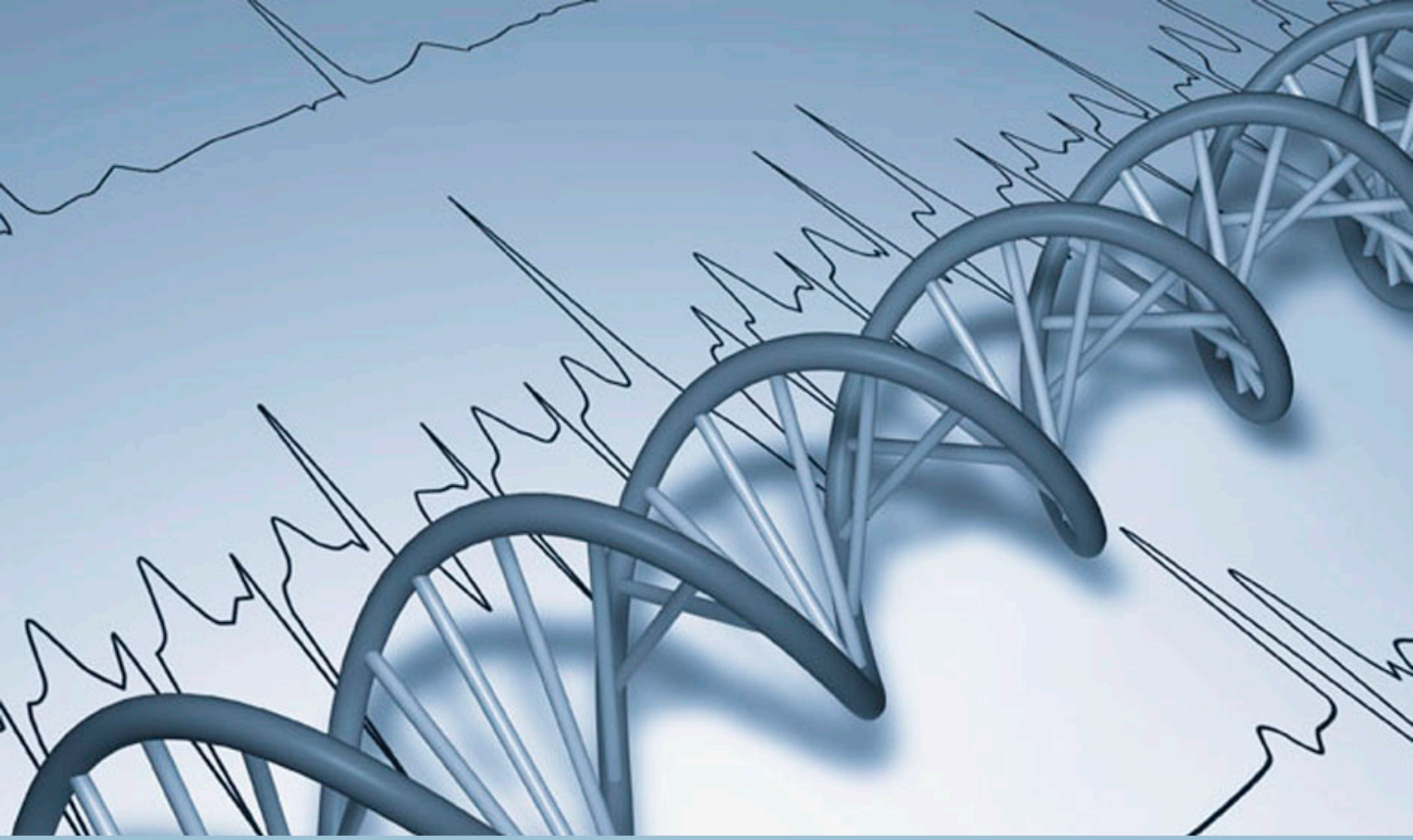
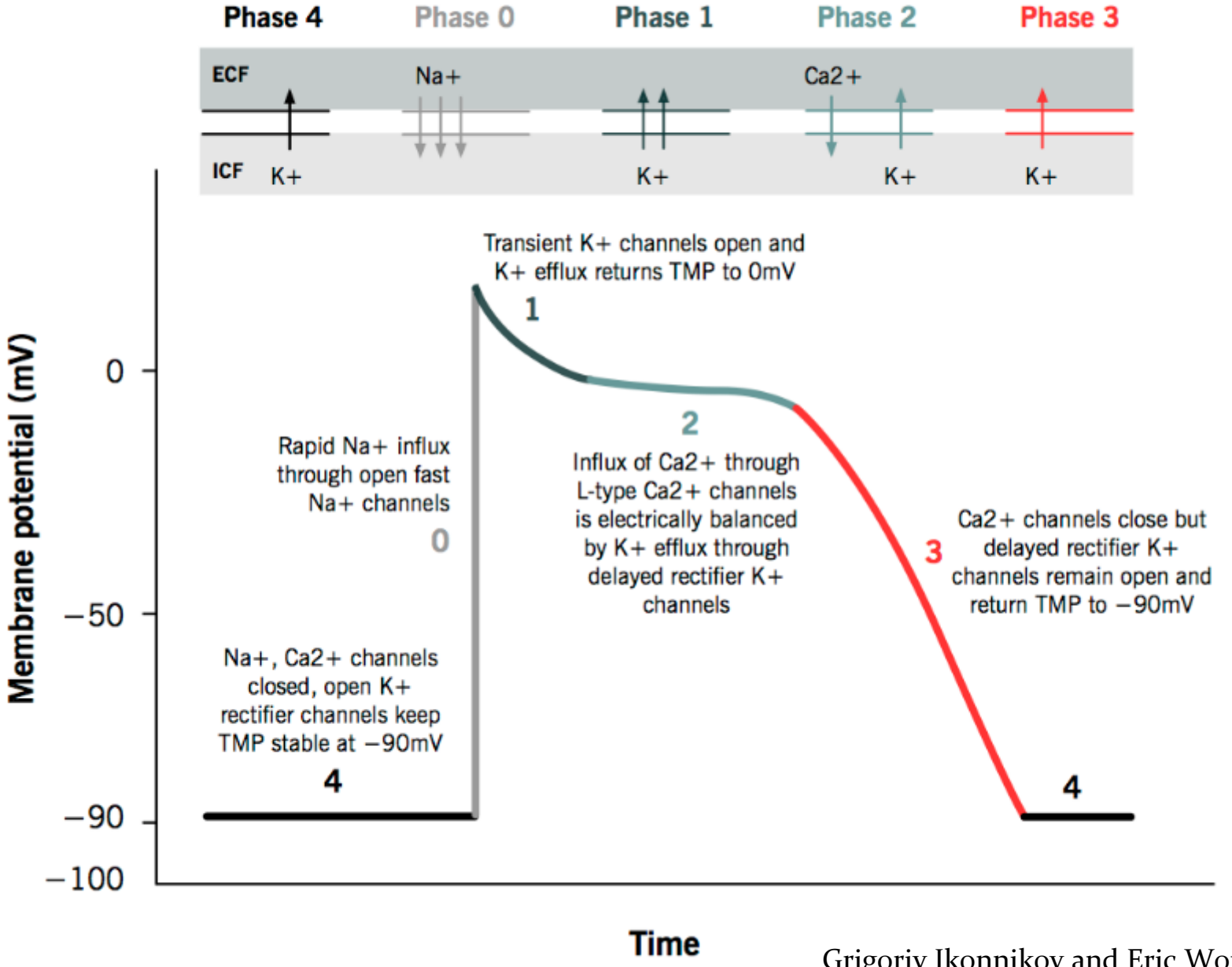


Which Genes Should Be Tested in LQTS and Why

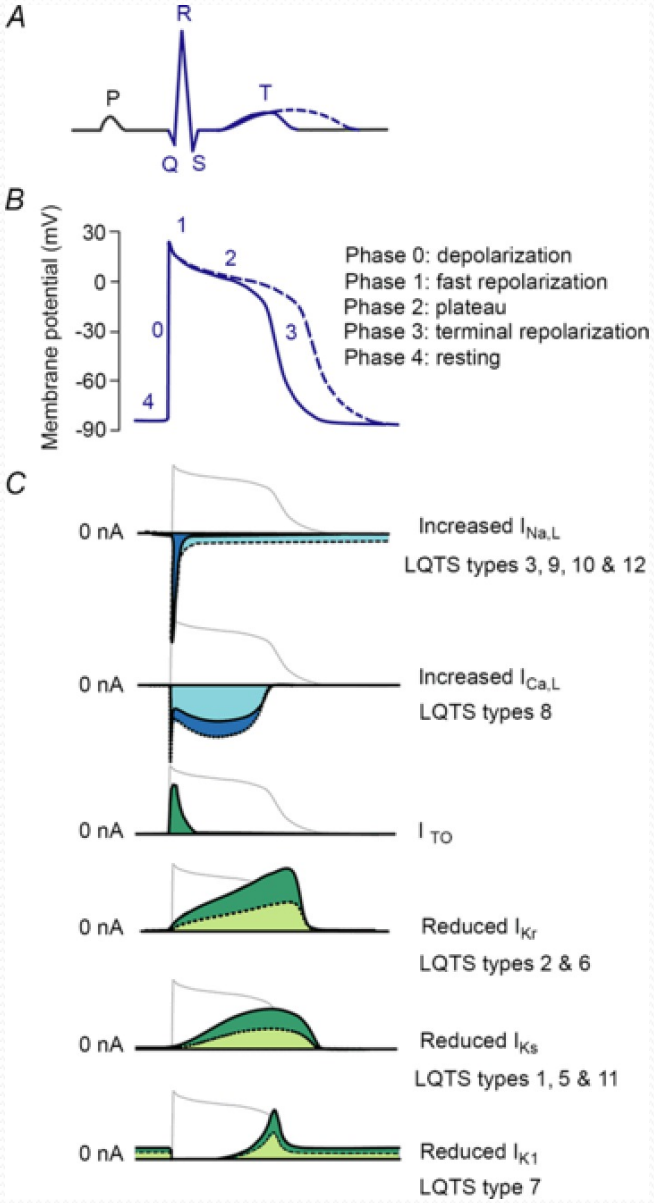
Z. Bhuiyan, MBBS, Ph.D

Cardiac Action Potential



Grigoriy Ikonnikov and Eric Wong

The cardiac electrical activity and the long QT syndrome



SCN5A, *CAV3*, *SCN4B*, *SNTA1*

CACNA1C

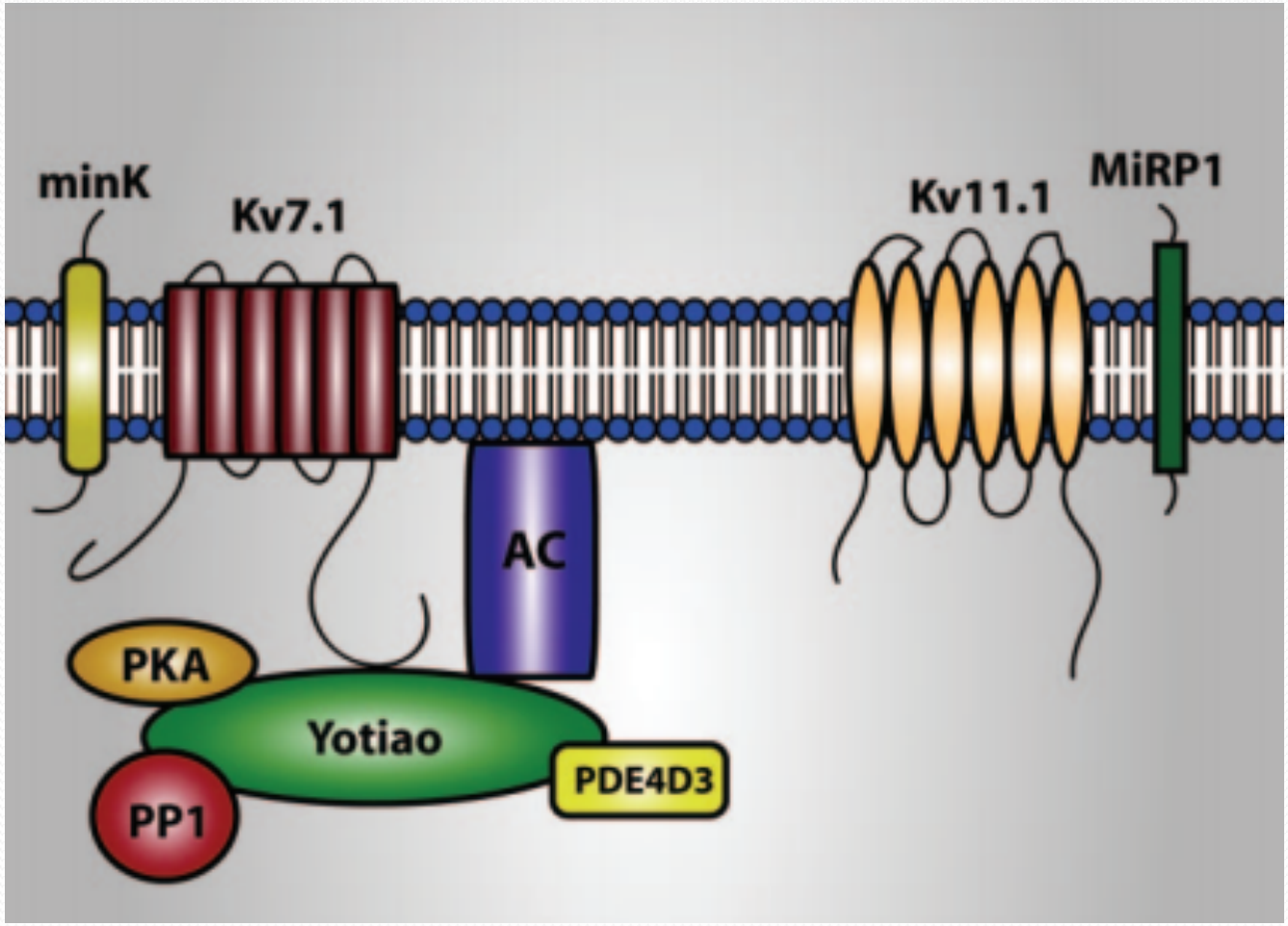
KCNH2, *KCNE2*

KCNQ1, *KCNE1*, *AKAP9*

KCNJ2

Amin et al. J Physiol. 2013; 591: 4125–4139.

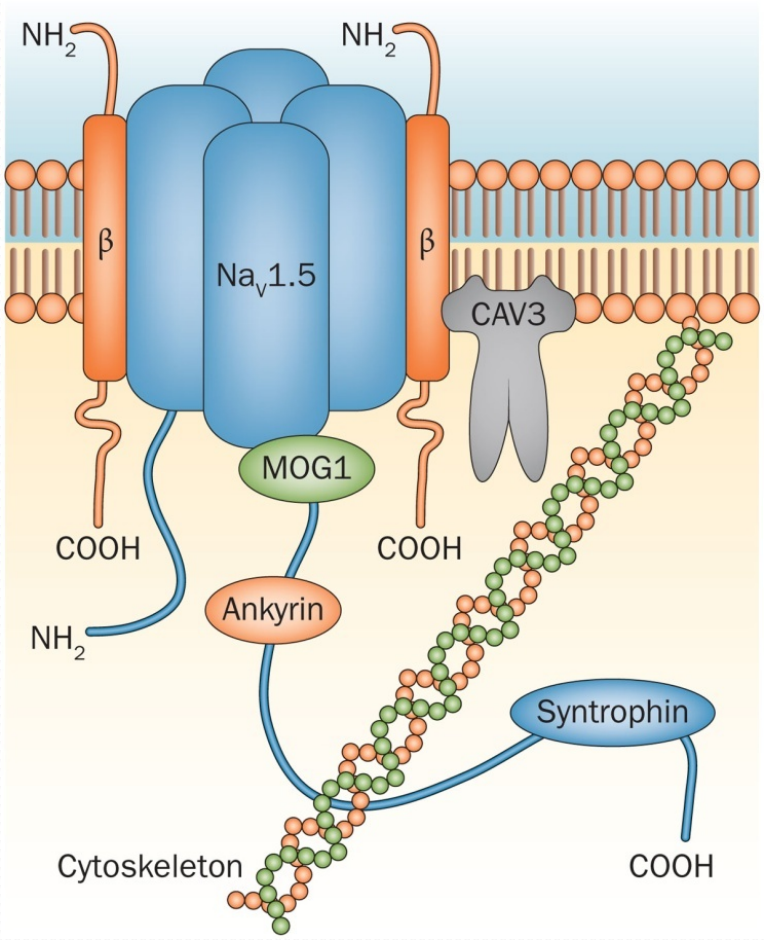
Cardiac IKs and IKr complexes in heart.



