Sekvenování nové generace v diagnostice vrozených arytmických syndromů

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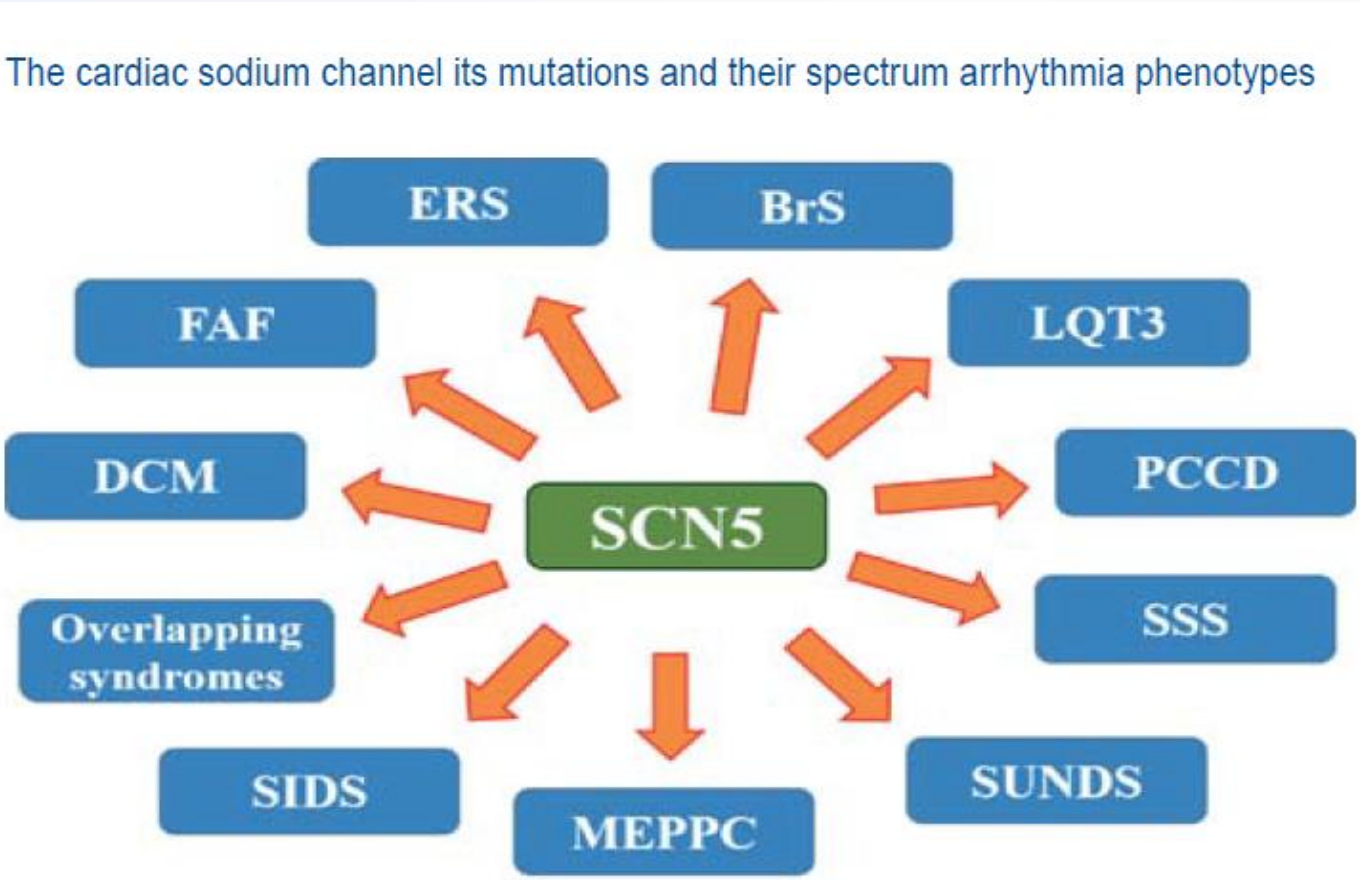
Genetická Heterogenita dědičných KVO

Kardiomyopatie	Arytmie	Aortopatie	VVV srdce
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*	*ANK2, CACNA1C, CALM1, CALM2, CASQ2, CAV3, KCNA5, KCNE1, KCNE2,* ***KCNH2****, KCNJ2, KCNJ5,* ***KCNQ1****,* ***SCN5A****, SNTA1, TRDN*	*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,* ***TGFBR1****, TGFBR2, TNXB*	*ACTA2, ELN, GATA4, GATA5, GATA6, JAG1, NKX2.5, NOTCH1, NOTCH2, PTPN11, TBX1, TBX20, TBX5, ZIC3*

Alelická Heterogenita!



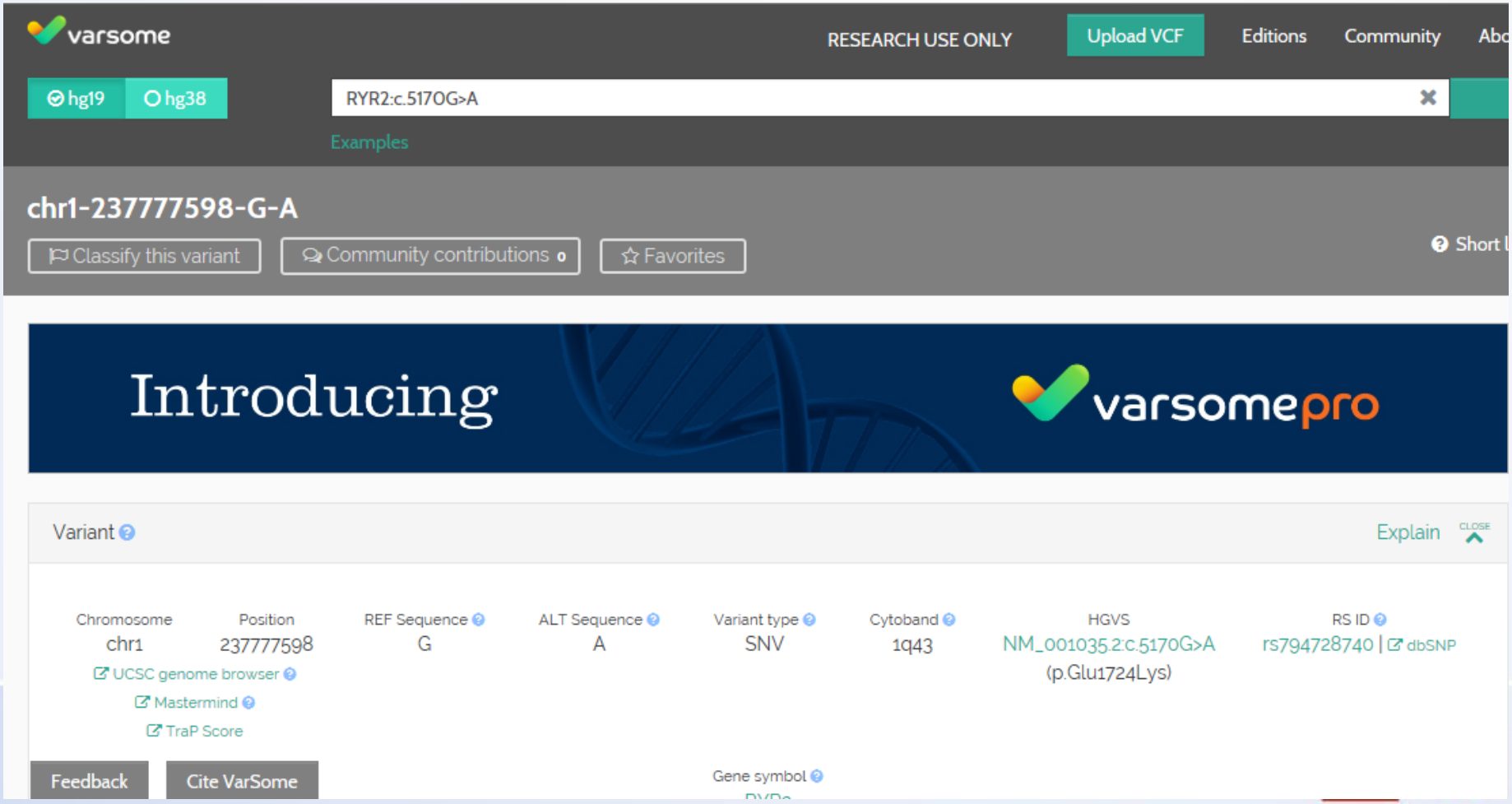
Pérez-Riera et al, J Hum Growth, 2016

Specifika jednotlivých genů!

