

Sekvenování nové generace v diagnostice vrozených arytmiických syndromů

MUDr. A. Křebsová PhD

IKEM Praha

Genetická Heterogenita dědičných KVO



Kardiomyopatie

ACTC1, ACTN2, BAG3, CSRP3, CTNNA3, DES, DSC2, DSG2, DSP, DTNA, FHL1, FLNA, FLNC, GLA, LAMP2, LDB3, LMNA, MIB1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYPN, NEXN, PKP2, PLN, PRKAG2, PTPN11, RAF1, RBM20, SGCD, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN, VCL

Arytmie

ANK2, CACNA1C, CALM1, CALM2, CASQ2, CAV3, KCNA5, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN5A, SNTA1, TRDN

Aortopatie

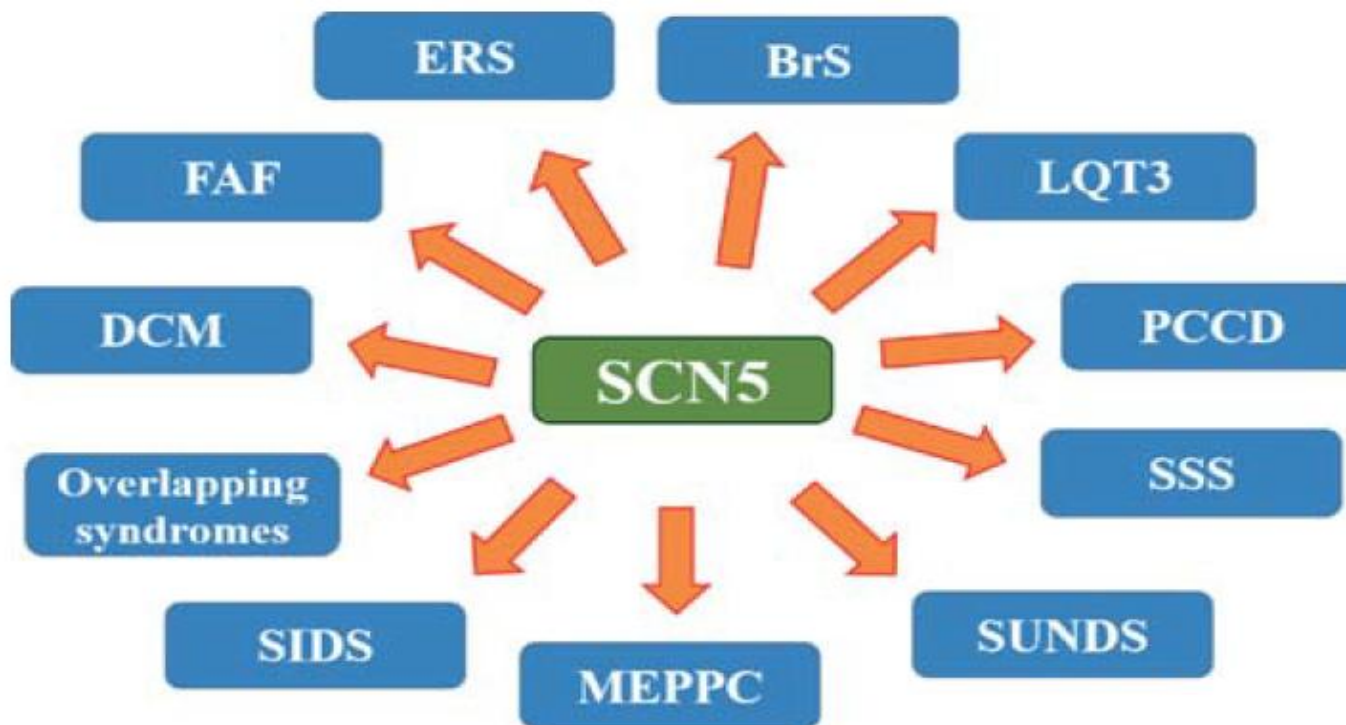
ACTA2, COL1A1, COL1A2, COL3A1, COL4A3, COL4A4, COL4A5, COL5A1, COL5A2, ELN, EMILIN1, FBN1, FBN2, LOX, MAT2A, MFAP5, MYH11, NOTCH1, PLOD1, SKI, SLC2A10, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFB1, TGFB2, TNXB

VVV srdce

ACTA2, ELN, GATA4, GATA5, GATA6, JAG1, NKX2.5, NOTCH1, NOTCH2, PTPN11, TBX1, TBX20, TBX5, ZIC3

Alelická Heterogenita!

