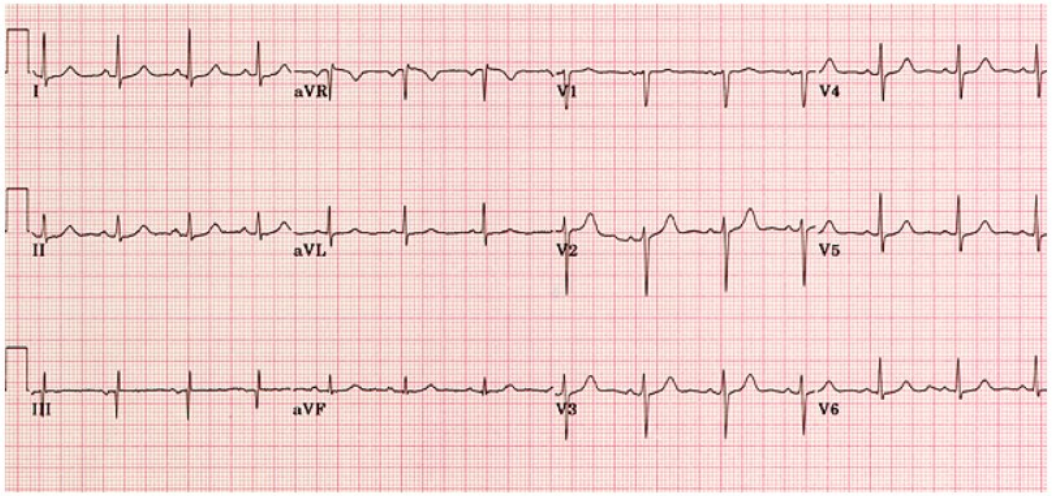
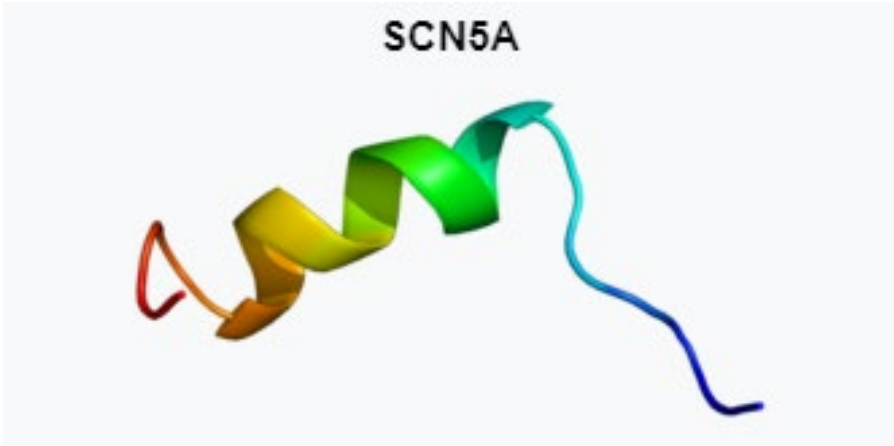
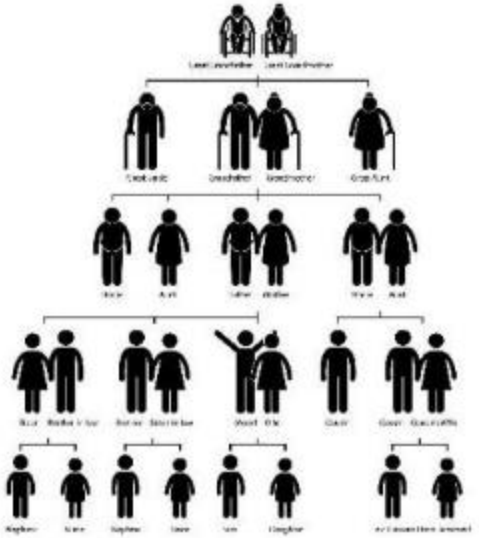
Amsterdam UMC
Universitair Medische Centra

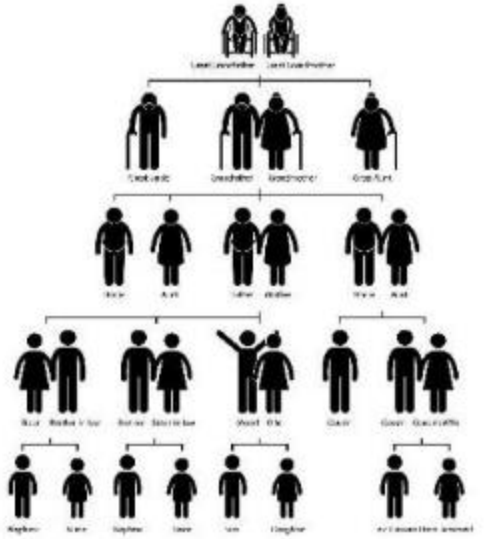
ERFELIJKHEID VAN BRUGADA SYNDROOM

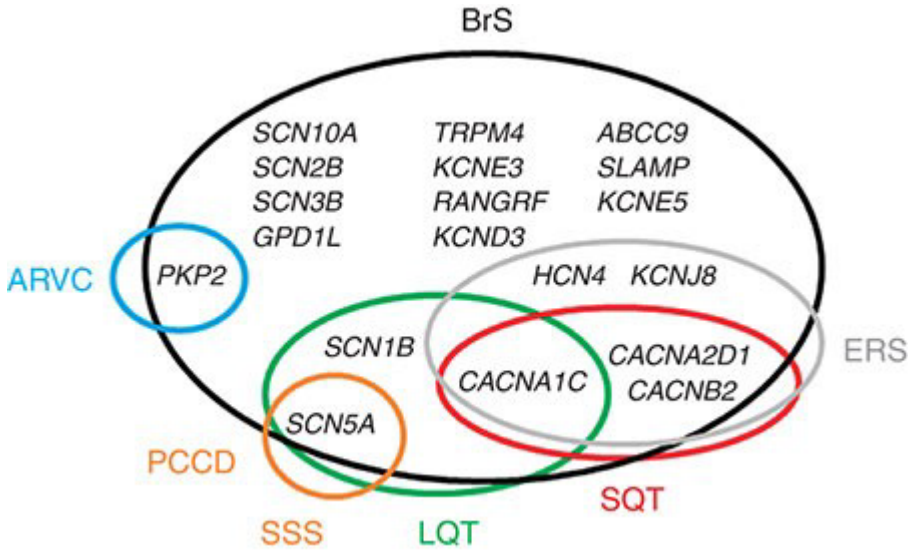
Dr. Saskia N. van der Crabben, Klinisch Geneticus Cardiogenetica
ERN GUARD-Heart for rare and low prevalence complex diseases of the heart