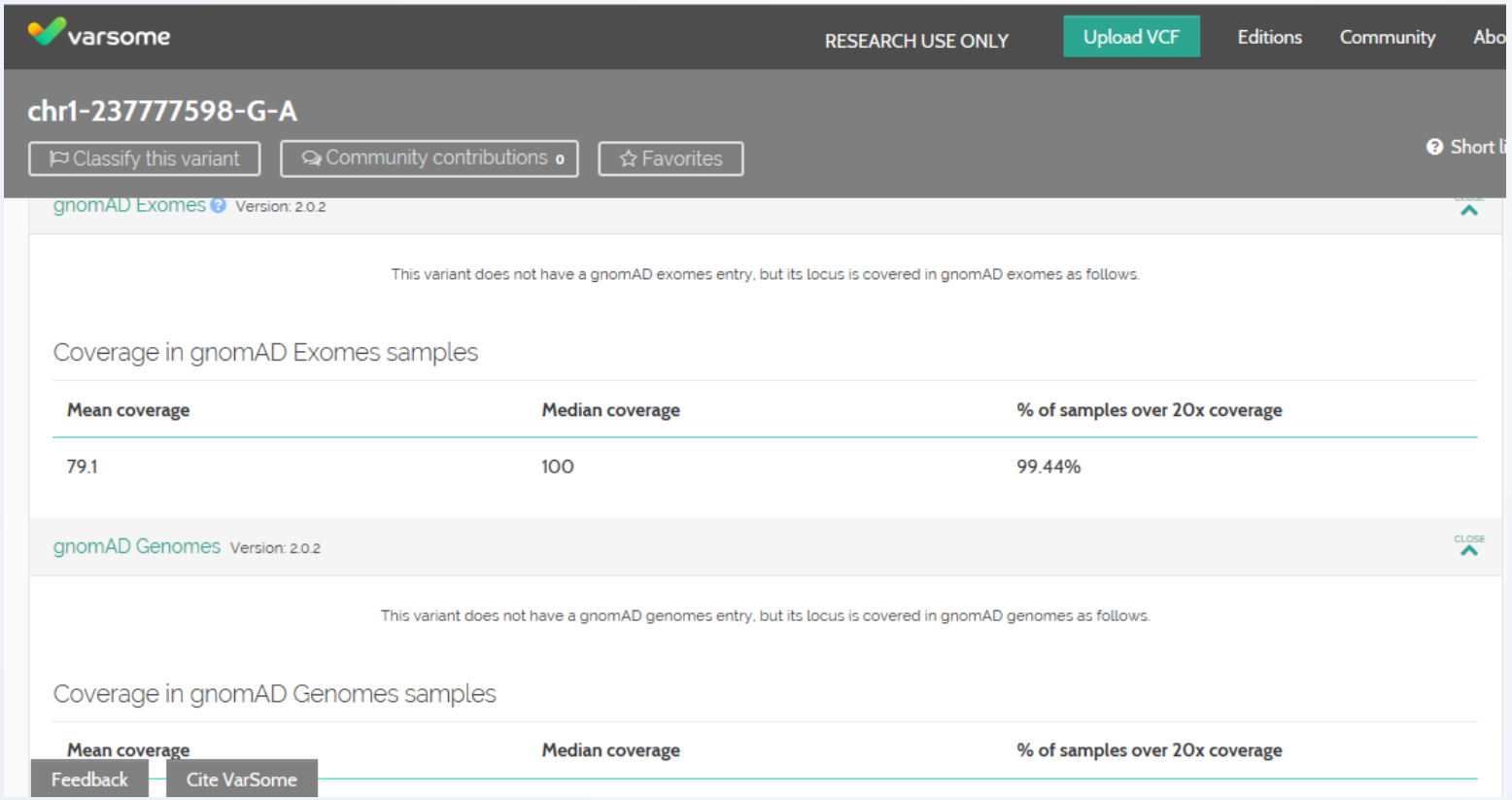
KCNH2- LOF	**KCNQ1** missence	**SCN5A** – kde?, LOF?
TTN -pouze STOP v určité lokalizaci	…	Populačně specifické varianty

DNA varianty specifické pro jednotlivé rodiny

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

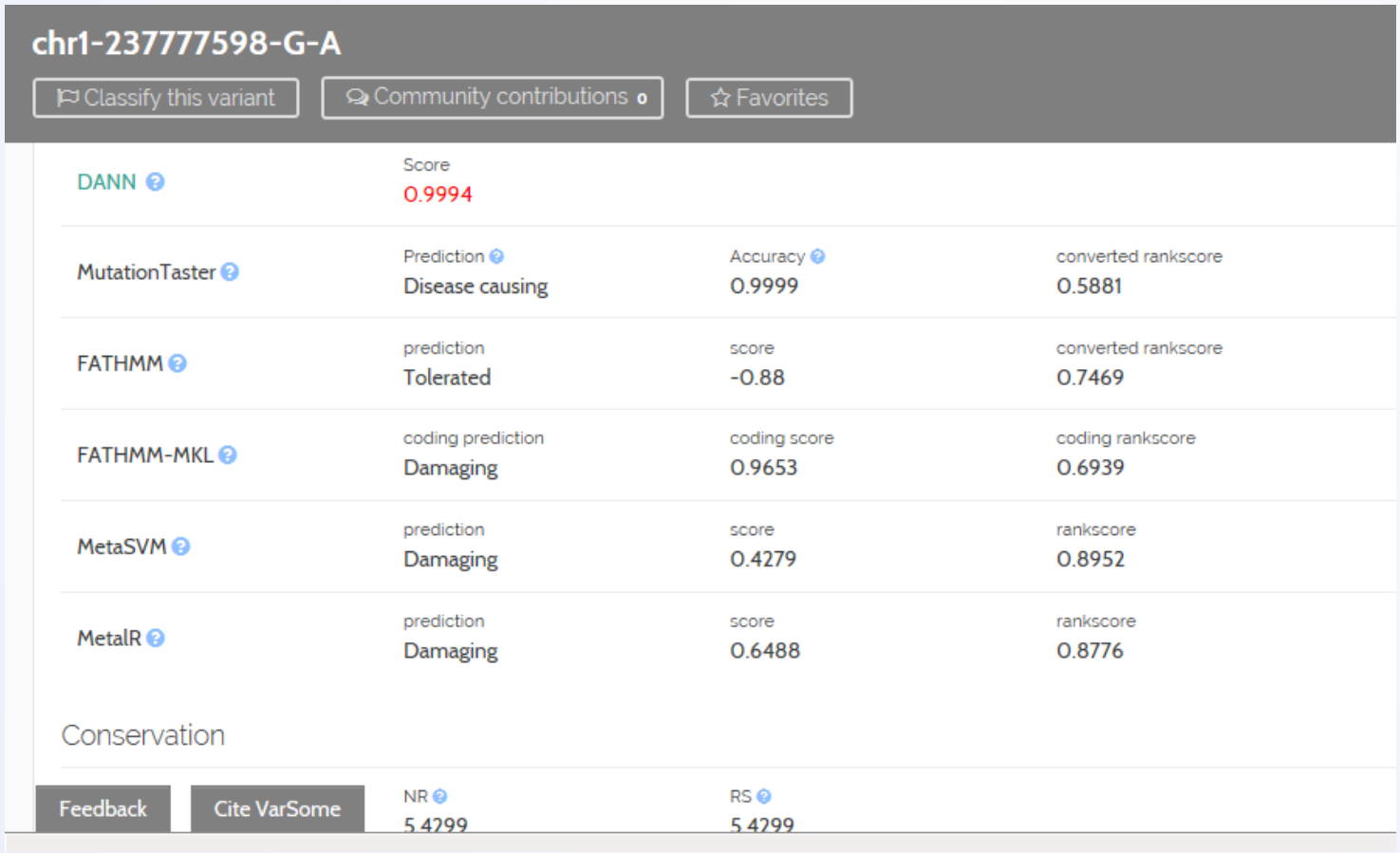


Přítomnost varianty v databázi ExAC (60 tis genomů)



Varianta je velmi vzácná!