The cardiac sodium channel its mutations and their spectrum arrhythmia phenotypes



Pérez-Riera et al, J Hum Growth, 2016

Specifika jednotlivých genů!

KCNH2- LOF

KCNQ1
missence

SCN5A – kde?,
LOF?

TTN -pouze
STOP v určité
lokalizaci

...

Populačně
specifické
varianty

DNA varianty specifické pro jednotlivé
rodiny

Dg. CPVT – RYR2 Varianta hodnocení v praxi (varsome)

The screenshot displays the VarSome web interface. At the top, the VarSome logo is on the left, and navigation links for 'RESEARCH USE ONLY', 'Upload VCF', 'Editions', 'Community', and 'About' are on the right. A search bar contains the variant 'RYR2:c.5170G>A'. Below the search bar, there are tabs for 'hg19' and 'hg38'. The main content area shows the variant 'chr1-237777598-G-A' with buttons for 'Classify this variant', 'Community contributions', and 'Favorites'. A large blue banner with a DNA double helix background reads 'Introducing varsomepro'. Below this, a 'Variant' section is open, showing a table of variant details. At the bottom, there are buttons for 'Feedback' and 'Cite VarSome', and a 'Gene symbol' field.

varsome

RESEARCH USE ONLY Upload VCF Editions Community About

hg19 hg38 RYR2:c.5170G>A

Examples

chr1-237777598-G-A

Classify this variant Community contributions Favorites Short L

Introducing varsomepro

Variant Explain

Chromosome	Position	REF Sequence	ALT Sequence	Variant type	Cytoband	HGVS	RS ID
chr1	237777598	G	A	SNV	1q43	NM_001035.2:c.5170G>A (p.Glu1724Lys)	rs794728740 dbSNP

UCSC genome browser Mastermind TraP Score

Feedback Cite VarSome Gene symbol

Přítomnost varianty v databázi ExAC (60 tis genomů)

varsome RESEARCH USE ONLY Upload VCF Editions Community About

chr1-237777598-G-A

Classify this variant Community contributions Favorites Short ID

gnomAD Exomes Version: 2.0.2

This variant does not have a gnomAD exomes entry, but its locus is covered in gnomAD exomes as follows.

Coverage in gnomAD Exomes samples

Mean coverage	Median coverage	% of samples over 20x coverage
79.1	100	99.44%

gnomAD Genomes Version: 2.0.2

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Coverage in gnomAD Genomes samples

Mean coverage	Median coverage	% of samples over 20x coverage
---------------	-----------------	--------------------------------

Feedback Cite VarSome

Varianta je velmi vzácná!

Predikční skóre patogenicity

chr1-23777598-G-A

Classify this variant Community contributions Favorites

DANN ?	Score	0.9994	
MutationTaster ?	Prediction ? Disease causing	Accuracy ? 0.9999	converted rankscore 0.5881
FATHMM ?	prediction Tolerated	score -0.88	converted rankscore 0.7469
FATHMM-MKL ?	coding prediction Damaging	coding score 0.9653	coding rankscore 0.6939
MetaSVM ?	prediction Damaging	score 0.4279	rankscore 0.8952
MetalR ?	prediction Damaging	score 0.6488	rankscore 0.8776

Conservation

Feedback Cite VarSome NR ? 5.4299 RS ? 5.4299

Spíše patogenní a v konservované části genu!

Možná funkční hodnocení varianty

chr1-23777598-G-A

Classify this variant Community contributions Favorites Short

LRT	prediction Deleterious	score 0.000011	converted rankscore 0.6292	Omega 0
MutationAssessor	prediction Medium	score 2.345	rankscore 0.6757	
Functional				
SIFT	prediction Damaging	score 0	converted rankscore 0.9122	
Provean	prediction Damaging	score -3.44	converted rankscore 0.6743	

Show citations

Beacon Network

Feedback Cite VarSome

CLOSE

Pravděpodobné porušení funkce proteinu

Opatrný verdikt programu

chr1-23777598-G-A

Classify this variant Community contributions Favorites Short L

ACMG Classification - Experimental - Educational use only Options Terms of use CLOSE

