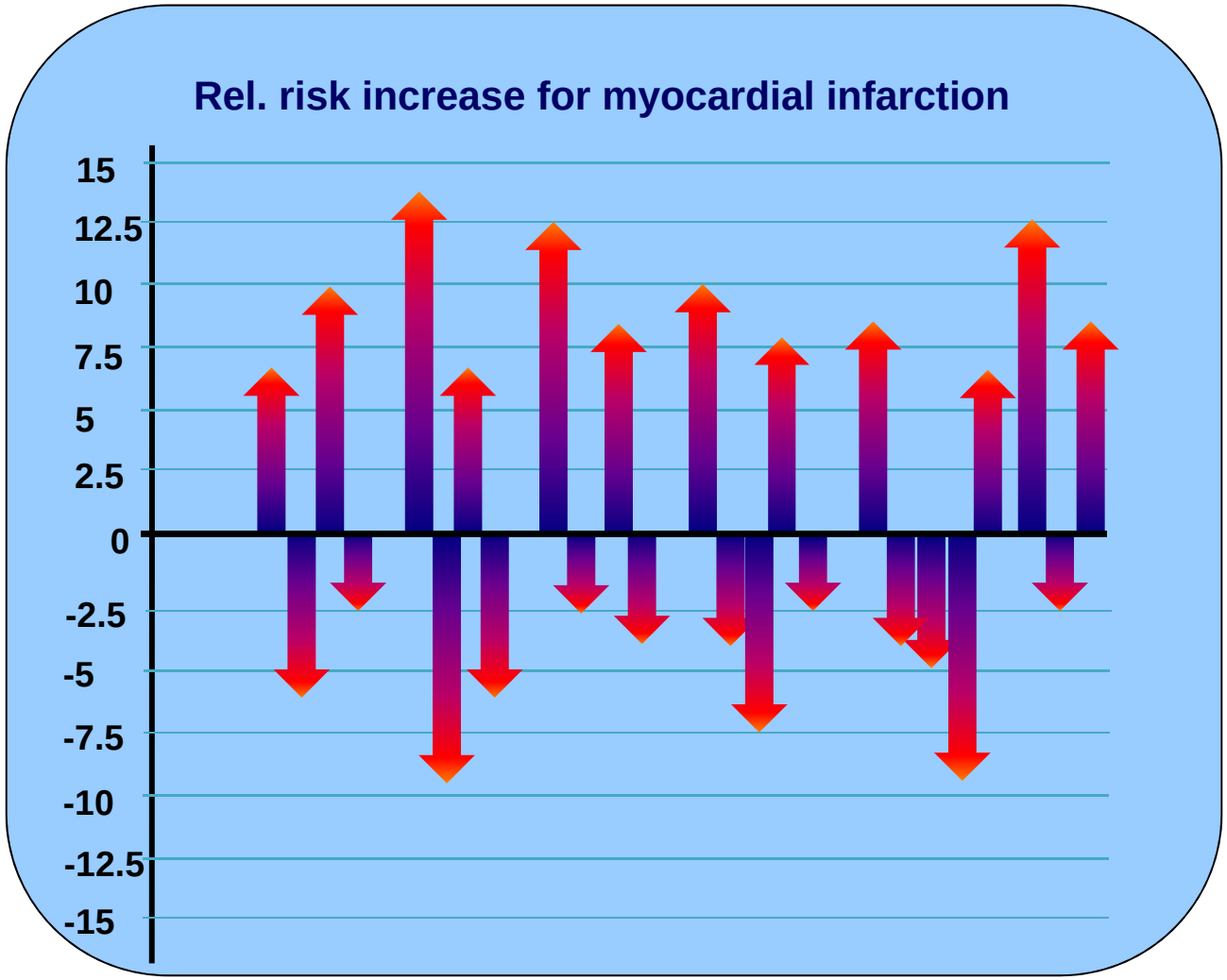
Computing individual probability



