THE GENETIC LANDSCAPE OF DILATED CARDIOMYOPATHY IN HUNGARY

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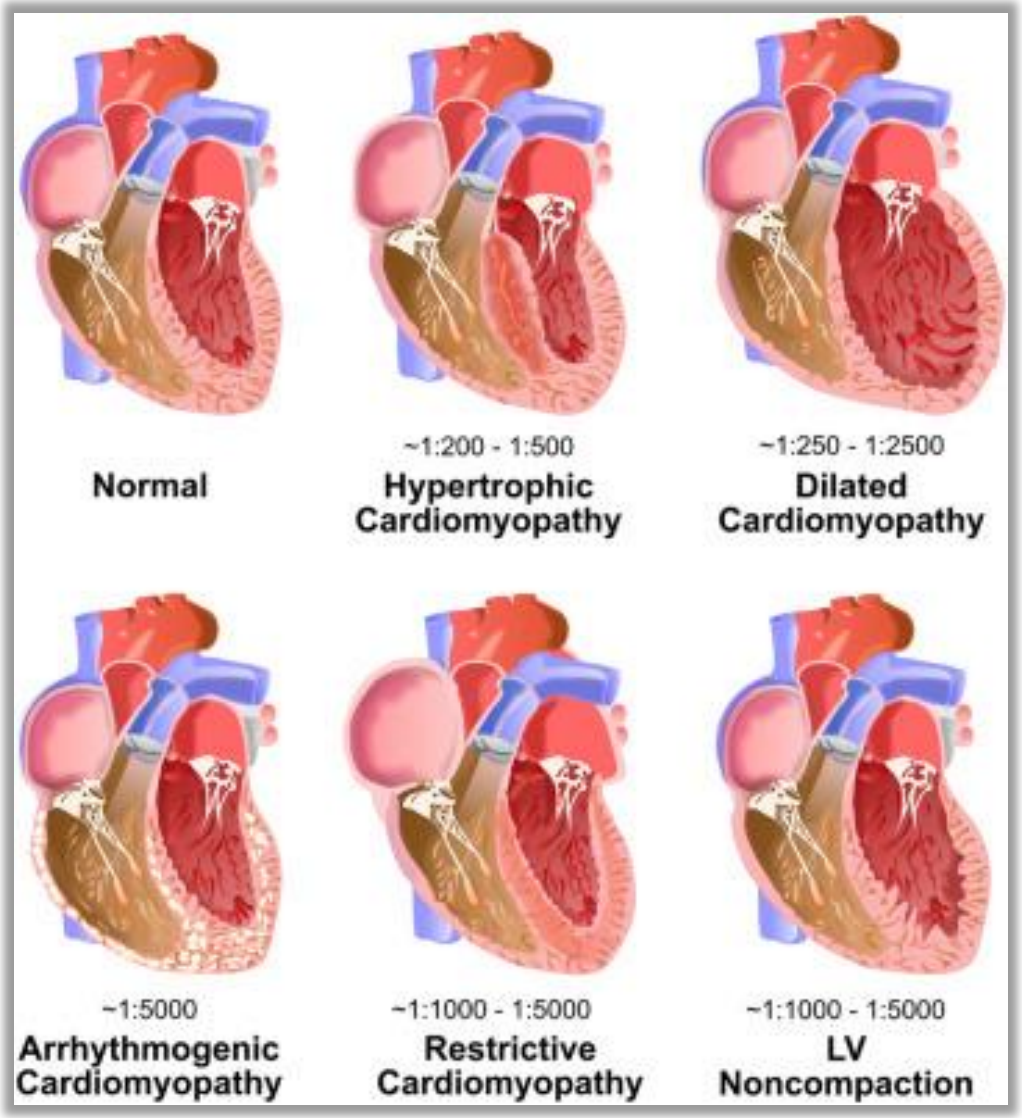
Cardiomyopathies



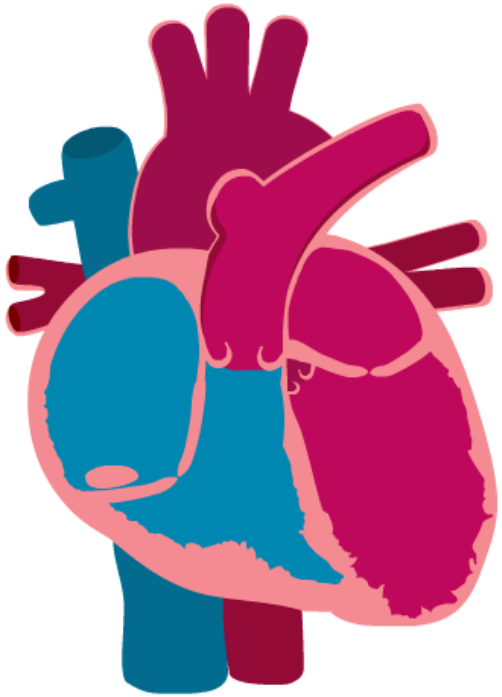
https://www.sciencedirect.com/science/article/abs/pii/S0828282X21000544