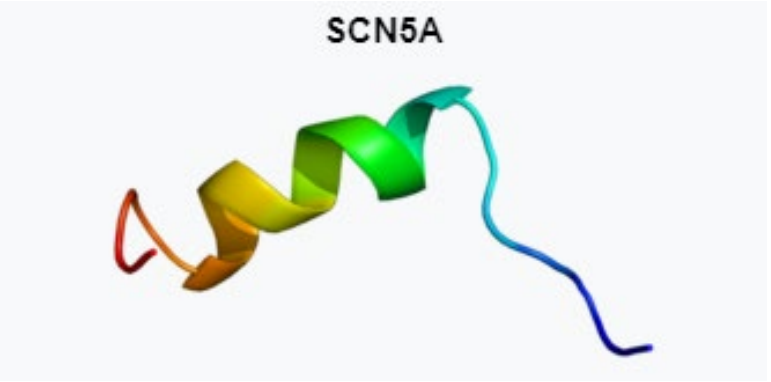

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

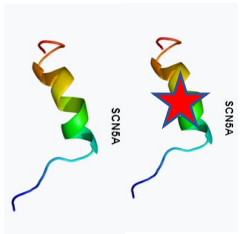

SCN5A

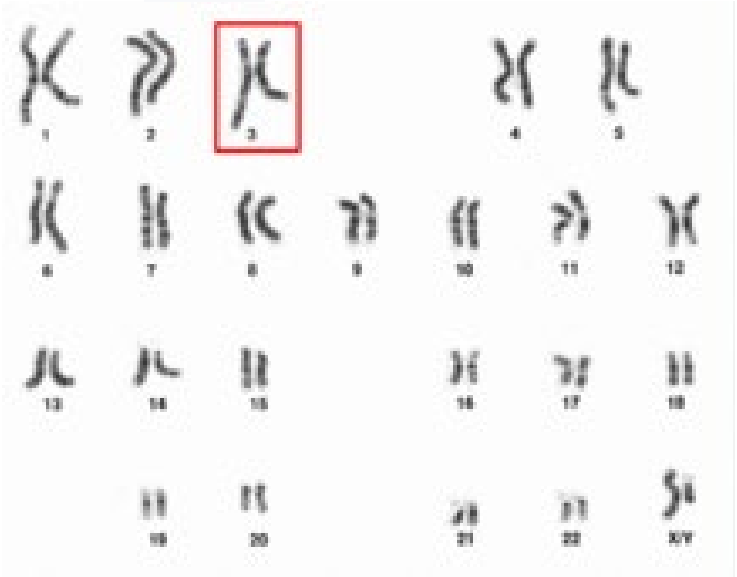


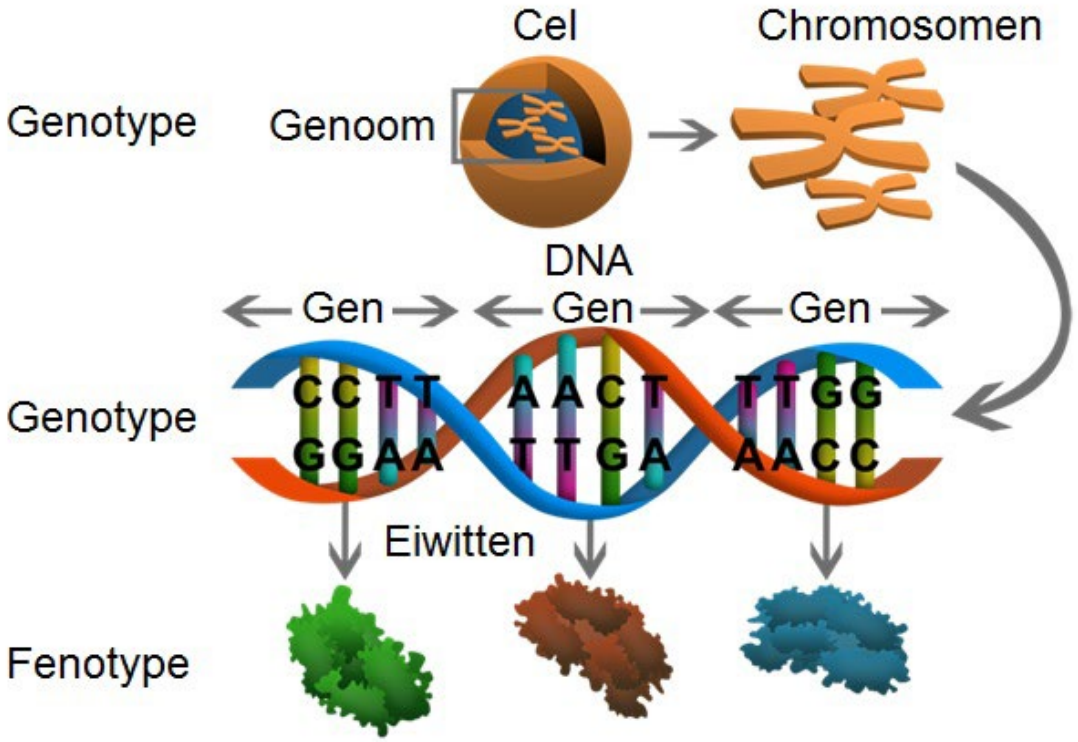


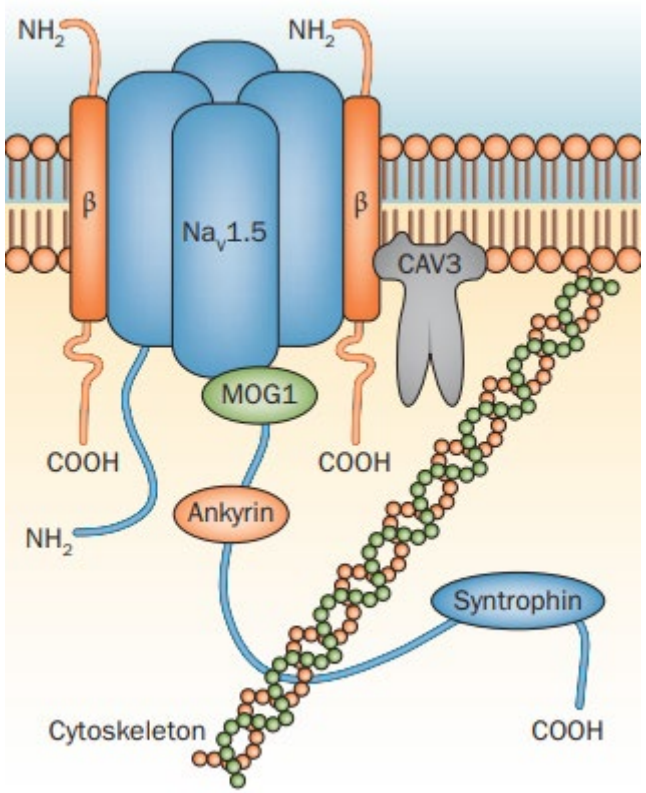

BrS
SCN10A
SCN2B
SCN3B
GPD1L
TRPM4
KCNE3
RANGRF
KCND3
ABCC9
SLAMP
KCNE5
ARVC
PKP2
HCN4
KCNJ8
SCN1B
CACNA1C
CACNA2D1
CACNB2
ERS
SCN5A
PCCD
SQT
SSS
LQT