In addition to interactions of channel and subunits for both complexes, the Kv7.1 subunit encoded by KCNQ1 also associates with yotiao (AKAP9) in heart, which recruits signaling molecules PP1, PKA, and phosphodiesterase 4D3 (PDE4D3) to the IKs complex. In brain, yotiao also associates with specific isoforms of adenylyl cyclase (AC).

Ackerman and Mohler. Circ Res. 2010;107:457-465.)

The $Na_v1.5$ (SCN5A) channel is part of a macromolecular complex



Liu, M. *et al.* (2014) Cardiac sodium channel mutations: why so many phenotypes? *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2014.85

Long QT Syndrome: Subdivision of genotyped patients

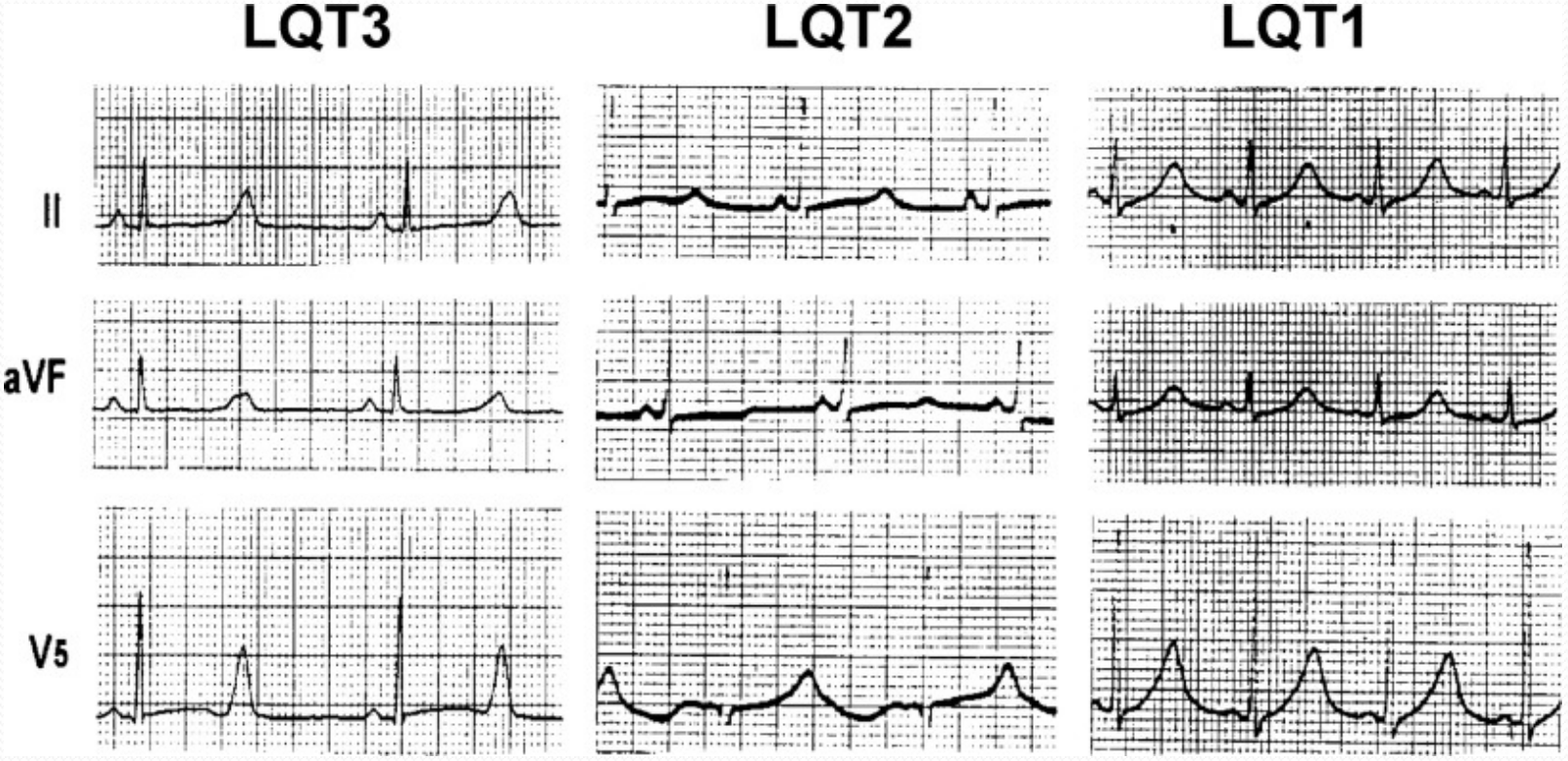
Type 1	*KCNQ1* (KvLQT1)	50%
Type 2	*KCNH2* (HERG)	35%
Type 3	*SCN5A*	8%
Type 5 & 6	*KCNE1, KCNE2*	< 5%
Type 4 & 7	*Ankyrin B, KCNJ2*	< 2%
Type 8 to type 16		

Long QT Syndrome: Subdivision of genotyped patients

Remaining LQTS	Gene	Protein	Current
Type 4	Ankyrin B	Ankyrin	Na+/K+ ATPase and others
Type 5	KCNE1	MinK	Iks ↓
Type 6	KCNE2	MiRP1	Ikr ↓
Type 7	KCNJ2	Kir2.1	Ik1 ↓
Type 8	CACNA1C	CaV1.2	ICa-L ↑
Type 9	CAV3	Caveolin 3	INa ↑
Type 10	SCN4B	SCNβ4 subunit	INa ↑
Type 11	AKAP-9	Yotiao	Iks ↓
Type 12	SNTA-1	Syntrophin-α1	INa ↑
Type 13	KCNJ5	Kir3.4	IkAch ↓
Type 14	CALM1	Calmodulin 1	Defective Ca2+ signalling
Type 15	CALM2	Calmodulin 2	
Type 16	CALM3	Calmodulin 3	

Type 17 or CPVT3: Bi-allelic mutation in TECRL gene

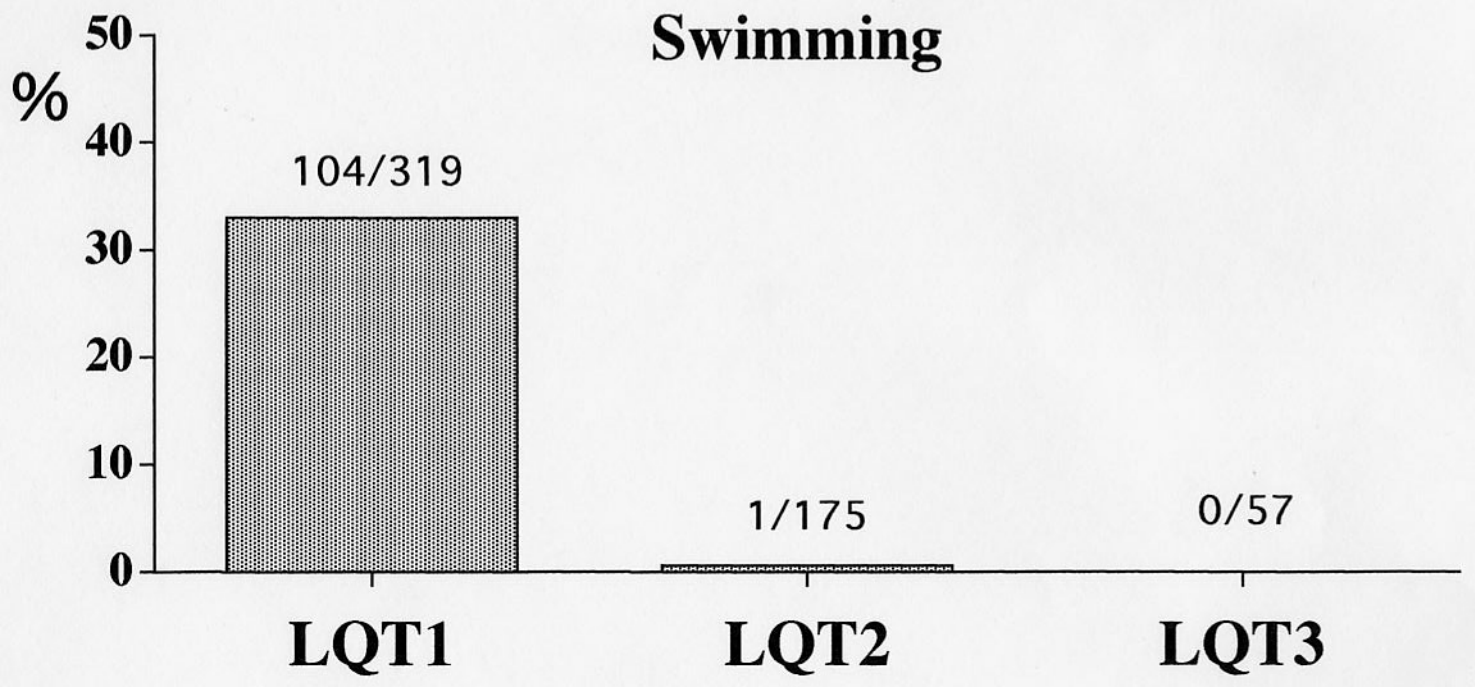
Genotype and ECG



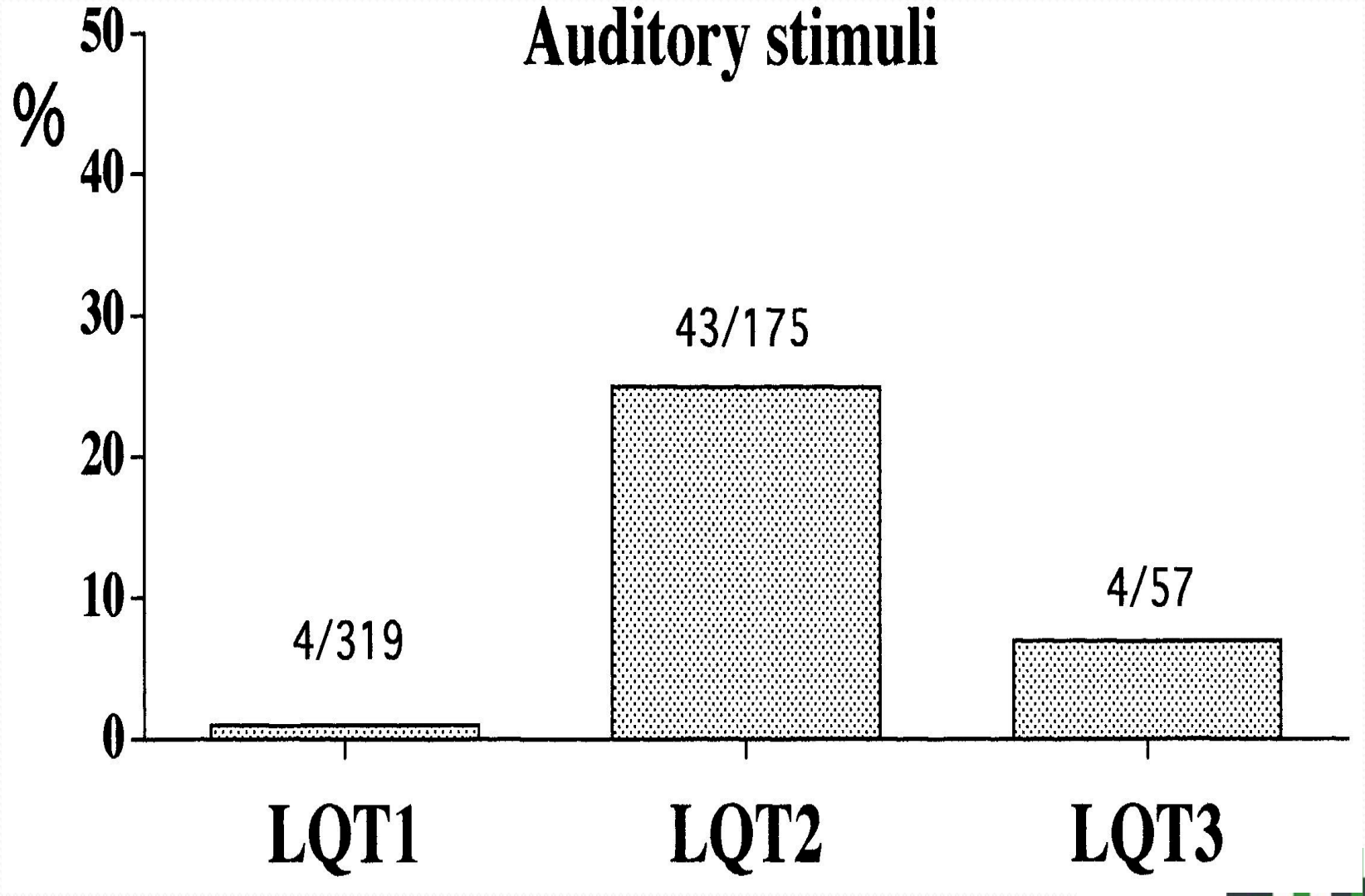
Distinctive T-Wave Patterns in the 3 Major LQTS Genotypes: LQT1: typical broad-based T-wave pattern (corrected QT [QTc] 570 ms); LQT2: typical bifid T-wave (QTc 583 ms); and LQT3: typical late-onset peaked/biphasic T-wave (QTc 573 ms).

Goldenberg and Moss. Journal of the American College of Cardiology, Volume 51, Issue 24, 2008, 2291–2300