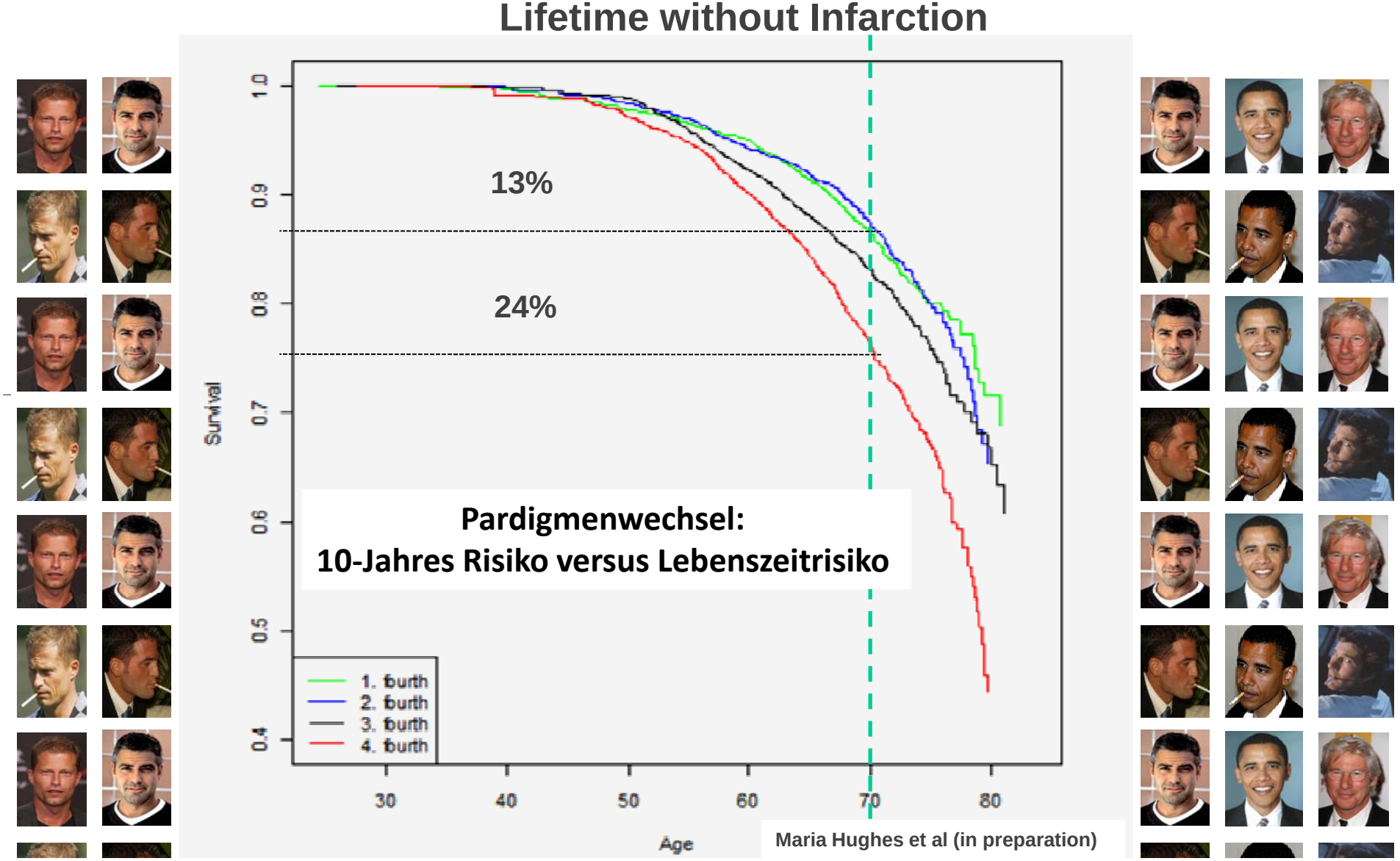
Computing individual probability



Relative Risiko verglichen mit wem?