Predikční skóre patogenicity



chr1-237777598-G-A

Classify this variant | Community contributions 0 | ☆ 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

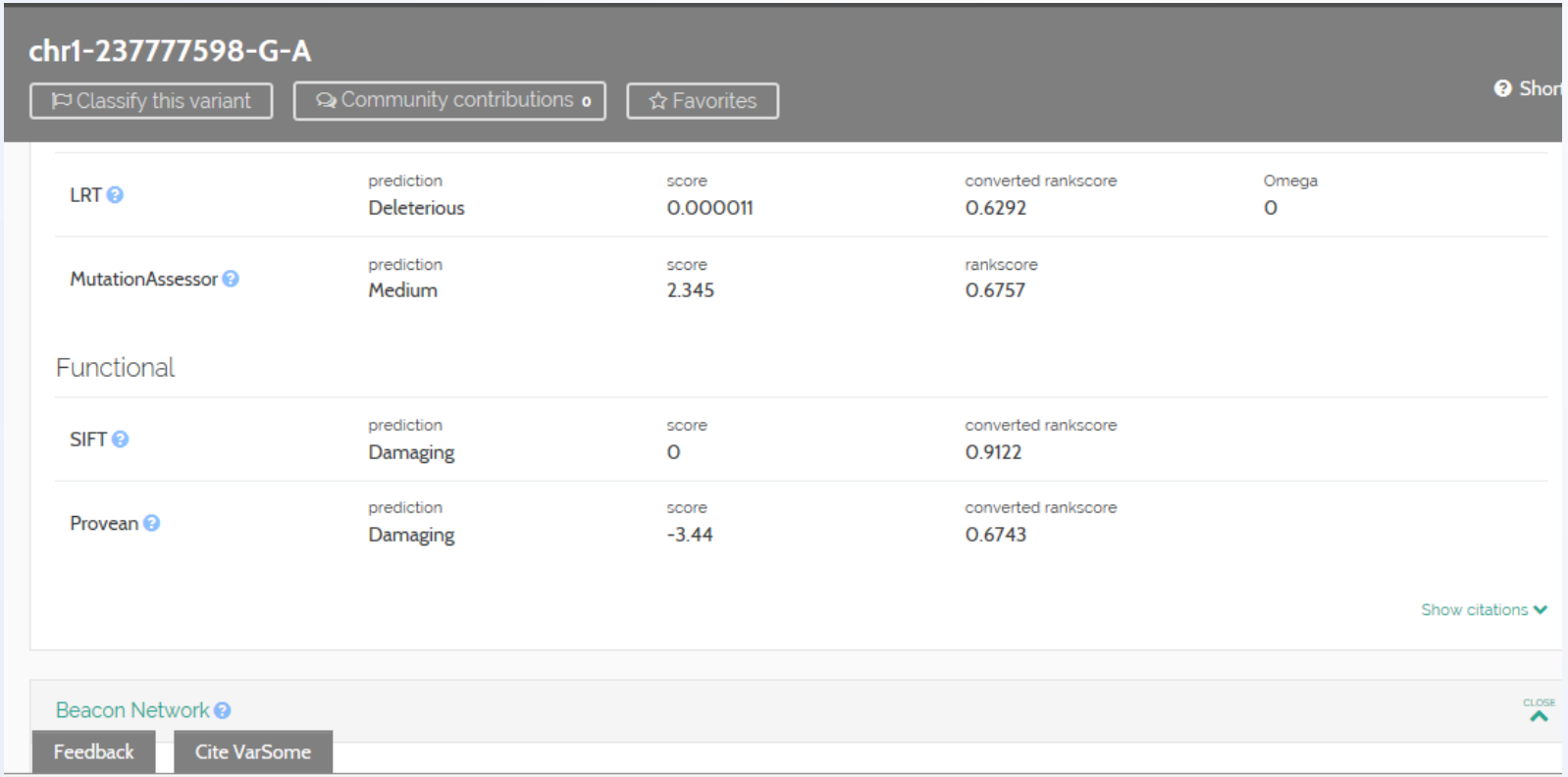
Conservation

Feedback | Cite VarSome

NR 5.4299	RS 5.4299

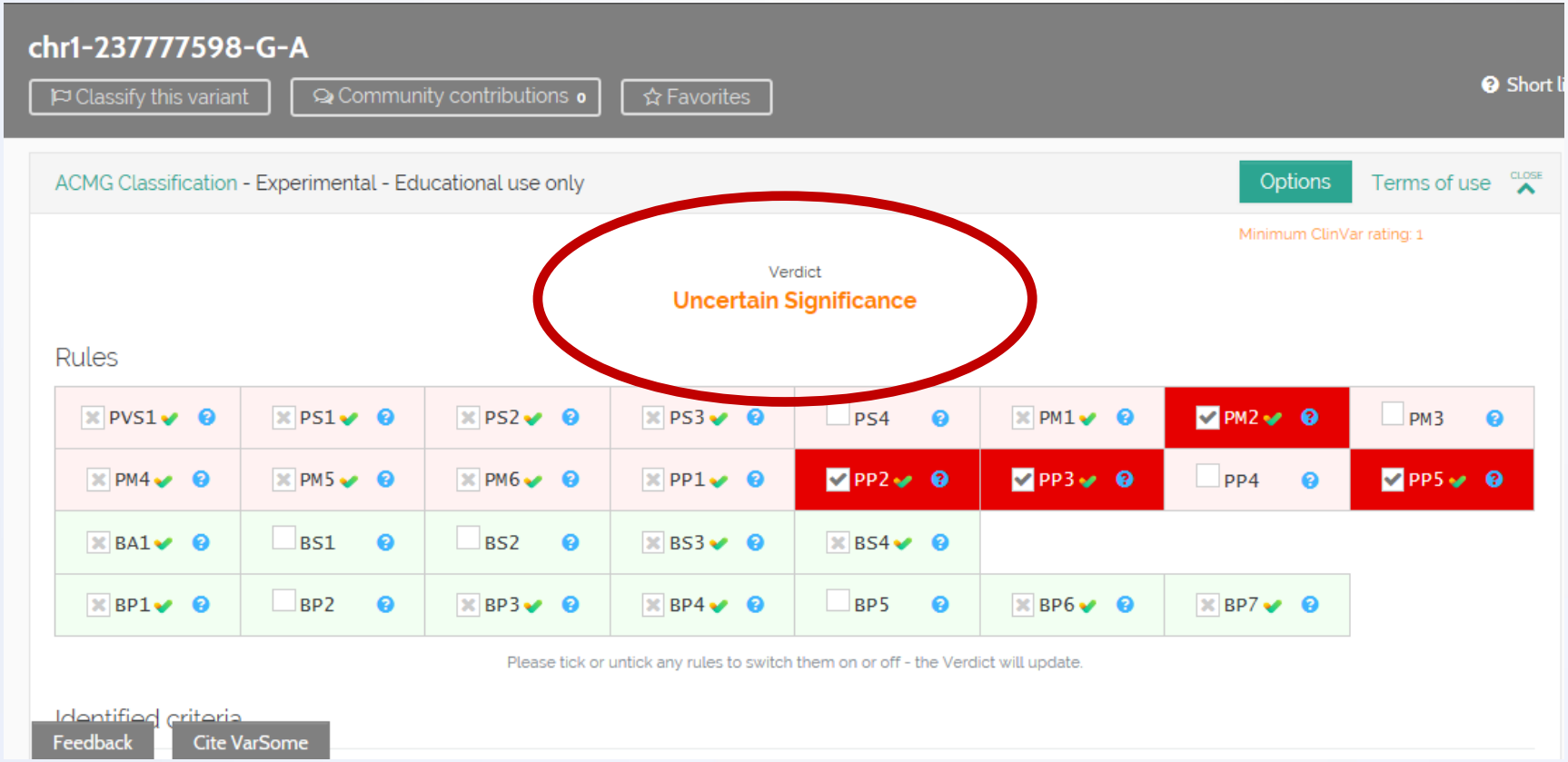
Spíše patogenní a v konservované části genu!

