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Translational Research in the Field of Inherited Arrhythmias

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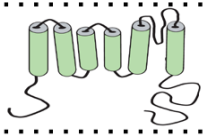
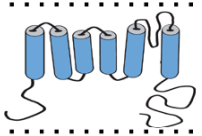
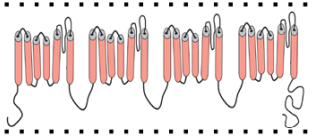
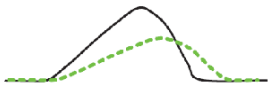
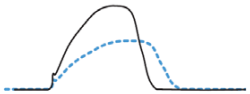
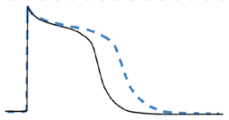
Czech Cardiovascular Research and Innovation Days, November 28-29, 2022, Prague, Czech Republic

Long QT Syndrome (LQT)

	Type 1	Type 2	Type 3
Gene	*KCNQ1*	*KCNH2*	*SCN5a*
Protein	$K_v7.1$ 	$K_v11.1$ 	$Na_v1.5$ 
Effect on current	I_{Ks} ↓ 	I_{Kr} ↓ 	$I_{Na,L}$ ↑ 
Effect on action potential			
Frequency among LQTS	± 35% 	± 30% 	≤ 10% 

Wilde *et al.*, Heart 2022, 108, 332-338

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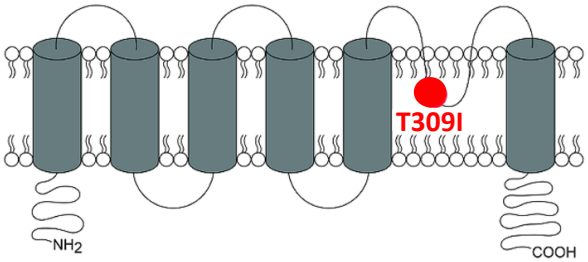
Long QT Syndrome (LQT)



Clinical characteristics of 30 Czech families with long QT syndrome and *KCNQ1* and *KCNH2* gene mutations: importance of exercise testing☆,☆☆

Irena Andrsova, MD,[a] Tomas Novotny, MD, PhD,[a,*] Jitka Kadlecova, DrS, PhD,[b] Alexandra Bittnerova, MA,[b] Pavel Vit, MD, PhD,[c] Alena Florianova, MD,[a] Martina Sisakova, MD,[a] Renata Gaillyova, MD, PhD,[b] Lenka Manouskova, RN,[a] Jindrich Spinar, MD, PhD[a]

Gene	Exon	Region	Nucleotide change	Amino acid change	References
KCNQ1	1	N-term	c.453_454insCC	p.P151fsX14	-
	3	S2-S3	c.569G>T	p.R190L†	[8]
	4	S4	c.674C>T	p.S225L	[9]
	6	S5	c.805_819del	p.269_273del	-
	6	Pore	c.916G>C	p.G306R	[8,10]
	7	Pore	c.926C>T	p.T309I*,‡	[8,11]
	7	Pore	c.935C>T	p.T312I	[8,10]
	7	Pore	c.940G>A	p.G314S	[8,12]
	7	S6	c.973G>A	p.G325R	[8,13]
	7	S6	c.1048G>C	p.G350R	[14]
	13	C-term	c.1645_1665del	p.M549_H555del	-
	14	C-term	c.1686G>C	p.R562S	-
	15	C-term	c.1760C>T	p.T587M	[8,15]
	15	C-term	c.1772G>A	p.R591H	[8,7]
	15	C-term	c.1772G>C	p.R591C	-
	16	C-term	c.1831G>A	p.D611N	[8]
	16	C-term	c.1893insC	p.P631fsX650†	[7]

Andrsova *et al.*, J Electrocardiol 2012, 45, 746-751

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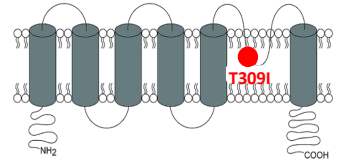
Long QT Syndrome (LQT)



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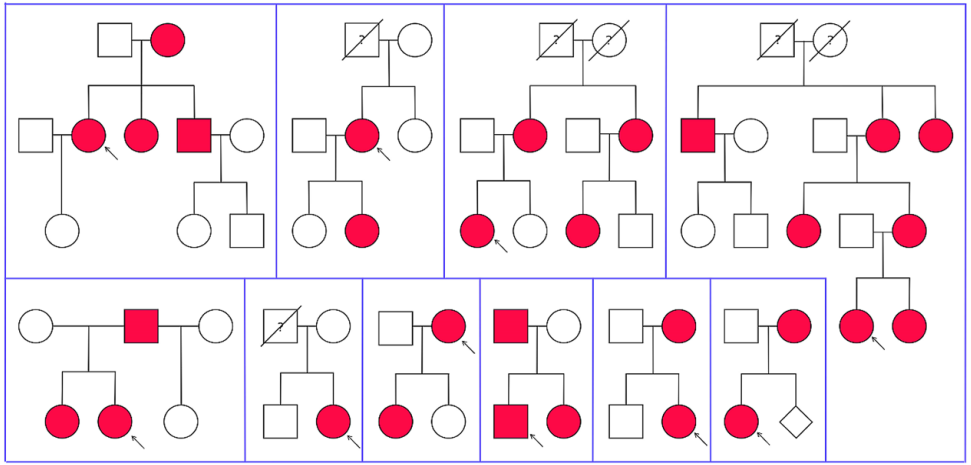

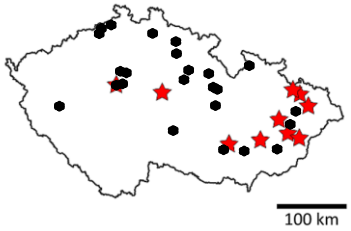

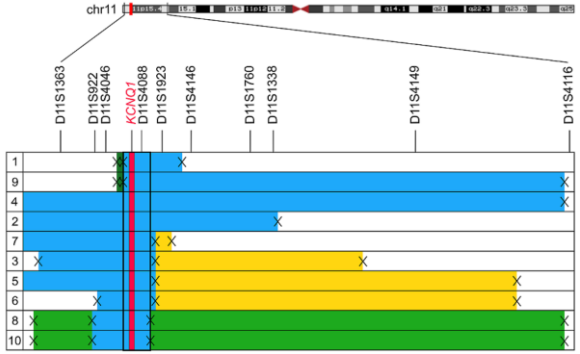

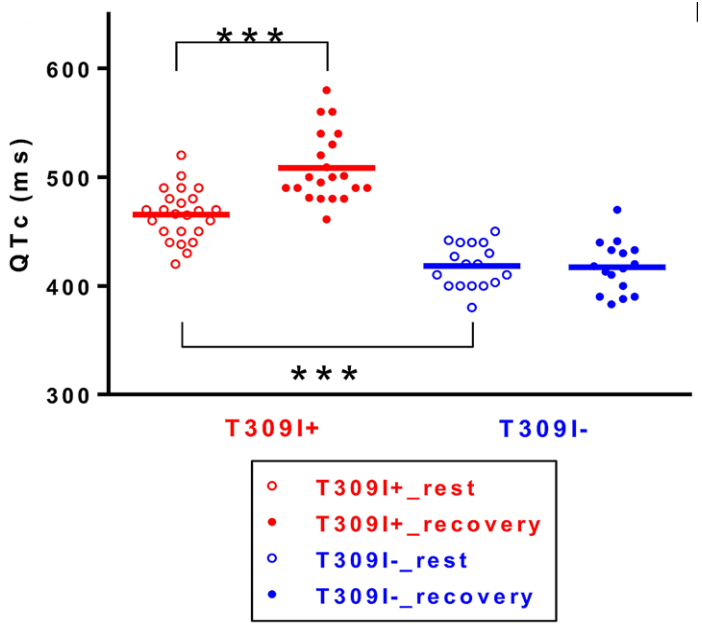

Synková *et al.*, Sci Rep 2021, 11, 3573

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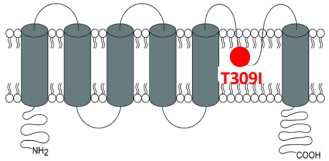
Long QT Syndrome (LQT)



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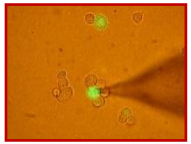
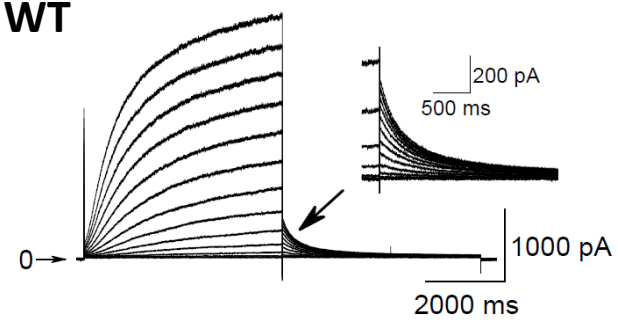
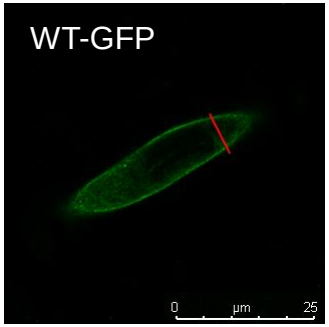
whole cell patch clamp