SCN5A

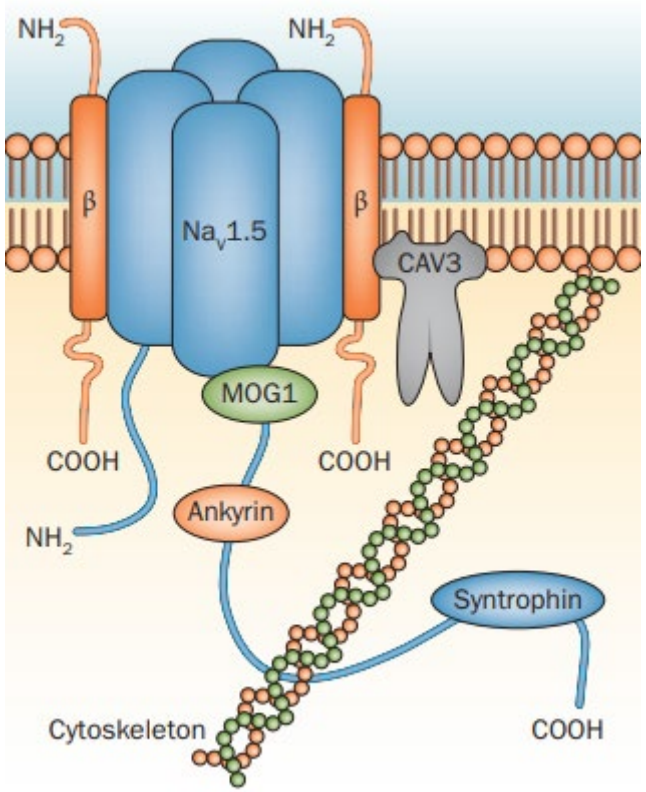

SCN5A
SCN5A



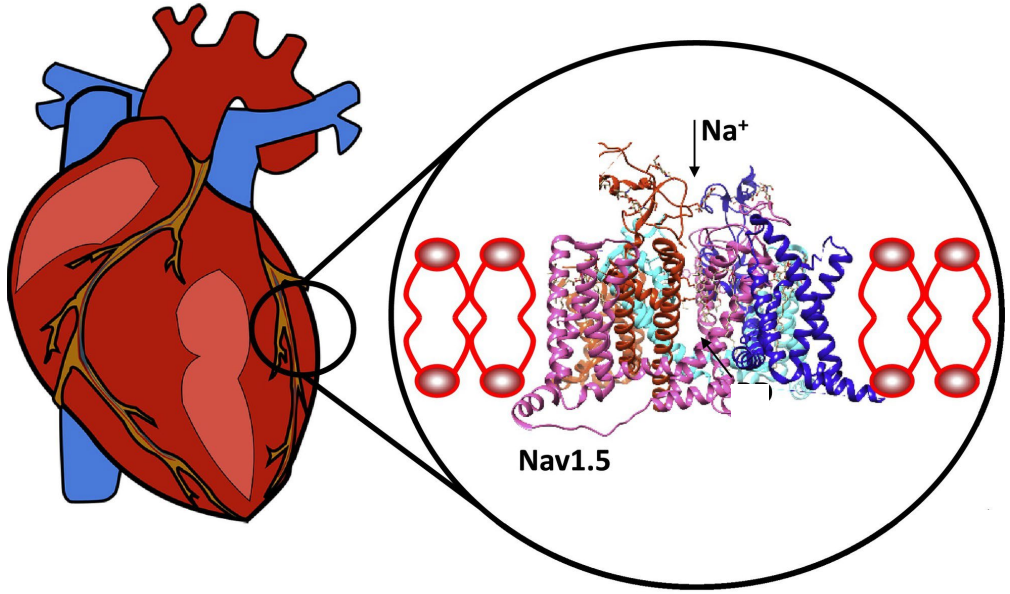


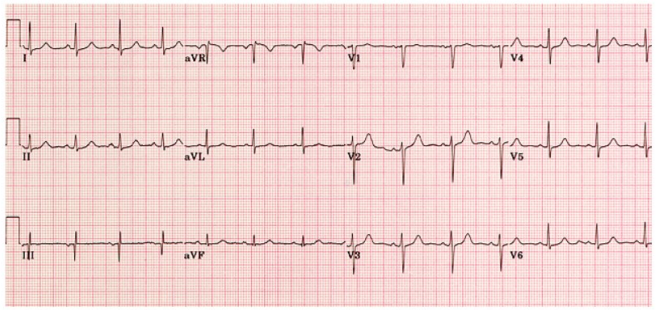


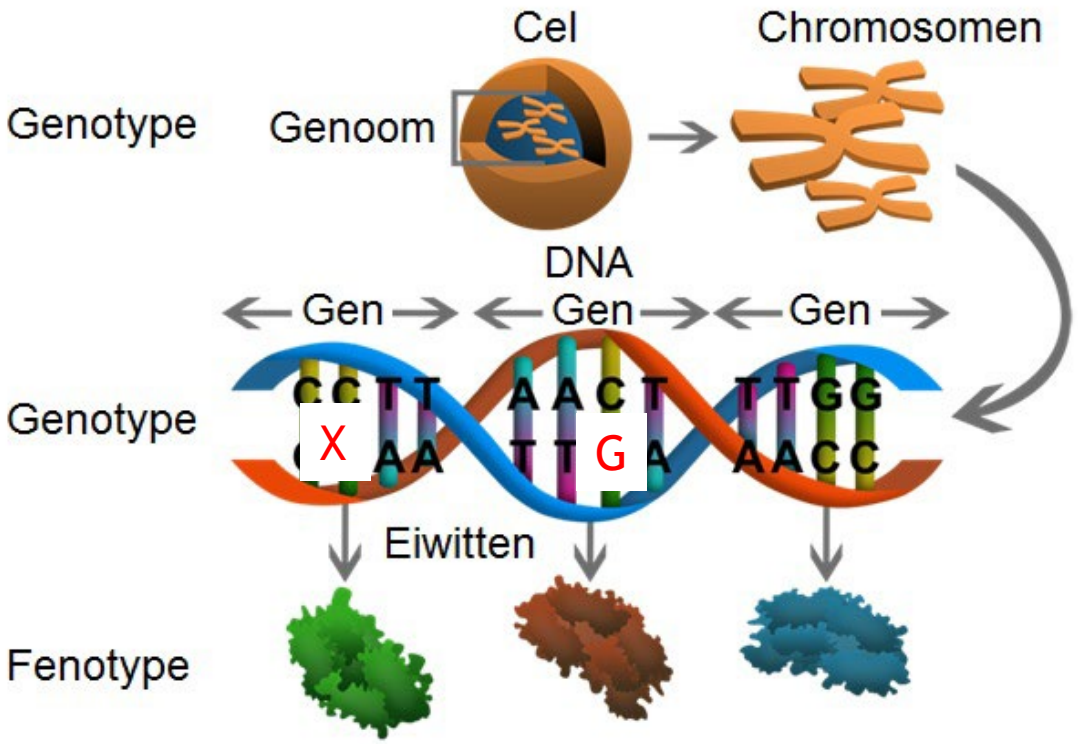
Liu, M. *et al. Nat. Rev. Cardiol.* **11**, 607–615 (2014)

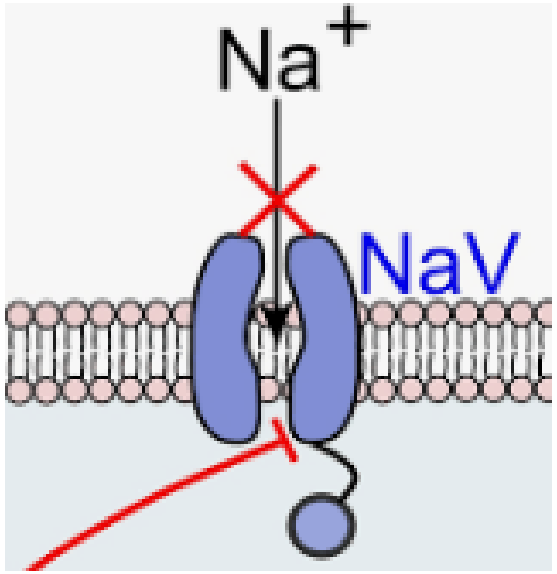


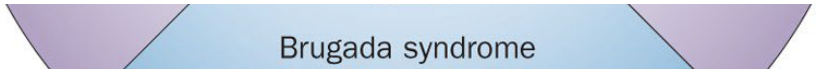
Liu, M. *et al. Nat. Rev. Cardiol.* **11**, 607–615 (2014)