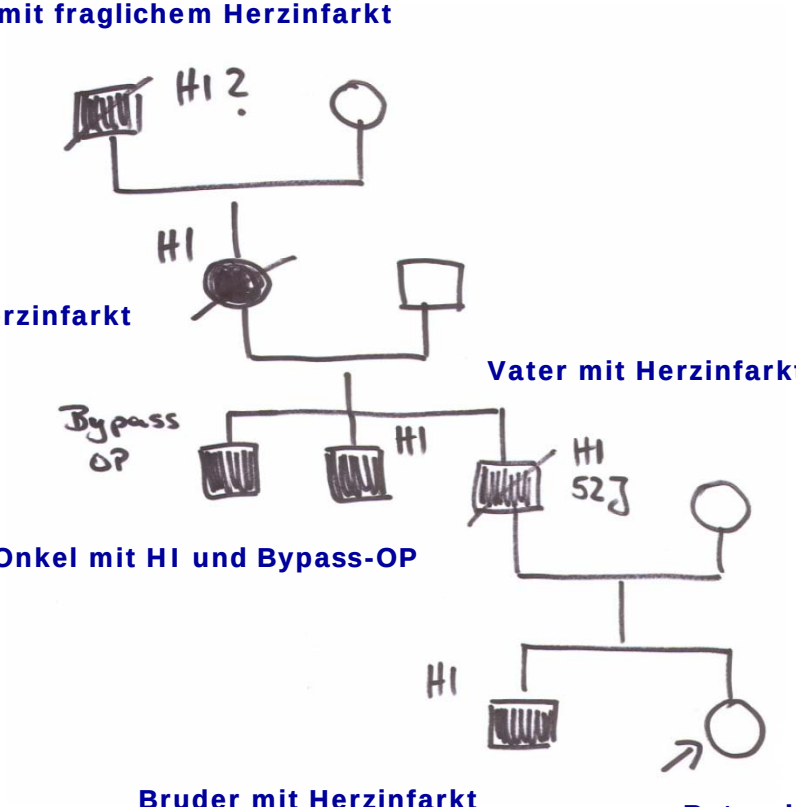
Who has a higher risk to suffer from MI within 10 years time?



„Ich fürchte, ich bin die nächste, die dran ist!“

Dr. Claudia Benndorf-Fehlandt (53)