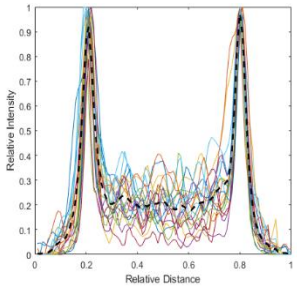


confocal microscopy

WT







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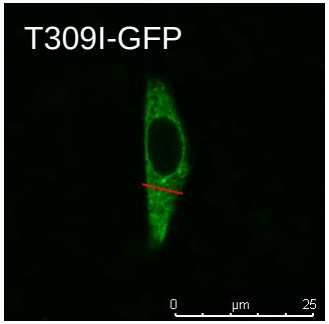

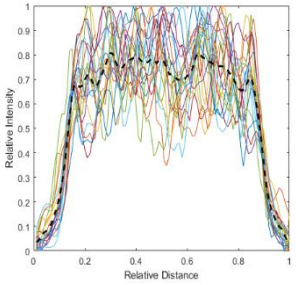

non-transfected cell

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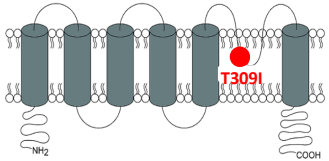
Long QT Syndrome (LQT)



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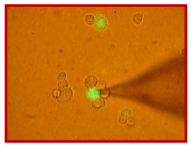
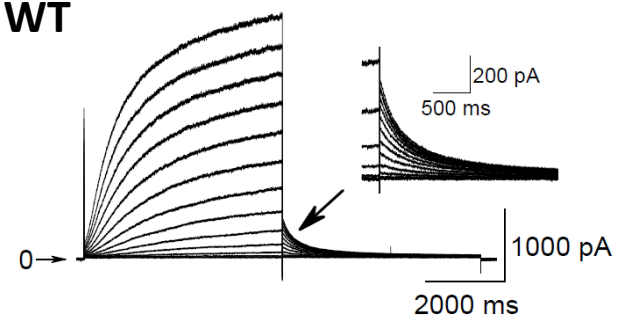
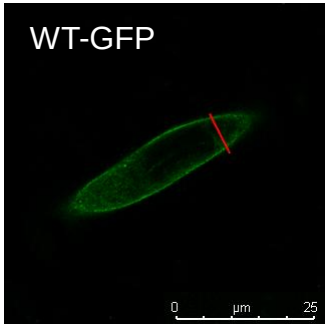
whole cell patch clamp

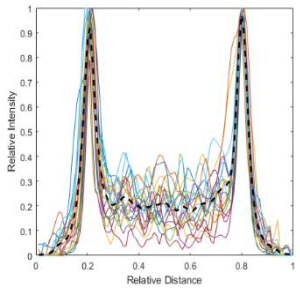


confocal microscopy

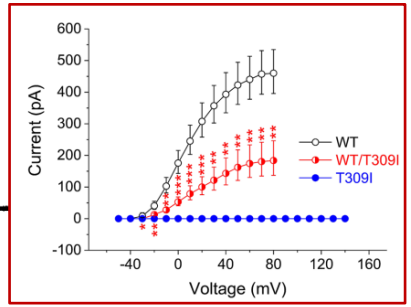
WT

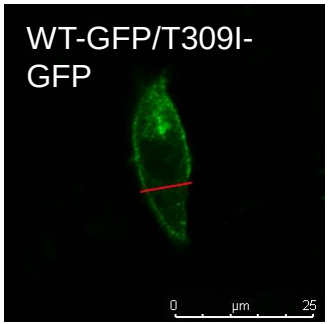


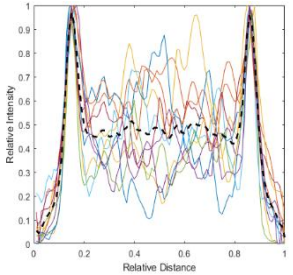




WT/T309I







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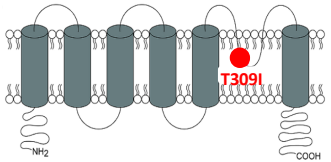

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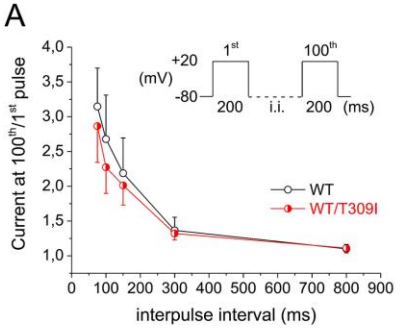