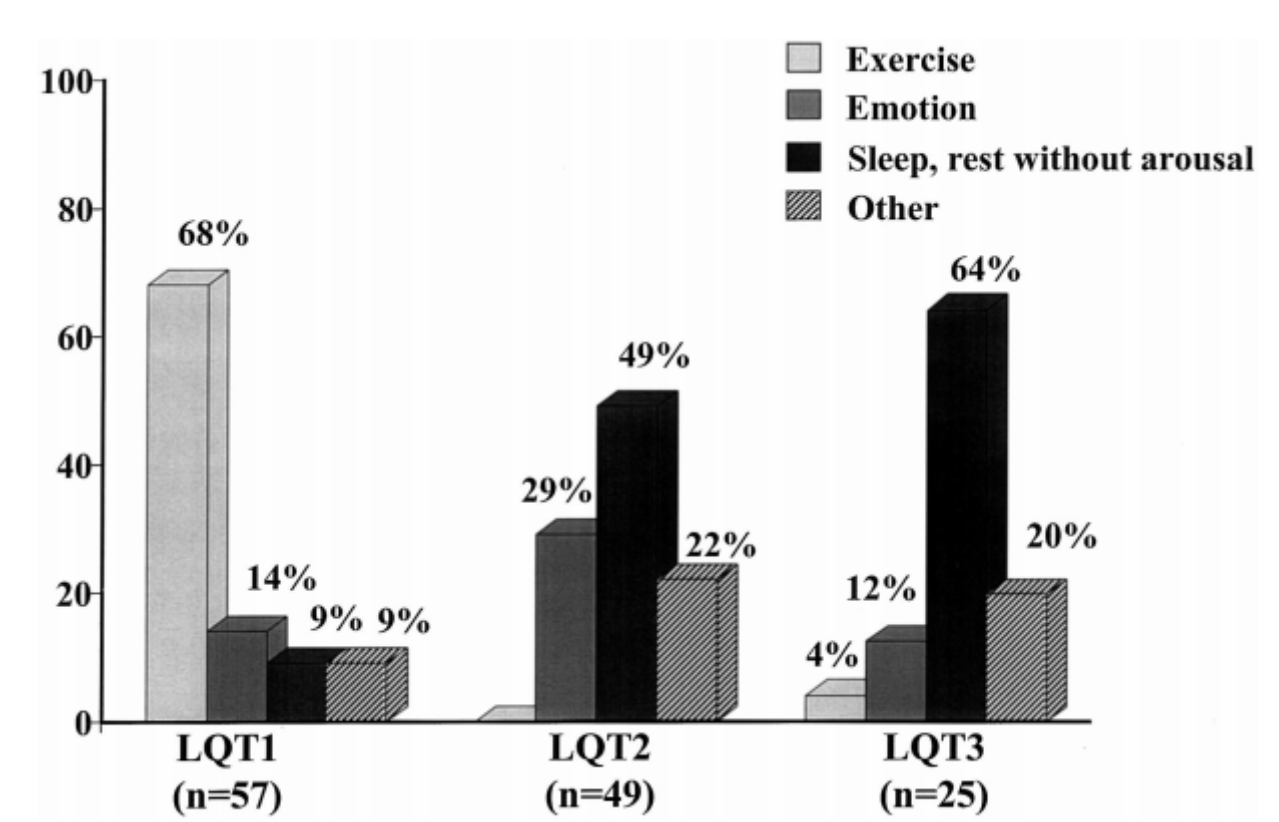
Genotype - Phenotype, LQT registry



Genotype - Phenotype, LQT registry

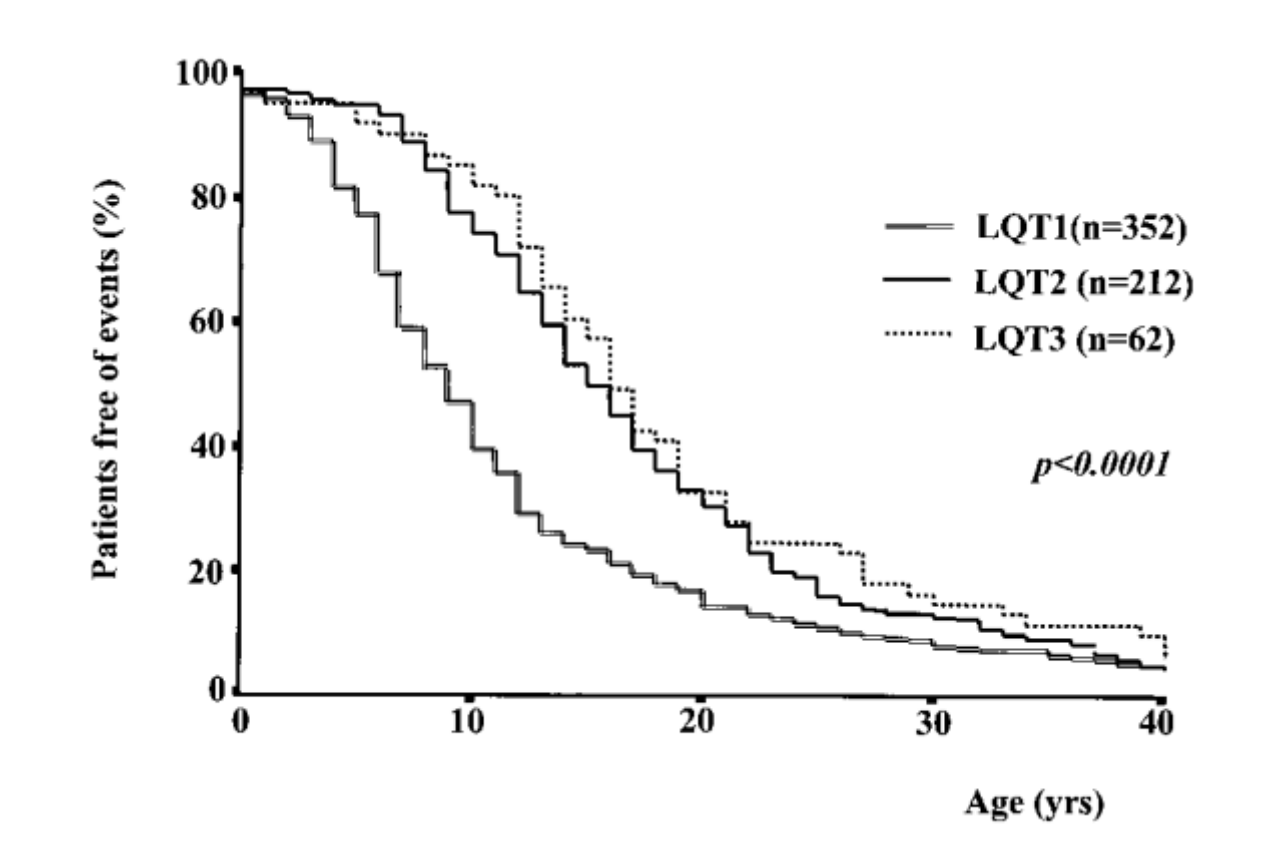


Triggers for cardiac events in LQT1, LQT2 and LQT3



Schwartz PJ et al. Circulation. 2001;103:89-95.

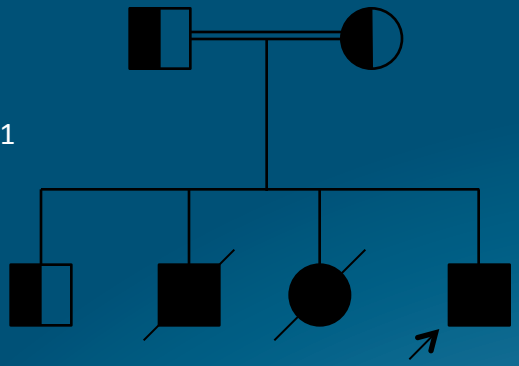
Kaplan-Meier cumulative survival curves showing time interval between birth and first cardiac event



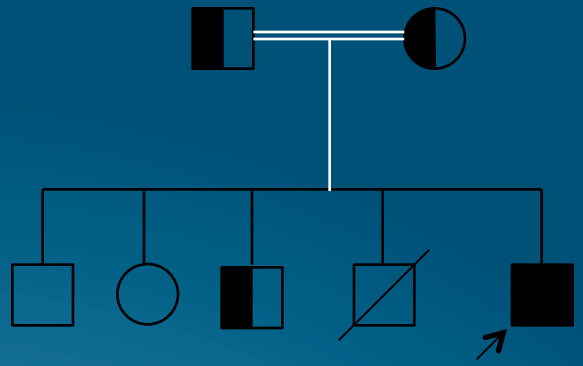
Schwartz PJ et al. Circulation. 2001;103:89-95.

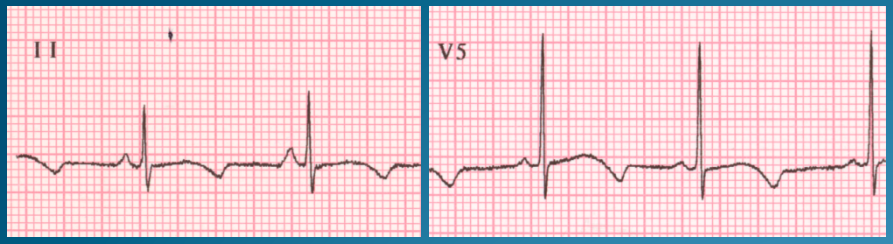
Exercise and Swimming induced long QT1

Family: 1

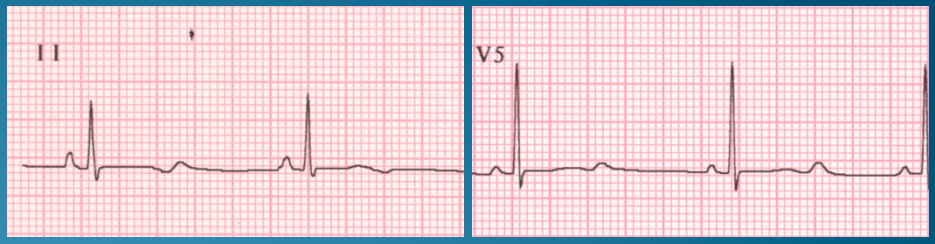


Family: 2



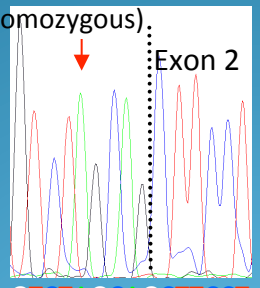


ECG from the proband of family: 1



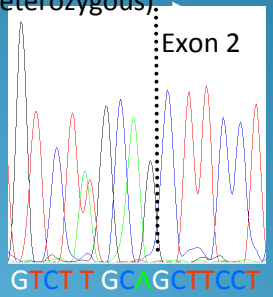
ECG from the proband of family: 2

T>A
(homozygous)



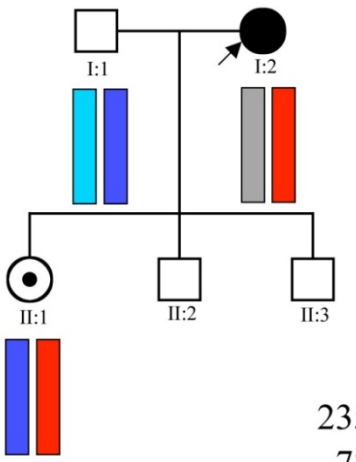
Patient

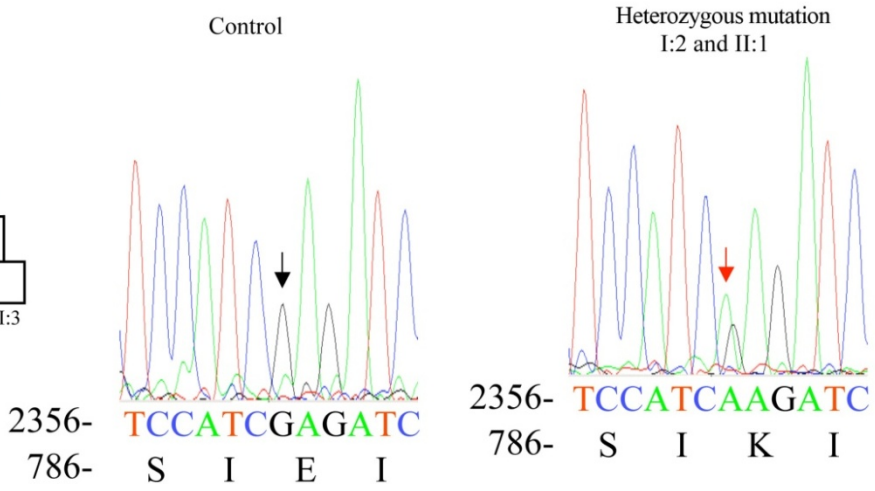
T>A
(heterozygous)



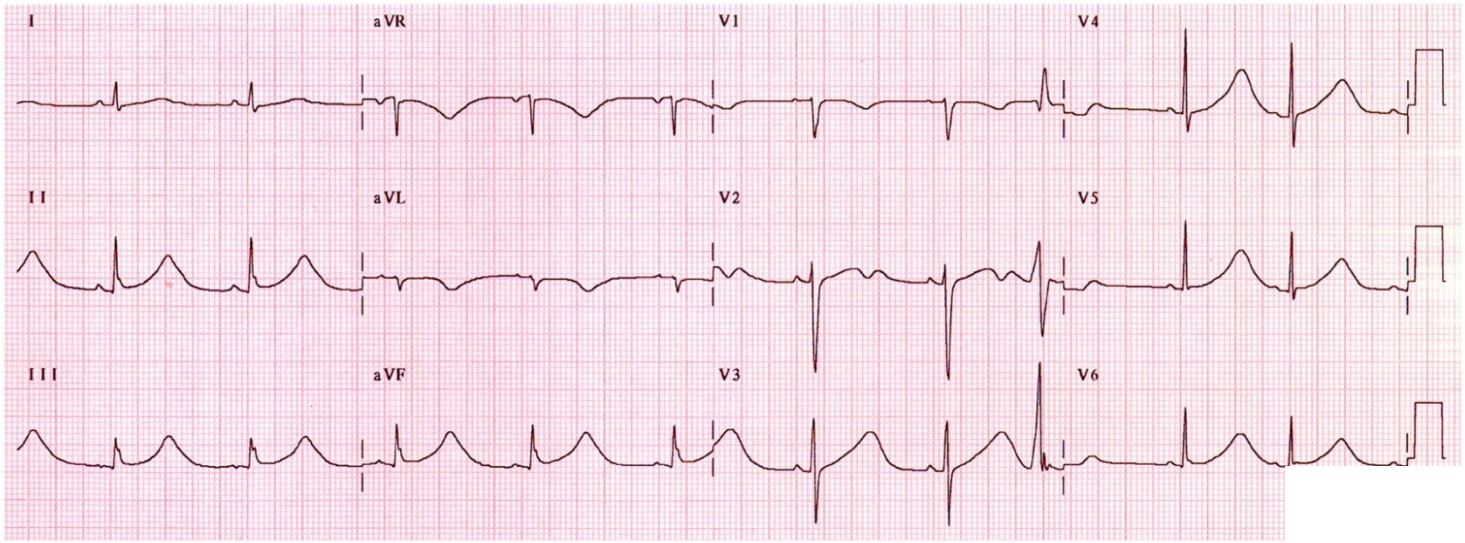
heterozygote carrier

Post-Partum Cardiac Arrest

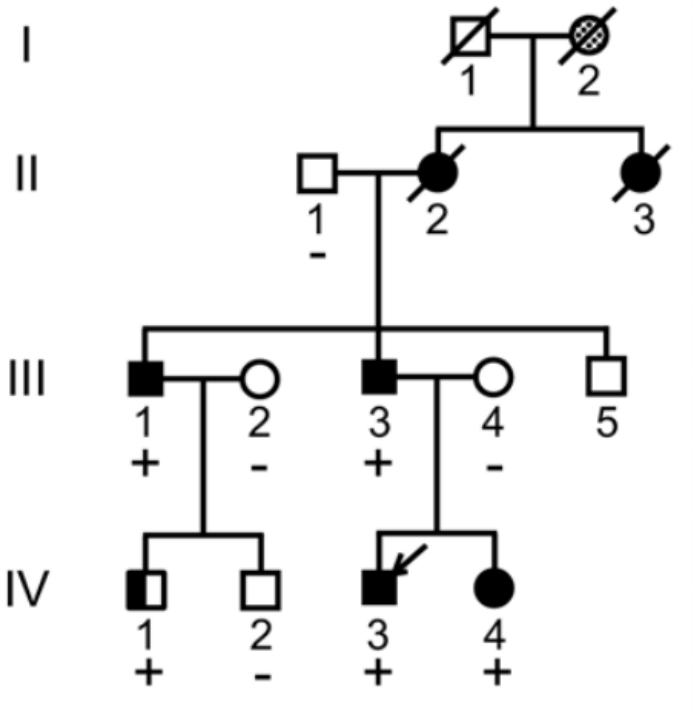


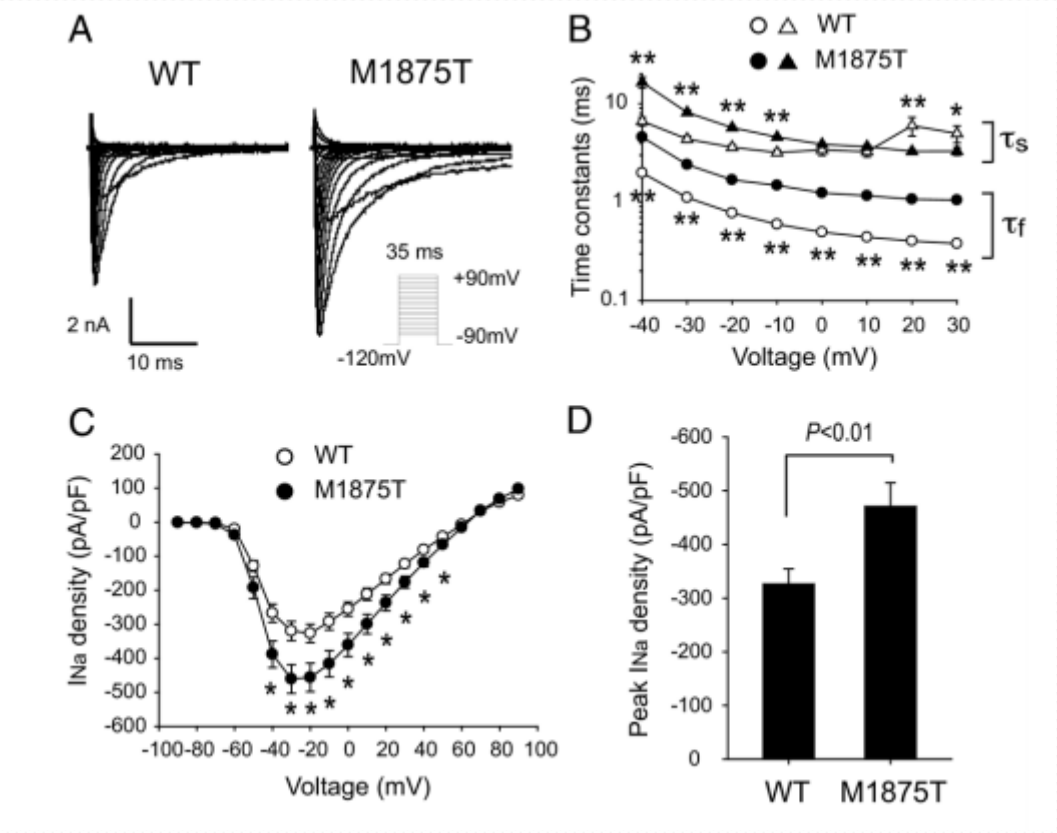


Human-	S	R	G	S	I	E	I	L	R	G	D
Mouse-	S	R	G	S	I	E	I	L	R	G	D
Rabbit-	S	R	G	S	I	E	I	L	R	G	D
Zebrafish-	S	R	G	S	I	E	I	L	R	D	D