Možná funkční hodnocení varianty

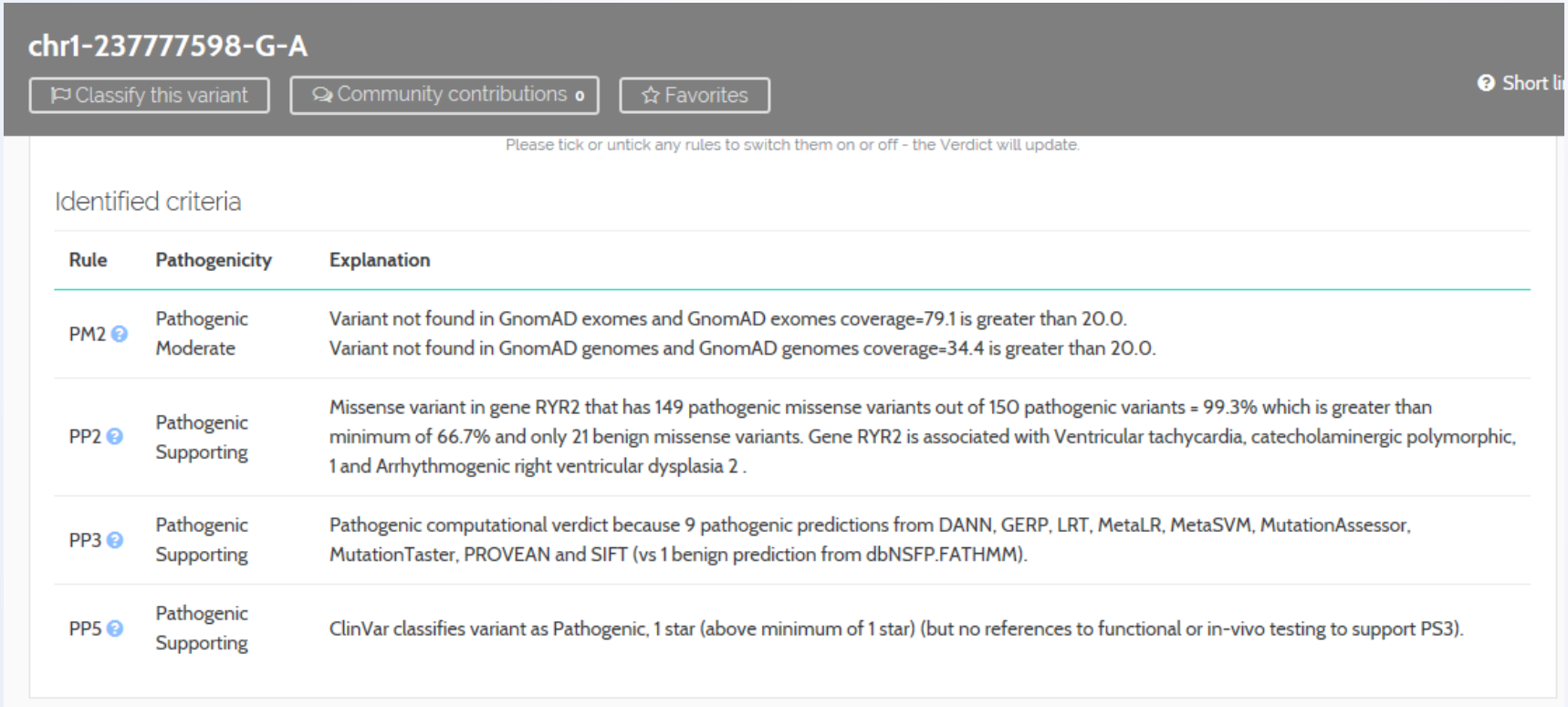


Pravděpodobné porušení funkce proteinu

Opatrný verdikt programu



Zdůvodnění!



chr1-237777598-G-A

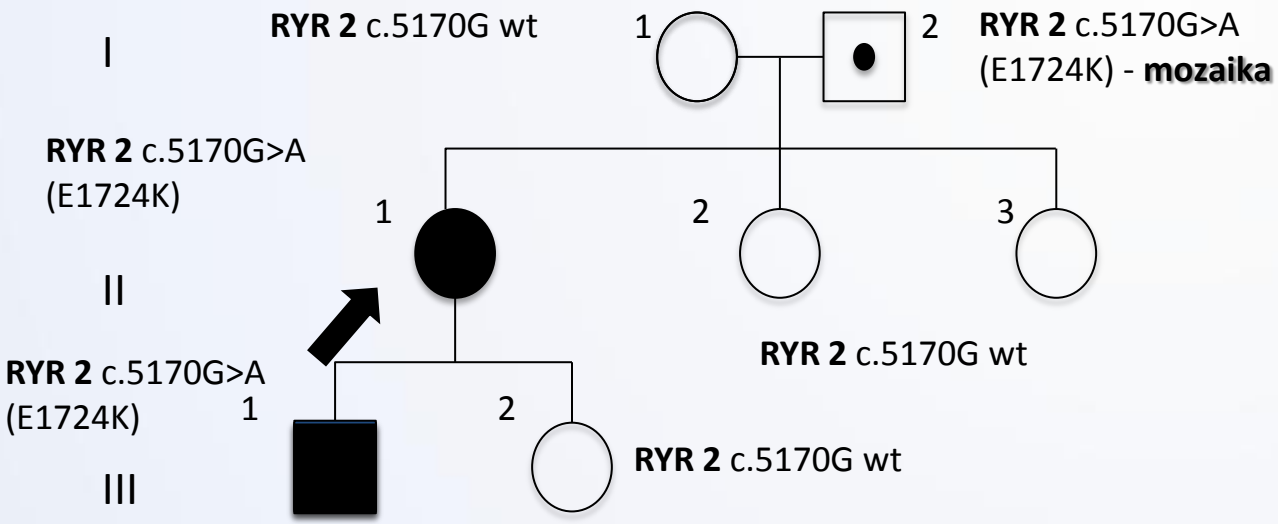
Classify this variant | Community contributions 0 | Favorites | Short li

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).