Verdict
Uncertain Significance

Minimum ClinVar rating: 1

Rules

<input checked="" type="checkbox"/> PVS1 ✓ ?	<input checked="" type="checkbox"/> PS1 ✓ ?	<input checked="" type="checkbox"/> PS2 ✓ ?	<input checked="" type="checkbox"/> PS3 ✓ ?	<input type="checkbox"/> PS4 ?	<input checked="" type="checkbox"/> PM1 ✓ ?	<input checked="" type="checkbox"/> PM2 ✓ ?	<input type="checkbox"/> PM3 ?
<input checked="" type="checkbox"/> PM4 ✓ ?	<input checked="" type="checkbox"/> PM5 ✓ ?	<input checked="" type="checkbox"/> PM6 ✓ ?	<input checked="" type="checkbox"/> PP1 ✓ ?	<input checked="" type="checkbox"/> PP2 ✓ ?	<input checked="" type="checkbox"/> PP3 ✓ ?	<input type="checkbox"/> PP4 ?	<input checked="" type="checkbox"/> PP5 ✓ ?
<input checked="" type="checkbox"/> BA1 ✓ ?	<input type="checkbox"/> BS1 ?	<input type="checkbox"/> BS2 ?	<input checked="" type="checkbox"/> BS3 ✓ ?	<input checked="" type="checkbox"/> BS4 ✓ ?			
<input checked="" type="checkbox"/> BP1 ✓ ?	<input type="checkbox"/> BP2 ?	<input checked="" type="checkbox"/> BP3 ✓ ?	<input checked="" type="checkbox"/> BP4 ✓ ?	<input type="checkbox"/> BP5 ?	<input checked="" type="checkbox"/> BP6 ✓ ?	<input checked="" type="checkbox"/> BP7 ✓ ?	

Please tick or untick any rules to switch them on or off - the Verdict will update.

Identified criteria
Feedback Cite VarSome

Zdůvodnění!

chr1-237777598-G-A

Classify this variant

Community contributions

Favorites

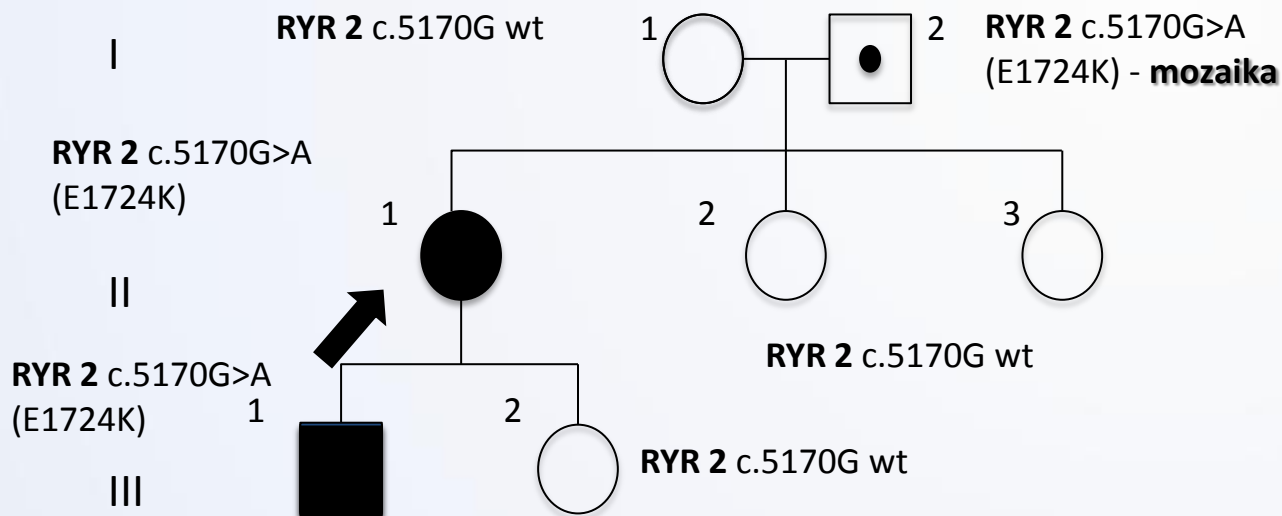
Short link

Please tick or untick any rules to switch them on or off - the Verdict will update.