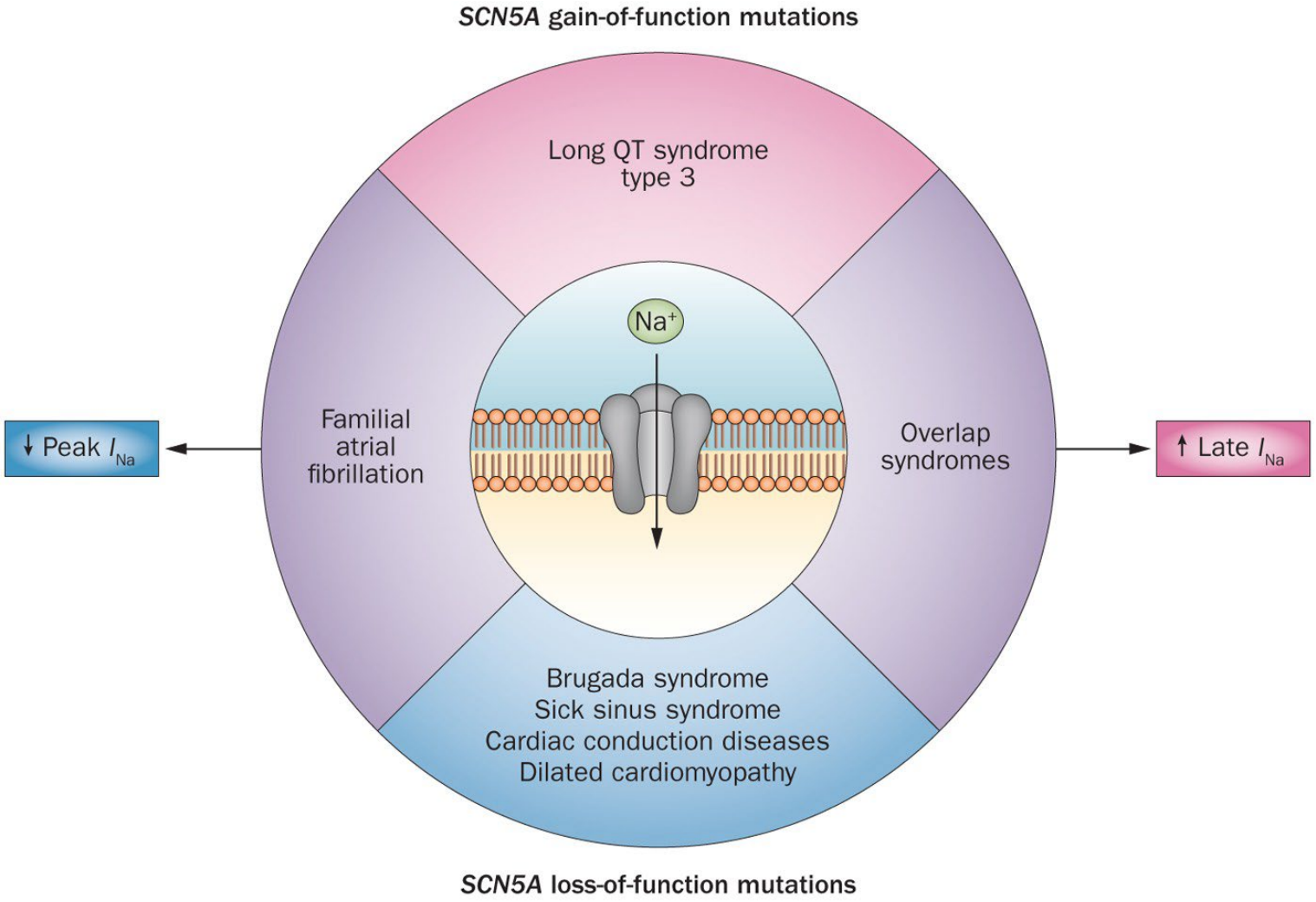



Cel
Chromosomen
Genotype
Genoom
DNA
Gen
Gen
Gen
Genotype
X
G
Eiwitten
Fenotype

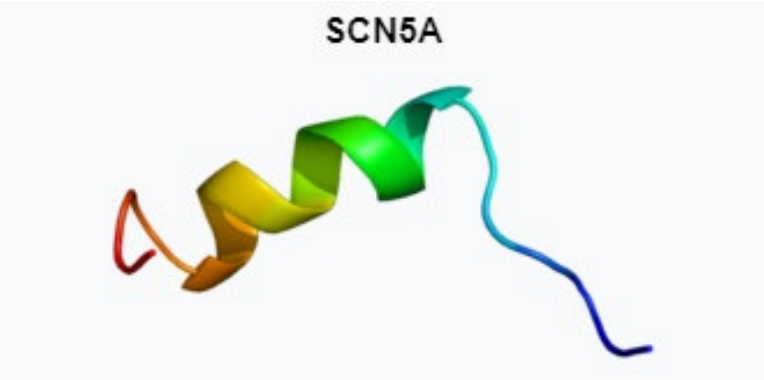

Na+
NaV



***SCN5A* loss-of-function mutations**

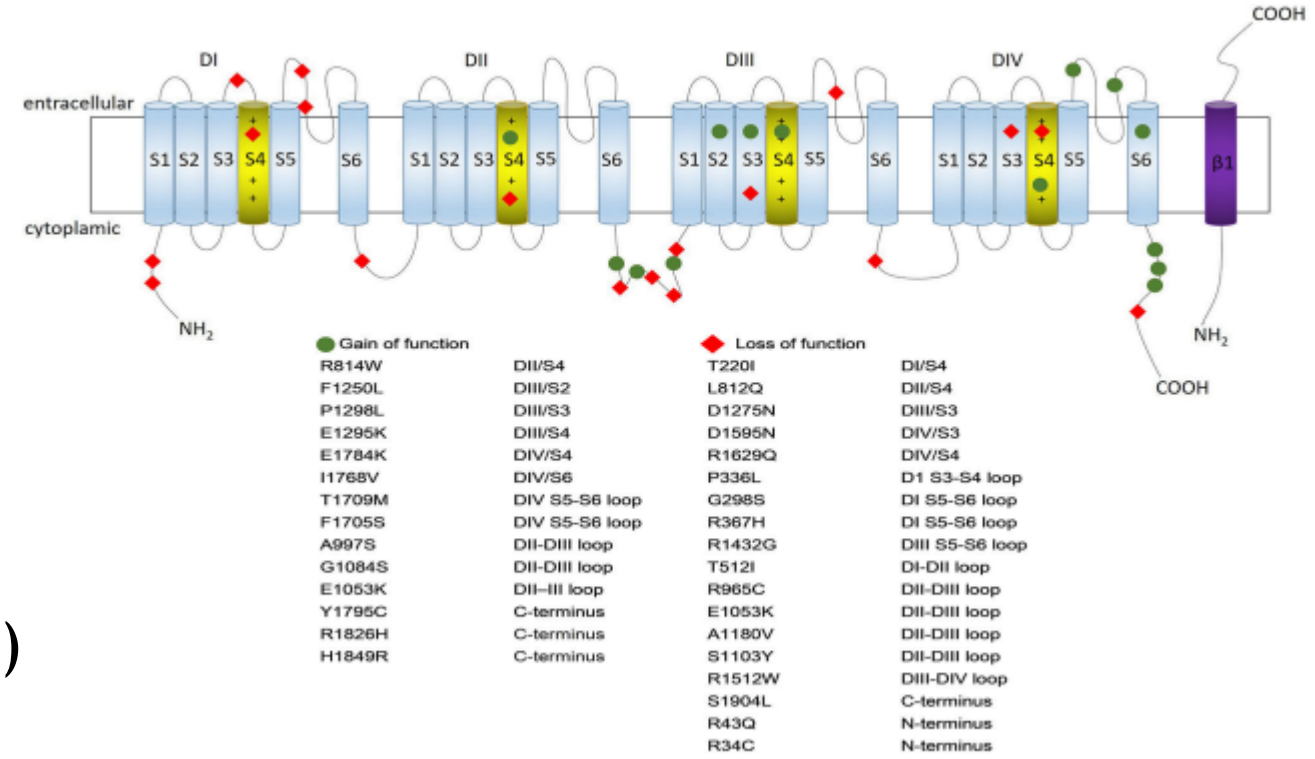


Liu, M. *et al. Nat. Rev. Cardiol.* **11**, 607–615 (2014)