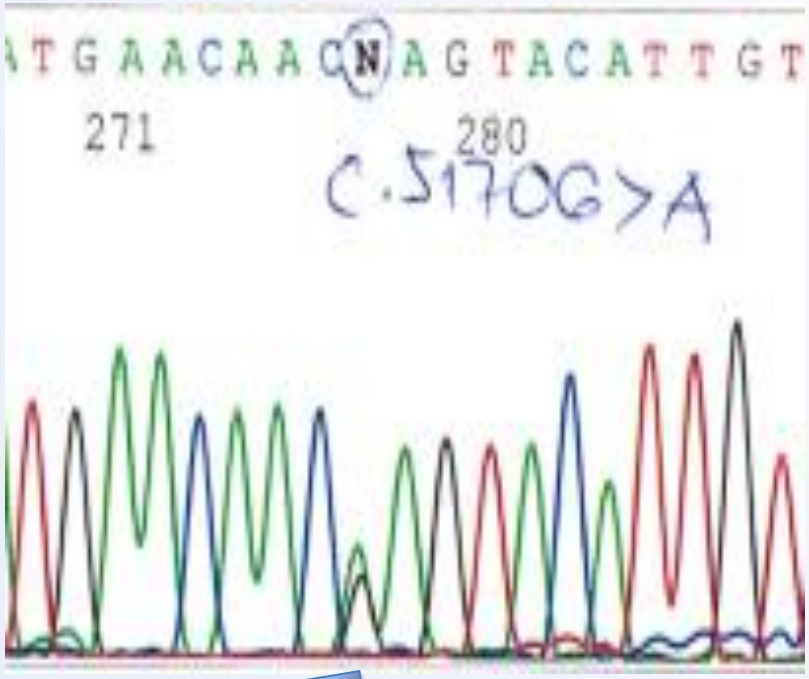
Segregace v rodině: PM6/PS2



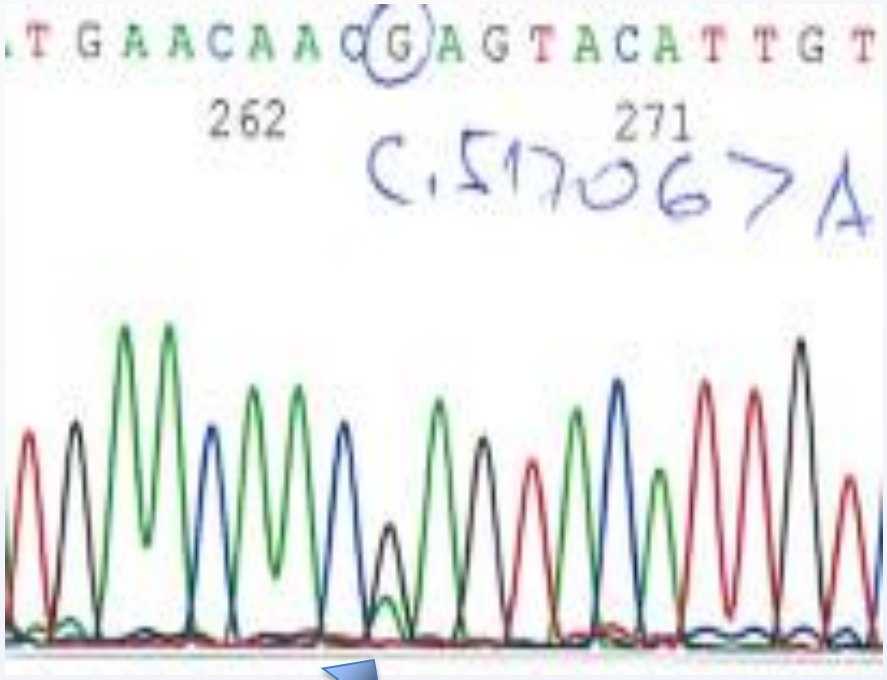
I-1: fibrilace síní před 50. rokem života a bez jiných rizikových faktorů
I-2: bez arytmií, v rodinné anamnéze bez SCD
II-1: CPVT
II-2 a 3: bez dokumentovaných arytmií
III-1: CPVT y při emocionálním vypětí či námaze
III-2: bez obtíží

Otec – somatická mozaika *RYR 2* mutace

Sanger sekvenace - proband



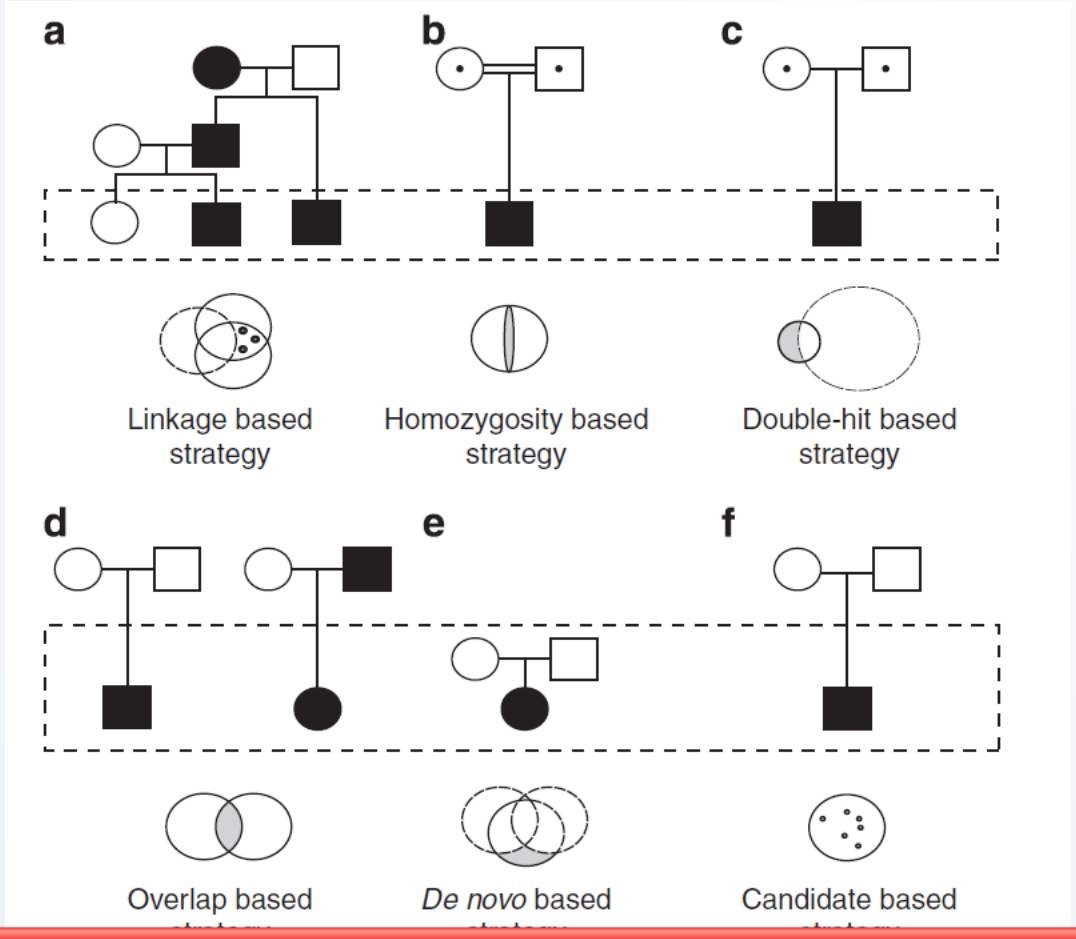
Sanger sekvenace - otec



Posouzení patogenicity

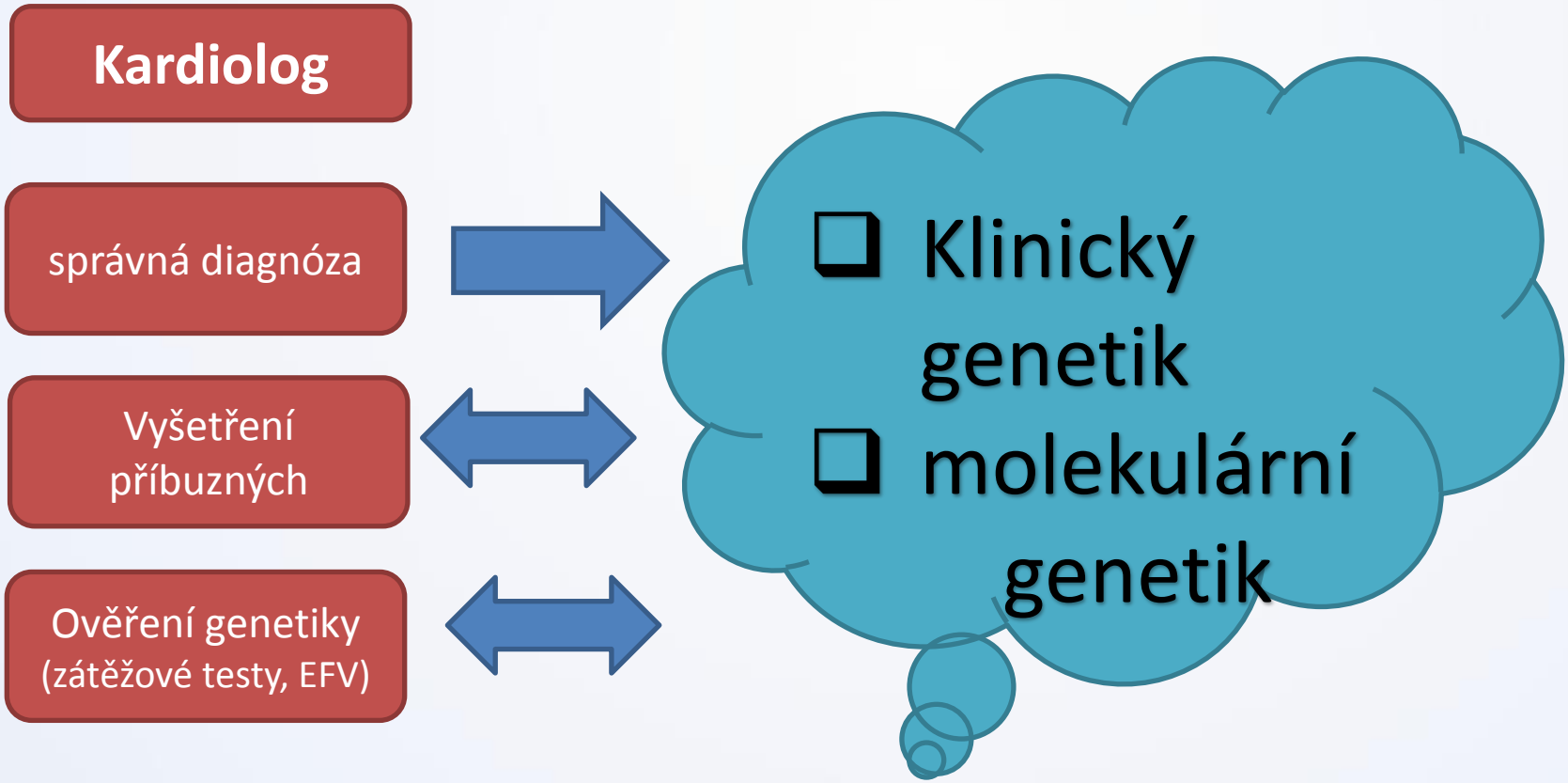
5	• Jistá patogenní mutace
4	• Pravděpodobná patogenní mutace
3	• Možná patogenní mutace (variant of unknown origin – VUS)
2	• Pravděpodobně nepatogenní mutace
1	• Jistě nepatogenní mutace

Koho vyšetřovat?!