Identified criteria

Rule	Pathogenicity	Explanation
PM2	Pathogenic Moderate	Variant not found in GnomAD exomes and GnomAD exomes coverage=79.1 is greater than 20.0. Variant not found in GnomAD genomes and GnomAD genomes coverage=34.4 is greater than 20.0.
PP2	Pathogenic Supporting	Missense variant in gene RYR2 that has 149 pathogenic missense variants out of 150 pathogenic variants = 99.3% which is greater than minimum of 66.7% and only 21 benign missense variants. Gene RYR2 is associated with Ventricular tachycardia, catecholaminergic polymorphic, 1 and Arrhythmogenic right ventricular dysplasia 2 .
PP3	Pathogenic Supporting	Pathogenic computational verdict because 9 pathogenic predictions from DANN, GERP, LRT, MetaLR, MetaSVM, MutationAssessor, MutationTaster, PROVEAN and SIFT (vs 1 benign prediction from dbNSFP.FATHMM).
PP5	Pathogenic Supporting	ClinVar classifies variant as Pathogenic, 1 star (above minimum of 1 star) (but no references to functional or in-vivo testing to support PS3).

Segregace v rodině: PM6/PS2



I-1: fibrilace síní před 50. rokem života a bez jiných rizikových faktorů

I-2: bez arytmií, v rodinné anamnéze bez SCD

II-1: CPVT

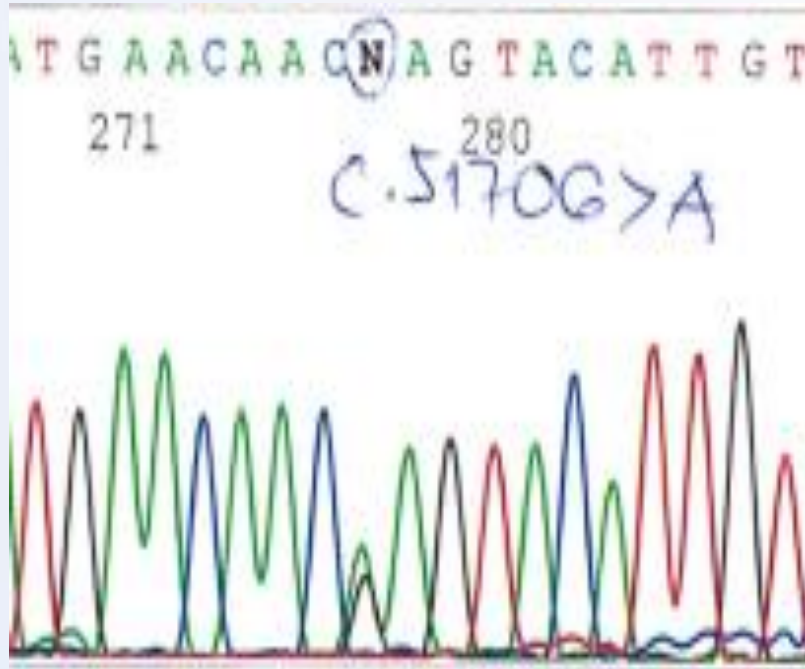
II-2 a 3: bez dokumentovaných arytmií

III-1: **CPVT** y při emocionálním vypětí či námaze

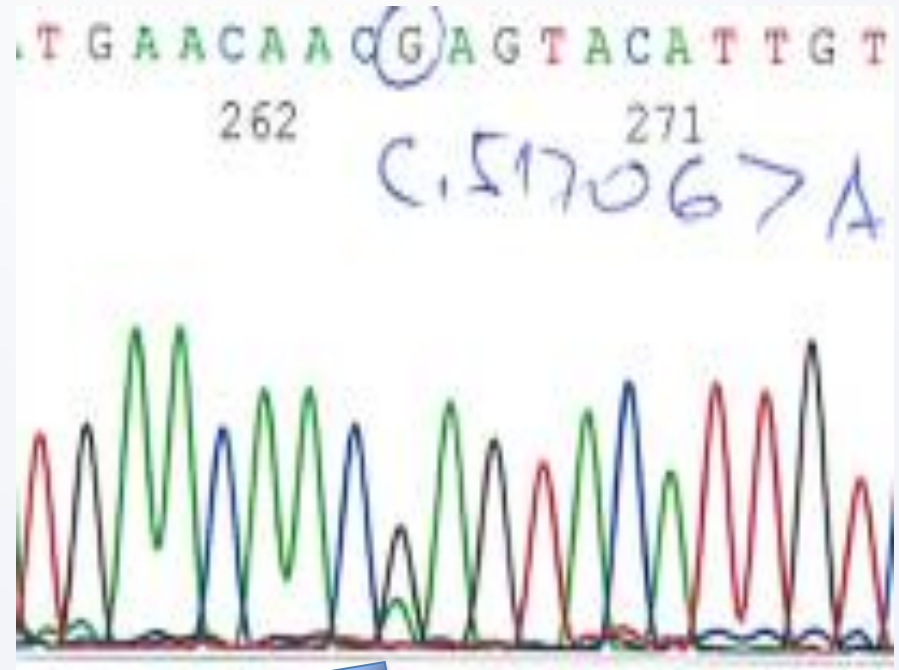
III-2: bez obtíží

Otec – somatická mozaika *RYR 2* mutace

Sanger sekvenace -
proband