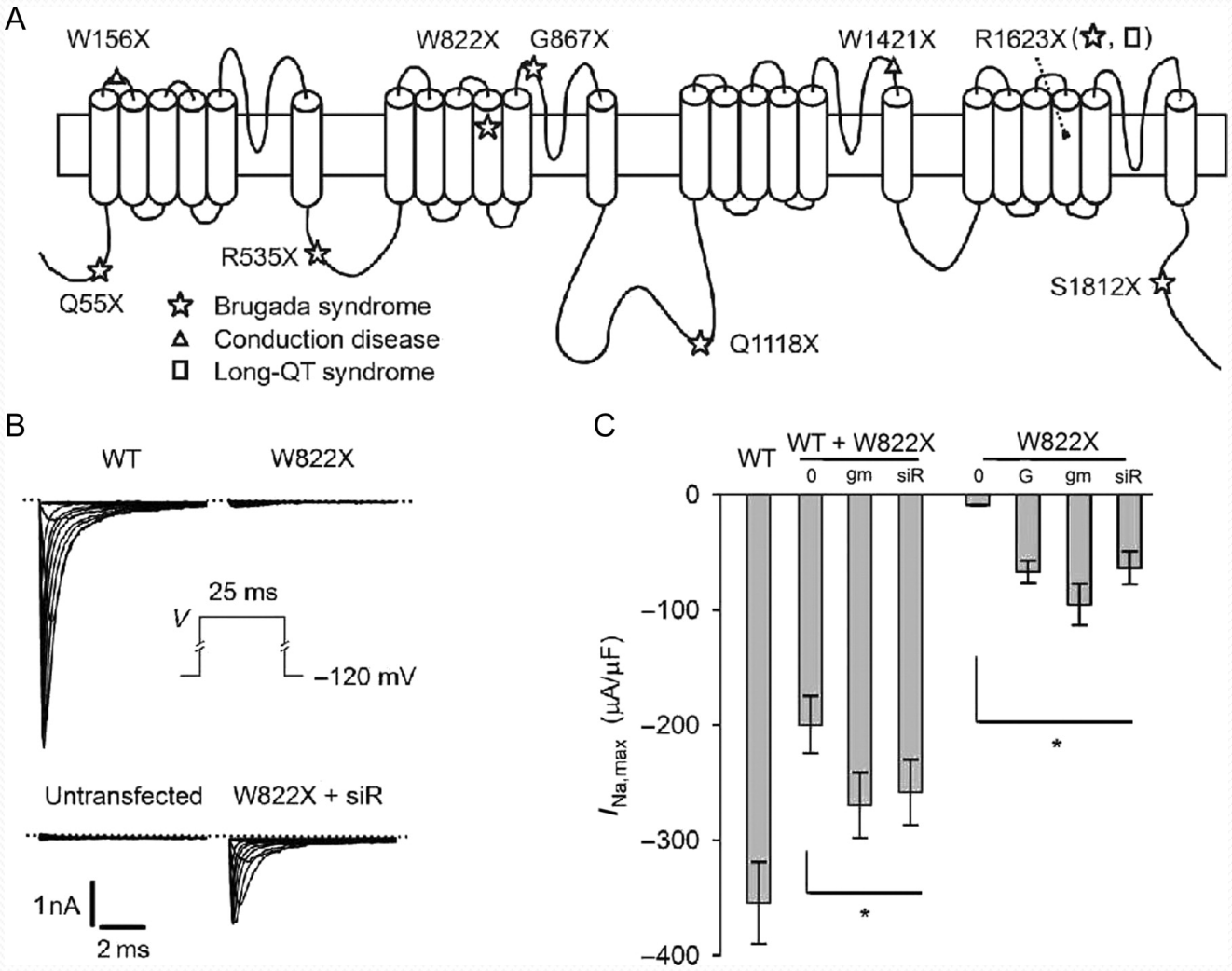
Gain of Function Mutation in SCN5A





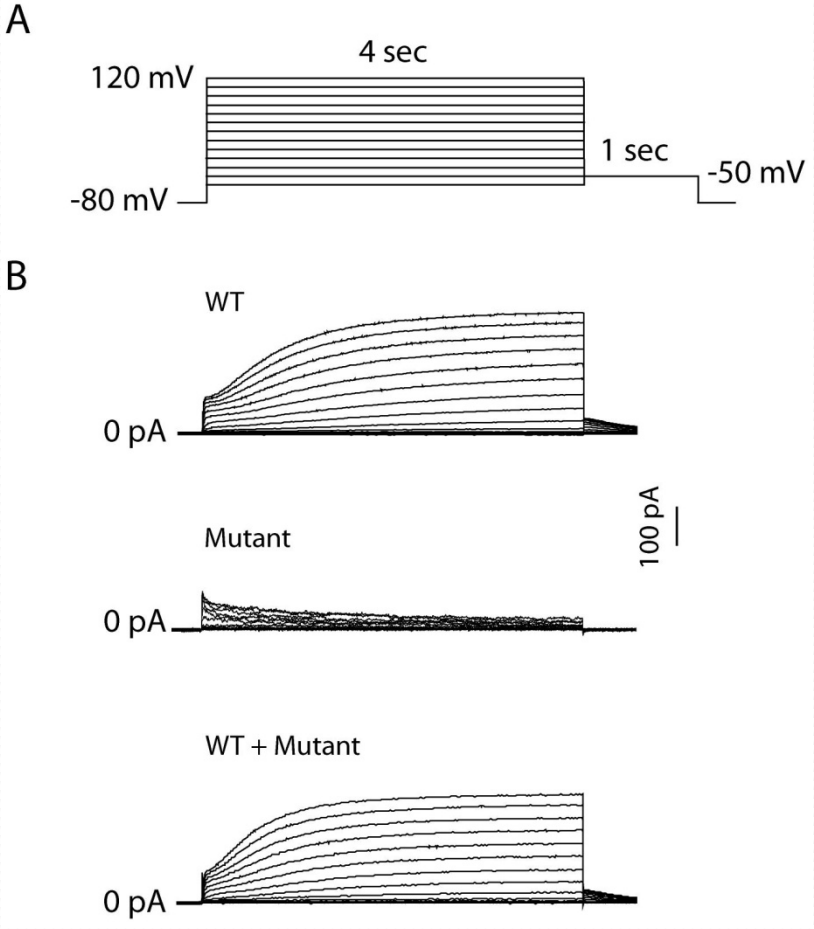
Makiyama et al. J Am Coll Cardiol. 2008;52:1326–34

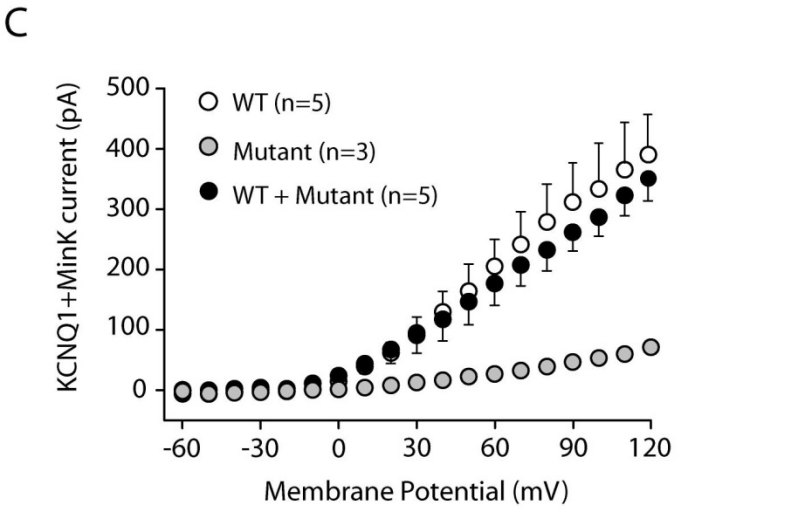
Loss of Function Mutations in SCN5A



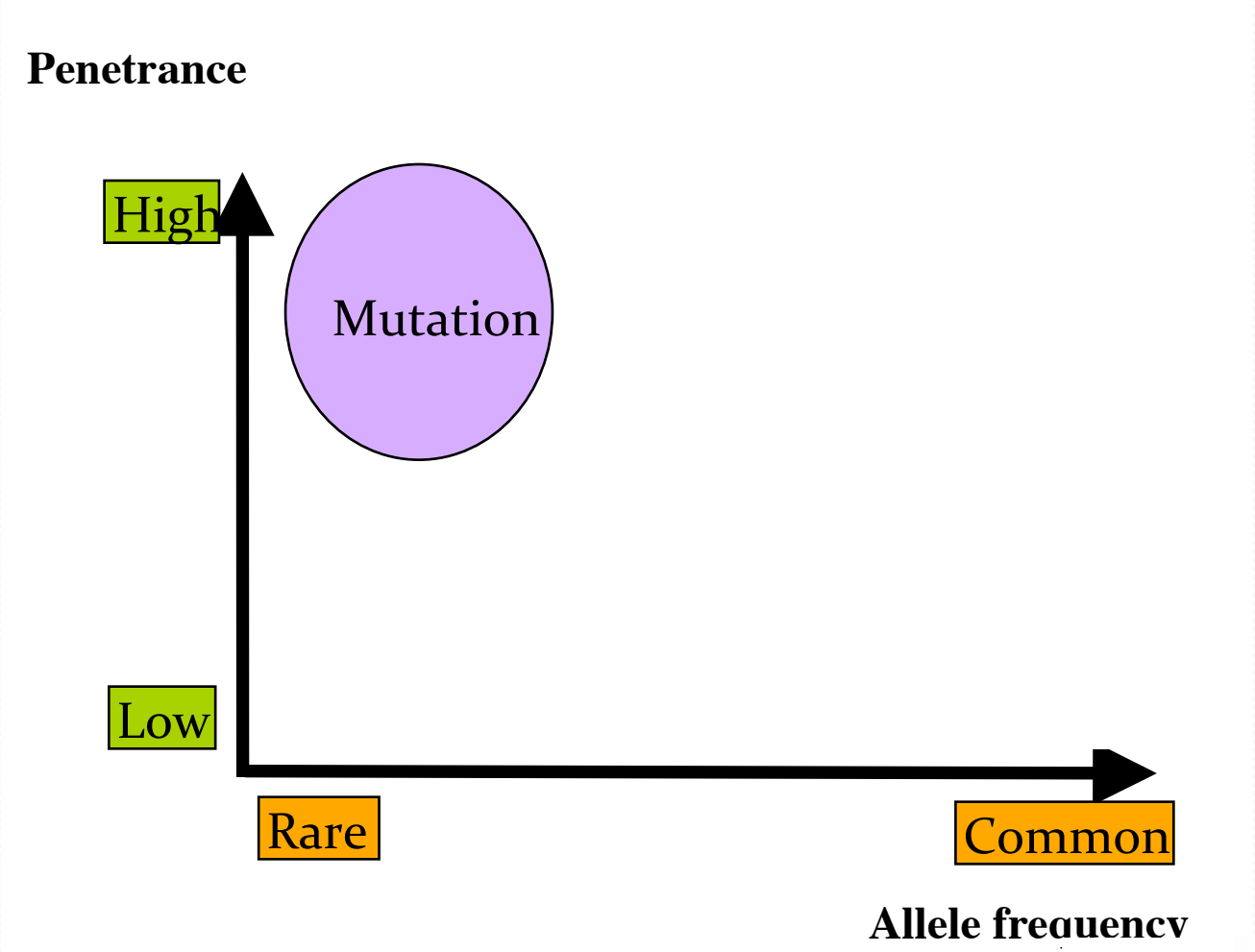
Siyong Teng et al. Cardiovasc Res 2009;83:473-480

Diminution or Loss of IKs current in LQT1 due to KCNQ1 Mutations

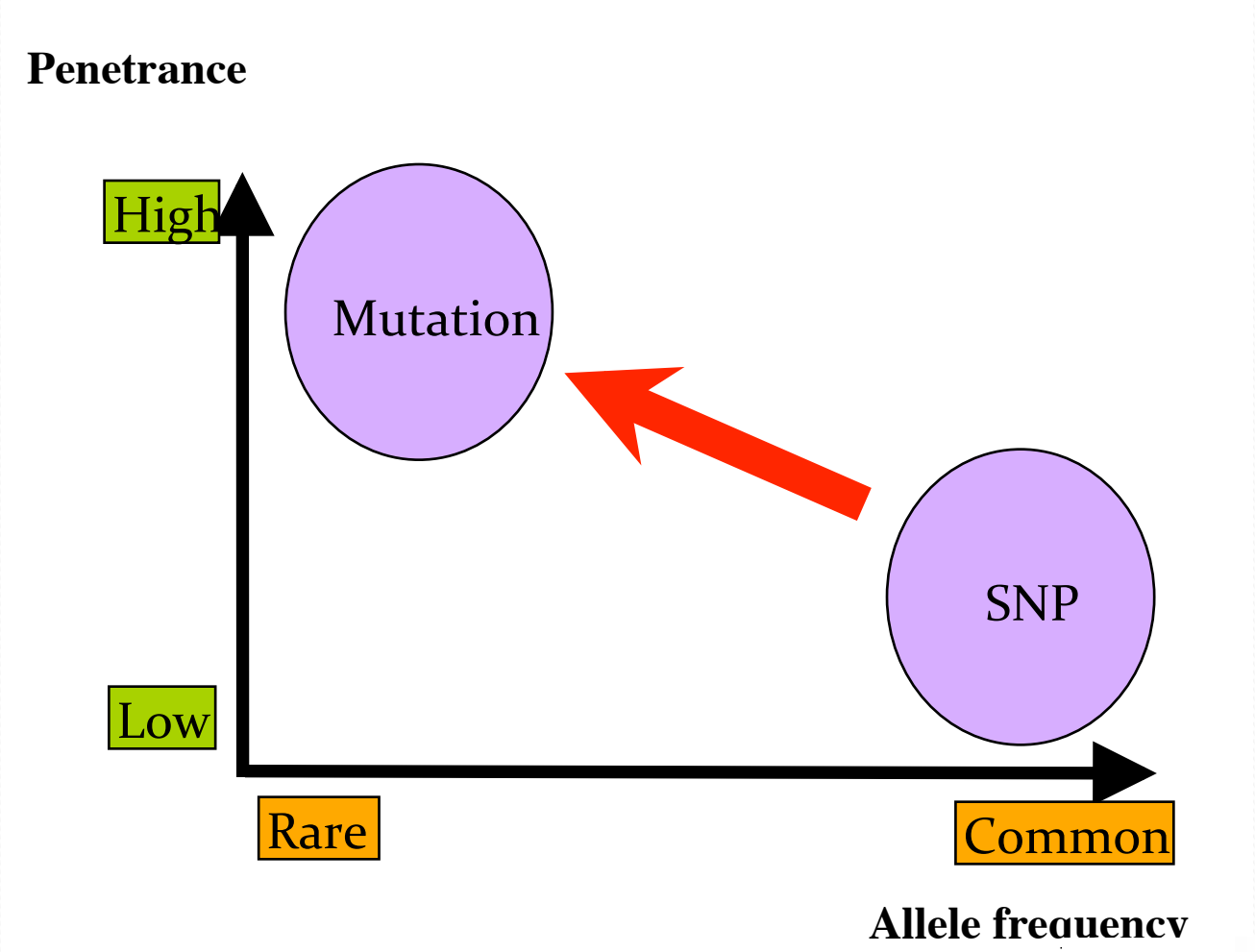




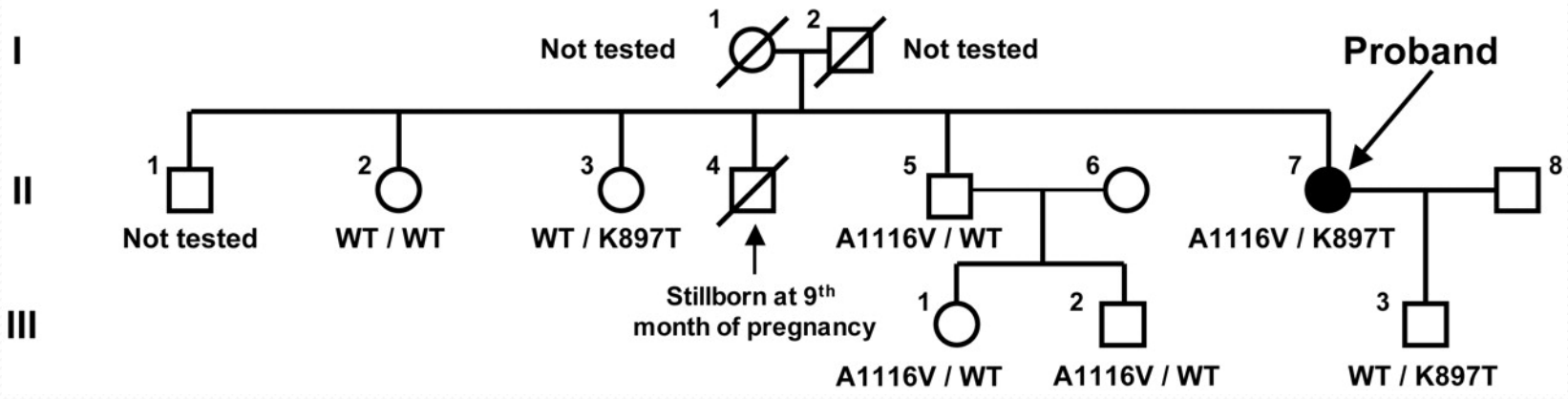
Mutations and common variants (SNPs)

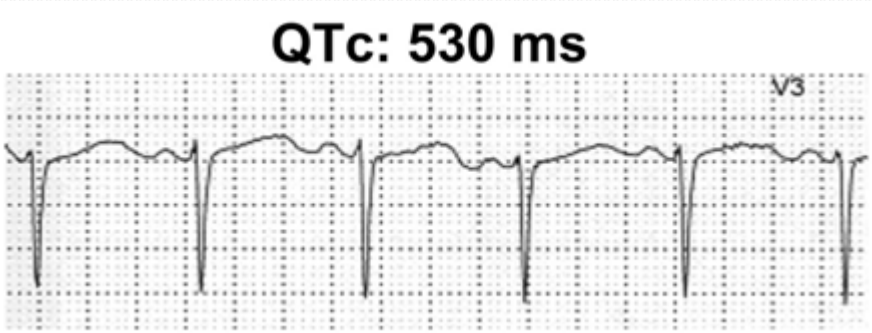


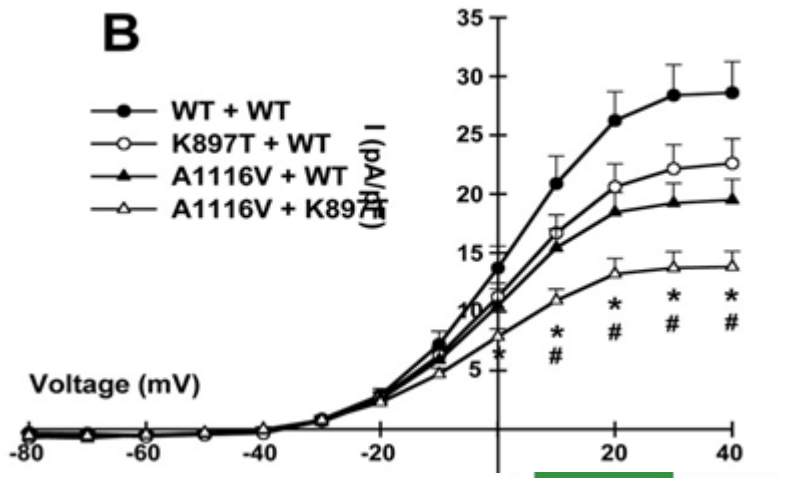
Mutations and common variants (SNPs)



Segregation of A1116V and K897T in the LQTS pedigree.