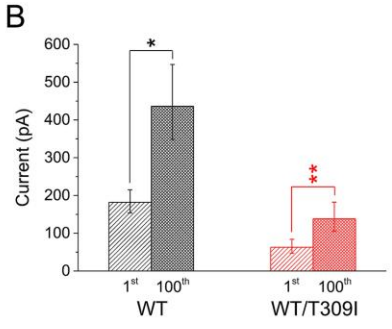

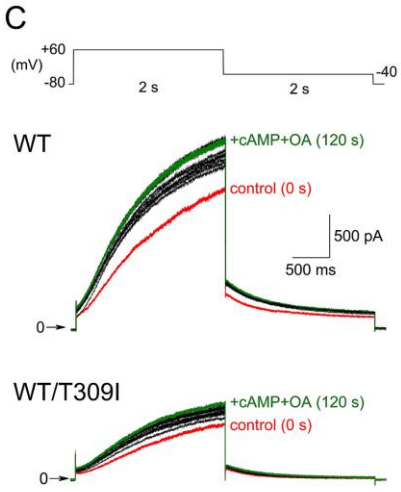

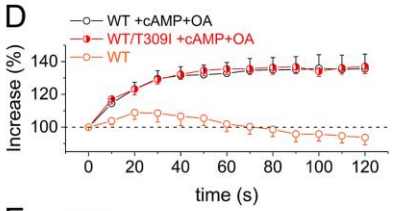

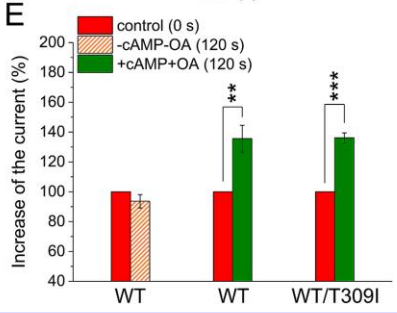

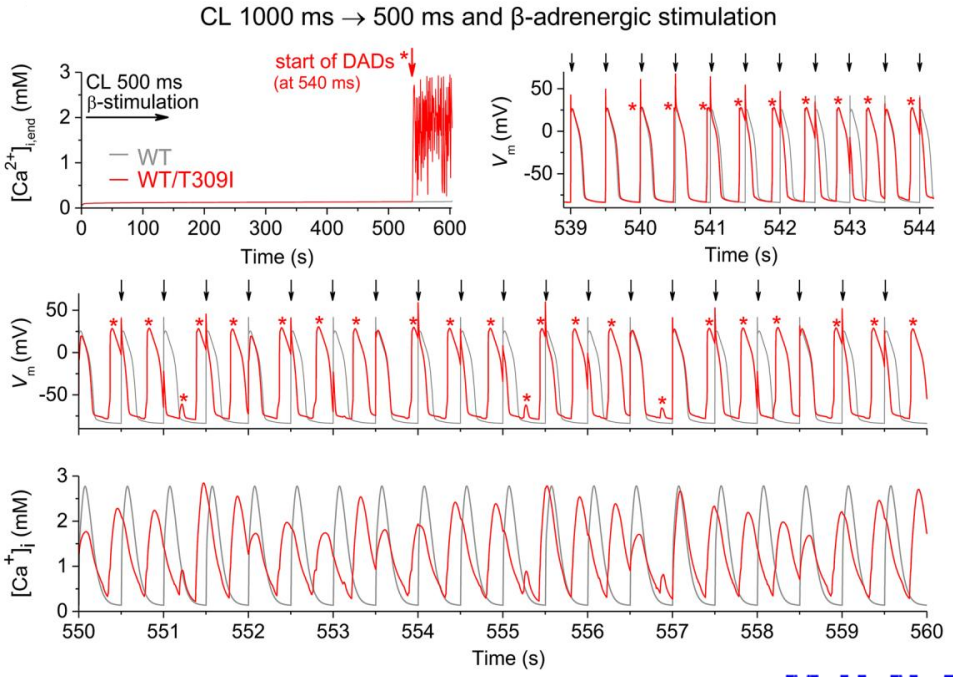

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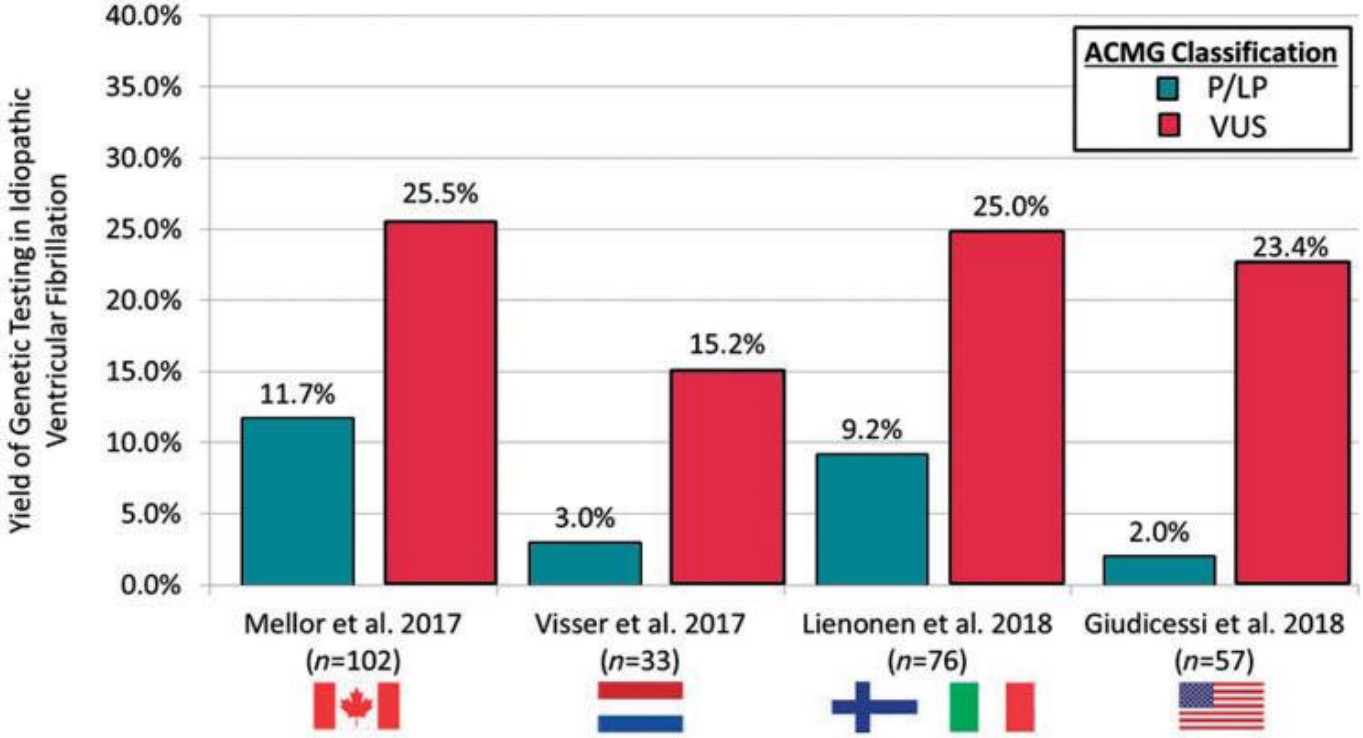
Synková *et al.*, Sci Rep 2021, 11, 3573

Idiopathic Ventricular Fibrillation (VF)



Conte *et al.*, Europace 2021, 23, 4-10

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Idiopathic Ventricular Fibrillation (VF)

	gene	protein variant		gene	protein variant
1	*KCNQ1*	Y111C	12	*PKP2*	E380K
2	*KCNH2*	R534C	13	*PKP2*	T50Sfs*61
3	*SCN4B*	P52R	14	*RYR2*	T279M
4	*HCN4*	D42H	15	*KCNH2*	P926Afs*14
5	*KCNH2*	R954C	16	*FLNC*	E1182Rfs*10
6	*DSP*	2836=	17	*DSP*	W867*
7	*KCNH2*	S1021Qfs*98; A228V	18	*RYR2*	T415I
8	*RYR2*	Y4734C	19	*DSP*	P2471L
9	*RYR2*	W4949R	20	*RYR2*	V2113M
10	*TTN*	R30773*	21	*CACNB2*	K267R
11	*TTN*	G4684*	22	*PKP2*	L436Hfs*11

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Idiopathic Ventricular Fibrillation (VF)

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9	*RYR2*	W4949R	20	*RYR2*	V2113M
10	*TTN*	R30773*	21	*CACNB2*	K267R
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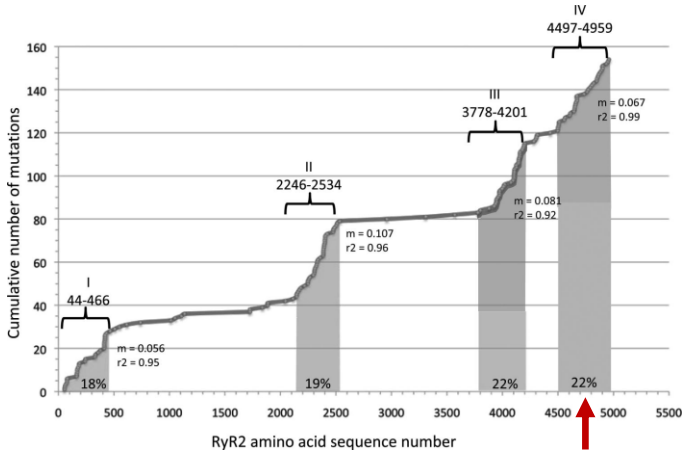
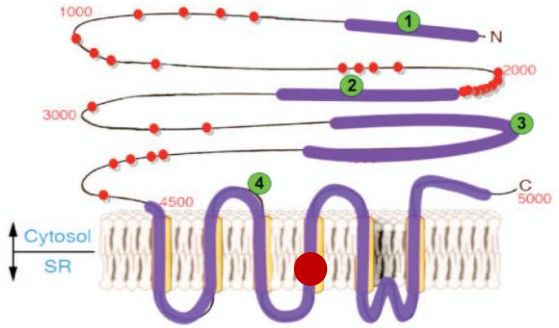
5	*KCNH2*	R954C
6	*DSP*	2836=
7	*KCNH2*	S1021Qfs*98; A228V
8	*RYR2*	Y4734C
9	*RYR2*	W4949R
10	*TTN*	R30773*
11	*TTN*	G4684*





Priori & Chen, Circ Res 2011, 108, 871-883

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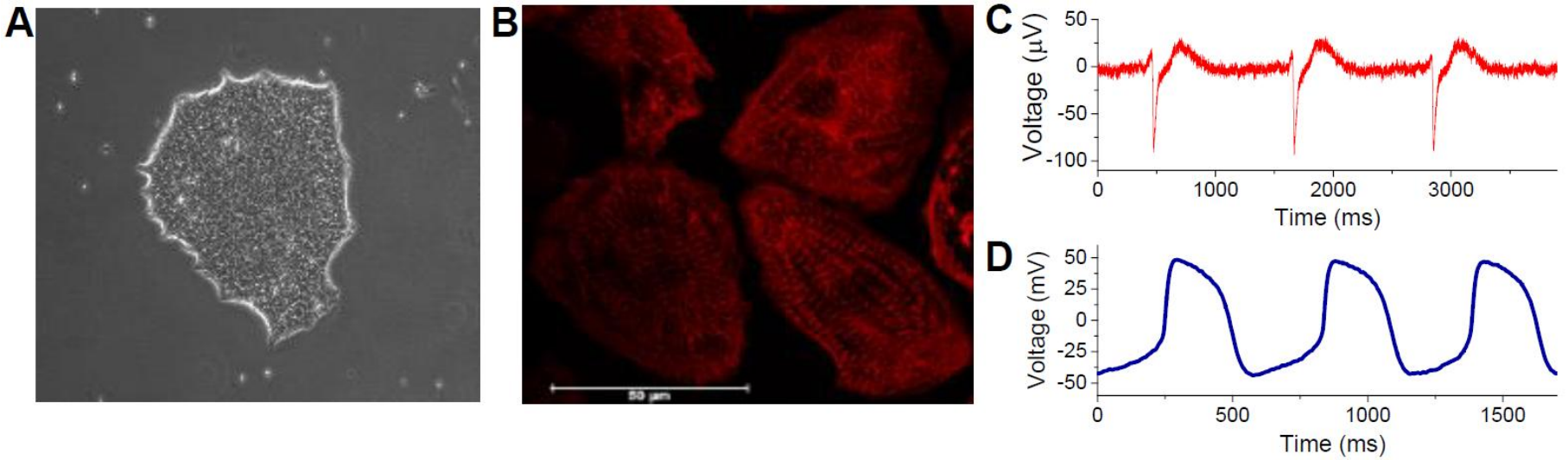
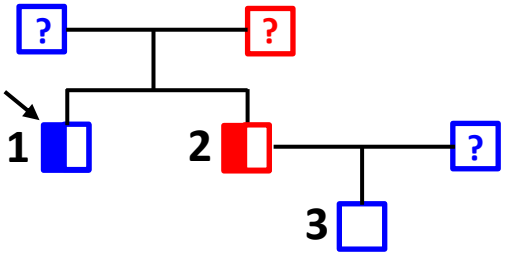
Idiopathic VF

Y4734C-RYR2



1) proband (iVF, Y4734C-RYR2)
2) proband´s sister (CPVT, Y4734C-RYR2)
3) proband´s nephew (healthy, WT-RYR2)