Sanger sekvenace - otec



Posouzení patogenicity

5

- Jistá patogenní mutace

4

- Pravděpodobná patogenní mutace

3

- Možná patogenní mutace (variant of unknown origin – VUS)

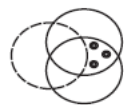
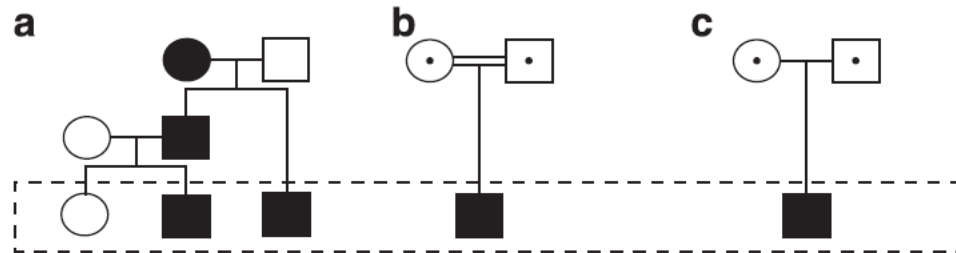
2

- Pravděpodobně nepatogenní mutace

1

- Jistě nepatogenní mutace

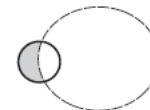
Koho vyšetřovat?!



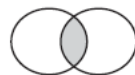
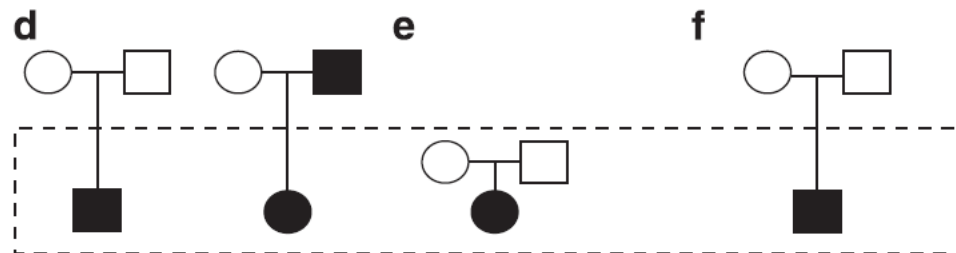
Linkage based strategy



Homozygosity based strategy



Double-hit based strategy



Overlap based strategy



De novo based strategy



Candidate based strategy

Rodiny



IKE
M

Kardiolog - Genetik

Kardiolog

správná diagnóza

Vyšetření
příbuzných

Ověření genetiky
(zátěžové testy, EFV)

- Klinický genetik
- molekulární genetik

Individualizovaná péče (léky/invasivní terapie/ICD)

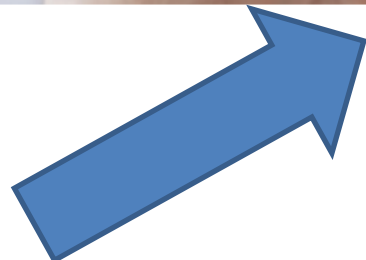


- Česká asociace akutní kardiologie
- Česká asociace ambulantních kardiologů
- Česká asociace intervenční kardiologie
- Česká asociace pro srdeční rytmus
- Česká asociace srdečního selhání
- Česká asociace kardiiovaskulárních zobrazovacích metod
- Chlopenní a vrozené srdeční vady v dospělosti
- Chorob myokardu a perikardu
- Kardio 35
- Kardiogenetika
- KardioTech
- Kardiiovaskulární farmakoterapie
- Kardiiovaskulární rehabilitace
- Kardiologických sester a spřízněných profesí
- Pediatrická kardiologie
- Plicní cirkulace
- Preventivní kardiologie