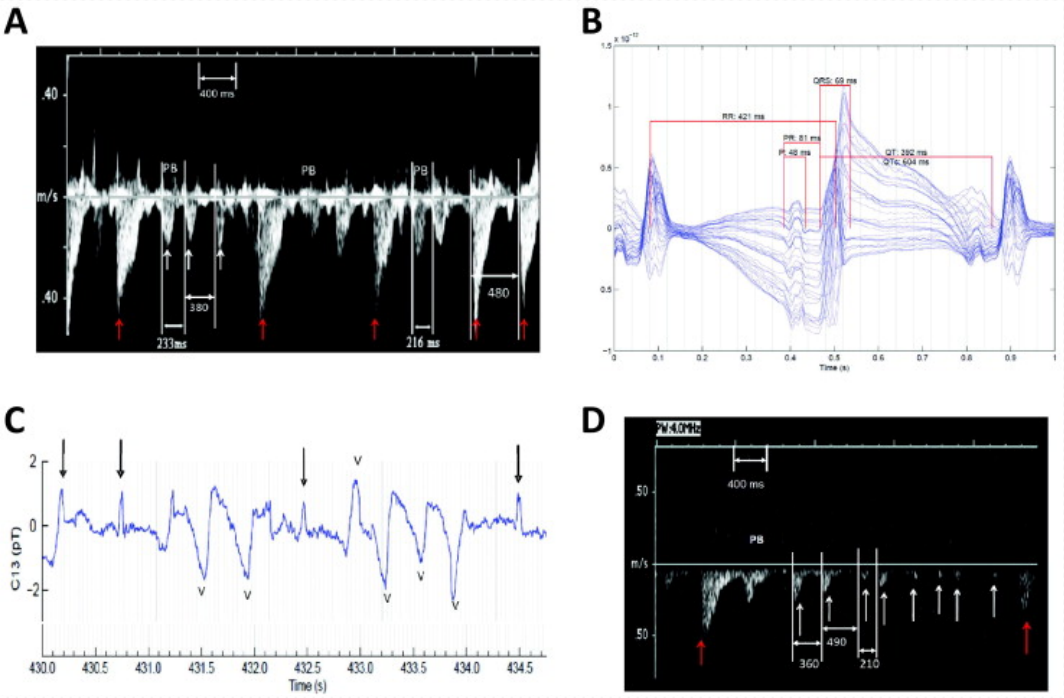






Lia Crotti et al. Circulation. 2005;112:1251-1258

LQTS in a fetus at 19 weeks' gestation presenting with ventricular tachycardia and severe hydrops fetalis: Fetal Doppler Echocardiogram and Magnetocardiogram.

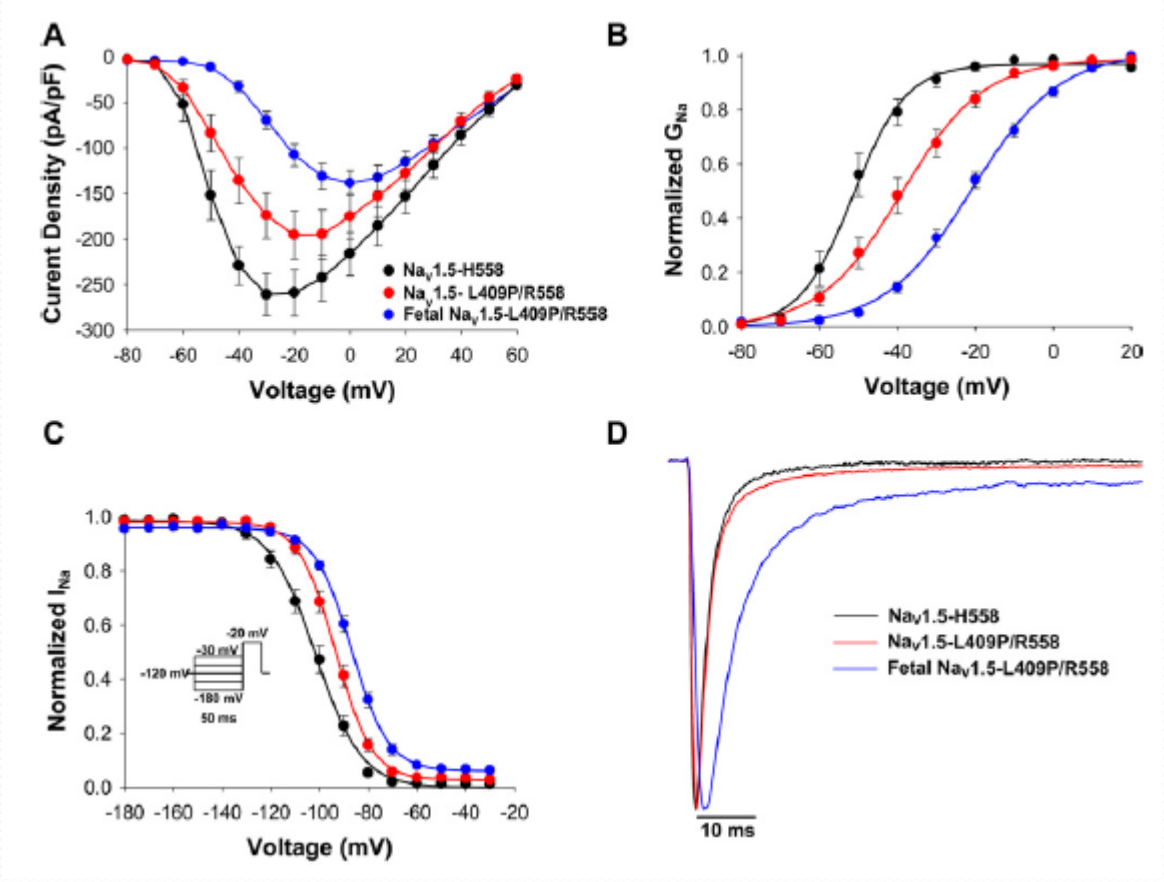


Normal conducted beats (red arrows) are interrupted by frequent premature beats and 2–3 beat runs of tachycardia with a variable cycle length (white arrows).

SCN5A: p.Leu409Pro

Murphy et al. Heart Rhythm. 2012;9: 590–597

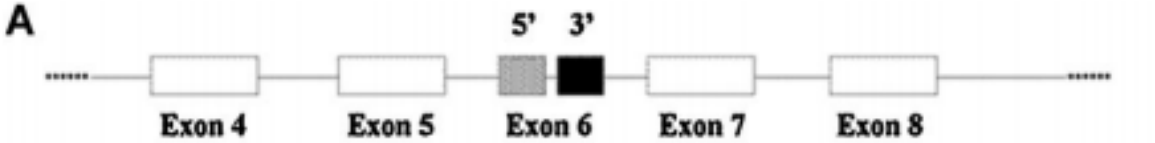
Effect of Leu409Pro Mutation in Neonatal and Adult SCN5A



Mutant channels show a sustained inward current during membrane depolarization

Murphy et al. Heart Rhythm. 2012;9: 590-597

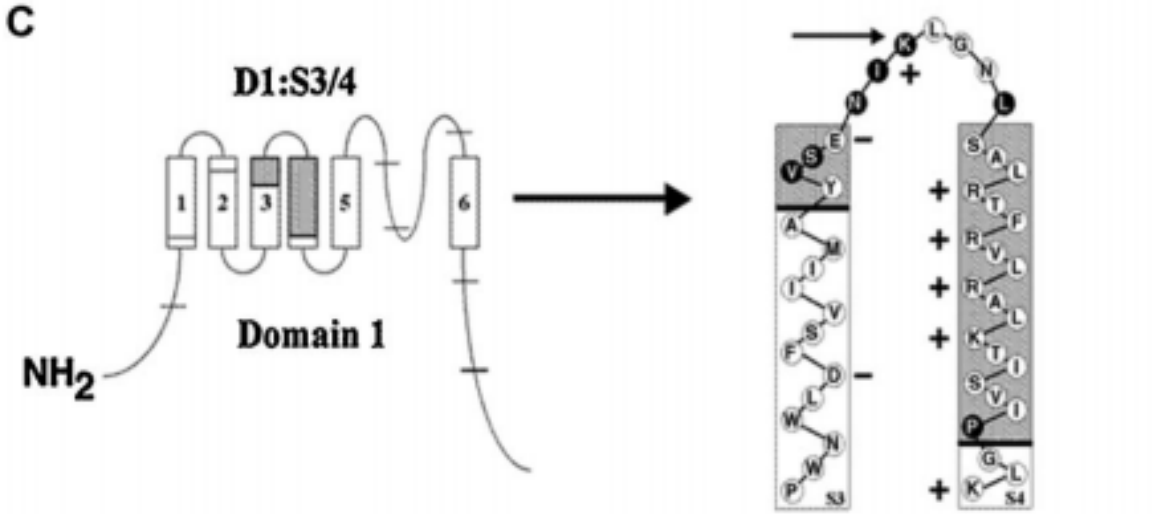
SCN5A: Neonatal vs Adult Isoform



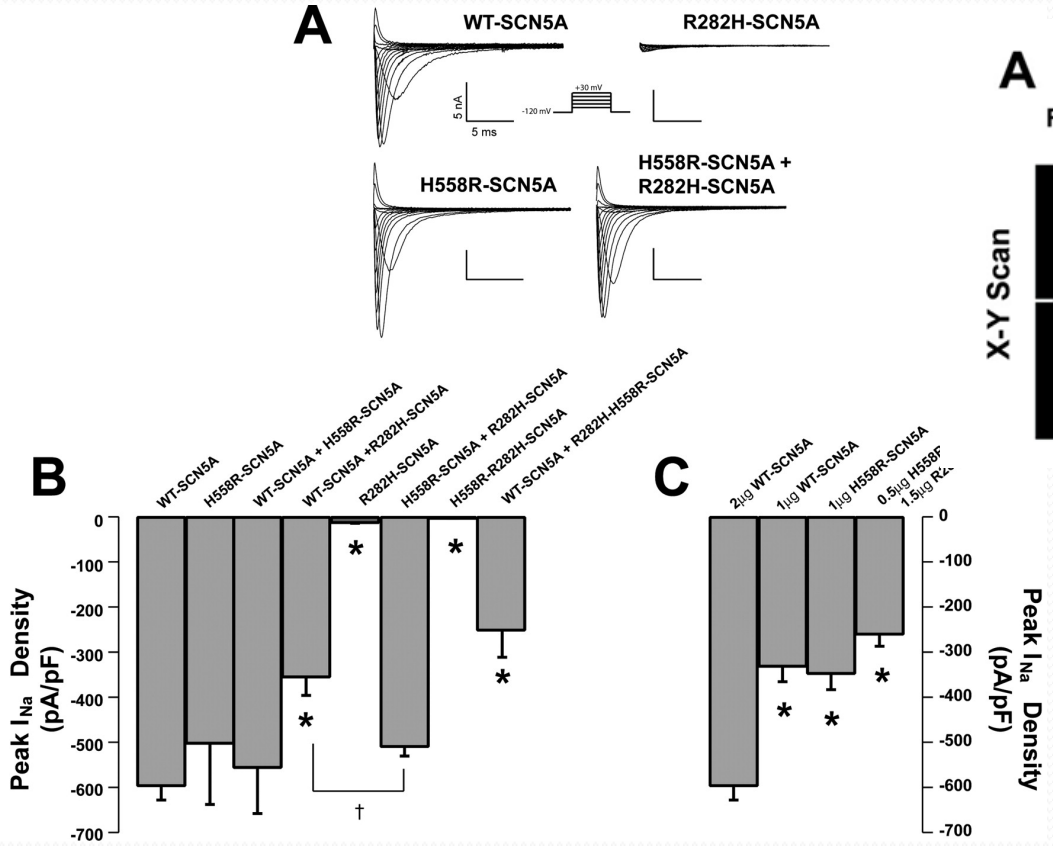
B

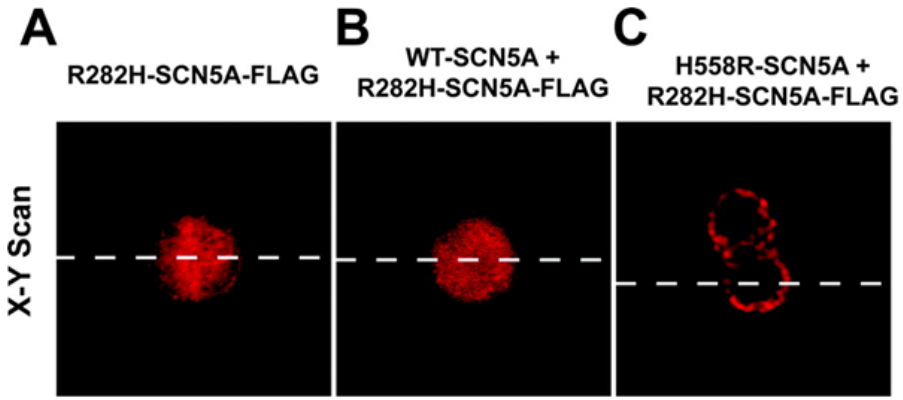
'Adult' $Na_V1.5$ (3') YTTEFVDLGNVSALRTFRVLRALKTISVIS

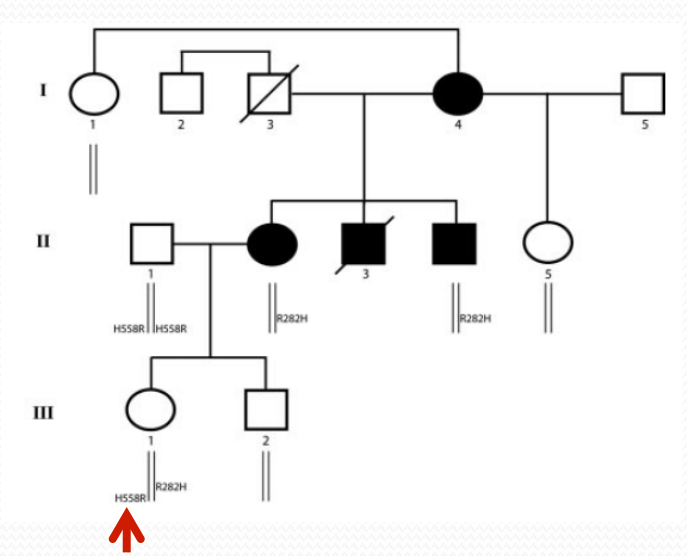
'Neonatal' $Na_V1.5$ (5') YVSENIKLGNLSALRTFRVLRALKTISVIP