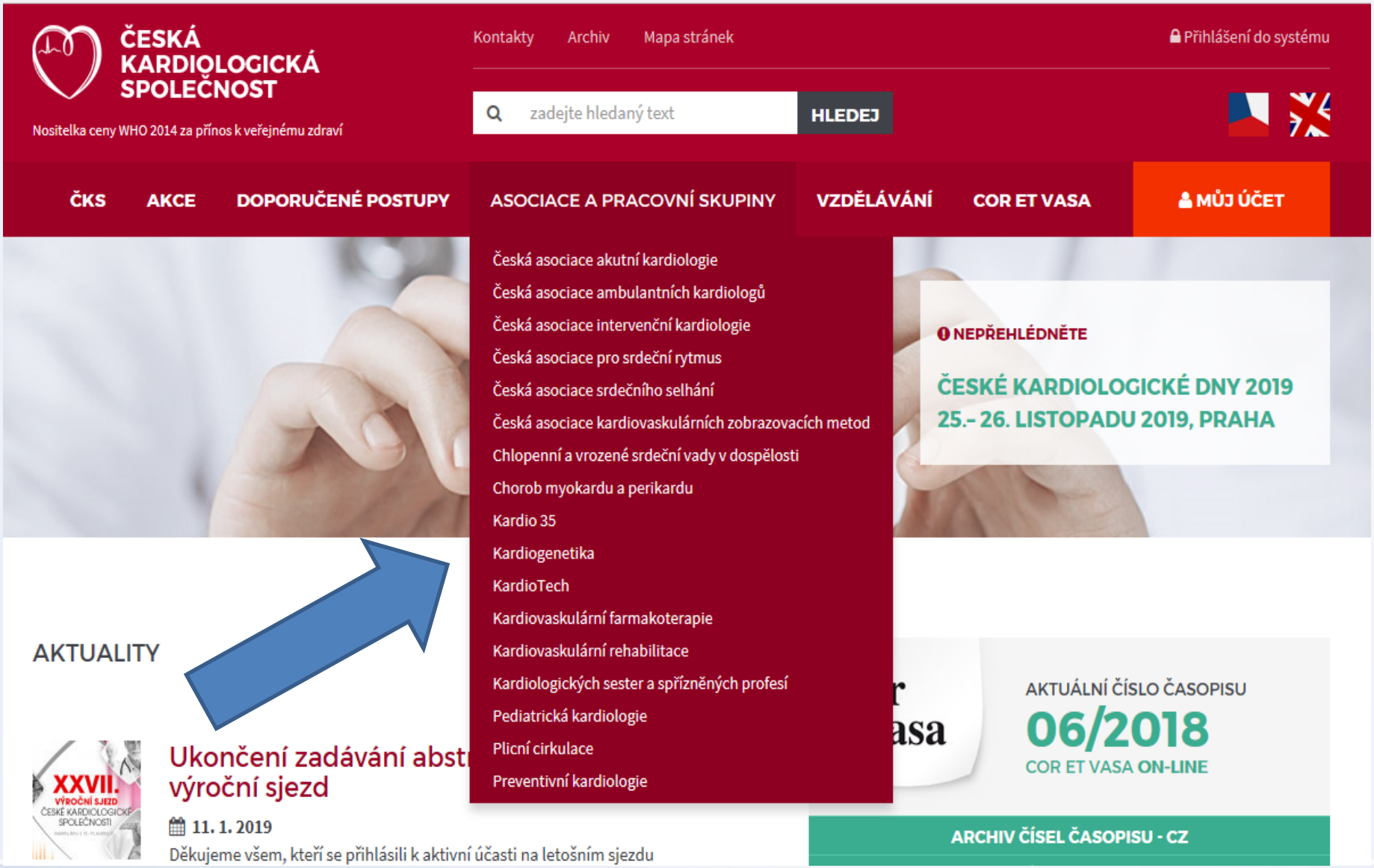


Rodiny

Kardiolog - Genetik



Individualizovaná péče (léky/invasivní terapie/ICD)



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Děkuji za pozornost!