NEPŘEHLÉDNĚTE

**ČESKÉ KARDIOLOGICKÉ DNY 2019
25.- 26. LISTOPADU 2019, PRAHA**

AKTUALITY



**Ukončení zadávání abstraktů
výroční sjezd**

11. 1. 2019

Děkujeme všem, kteří se přihlásili k aktivní účasti na letošním sjezdu

asa

AKTUÁLNÍ ČÍSLO ČASOPISU

06/2018
COR ET VASA ON-LINE

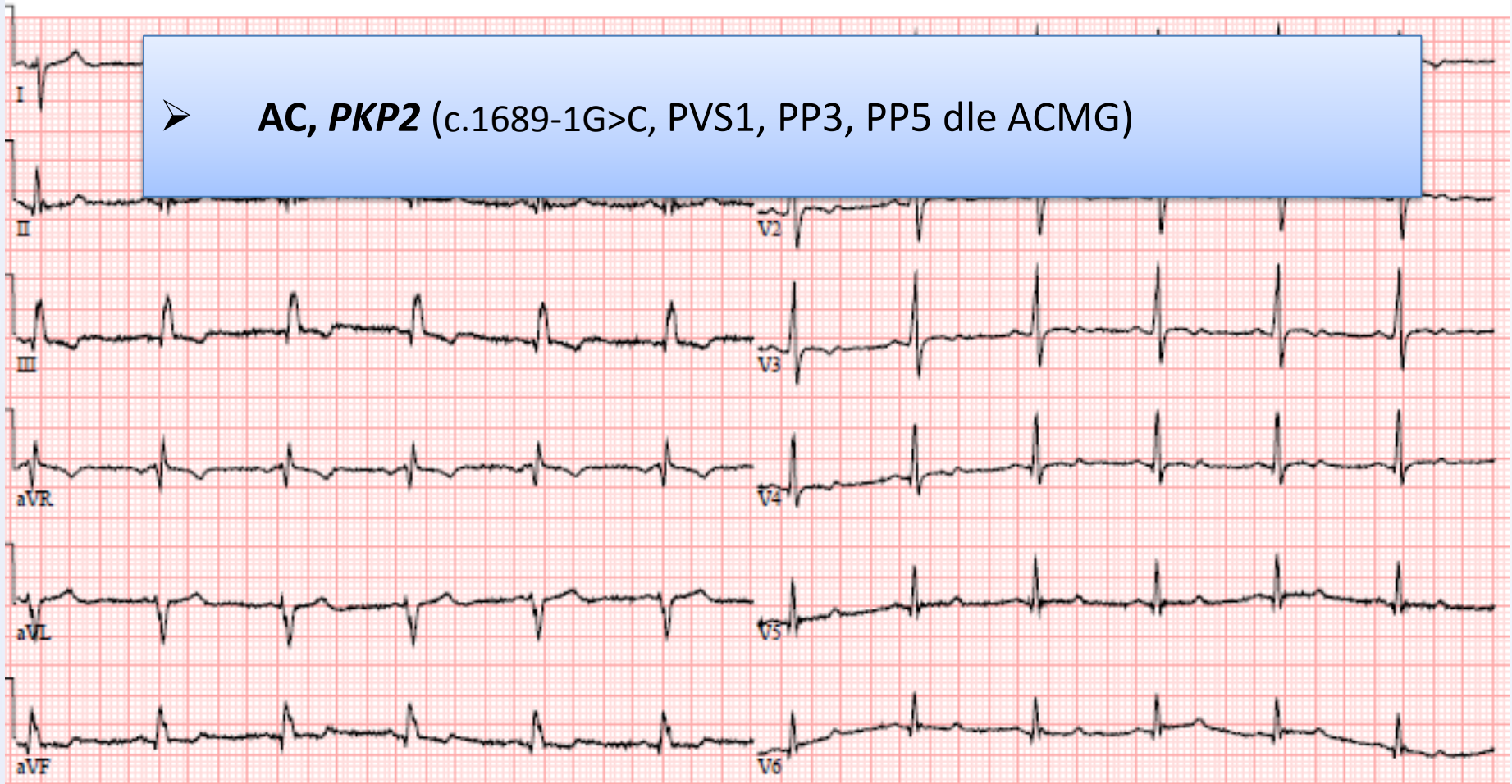
ARCHIV ČÍSEL ČASOPISU - CZ



Děkuji za pozornost!
alice.krebsova@ikem.cz

iVF? – mladý fotbalista

➤ **AC, PKP2** (c.1689-1G>C, PVS1, PP3, PP5 dle ACMG)