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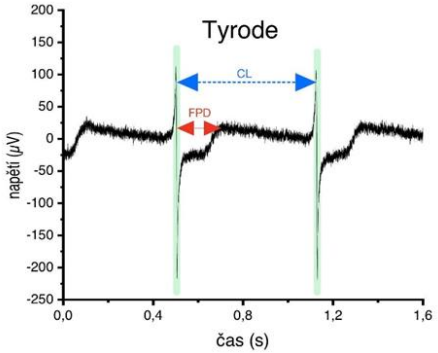
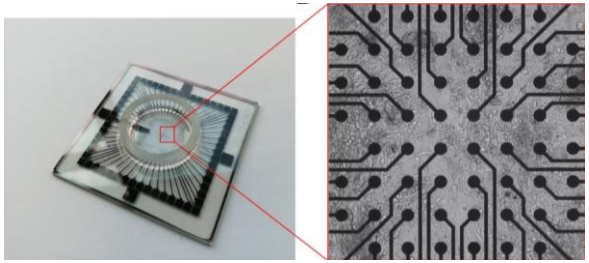
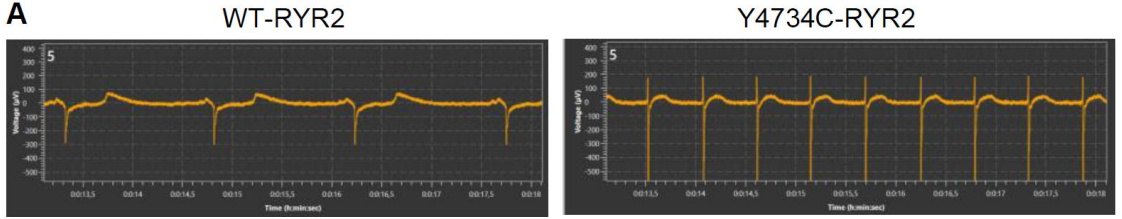
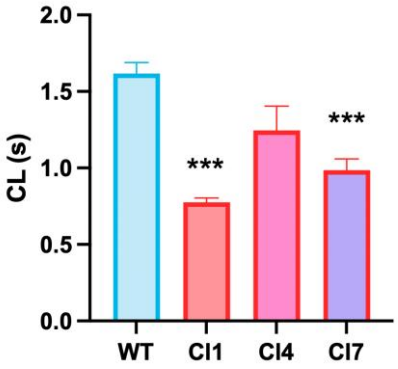
Idiopathic VF

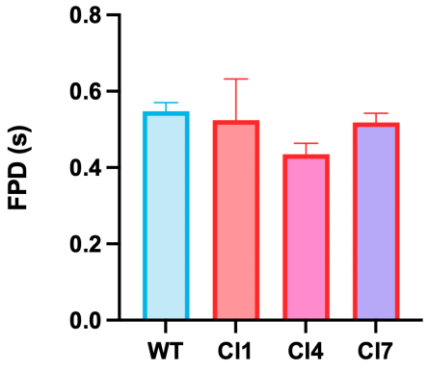
Y4734C-RYR2

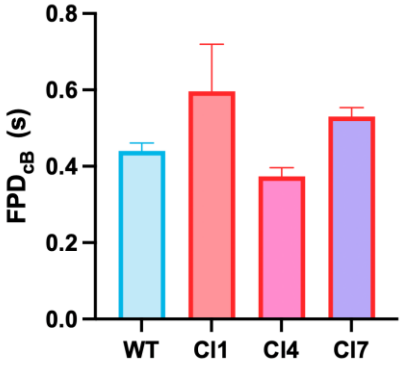


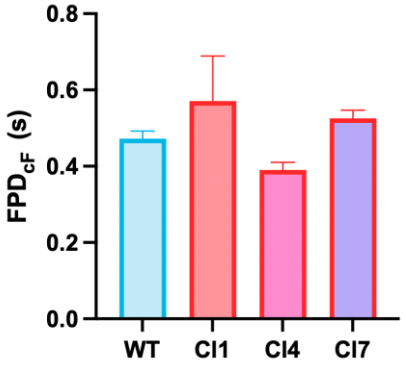








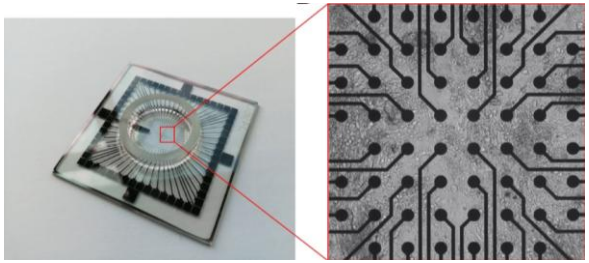




(unpublished data)

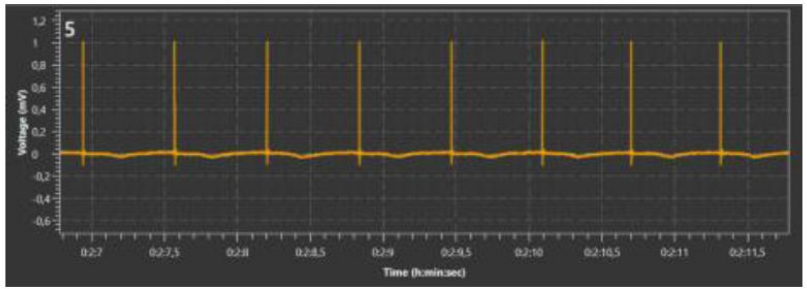
MUNI MED

Idiopathic VF

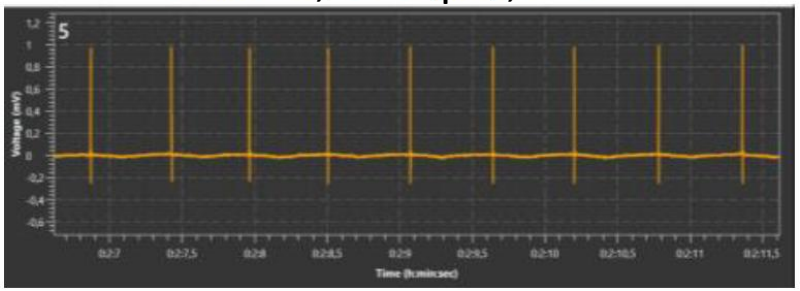


Y4734C-RYR2

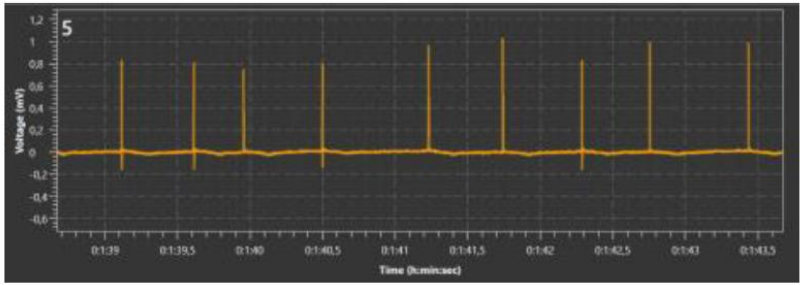
5 mM K^+, iso 0 µM, 37 °C (control)



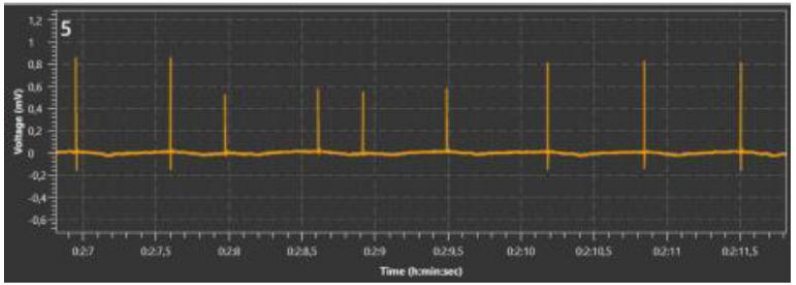
3 mM K^+, iso 0 µM, 37 °C



3 mM K^+, iso 1 µM, 37 °C



3 mM K^+, iso 1 µM, 40 °C



JNI MED

(unpublished data)

Translational research in the field of inherited arrhythmias…

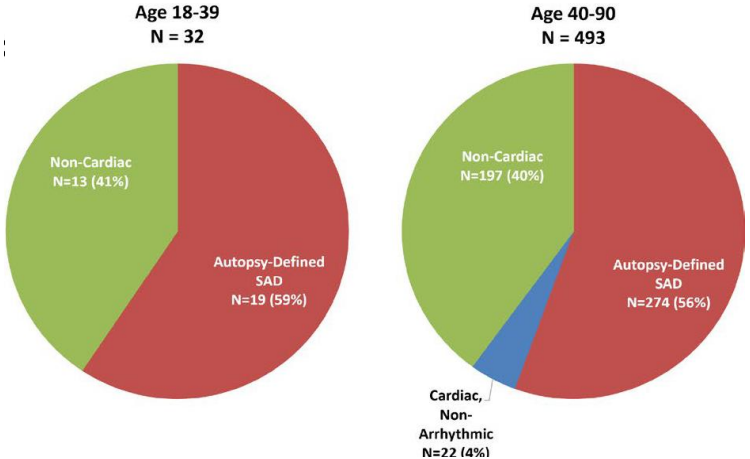
- … is key to confirmation of the pathogenic character of a variant – genotype-phenotype correlation.
- … can better explain arrhythmogenesis and help to find a more specific treatment/prevention in the future.