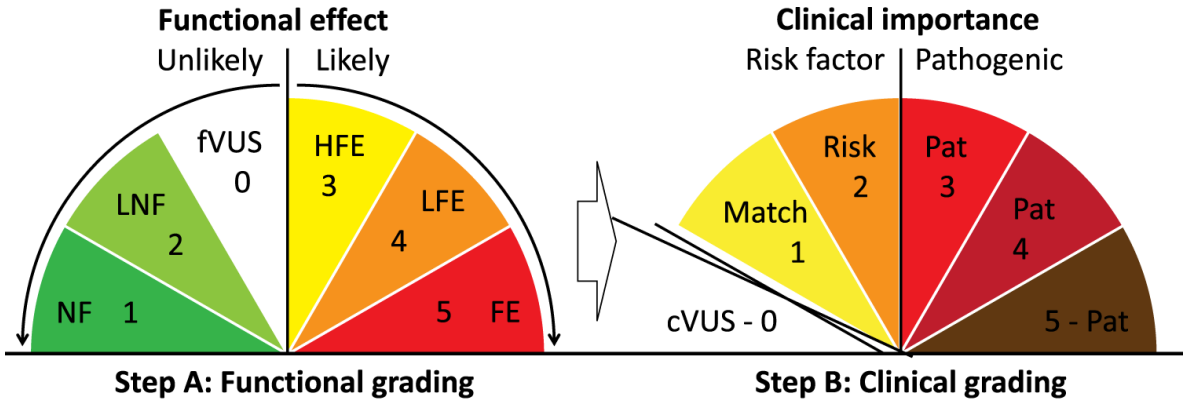


- Klasse 5
- Klasse 4
- Klasse 3 of VUS

(variant of unknown significance)



Li W. et al. Front Physiol, 2018



Step A: Functional grading

Step B: Clinical grading

NF	= Normal Function
LNF	= Likely Normal Function
fVUS	= functional VUS
HFE	= Hypothetical Functional Effect
LFE	= Likely Functional Effect / hypomorphic allele
FE	= Functional Effect (e.g. LoF or GoF)

cVUS	= clinical VUS
Match	= right type of gene for this phenotype
Risk	= known risk factor / variant-of-interest
Pat	= pathogenic variant, penetrance-graded when known

A **ACMG classification or ABC functional grading**

ACMG classification		ABC functional "A" grading
Pathogenic	**P**	**5** Proven functional effect
Likely pathogenic	**LP**	**4** Likely functional effect
		4 Hypomorphic allele
VUS	**«VUS+»**	**3** VUS with hypothetical effect
VUS		**0** VUS that cannot be classified
Likely benign	**LB**	**2** Likely normal function
Benign	**B**	**1** Normal function

B **Genotype-phenotype-based grading if A >2, giving a combined functional + clinical class**

Clinical "B" grading	Combined class clinical + functional	
5 Pathogenic, high penetrance	(+ 5)	**A**
4 Pathogenic, moderate penetrance	(+ 5)	**B**
3 Pathogenic	(+ 5)	**C**
2 Risk factor / susceptibility finding	(+ 4-5)	**D**
1 Potential gene-phenotype match	(+ 3-4)	**E**
0 No genotype-phenotype match	(+ 3)	**F**
	(0-2)	**0**

C **Selection of a standard comment based on combined class and clinical question**

Houge G. et al, Eur J Hum Genet 2022

CLINVAR

Germline classification

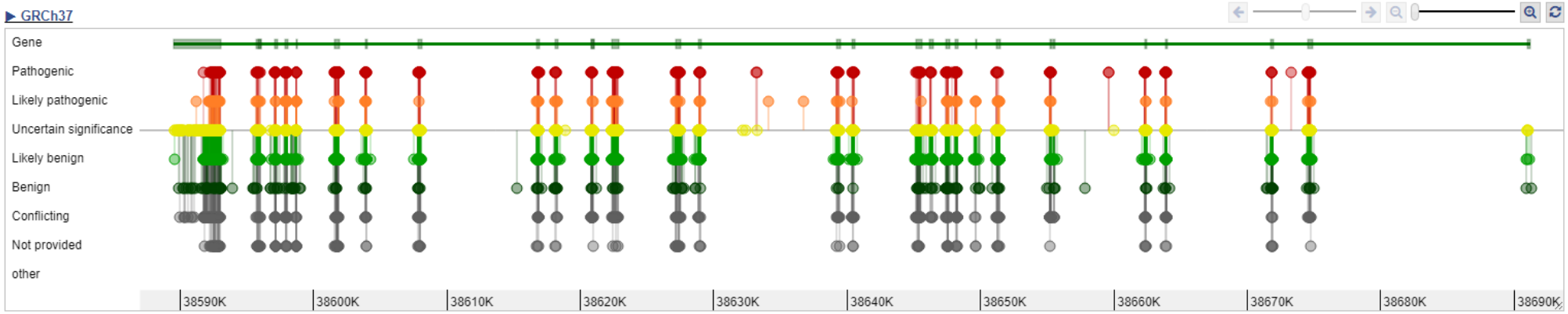
- [ ] Conflicting classifications (347)
- [ ] Benign (181)
- [ ] Likely benign (1,223)
- [ ] Uncertain significance (1,937)
- [ ] Likely pathogenic (187)
- [ ] Pathogenic (330)