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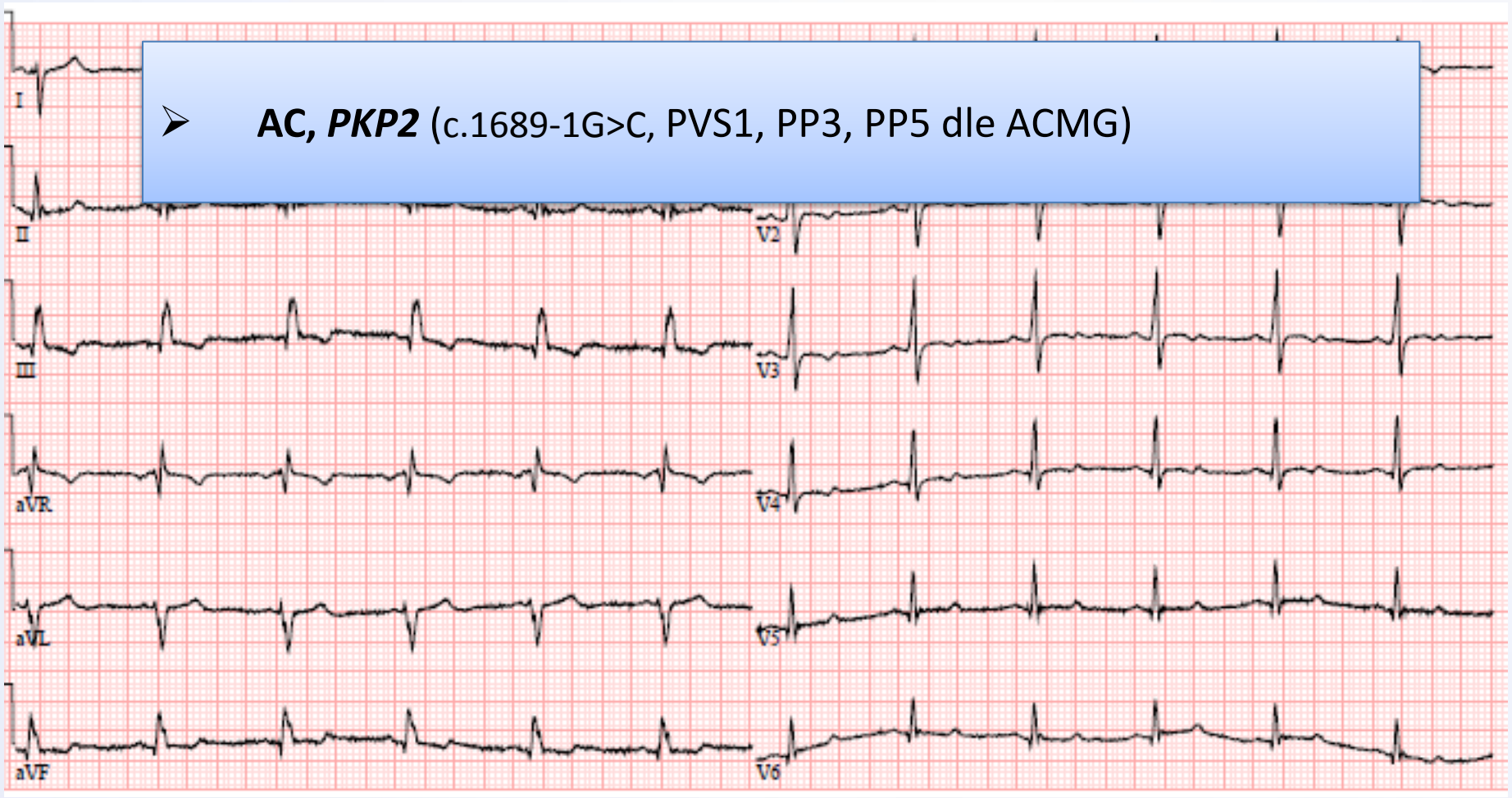
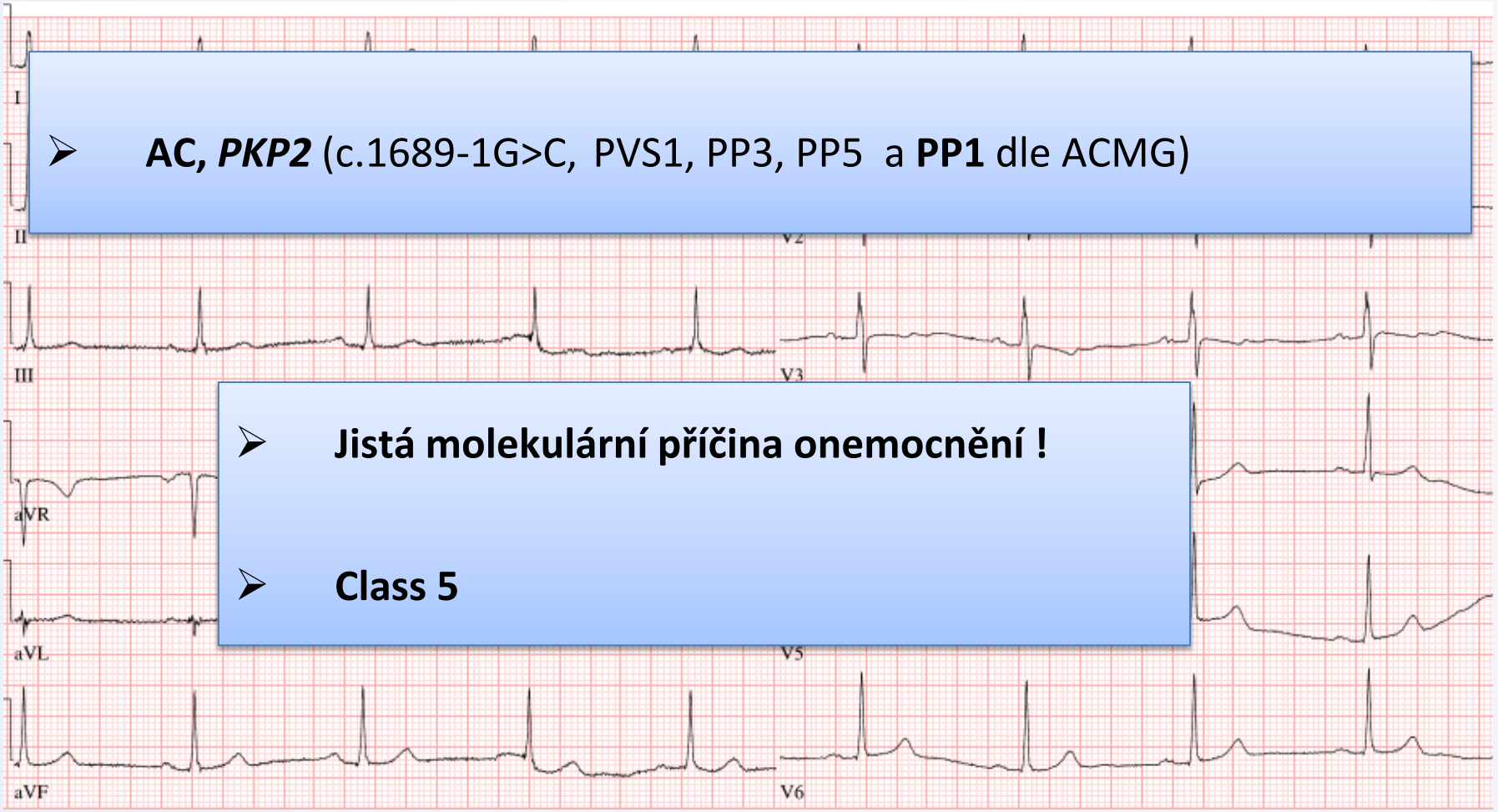
iVF? – mladý fotbalista



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

Klidové EKG matky

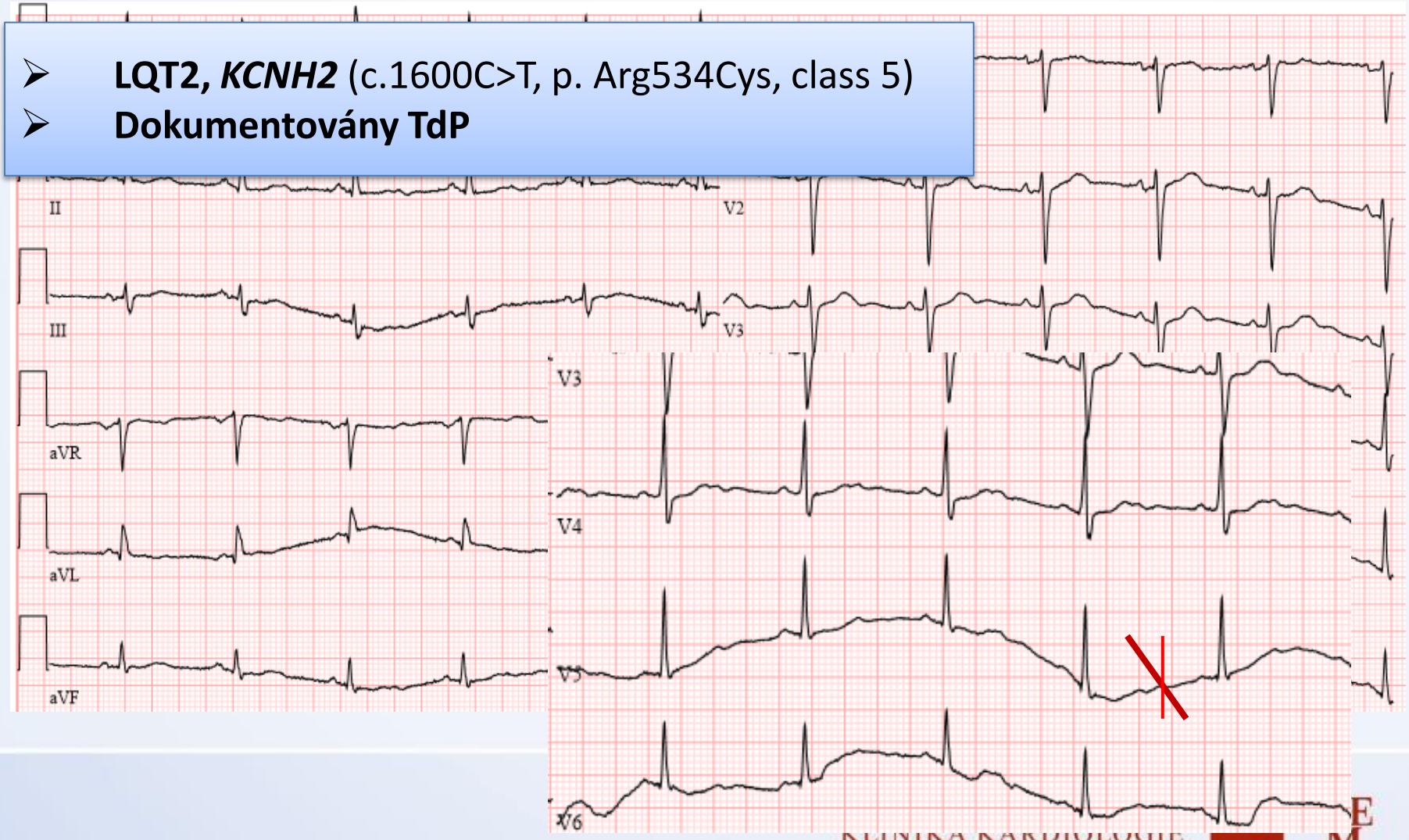


- **AC, *PKP2*** (c.1689-1G>C, PVS1, PP3, PP5 a **PP1** dle ACMG)