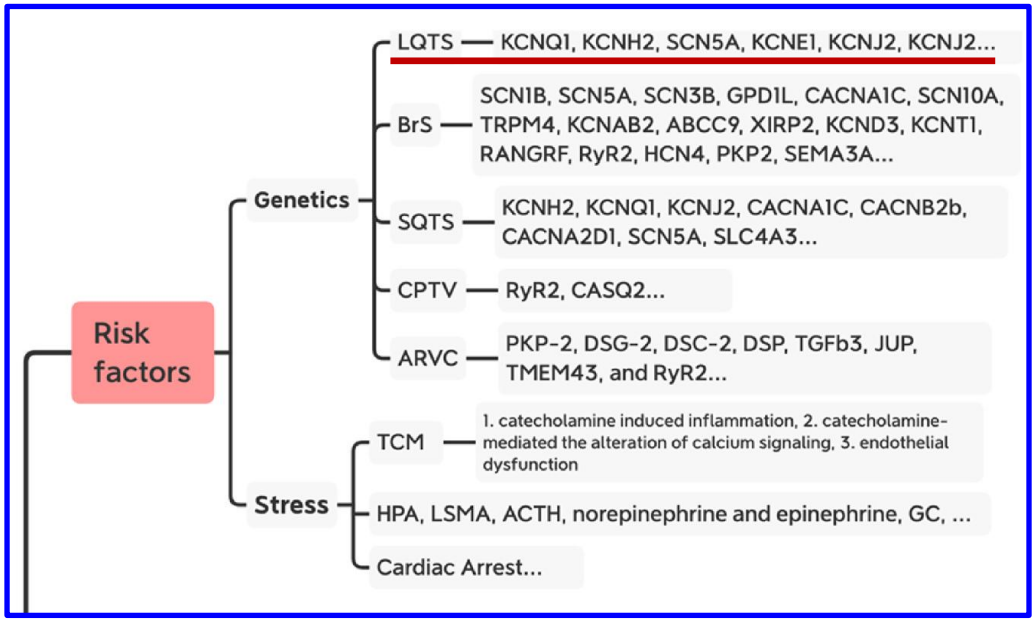
Thank you for your attention!

Supported by the grant projects NV16-30571A (2016-2020) and NU22-02-00348 (2022-2025) and the conceptual development of research organization (FNBr, 65269705) provided by the Ministry of Health of the Czech Republic and by the Specific University Research Grant of the Masaryk University MUNI/A/1133/2021 provided by the Ministry of Education, Youth and Sports of the Czech Republic.

MUNI MED

Sudden Cardiac Death & Inherited Arrhythmias





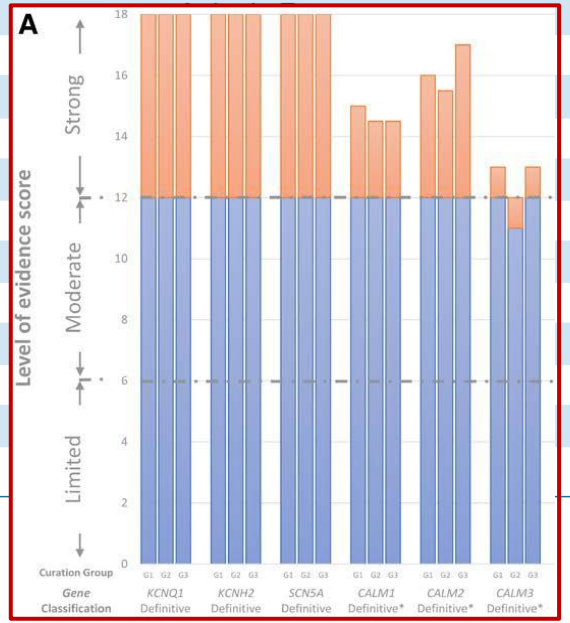
Chahine *et al.*, J Am Heart Assoc 2022, 11, e023446

Lou *et al.*, J Forensic Leg Med 2022, 87, 102332

MUNI MED

Long QT Syndrome (LQT)

LQT Subtype	Gene	Protein	Current
LQT1	*KCNQ1*	KCNQ1 (Kv7.1)	↓ I_{Ks}
LQT2	*KCNH2*	hERG (Kv11.1)	↓ I_{Kr}
LQT3	*SCN5A*	$Na_v1.5$	↑ I_{Na}
LQT4 (ankyrin-B syndrome)	*ANK2*		Multichannel interactions
LQT5	*KCNE1*		↓ I_{Ks}
LQT6	*KCNE2*		↓ I_{Kr}
LQT7 (Andersen-Tawil syndrome type 1)	*KCNJ2*		↓ I_{K1}
LQT8 (Timothy syndrome)	*CACNA1C*		↑ I_{Ca}
LQT9	*CAV3*		↑ I_{Na}
LQT10	*SCN4B*		↑ I_{Na}
LQT11	*AKAP9*		↓ I_{Ks}
LQT12	*SNTA1*		↑ I_{Na}
LQT13	*KCNJ5*		↓ I_{KACh}
LQT14	*CALM1*		Multichannel interactions
LQT15	*CALM2*		Multichannel interactions

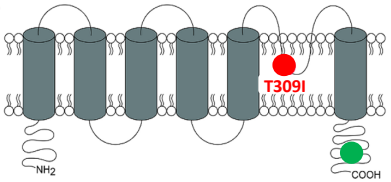


Bohnen *et al.*, Physiol Rev 2017, 97, 89-134

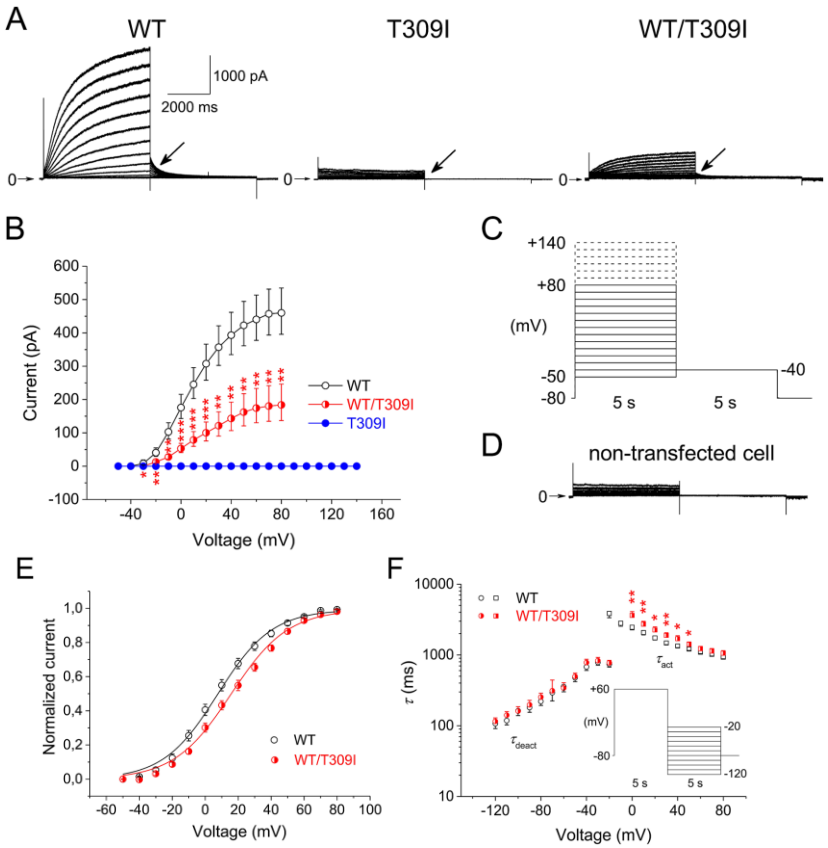
Adler *et al.*, Circulation 2020, 141, 418-428

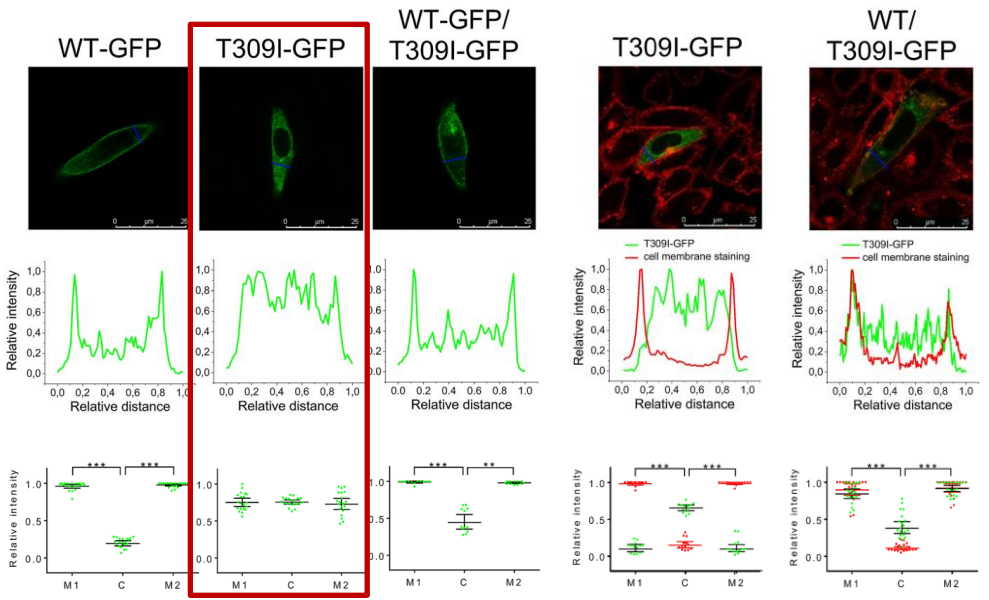
MUNI MED

Long QT Syndrome (LQT)



T309I

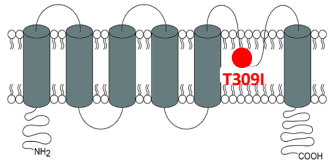




Synková *et al.*, Sci Rep 2021, 11, 3573

MUNI MED

Long QT Syndrome (LQT)