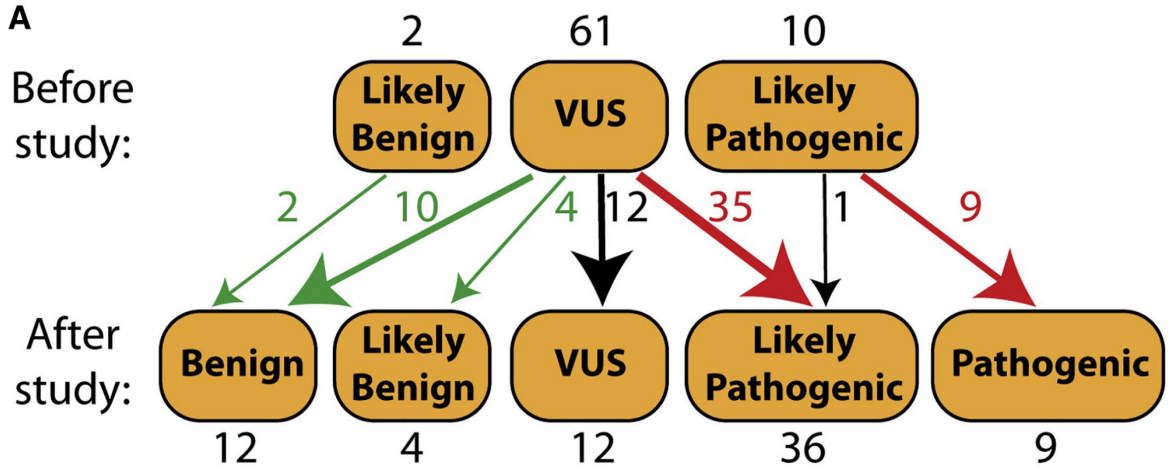
Types of conflicts

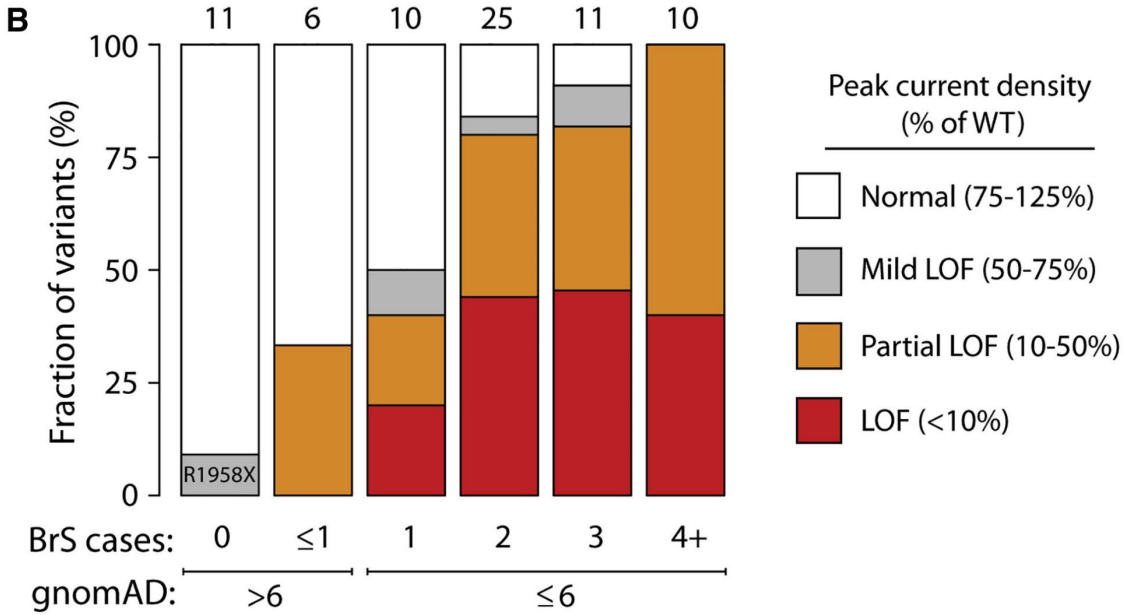
- [ ] P/LP vs LB/B (4)
- [ ] P/LP vs VUS (113)
- [ ] VUS vs LB/B (238)