Rescue of the Aberrant function by H558R Polymorphism: In Vitro



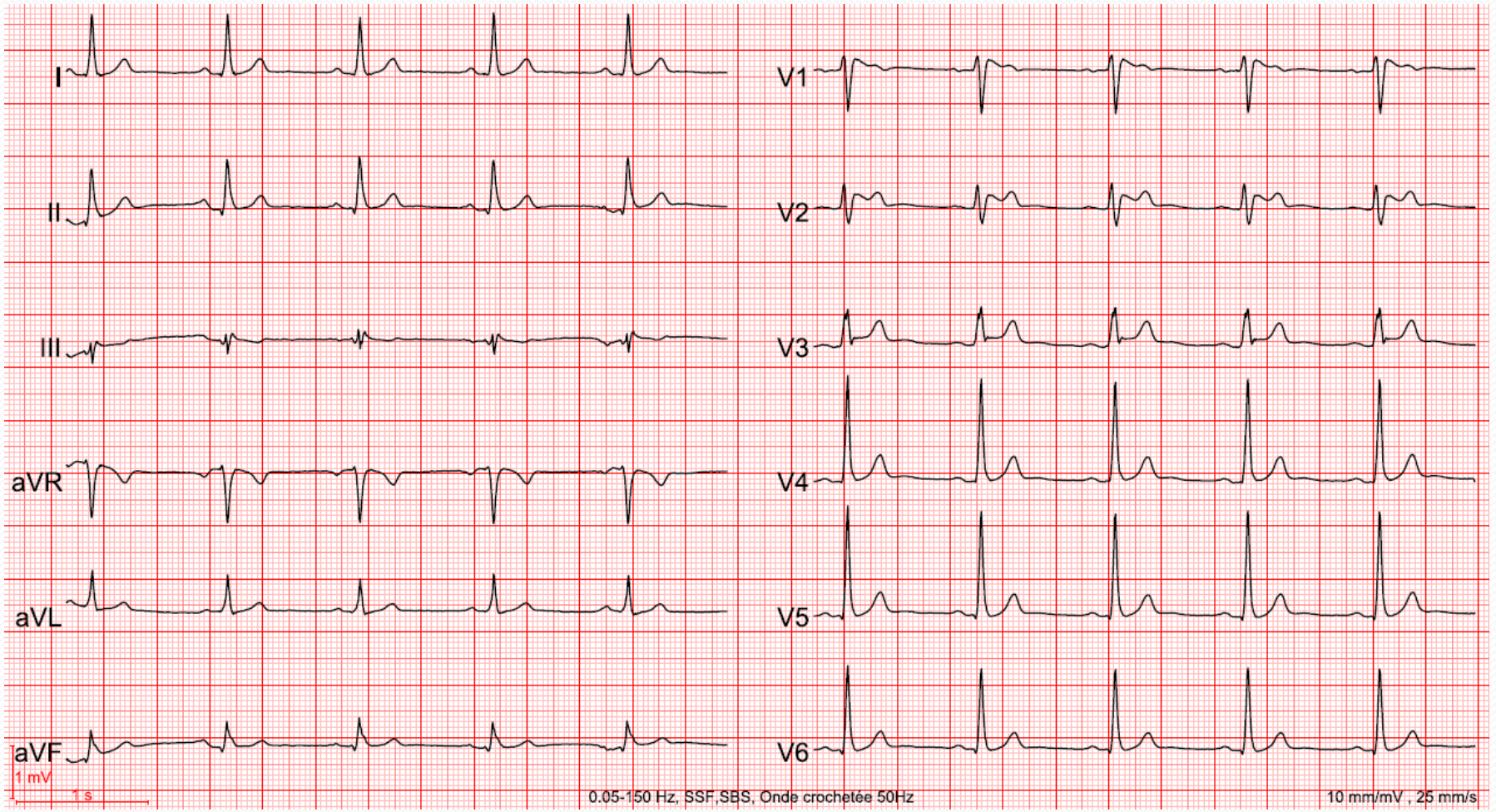




Steven Poelzing et al. Circulation. 2006;114:368-376

Such SNP influence still requires more Clinical studies

Non-symptomatic son of a Symptomatic (Syncope) Mother

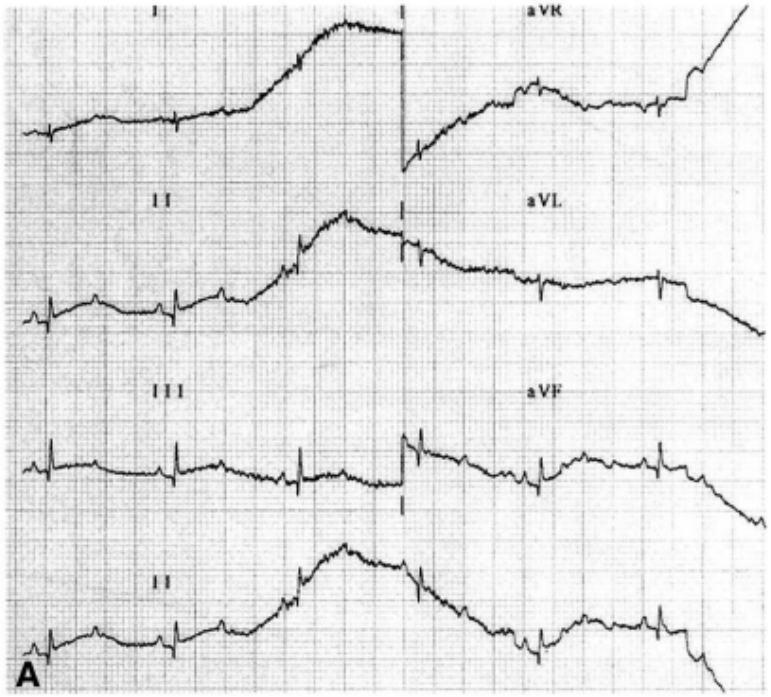


Our patient data

Het: Arg282Gly
Het: His558Arg

SCN5A

Long QT syndrome in neonates : Conduction disorders associated with HERG mutations and sinus bradycardia with KCNQ1 mutations



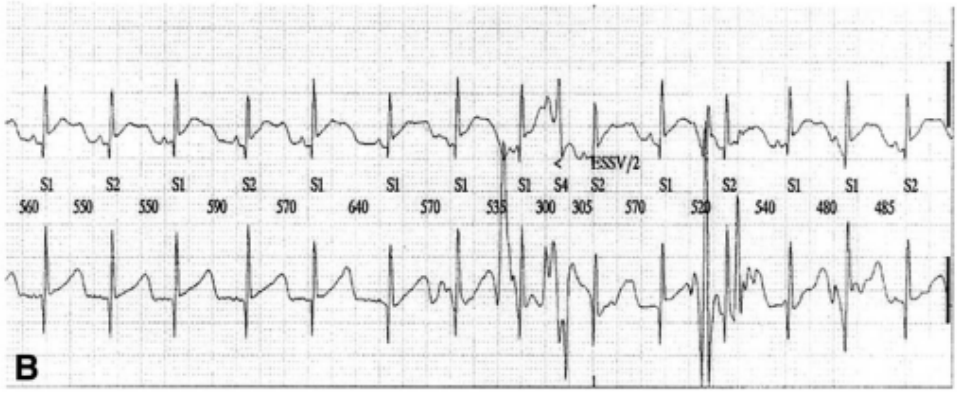


Figure 1. Electrocardiographic **(A)** and Holter **(B)** recordings of a one-day-old neonate with bradycardia attributable to 2:1 atrioventricular block (AVB). The Holter recording showed 1:1 sinus rhythm periods, thus demonstrating that the AVB was intermittent. Furthermore, the notched T-wave morphology pointed to a mutation in *HERG*, which was identified.

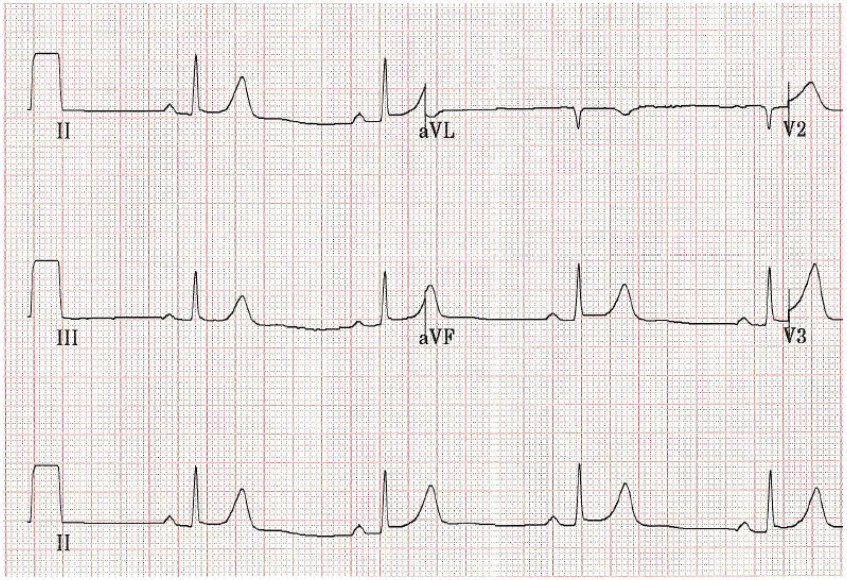
Jean-Marc Lupoglazoff et al. Journal of the American College of Cardiology. 2004; 43: 826–830

Long QT syndrome in neonates : Conduction disorders associated with HERG mutations and sinus bradycardia with KCNQ1 mutations

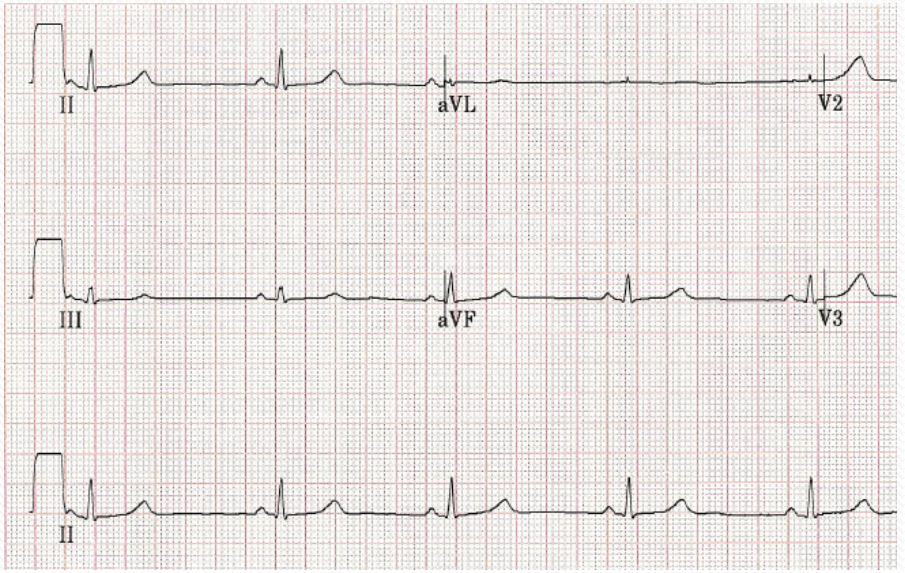
Patient Number/Gender	Circumstances of Diagnosis	ECG QTc (ms) VR (beats/min)	Initial Therapy	Outcome Follow-Up	Genotype
16/M	Fetal bradycardia	527 65	Propranolol	AS at 8 yrs	*KCNQ1* R231C (de novo mutation)
17/M	Neonatal bradycardia	500 90	Propranolol	AS at 7 yrs	*KCNQ1* R174H by MT
18/F	Fetal bradycardia	480 90	Propranolol	AS at 4 yrs	*KCNQ1* g.1258 ins A by MT
19/M	Neonatal bradycardia	460 95	Propranolol	AS at 6 yrs	*KCNQ1* A590T by MT
20/F	Fetal bradycardia	550 90	Propranolol	AS at 2 yrs	*KCNQ1* G325R by MT
21/M	Fetal bradycardia	545 94	Propranolol	AS at 2 months	*KCNQ1* R231C by MT
22/M	Neonatal bradycardia	560 95	Propranolol	AS at 3 yrs	*KCNQ1* g.dup524–534 by MT
23/M	Fetal bradycardia	503 69	Acebutolol	AS at 2 yrs	*KCNQ1* R231C by MT

Jean-Marc Lupoglazoff et al. Journal of the American College of Cardiology. 2004; 43: 826–830