Uropa mit fraglichem Herzinfarkt



Oma mit Herzinfarkt

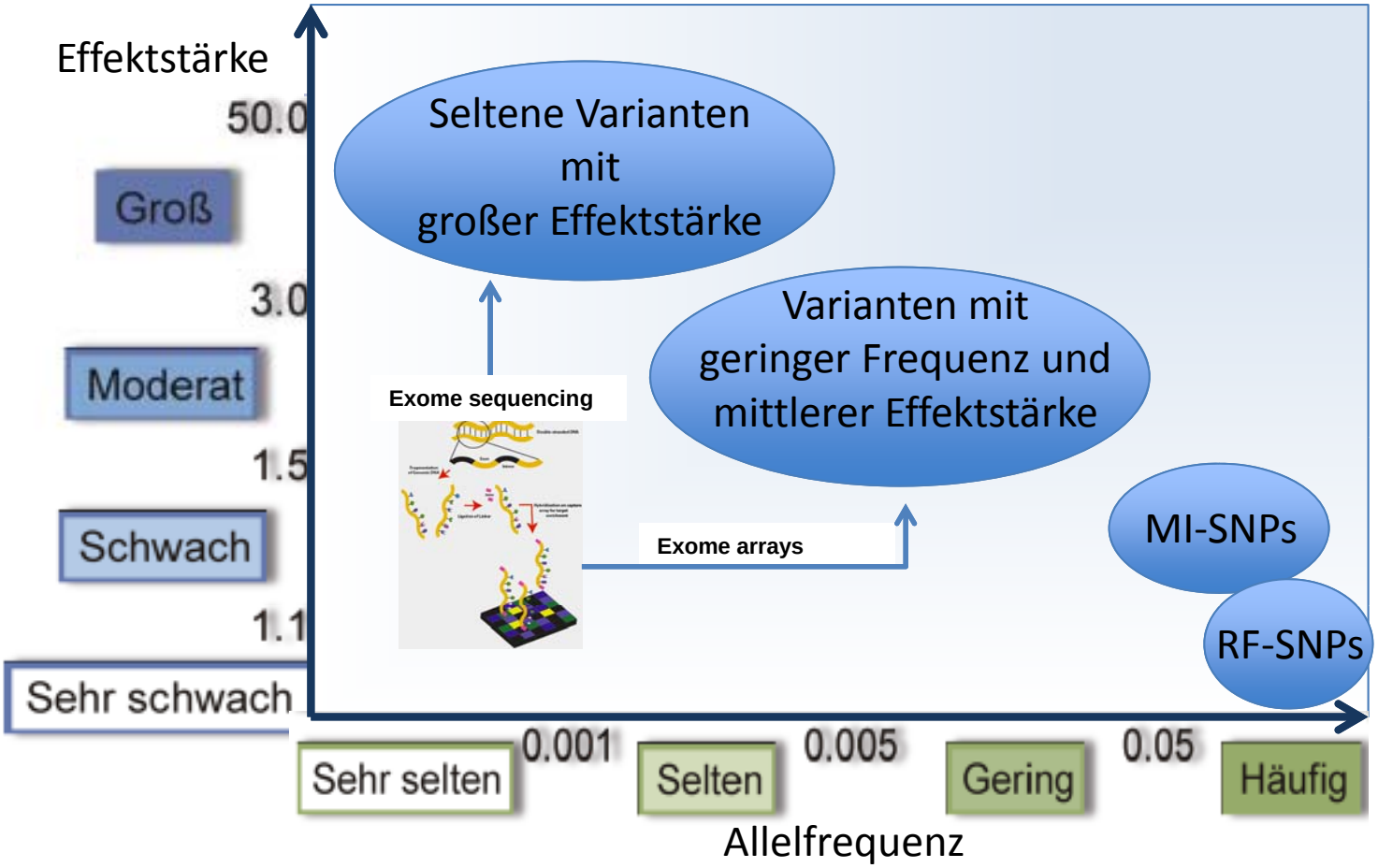
Vater mit Herzinfarkt

Zwei Onkel mit HI und Bypass-OP

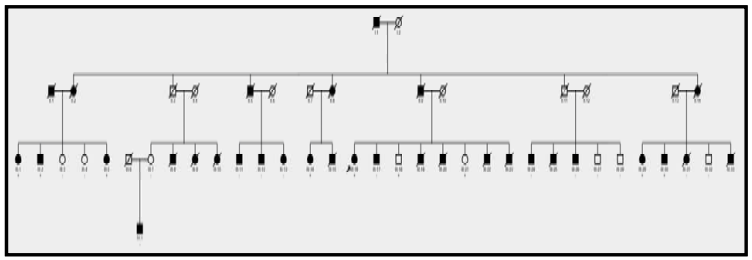
Bruder mit Herzinfarkt

Ratsuchende

Problem: Missing heritability

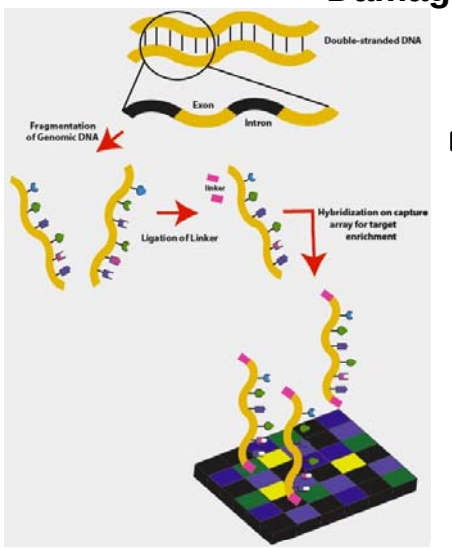


From an unusual family to a new mechanism of myocardial infarction



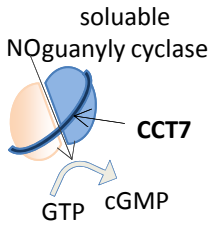
⇨

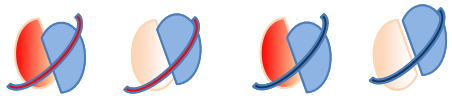
Exome sequencing



⇨

Damaging mutations in: ***GUCY1A3****
CCT7*
ETFDH
GCLC





2 mutations : 100% affected
1 mutation : 60% affected ⇨ **2-point LOD score = 5.68!**
0 mutation : 20% affected