Graphical view of search results ▲

▶ GRCh37







Glazer AM et. Al, Am J Human Genet 2020

Multidisciplinair Cardiogenetica Team

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Cardiologist

Dr M Baars
Clinical geneticist

Dr SN van der Crabben
Clinical geneticist

Dr W Kok
Cardiologist

Dr AC Houweling
Clinical geneticist

Prof dr Y Pinto
Cardiologist

Prof dr N Blom
Pediatric cardiologist

Prof dr JWM Niessen
Pathologist

Dr AJA Groffen
Molecular geneticist

Dr EA Nannenberg
Clinical geneticist

Dr AMC Vermeer
Clinical geneticist

Dr C van der Werf
Cardiologist

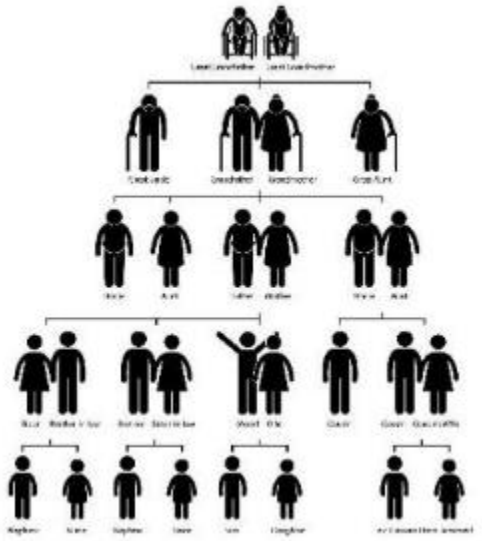
Prof dr AAM Wilde
Cardiologist

Drs J Nijman
Genetic counsellor

Drs MW Wagenaar
Physician assistant

Dr SA Clur
Pediatric cardiologist

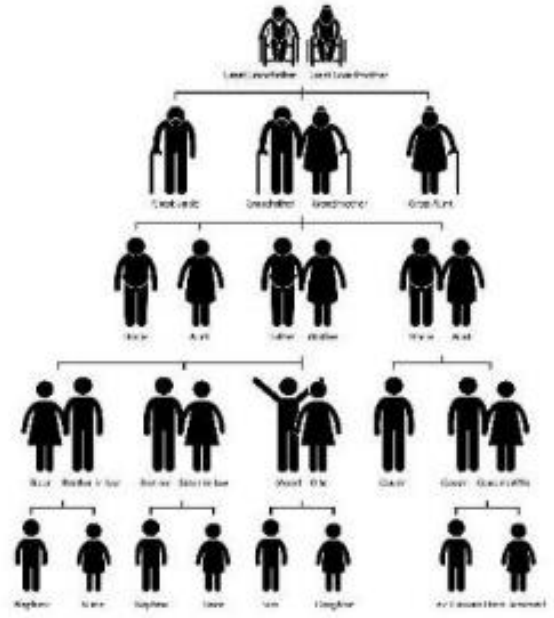
Dr IM Kuipers
Pediatric cardiologist

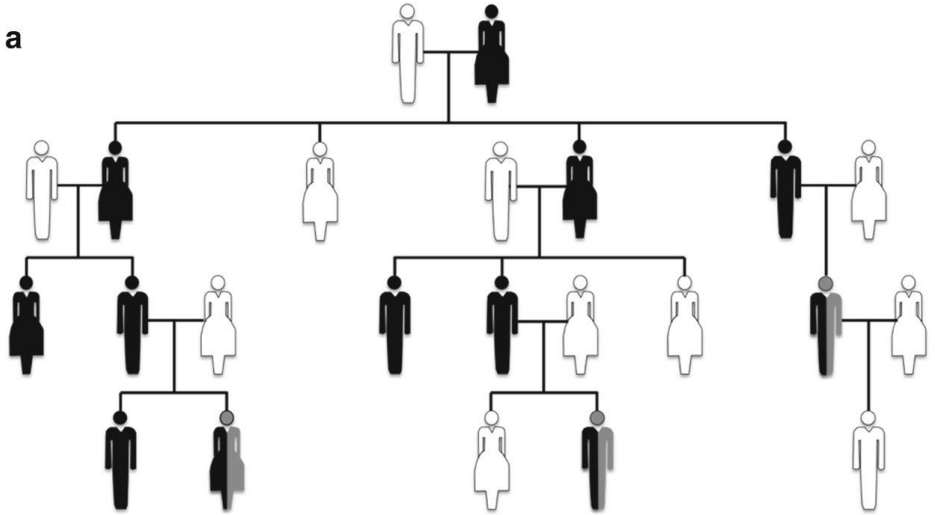


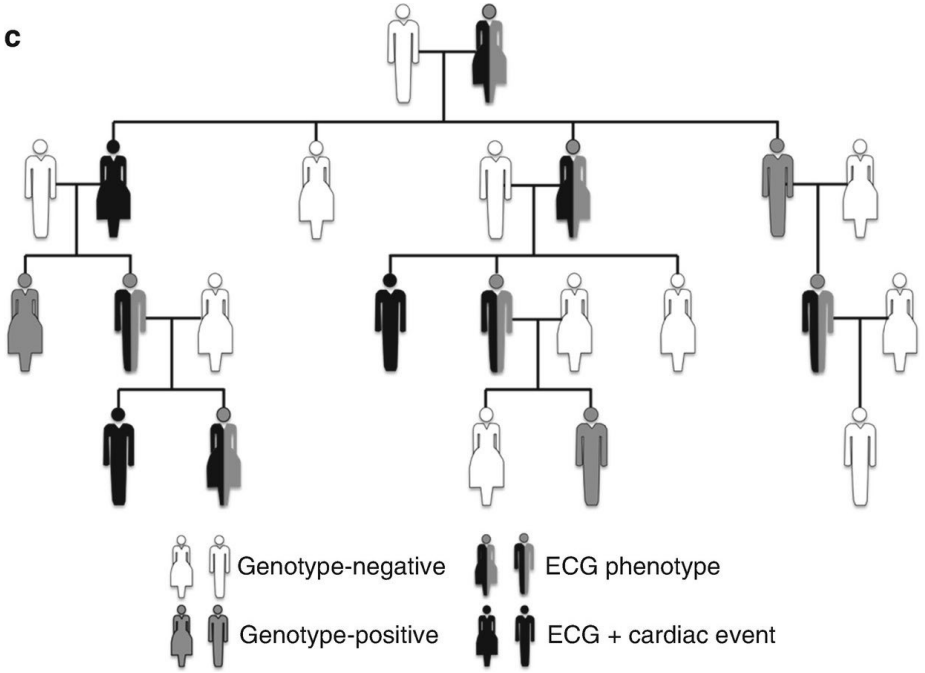

What is
Genetic
Counseling?