Sinus Bradycardia with KCNQ1 mutations in Adult



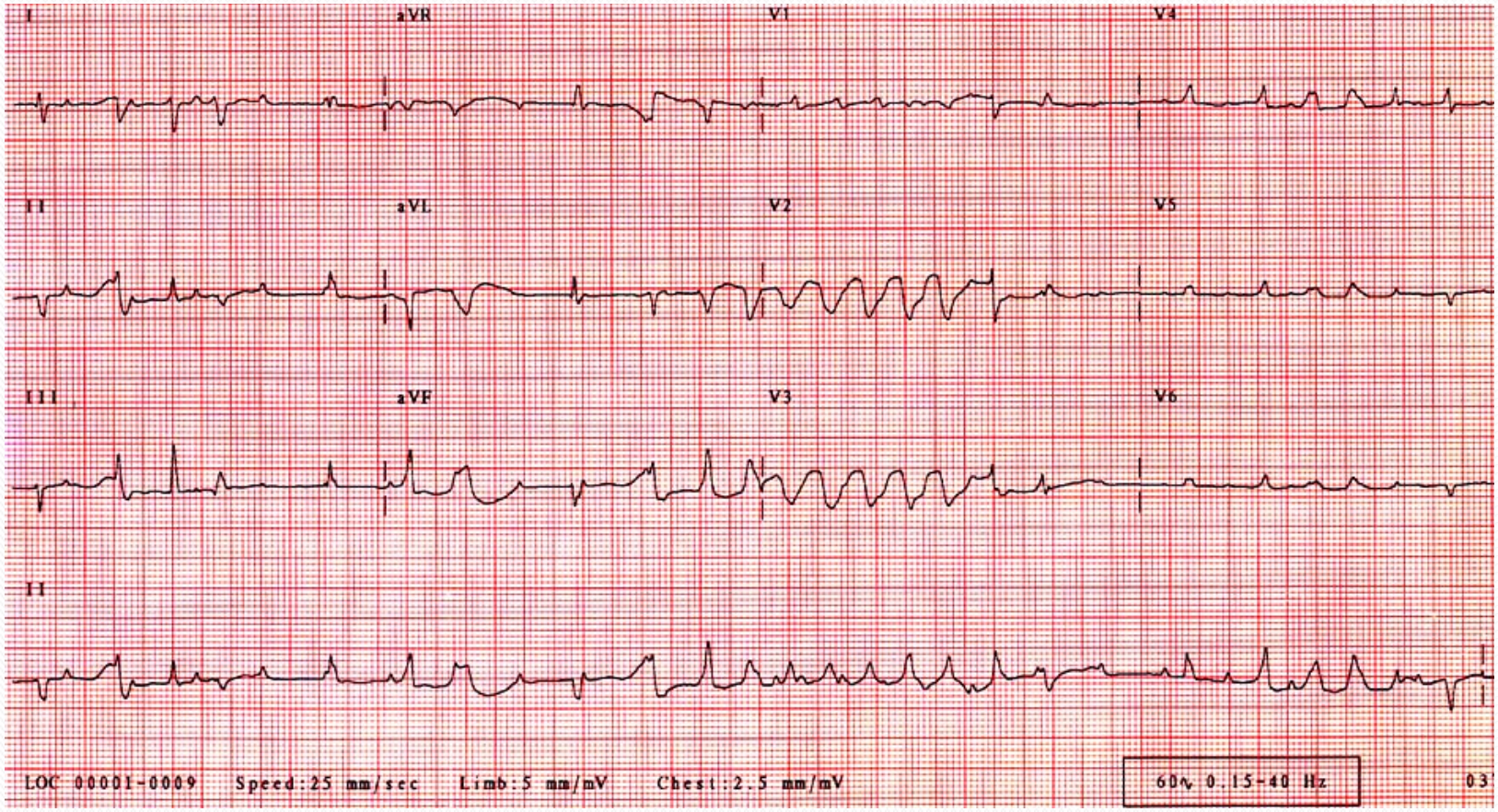
Father: 46 b/min



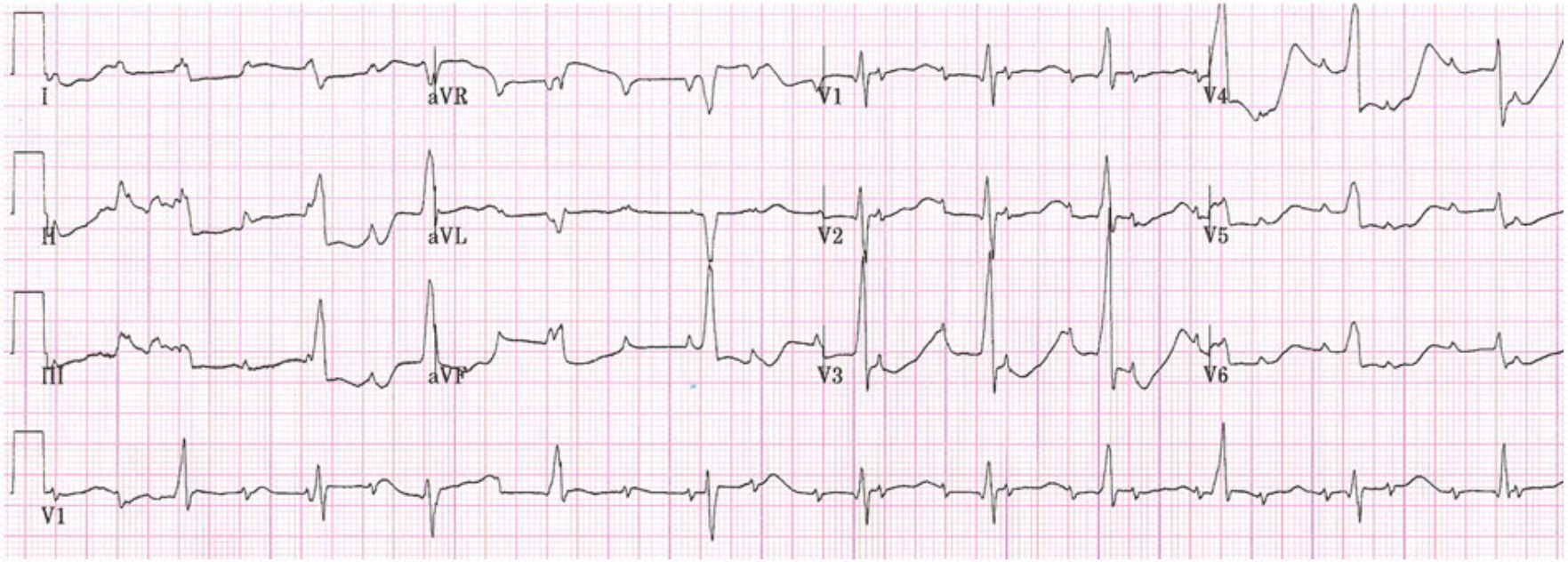
Mother: 53 b/min

Heterozygous c.387-5T>A Mutation

ECG: First day

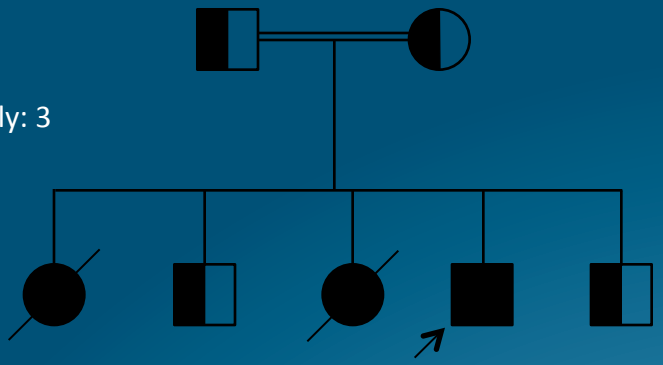


ECG of the Neonate

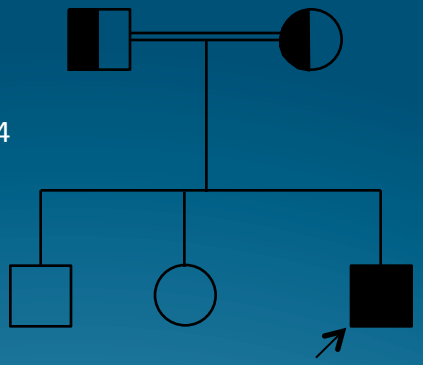


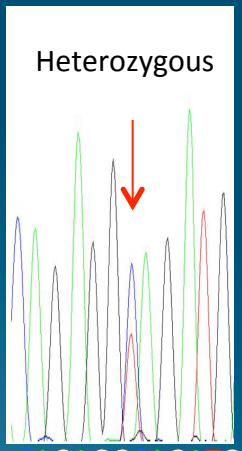
Bi-Allelic Mutation in KCNH2 Gene

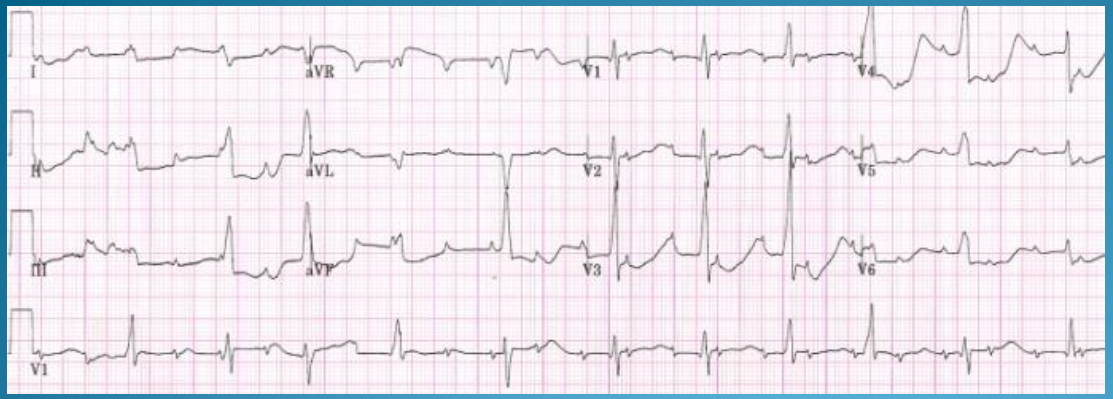
Family: 3



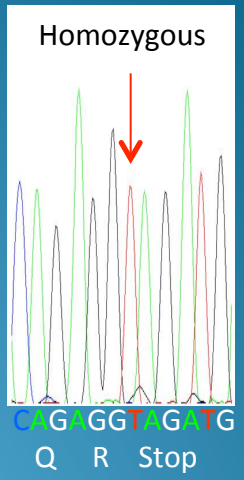
Family: 4



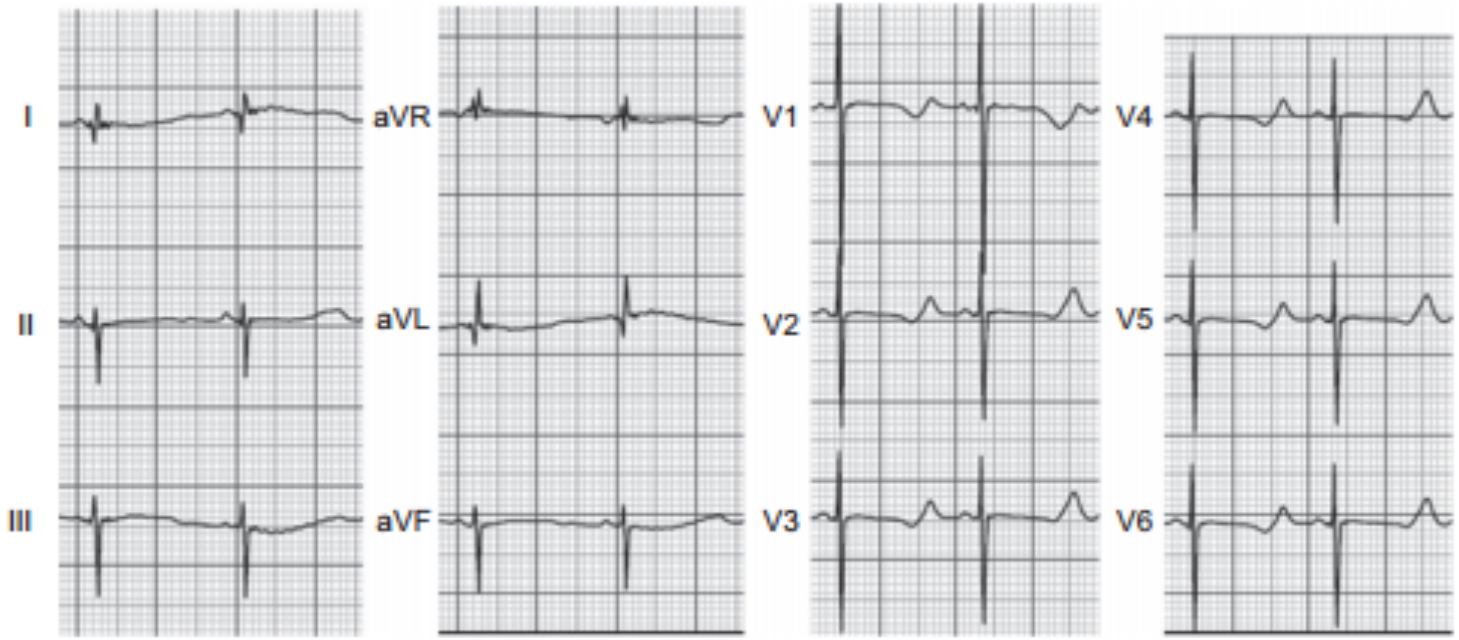




ECG from the proband of family: 4



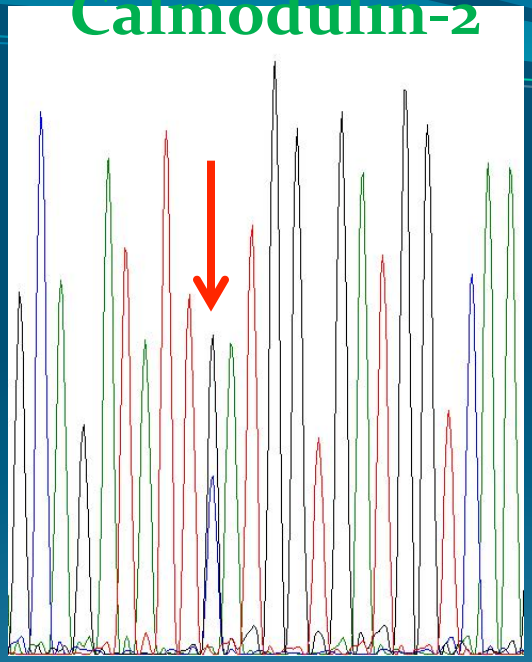
Calm-2 mutation and long QT syndrome



Standard 12-lead electrocardiogram from case 1 recorded at presentation. The rhythm was sinus at 83 beats/min with a prolonged QT interval (corrected QT interval 651 ms). Evidence for T-wave alternans was present in lead II.

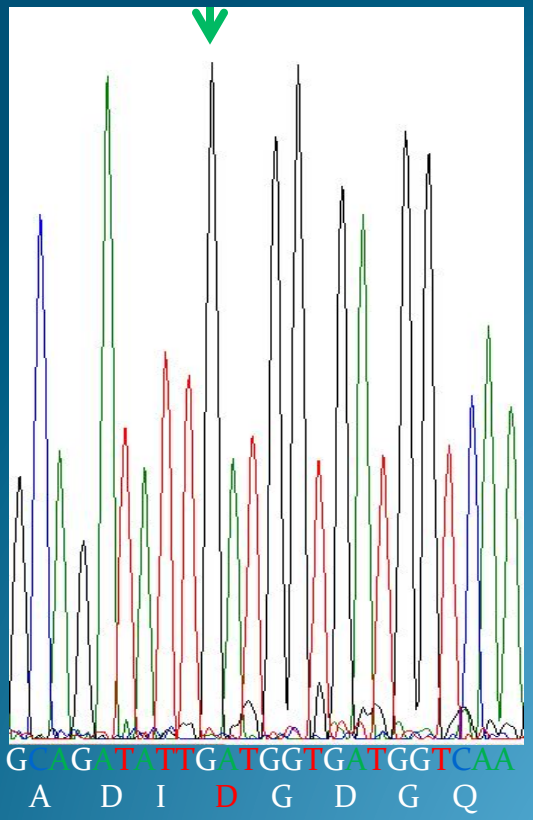
Heart Rhythm 2016;13:2012–2019

Calmodulin-2



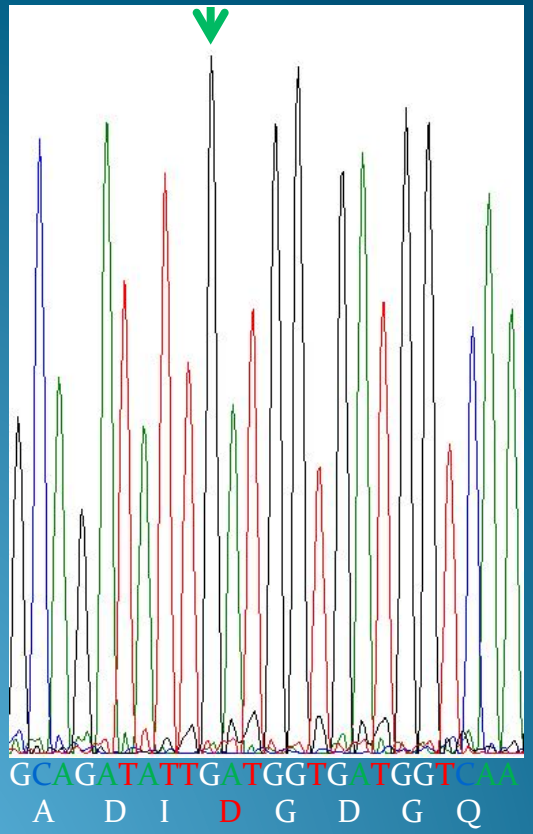
Child

GAT>CAT
Asp(D) > His(His)

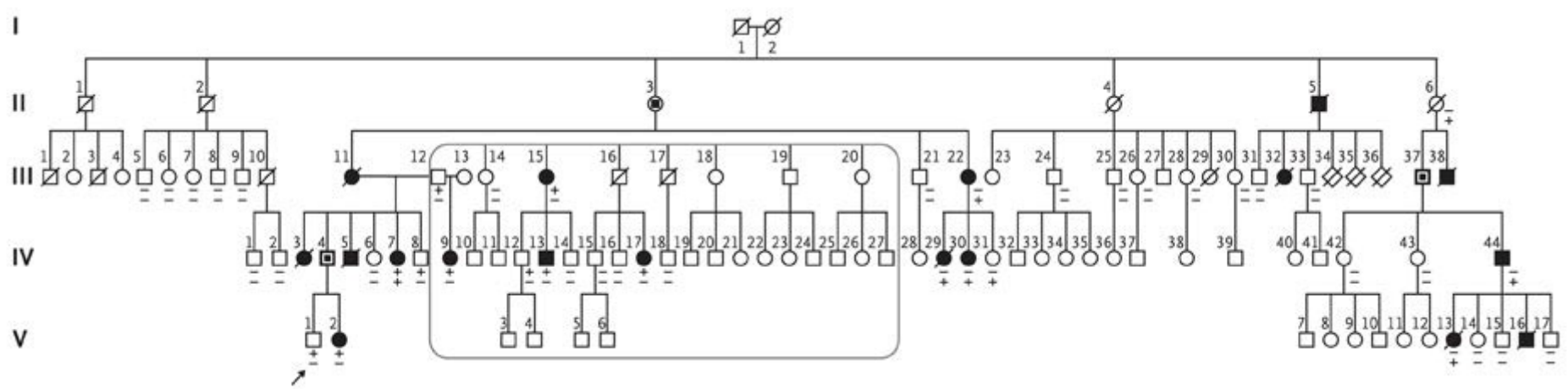


Father

Mother



Pedigree of Five Generations of a Family with the Long-QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia.



Beckmann BM, Wilde AA, Kääb S. Dual inheritance of sudden death from cardiovascular causes. N Engl J Med. 2008;358:2077-8.