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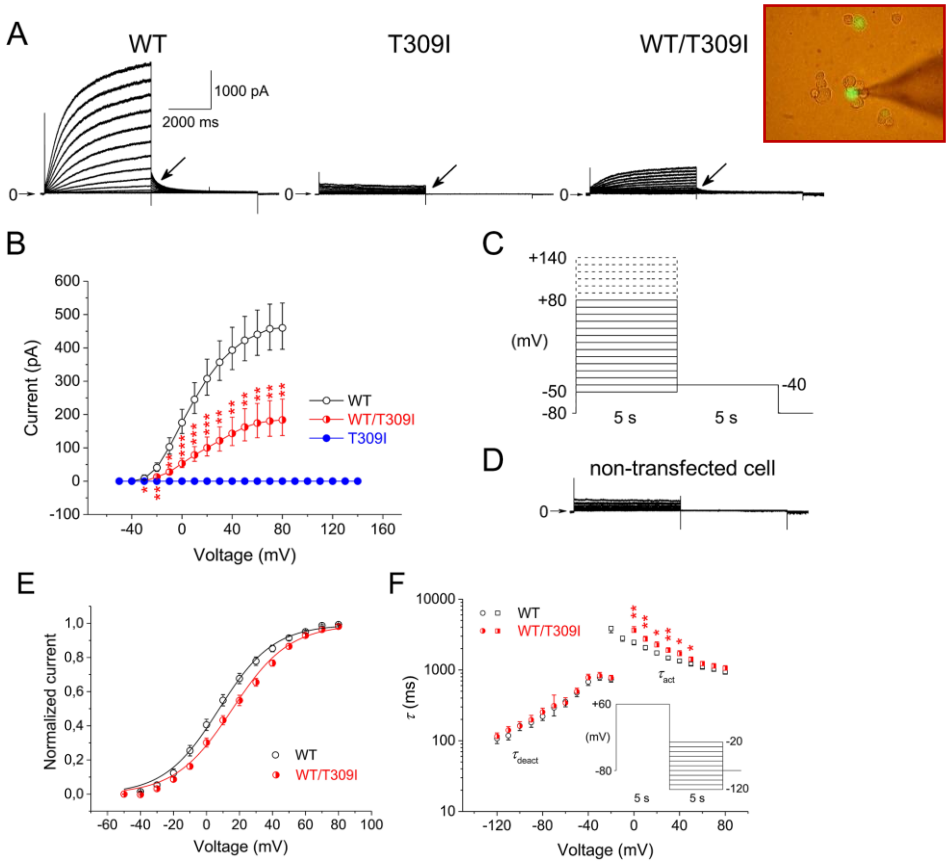

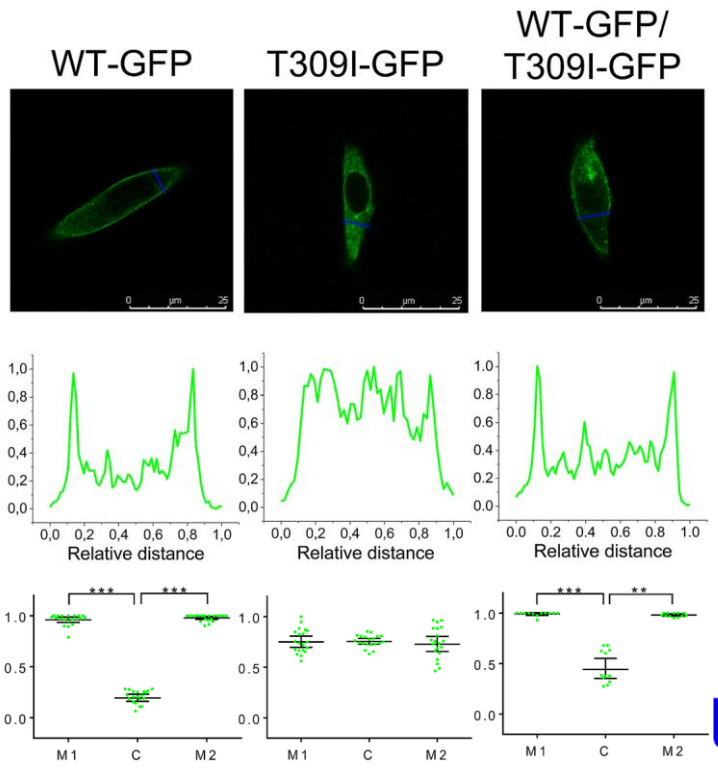

Synková *et al.*, Sci Rep 2021, 11, 3573

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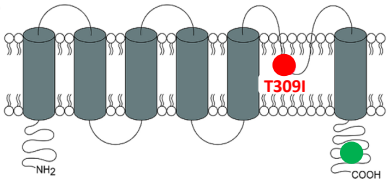
Long QT Syndrome (LQT)



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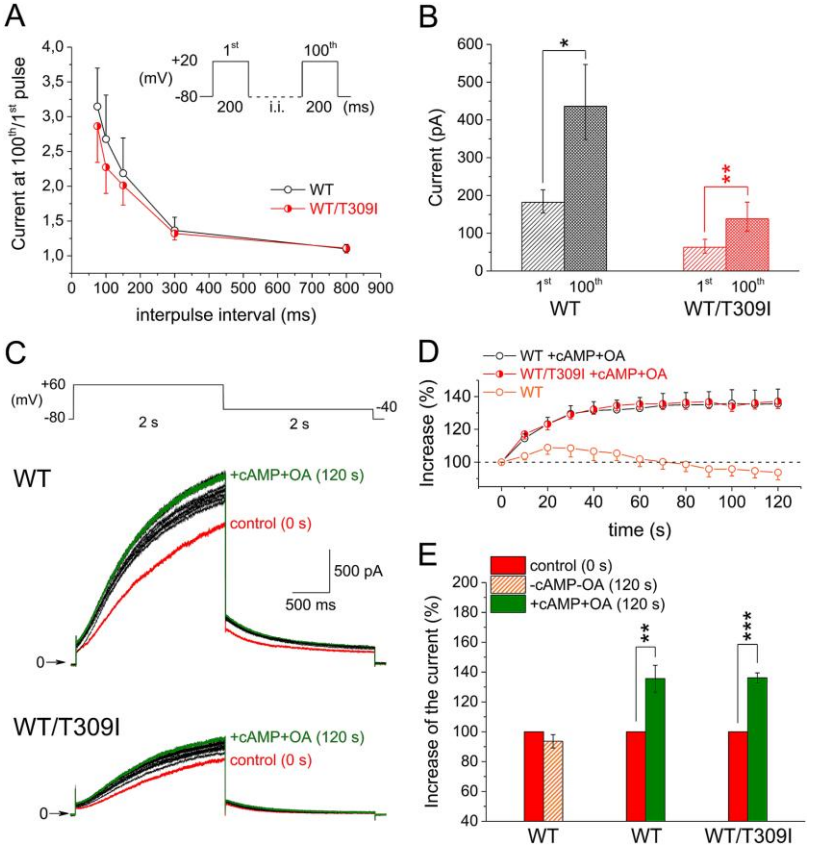