- **Jistá molekulární příčina onemocnění !**
- **Class 5**

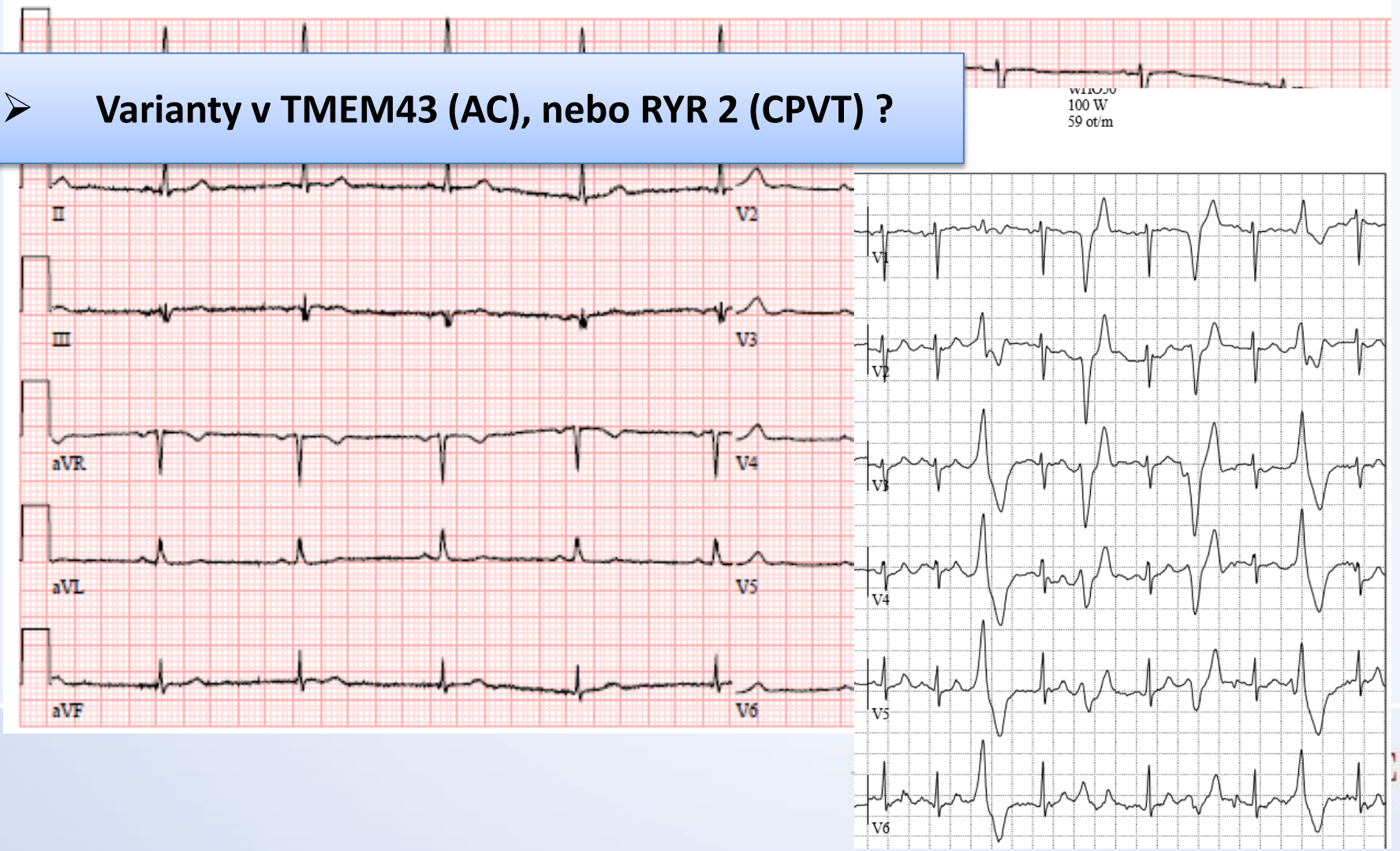
iVF? – žena, 64 let, na výletě

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

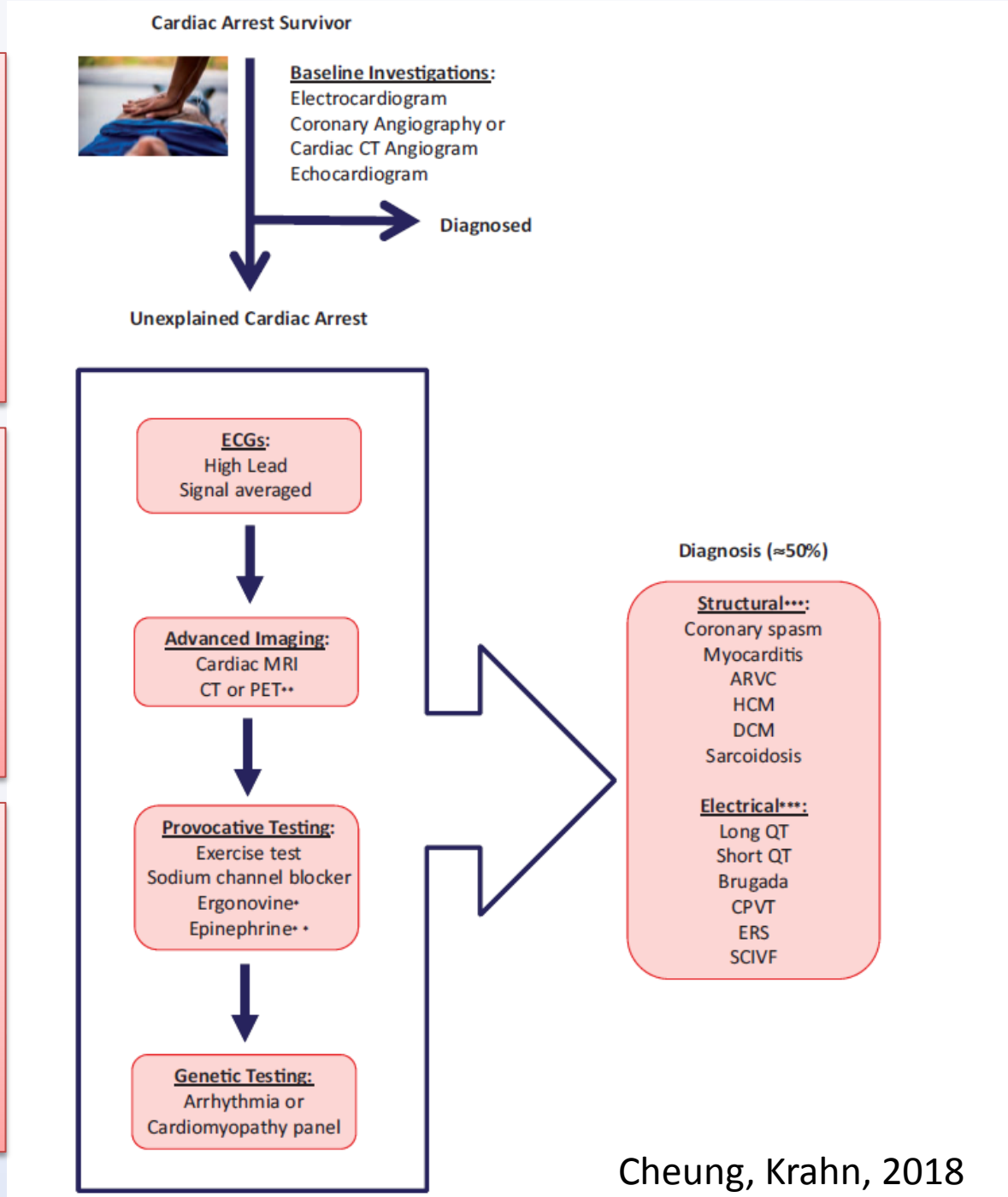


LQT? – 18 let, žena, KPR na maturitním plese

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



- ❑ **Nutné podrobné vyšetření po KPR**
- ❑ **Kaskádový rodinný screening vhodný**
- ❑ **Opatrnost v hodnocení výstupů NGS!**



Cheung, Krahn, 2018