Challenging Case

Kingdom of Saudi Arabia
Ministry of National Guard - Health Affairs
King Abdulaziz Medical City

R. 19-2-16

16 February 2016
8 Jamada El Oula 1437

Division of Pediatric Cardiology

SECTION HEAD
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Fahad Al Habshan, *MD, FESC*
Omar Al Tamimi, *MD*
Saleh Al Ghamdi, *MD*
Abdu Al Khatabi, *MD*
Mesud Yelbuz, *MD*
Zaheer Ahmad, *MD*
Ahmed Alomrani, MD, *FSCAI, FACC*

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Email: pedcardio@ngha.med.sa
✉ Mail Code 1420

Patient's Name : *ALSAHALY, NWAIR*
MRN : *2637906*

26367
26368 Father
26369 Mother

TO: M.Z.A. BHUIYAN
Head of Molecular Diagnostic Laboratory
Service of Medical Genetics, BN19_509
University Hospital Lausanne, Switzerland

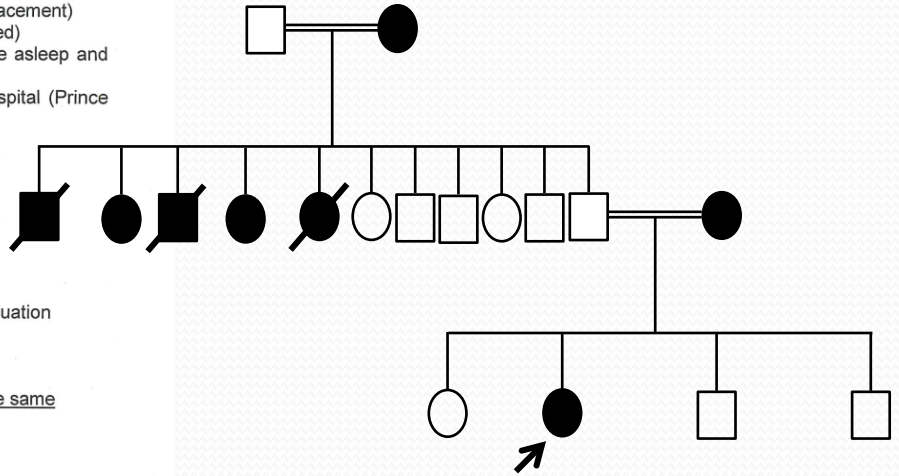
N is an 11-year-old with history of Loss of consciousness.
1st time in school, 4 months back; for seconds; no abnormal movement; no loss of consciousness; it occurs while standing; no postictal hypoactivity.

2nd time two weeks after the first event; while standing also, after playing in school for seconds, she has history of dizziness with change in position from sitting to standing position, frequently on daily basis. This dizziness associated with palpitation, no sweating. No more loss of consciousness. She has history of chest pain in the left nipple area, very localized; on /off; most likely while sitting. No cyanosis. She has history of poor appetite.

Family History:
Parents are first degree cousins: Grandmother (paternal side) had Long QT3 based on genetic testing and underwent an AICD implantation with regular follow-up with adult EP Team. (History of dizziness prior to AICD placement)

1. Auntie died at age of 13 year suddenly (Diagnosis: not confirmed)
2. Uncles died at age of 23 year and the other 20 year old (while asleep and sitting in the car.
3. Younger uncle had AICD; on regular follow-up in different hospital (Prince Sultan Cardiac Center. Not sure about the Diagnosis)

No other family member.
No family history of hearing deafness.



Physical Examination:
Conscious, alert, no Dysmorphism
CVS: S1, S2, No
GI: soft, lax, no organomegally
Detailed genetic testing are included in this report for your kind evaluation and feedback.

N.B.
Father is negative for genetic testing. Alive Auntie is positive for the same gene. Grandmother is positive for the same gene. (on AICD)

Dr. Saleh Al Ghamdi
BN 35954 PG 4469

Written by Consultant/Electrophysiologist (BN36519) Saleh Al Ghamdi
Pediatric Cardiology, King Abdulaziz Cardiac Center

Challenging Case

ID:2637906

KING ABDULAZIZ CARDIAC CENTER

15-MAY-2005 (10 yr)
Female Unknown

Room:ECG
Loc:32

Vent. rate	84	BPM
PR interval	164	ms
QRS duration	84	ms
QT/QTc	370/437	ms
P-R-T axes	53 53	52

Pediatric ECG Analysis

Normal sinus rhythm
Possible Left atrial enlargement
PEDIATRIC ANALYSIS - MANUAL COMPARISON REQUIRED
When compared with ECG of 15-NOV-2015 13:16,
PREVIOUS ECG IS PRESENT

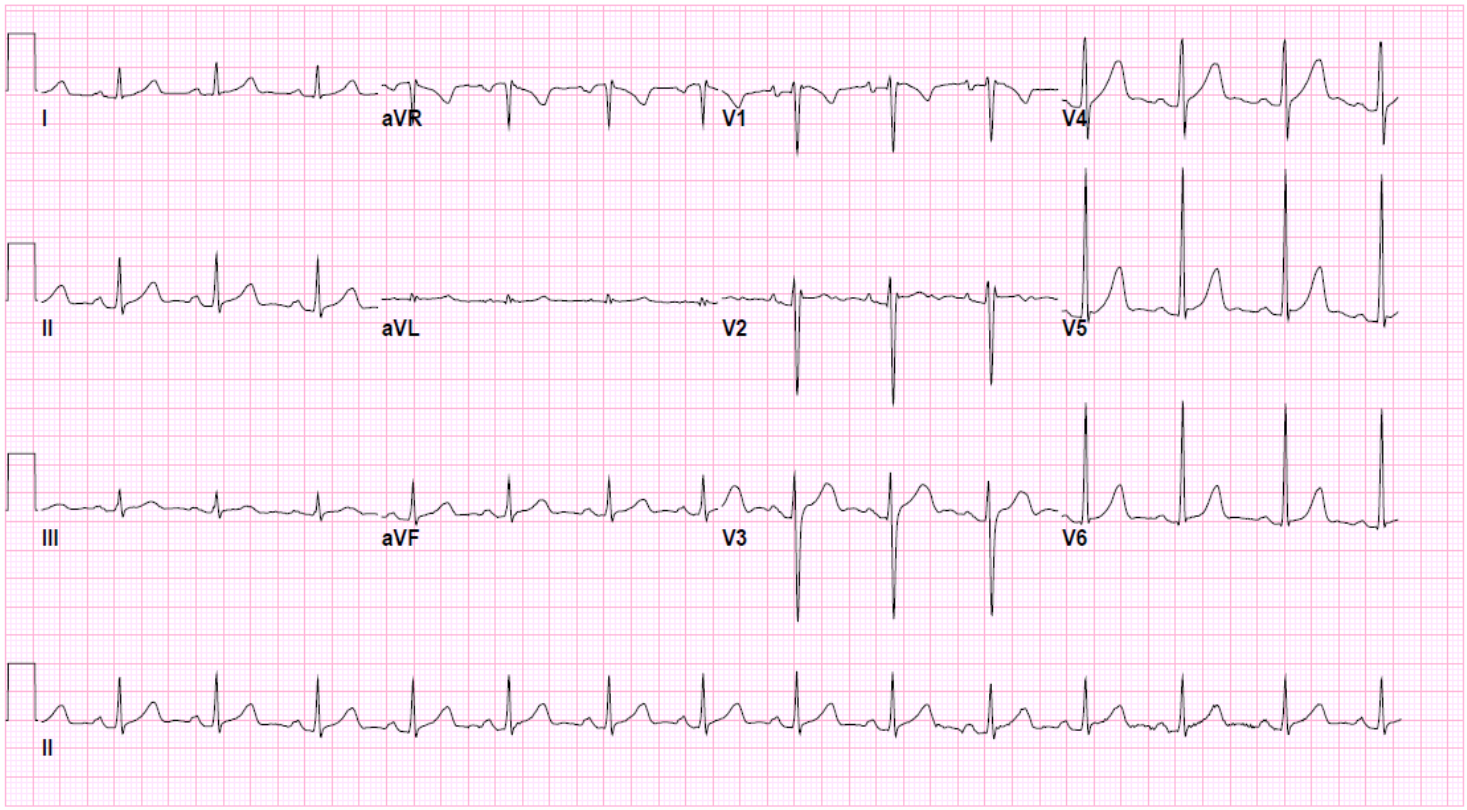
Technician:LEONORA VILLAPANDO
Test ind:ROUTINE

Referred by: PEDS

Confirmed By: : :

ECG 55-18:

COMMENTS::

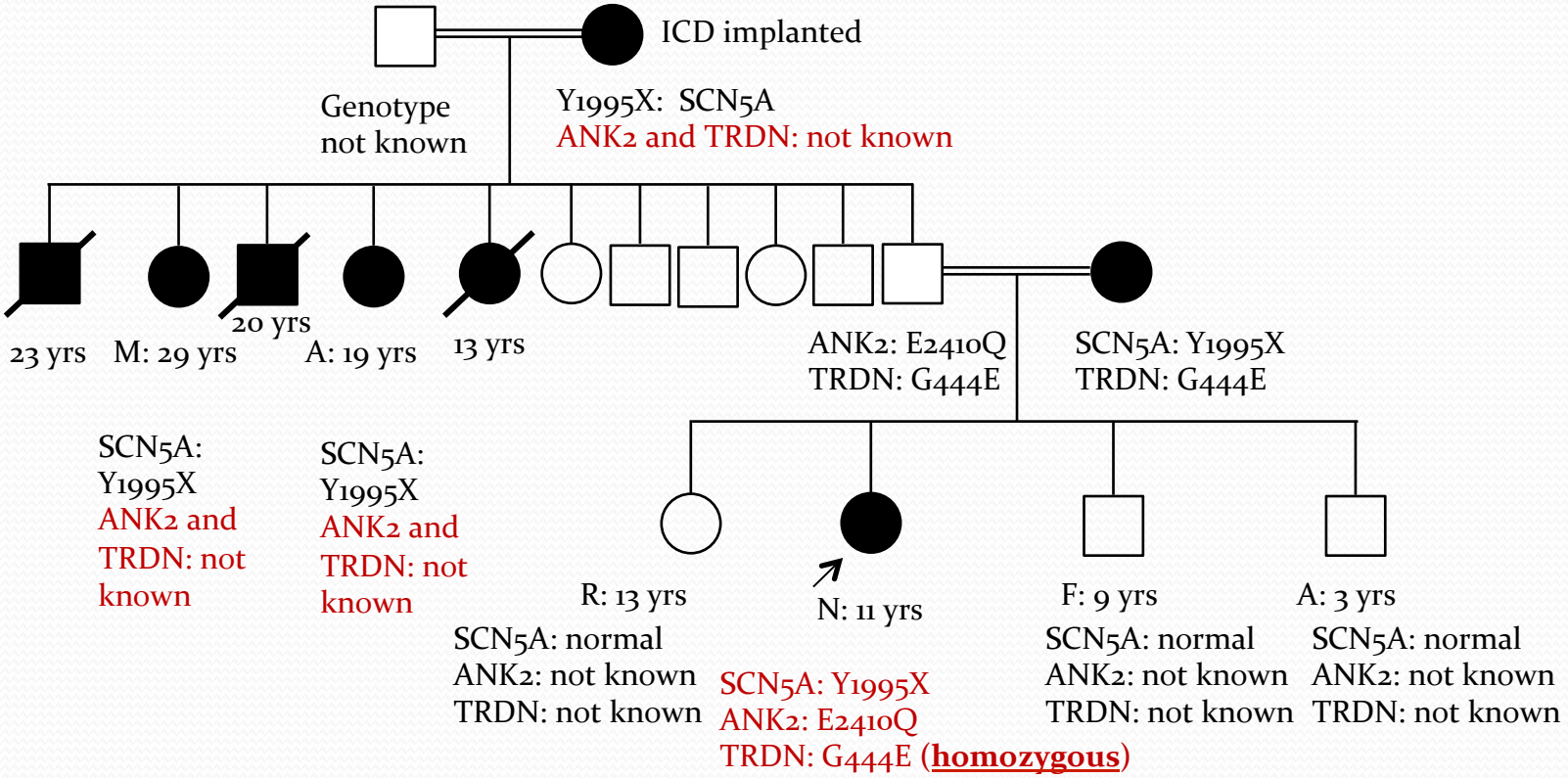


25mm/s 10mm/mV 40Hz 7.1.1 12SL 239 CID: 168

EID:234 EDT: 15:54 07-FEB-2016 ORDER:

Page 1 of 1

Genotype: Is there a Synergy between SCN5A and ANK2 ?



My suspicion goes for SCN5A and ANK2. TRDN (G444E) is possibly a polymorphism in Arab population ??

Genotype of the Deceased are not known

Challenging Case

KING ABDULAZIZ CARDIAC CENTER

19-MAY-2014 (4 days)
Male Unknown

Room:PCICU10
Loc:29

Vent. rate	139	BPM
PR interval	116	ms
QRS duration	142	ms
QT/QTc	332/505	ms
P-R-T axes	83 89	27

** ** ** ** * Pediatric ECG Analysis * ** ** ** **
Sinus rhythm with Fusion complexes
Right atrial enlargement
Left bundle branch block
No previous ECGs available

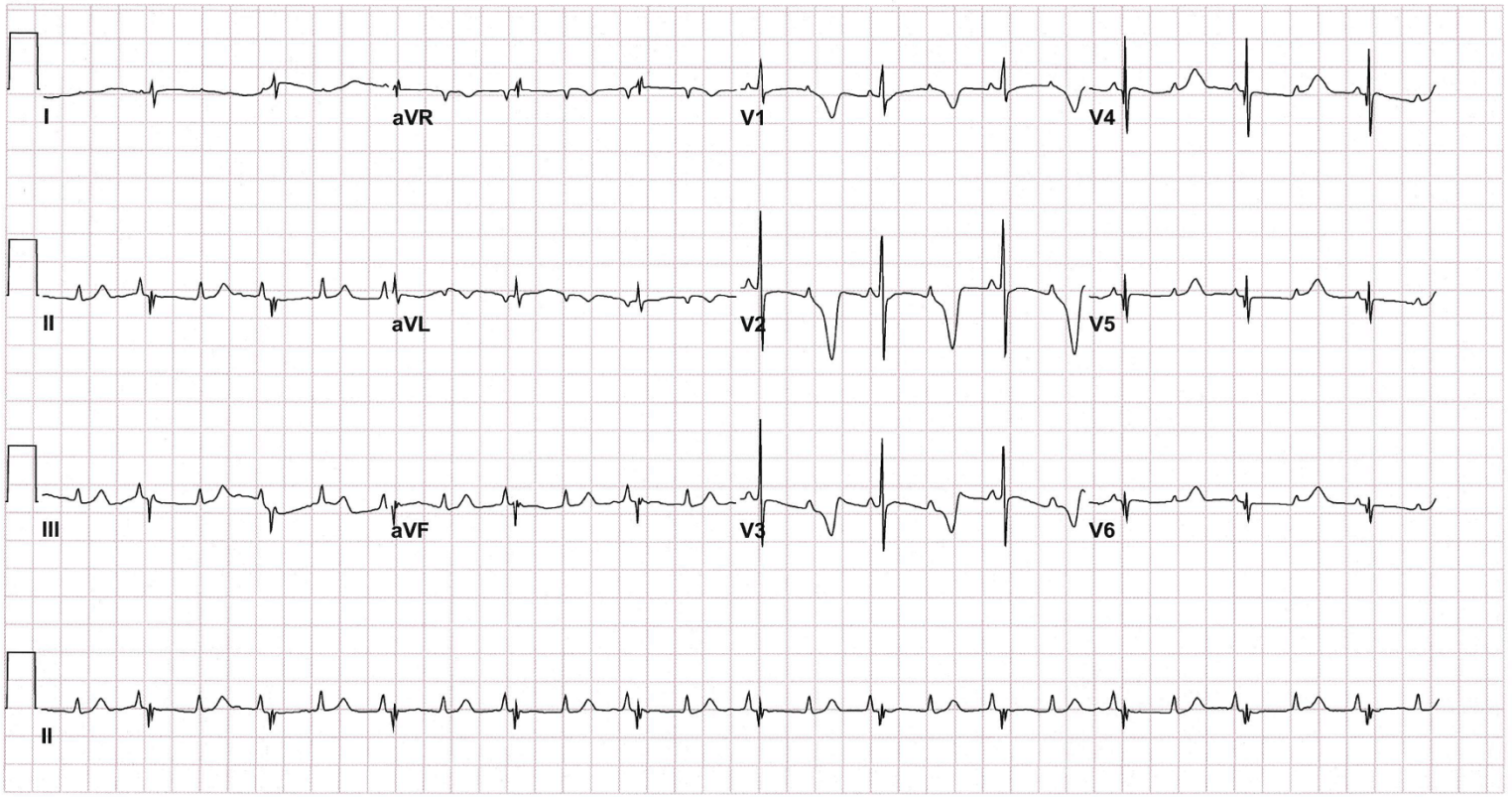
Technician:MARTHA BACOLOD
Test ind:PRE OP

Referred by: PEDS

Confirmed By: : :

COMMENT:

ECG 55-17:Yes



25mm/s 10mm/mV 40Hz 7.1.1 12SL 239 CID: 167

EID:222 EDT: 16:14 23-MAY-2014 ORDER: ACCOUNT: 2556797

Blind monks examining an elephant

Itcho Hanabusa (1652–1724).

Conclusion

- Clinical Phenotype, Family History for the Disease, ECG phenotype, QTc interval
- Main Genes: KCNQ1, KCNH2, SCN5A
- Important genes: KCNE1, KCNE2, ANK2
- Rare but very important: CALM1, CALM2, CALM3, TECRL
- Occasionally Multiple Genes might be involved
- Once again: Clinical Phenotype should not be forgotten

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- Multiple Genes might be involved
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Thank you!