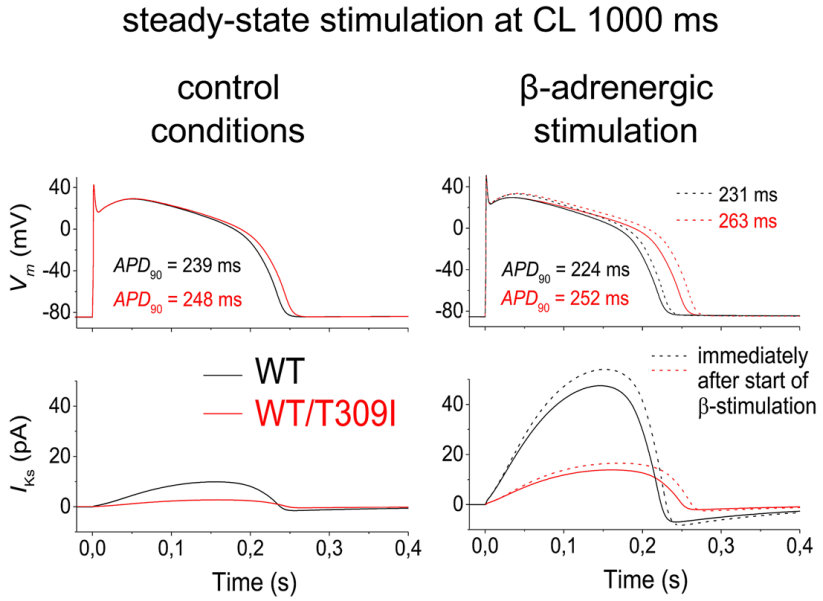

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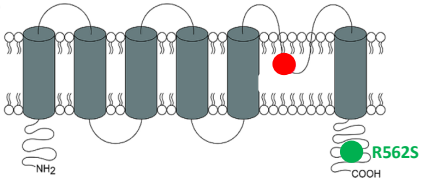
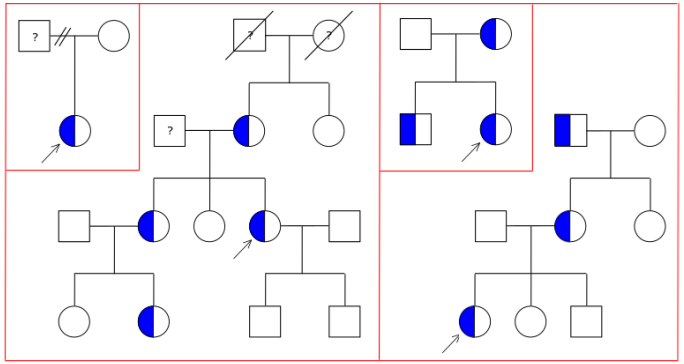
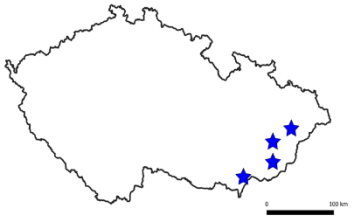
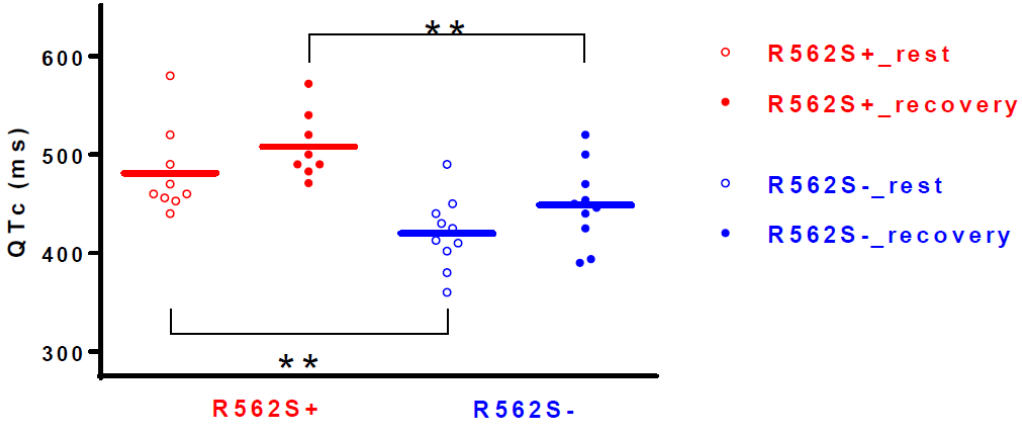
Long QT Syndrome (LQT)



R562S







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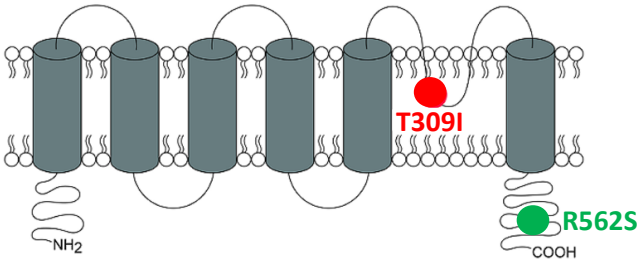
rodina												
1	247	108	119	X	213	406						
2	249	118	121	X	213	402	198	93	269	223		
3	251	96	125	X	213	402	198	93	269	227	210	
4	251	96	125	X	213	402	198	93	269	227	204	

(unpublished data)

MUNI MED

Long QT Syndrome (LQT)



Clinical characteristics of 30 Czech families with long QT syndrome and *KCNQ1* and *KCNH2* gene mutations: importance of exercise testing☆,☆☆

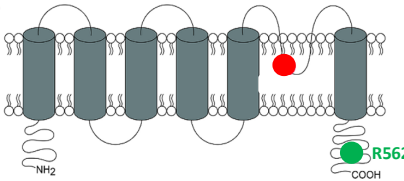
Irena Andrsova, MD,[a] Tomas Novotny, MD, PhD,[a,*] Jitka Kadlecova, DrS, PhD,[b] Alexandra Bittnerova, MA,[b] Pavel Vit, MD, PhD,[c] Alena Florianova, MD,[a] Martina Sisakova, MD,[a] Renata Gaillyova, MD, PhD,[b] Lenka Manouskova, RN,[a] Jindrich Spinar, MD, PhD[a]

Gene	Exon	Region	Nucleotide change	Amino acid change	References
KCNQ1	1	N-term	c.453_454insCC	p.P151fsX14	-
	3	S2-S3	c.569G>T	p.R190L†	[8]
	4	S4	c.674C>T	p.S225L	[9]
	6	S5	c.805_819del	p.269_273del	-
	6	Pore	c.916G>C	p.G306R	[8,10]
	7	Pore	c.926C>T	p.T309I*,‡	[8,11]
	7	Pore	c.935C>T	p.T312I	[8,10]
	7	Pore	c.940G>A	p.G314S	[8,12]
	7	S6	c.973G>A	p.G325R	[8,13]
	7	S6	c.1048G>C	p.G350R	[14]
	13	C-term	c.1645_1665del	p.M549_H555del	-
	14	C-term	c.1686G>C	p.R562S	-
	15	C-term	c.1760C>T	p.T587M	[8,15]
	15	C-term	c.1772G>A	p.R591H	[8,7]
	15	C-term	c.1772G>C	p.R591C	-
	16	C-term	c.1831G>A	p.D611N	[8]
	16	C-term	c.1893insC	p.P631fsX650†	[7]

Andrsova *et al.*, J Electrocardiol 2012, 45, 746-751

MUNI MED

Long QT Syndrome (LQT)



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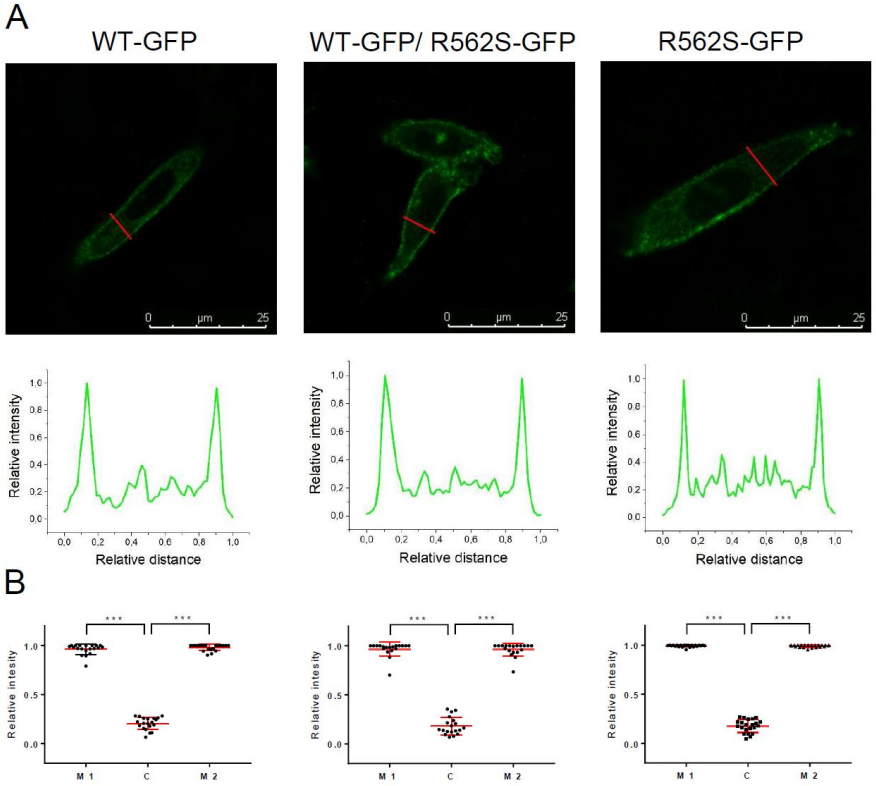

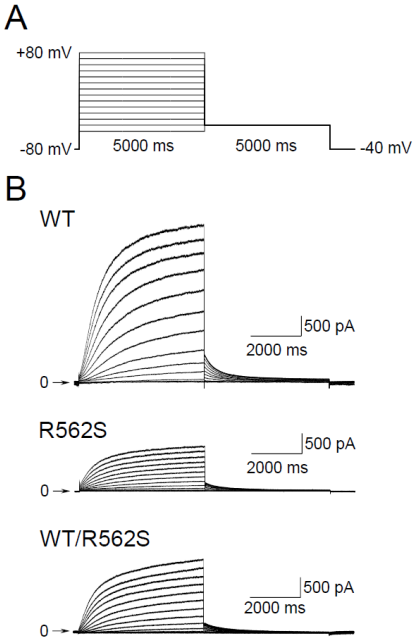

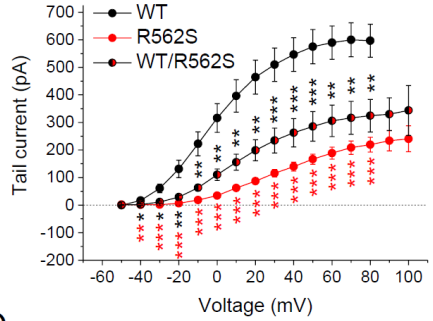

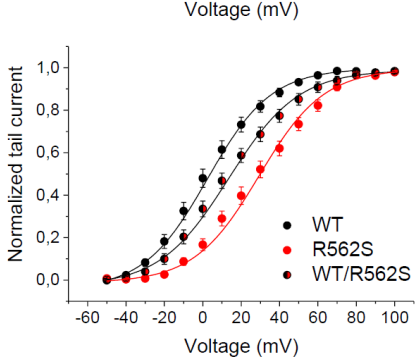

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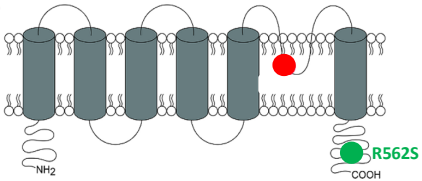
Long QT Syndrome (LQT)