Jeanette Erdmann, Stephanie Tennstedt, Anja Medack, Frank Kaiser, **Lübeck**
Ulrike Esslinger, Klaus Stark, Markus Fischer, Christian Hengstenberg, **Regensburg**
Tim Strom, Thomas Meitinger, **München**

- **„Monogene Erkrankungen“**

  Herzmuskelerkrankungen

  Rhythmusstörungen

Genetik der Kardiomyopathien

Tab. 2 Krankheitsgene der DCM und HCM

Proteinlokalisation	Genname	Symbol	DCM	HCM
Zellmembran	Caveolin 3	*CAV3*		+
	M_2-Muskarinrezeptor	*CHRM2*	+	
	Dystrophin	*DMD*	+	
	Laminin α_4	*LAMA4*	+	
	Presenilin 1/2	*PSEN1/2*	+	
	β-Sarkoglykan	*SCGB*	+	
	δ-Sarkoglykan	*SGCD*	+	
Zellkern/Kernmembran	Emerin	*EMD*	+	
	„Eyes absent 4"	*EYA4*	+	
	„Four-and-a-half LIM protein 2"	*FHL2*	+	
	Lamin A/C	*LMNA*	+	
	Thymopoietin	*TMPO*	+	
Z-Scheibe/Zytoskelett	α-Actinin 2	*ACTN2*	+	+
	„Cardiac muscle LIM protein"	*CSRP3*		+
	Desmin	*DES*	+	
	α-Dystrobrevin	*DTNA*	+	
	„Integrin-linked kinase"	*ILK*	+	
	„LIM binding domain 3"	*LDB3*	+	+
	Myozenin 2 (Calsarcin 1)	*MYOZ2*	+	+
	Myopalladin	*MYPN*	+	
	Nebulette	*NEBL*	+	
	Nexilin	*NEXN*	+	+
	Telethonin	*TCAP*		+
	Titin	*TTN*	+	+
	Vinculin	*VCL*		+
Sarkomer	α-kardiales Aktin 1	*ACTC*	+	+
	Myosinbindendes Protein C	*MYBPC3*	+	+
	α-Myosin, schwere Kette	*MYH6*	+	+
	β-Myosin, schwere Kette	*MYH7*	+	+
	Regulatorisches Myosin, leichte Kette	*MYL2*	+	+
	Essenzielles Myosin, leichte Kette	*MYL3*		+
	„Myosin light chain kinase"	*MYLK2*		+
	Kardiales Troponin C	*TNNC1*	+	+
	Kardiales Troponin I	*TNNI3*	+	+
	Kardiales Troponin T	*TNNT2*	+	+
	α-Tropomyosin	*TPM1*	+	+
Mitochondrium	Tafazzin	*G4.5*	+	
Ionenkanäle/-regulatoren	ATP-sensitiver Kaliumkanal/SURA2	*ABCC9*	+	
	Calreticulin 3	*CALR3*		+
	Phospholamban	*PLN*	+	+
	Kardialer Ryanodinrezeptor	*RyR2*	+	
	Natriumkanal Typ V	*SCN5A*	+	
Glanzstreifen	Desmoplakin	*DSP*	+	
	Junctophilin 2	*JPH2*		+
	Plakoglobin	*JUP*	+	
	Metavinculin	*VCL*	+	
Verschiedenes	„BCL-2 associated athanogene 3"	*BAG3*	+	
	α-Crystallin B	*CRYAB*	+	
	RNA-bindendes Protein 20	*RBM20*	+	