Klidové EKG matky

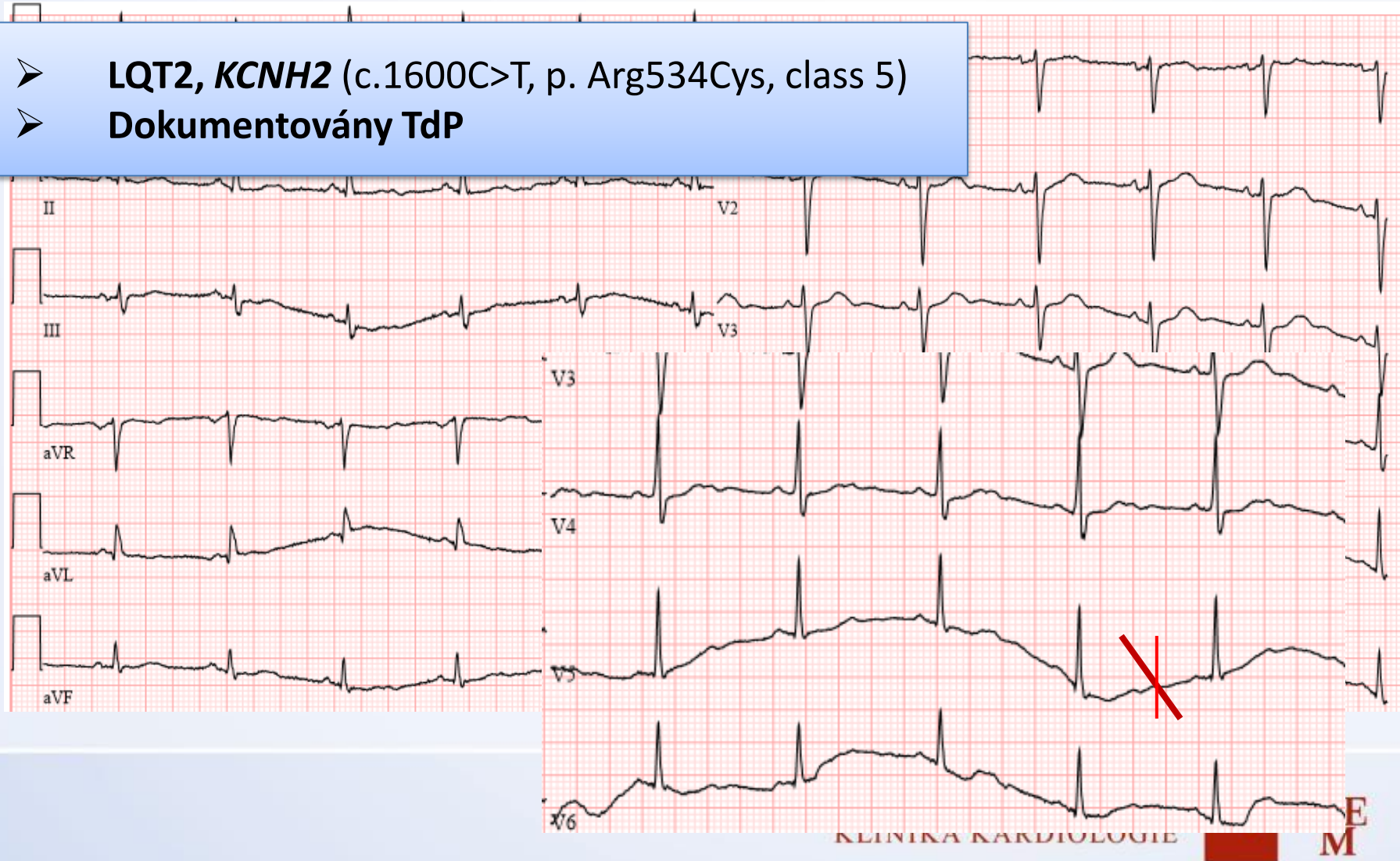
➤ **AC, PKP2** (c.1689-1G>C, PVS1, PP3, PP5 a **PP1** dle ACMG)