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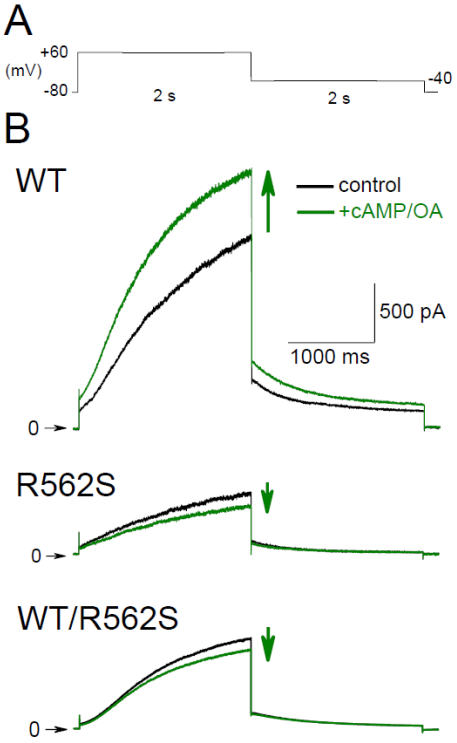
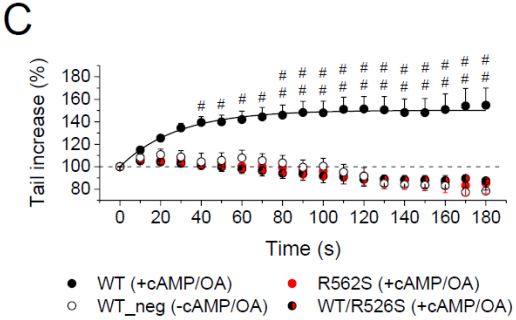
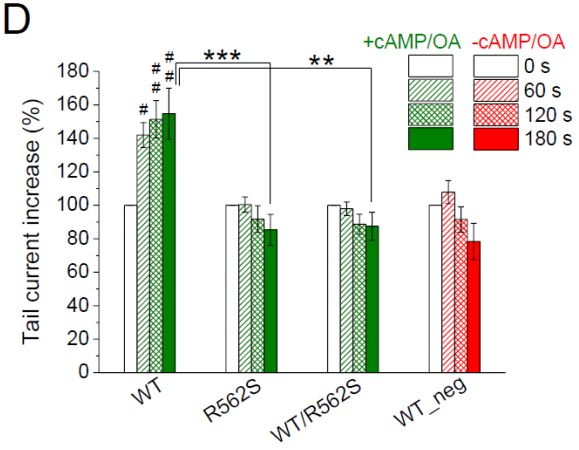
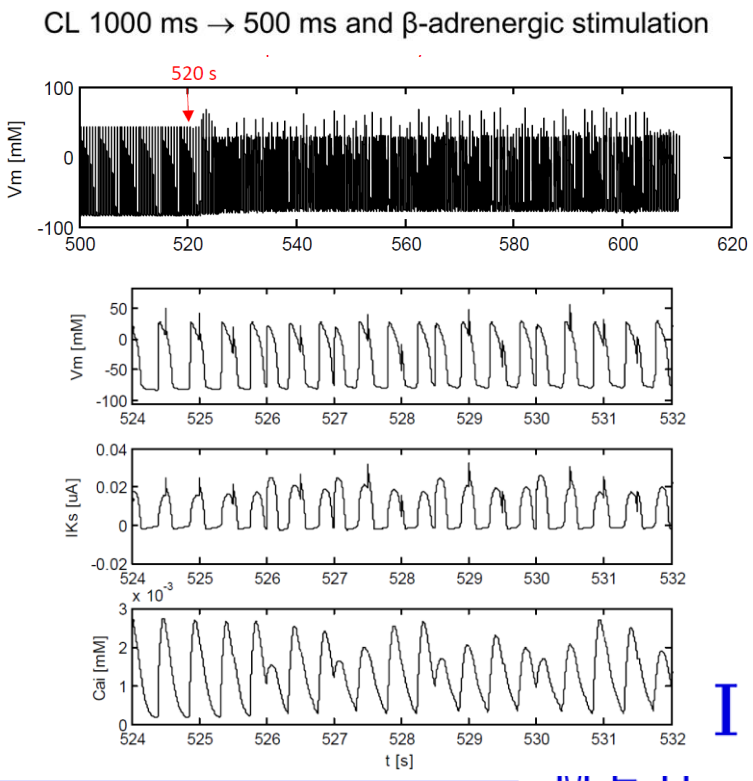








(unpublished data)

Idiopathic Ventricular Fibrillation (VF)

Table I Diagnostic assessment of patients with IVF

Study	Number of patients with initial diagnosis of IVF	Exercise testing	CMR	Cardiac CT/coronary angiogram	Ergonovine challenge	Sodium-channel blockers challenge	EPS/cardiac mapping	Endocardial biopsy	Genetic testing	Number of patients with true IVF
Krahn *et al.*[5]	63	100%	100%	100%	NP	100%	NR	1.6%	30%	28 (44%)
Sekiguchi *et al.*[17]	64	27/64	100%	100%	NR	NR	76%	NR	0%	40 (62%)
Visser *et al.*[34]	33	NR	NR	NR	NR	58%	NR	NR	100%	32 (97%)
Leinonen *et al.*[8]	76	75%	62%	NR	NR	NR	51%	29%	NR	69 (91%)
Haissaguerre *et al.*[20]	24	NR	NR	NR	NR	100%	100%	NR	17/24	24 (100%)
Waldmann *et al.*[13]	49	8.2%	81.6%	100%	38.8%	43%	24.5%	0	18.4%	46 (94%)
Giudicessi and Ackerman[14]	67	88%	73%	86%	NR	27%	61%	6%	73%	67 (100%)
Conte *et al.*[23]	245	80%	65%	100%	NR	64%	59%	1.6%	18%	245 (100%)
Frontera *et al.*[25]	54	83%	70%	44%	NR	69%	63%	13%	87%	37 (68%)
Cunningham *et al.*[28]	46	41%	57%	11%	NR	NP	NR	4%	72%	22 (48%)

CMR, cardiac magnetic resonance; CT, computed tomography; EPS, electrophysiology study; IVF, idiopathic ventricular fibrillation.

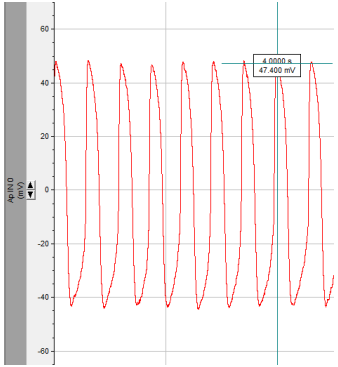
Conte *et al.*, Europace 2021, 23, 4-10

MUNI MED

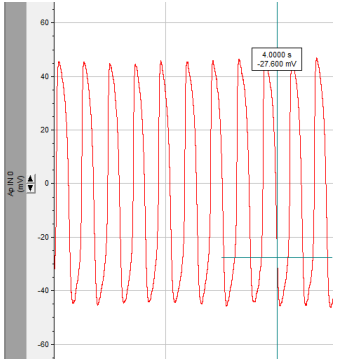
Idiopathic VF

Y4734C-RYR2

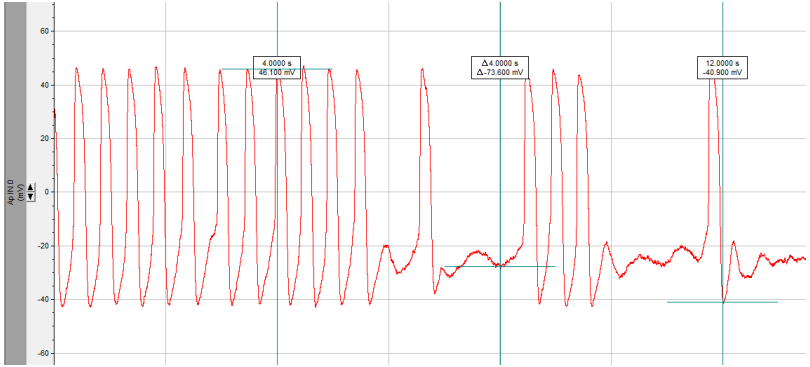
Tyr, 5 mM K^+

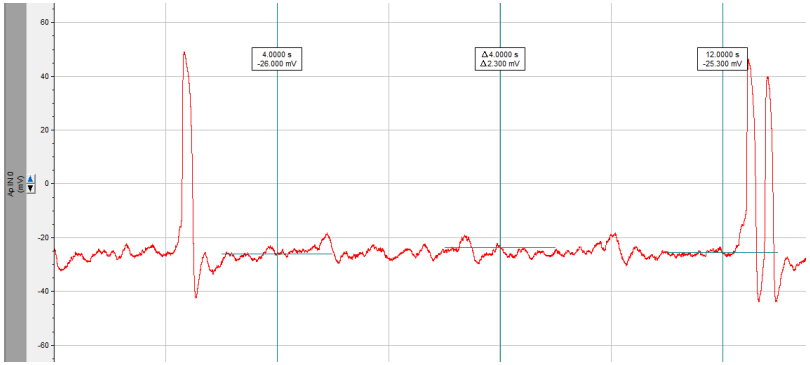


Tyr, 3 mM K^+



Tyr, 3 mM K^+ + 1 µM isoprenalin





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