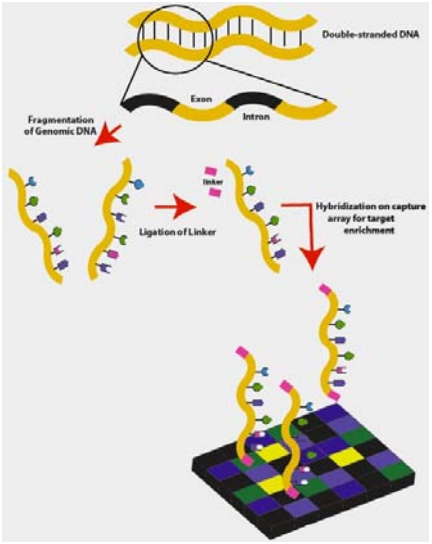
+ Etabliertes Krankheitsgen. **DCM** Dilatative Kardiomyopathie; **HCM** hypertrophe Kardiomyopathie.

Meder B und Katus H
Internist 2012 · 53:408–418

Large scale exome sequencing

Kardiomyopathie/Herzrhythmusstörung

Exome sequencing



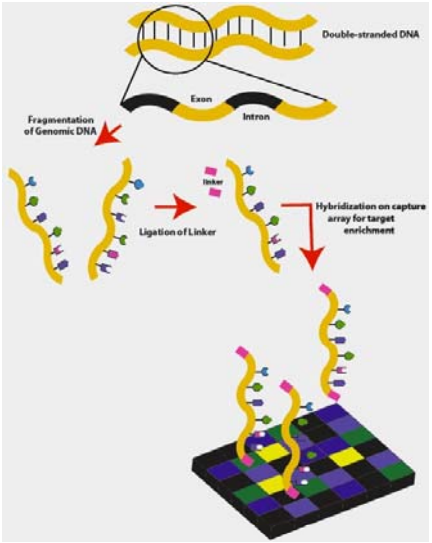
Large scale exome sequencing

Dilatative Kardiomyopathie

312 DCM Patienten

246 Kontrollen

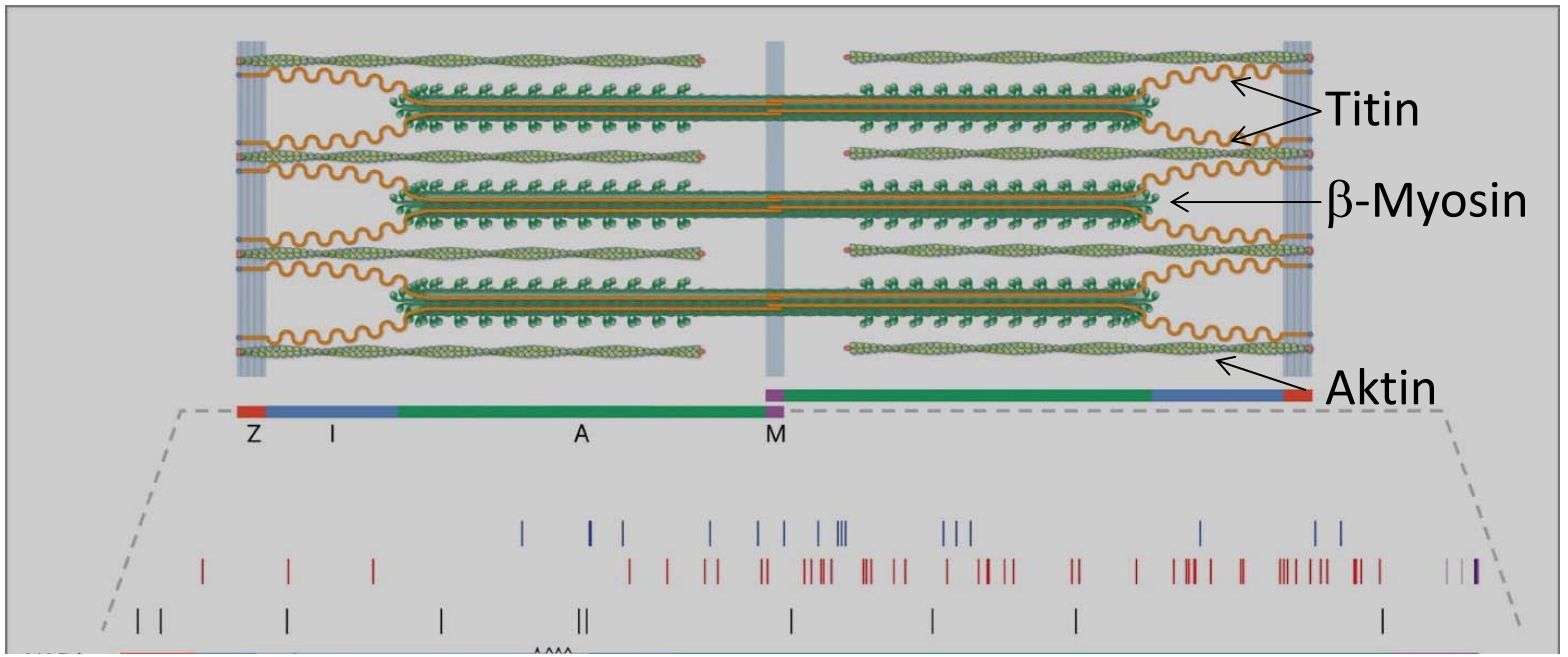
Exome sequencing