➤ **Jistá molekulární příčina onemocnění !**

➤ **Class 5**

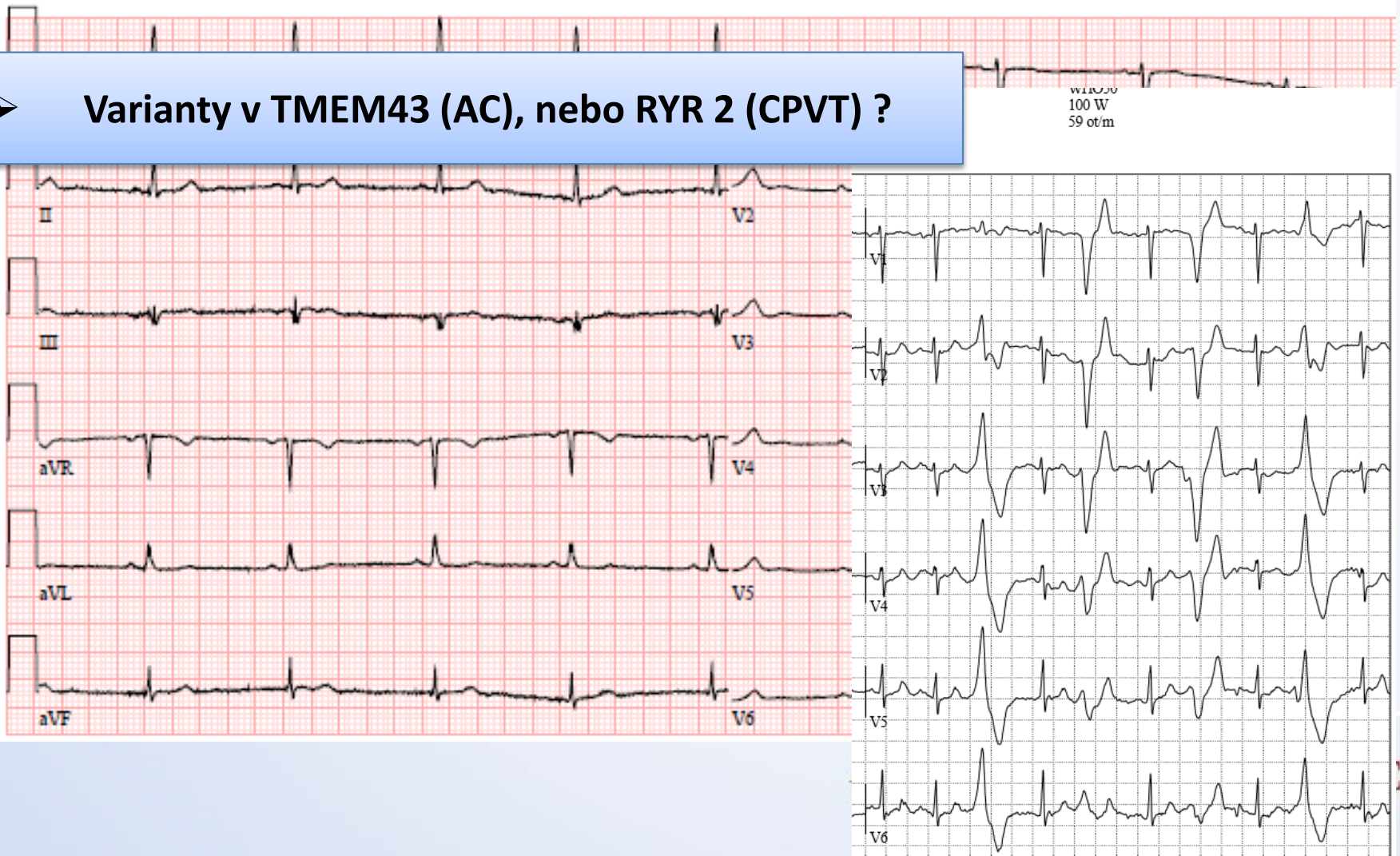
iVF? – žena, 64 let, na výletě

- LQT2, *KCNH2* (c.1600C>T, p. Arg534Cys, class 5)
- Dokumentovány TdP



LQT? – 18 let, žena, KPR na maturitním plese

➤ Varianty v TMEM43 (AC), nebo RYR 2 (CPVT) ?



☐ **Nutné podrobné vyšetření po KPR**

☐ **Kaskádový rodinný screening vhodný**

☐ **Opatrnost v hodnocení výstupů NGS!**