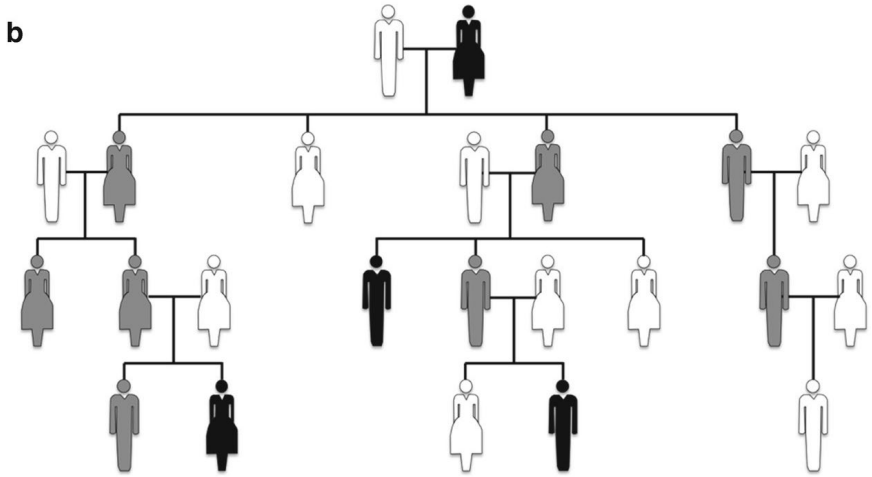
Klasse 5 SCN5A variant

DNA-test

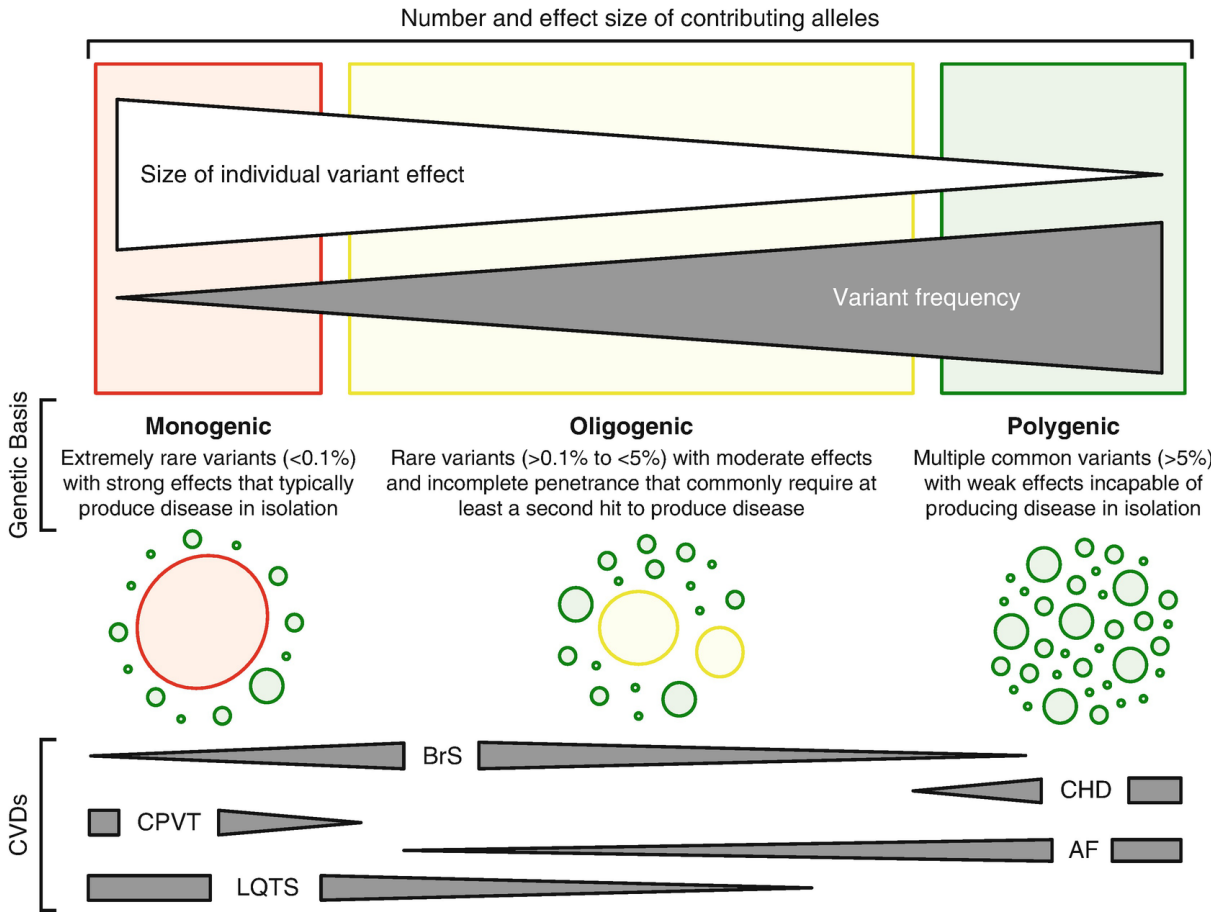






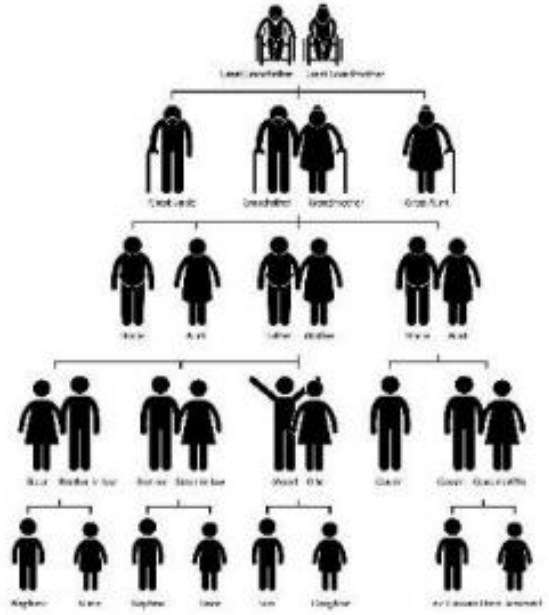


Giudicessi JR and Ackerman MJ, Cardiac Repolarization 2019


Number and effect size of contributing alleles
Size of individual variant effect
Variant frequency
Genetic Basis
Monogenic
Extremely rare variants (<0.1%) with strong effects that typically produce disease in isolation
Oligogenic
Rare variants (>0.1% to <5%) with moderate effects and incomplete penetrance that commonly require at least a second hit to produce disease
Polygenic
Multiple common variants (>5%) with weak effects incapable of producing disease in isolation
CVDs
BrS
CHD
CPVT
AF
LQTS

Klasse 4/4 SCN5A variant

DNA-test



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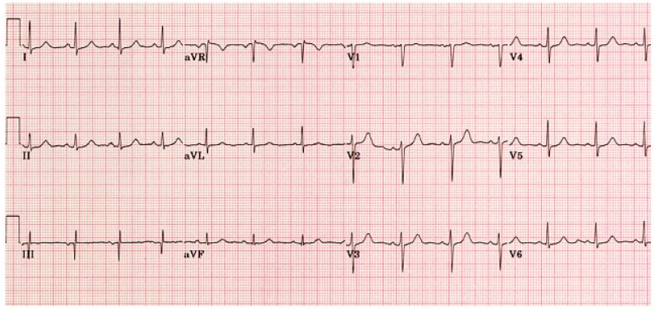
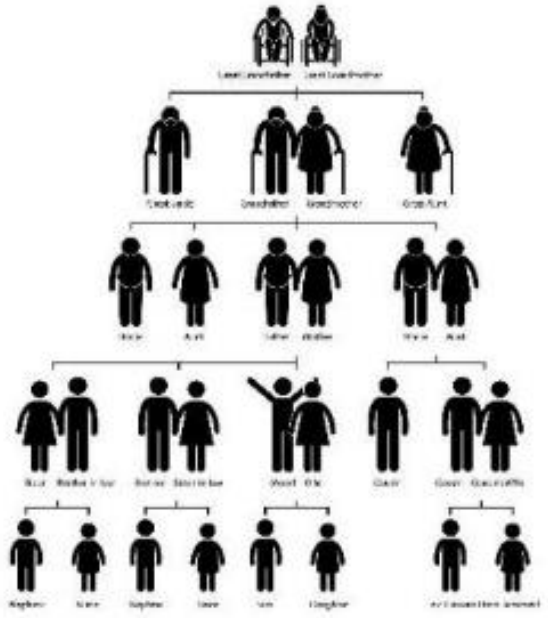


VUS SCN5A (of geen)



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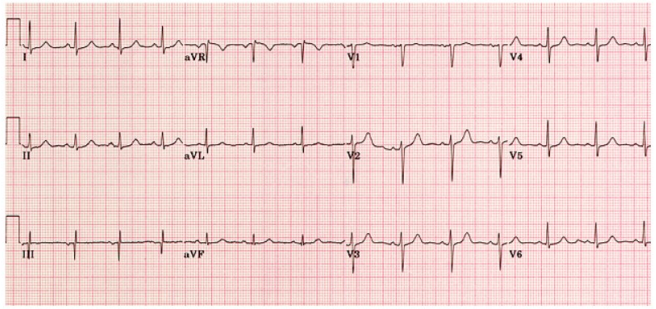


+

DNA-test

RESEARCH HIGHLIGHTS

GENE THERAPY

Gene therapy for Brugada syndrome

A novel mouse model of Brugada syndrome (BrS) is used to demonstrate that gene therapy targeting the protein trafficking regulator MOG1 (also known as RAN guanine nucleotide release factor) can successfully reverse the cardiac functional abnormalities associated with BrS. These findings were published in *Science Translational Medicine*.

Patients with BrS, an inherited arrhythmia syndrome characterized by ventricular tachycardia (VT) or fibrillation, have limited treatment options. Variants in *SCN5A* (encoding cardiac sodium channel $Na_v1.5$) are the cause of BrS in 25–30% of patients. Yu and colleagues generated a knock-in mouse model of BrS using the *Scn5a* variant p.G1746R, which corresponds to the p.G1743R variant that has been identified in some families with BrS. This $Scn5a^{G1746R/+}$ mouse model recapitulated several clinical features of BrS, including ST-segment abnormality, spontaneous VT and syncope. The researchers subsequently used the mouse model to test the efficacy of gene therapy for BrS.

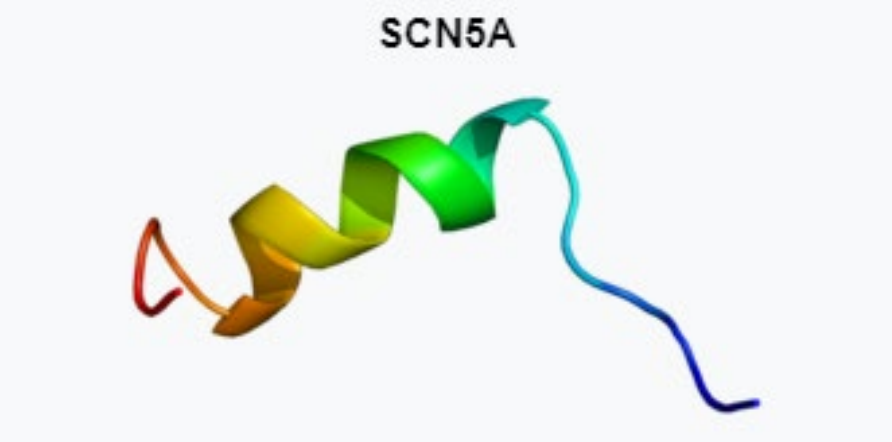
As the *SCN5A* coding sequence is too large to be cloned into adeno-associated virus (AAV) vectors, the investigators instead devised a gene therapy approach targeting MOG1, a chaperone protein involved in trafficking of $Na_v1.5$ to the cell surface. AAV9-Mog1 gene therapy increased cell surface levels of $Na_v1.5$ and reversed the features of BrS in $Scn5a^{G1746R/+}$ mice by normalizing the cardiac action potential, abolishing J waves and preventing VT. Furthermore, in humanized knock-in mice overexpressing the *SCN5A* mutation p.D1275N, which is implicated in dilated cardiomyopathy and cardiac conduction disorders, AAV9-Mog1 gene therapy attenuated the cardiac arrhythmia and cardiomyopathy phenotype by increasing fractional shortening and ejection fraction and reducing the incidence of heart block, sinus pause and sinus arrhythmias.

Together, these findings highlight a potential gene therapy strategy for BrS and a novel approach for other diseases caused by variants in large genes that exceed the loading capacity of AAV vectors.

Karina Huynh

Nature 2022

Conclusie



- Variant interpretatie + counseling in multidisciplinaire academische setting