Herman DS et al. N Engl J Med 2012;366:619-628.

Dilatative Kardiomyopathie

Titin Mutationen als Hauptursache der DCM



Bei 27% von DCM Patienten fanden sich Titin Mutationen
(bei Kontrollen 3%, $P=9\times10^{-14}$)

Herman DS et al. N Engl J Med 2012;366:619-628.

Dilatative Kardiomyopathie

Titin Mutationen als Hauptursache der DCM

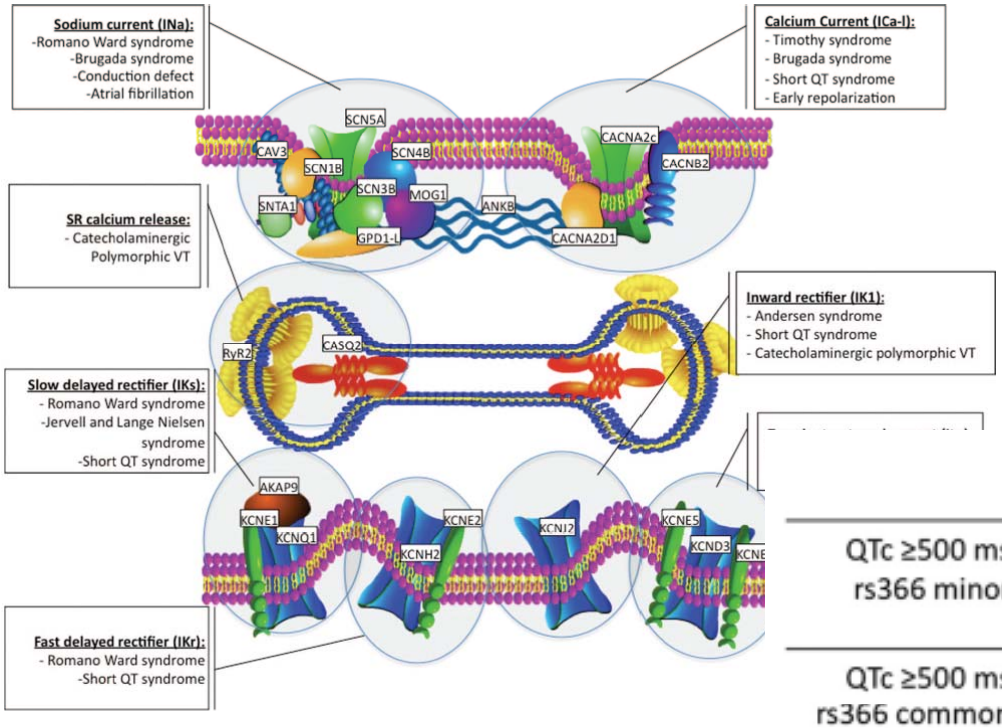
aber

Wenn man 10.000 Gesunde sequenziert – findet man
300 Titin Mutationen, obwohl
von 10.000 Personen nur 5 eine DCM entwickeln.

Bei 27% von DCM Patienten fanden sich Titin Mutationen
(bei Kontrollen 3%, $P=9\times10^{-14}$)

Herman DS et al. N Engl J Med 2012;366:619-628.

Genetik der Herzrhythmusstörungen



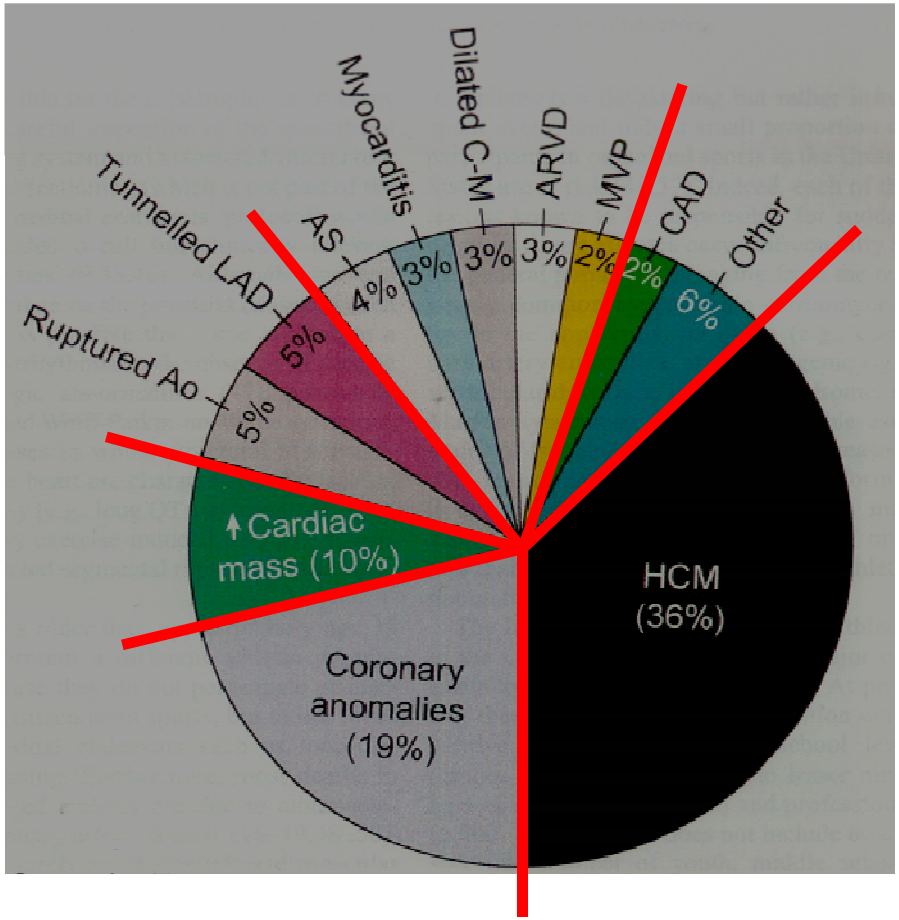
LQTS risk stratification scheme

QTc ≥500 ms rs366 minor	4.08	6.24	7.18	10.97
QTc ≥500 ms rs366 common	2.78	4.25	4.89	7.47
QTc <500 ms rs366 minor	1.47	2.24	2.58	3.95
QTc <500 ms rs366 common	1	1.53	1.76	2.69
	LQT1 Males	LQT1 Females	LQT2/3 Males	LQT2/3 Females

HR <2 | HR 2 - 4 | HR > 4 ≤ 5 | HR > 5

Napolitano et al
***Circulation*. 2012;125:2027-2034**

Sport und plötzlicher Herztod:



Prinzipien:

1. jeder trägt viele Risikoallele
2. multiple Gen/Gen // Umwelt Interaktionen
3. komplexere Risikoprädiktion
4. komplexere Beratungssituation