Heterogeneous group of disease

Based on morphology and functional differences:

- Hypertrophic (HCM)
- Dilated (DCM)
- Arrhythmogenic (ARVC, AC)
- Restrictive (RCM)
- Not classified:
  - Left ventricular non-compact (LVNC)
  - Tako-tsubo (TTC)

Dilated cardiomyopathy



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Dilatation and systolic dysfunction of the left or both ventricles

One of the major cause of heart failure

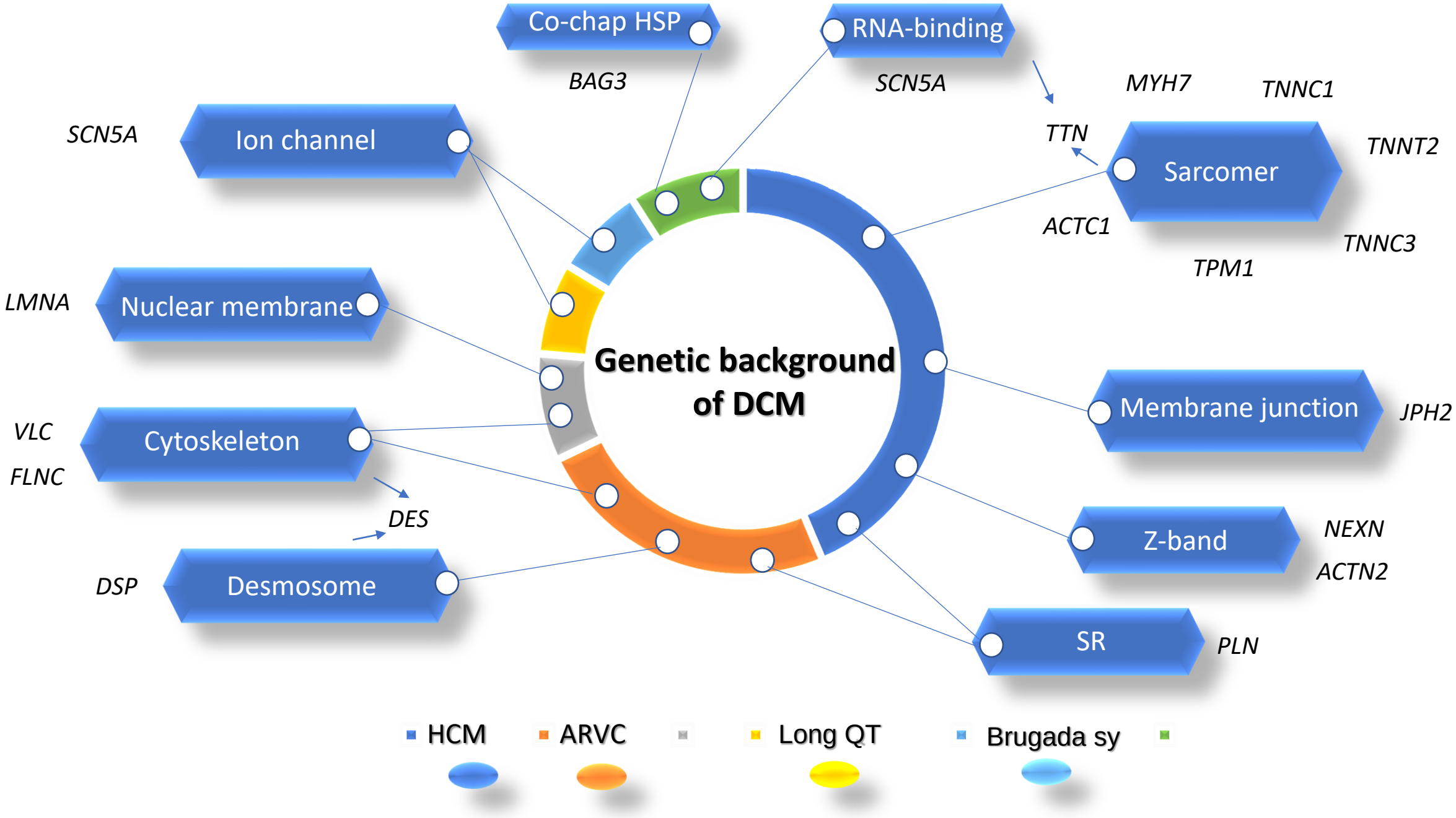
Leading cause of heart transplantation

Prevalence:

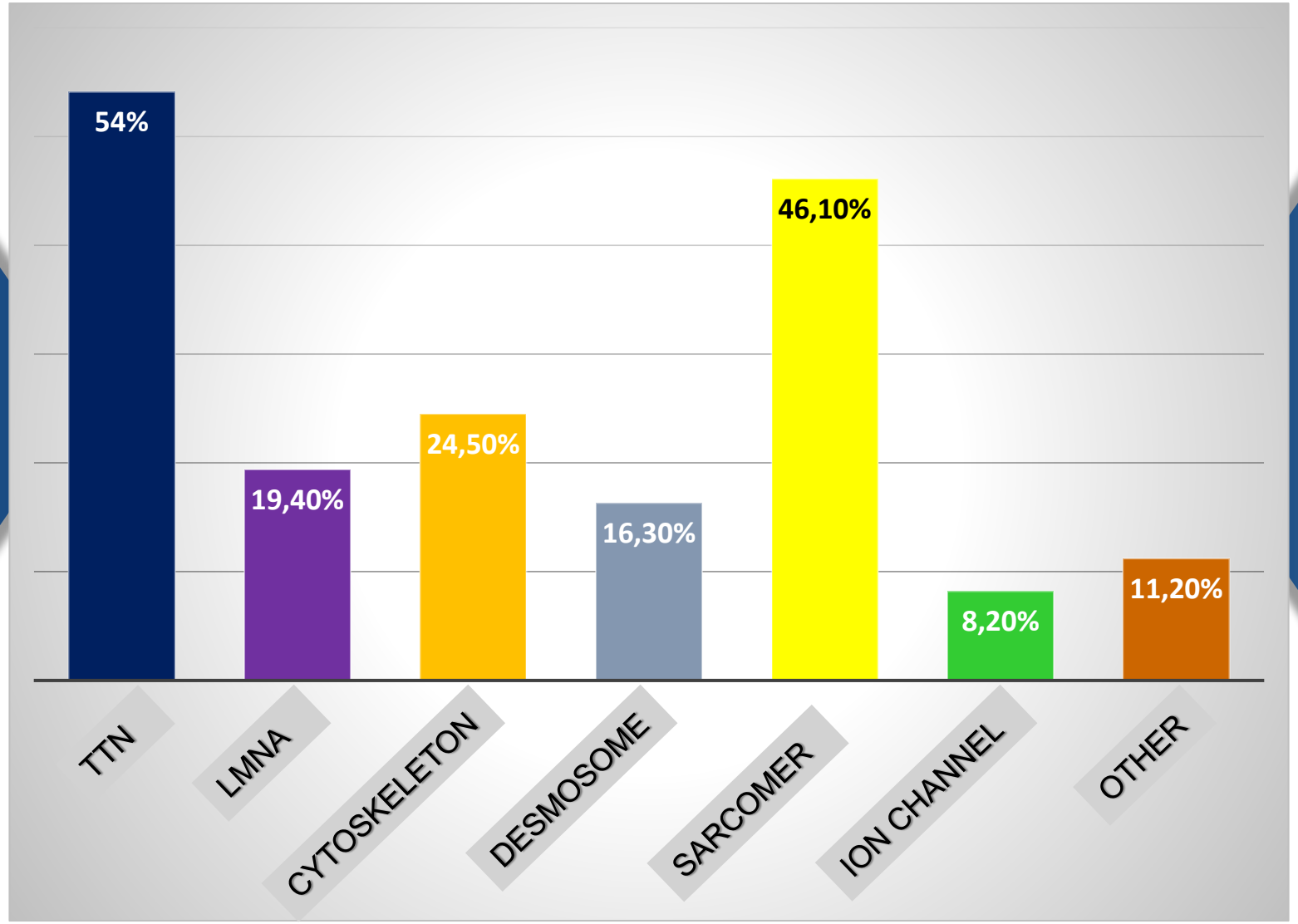
- In heart failure population: 1:250-400
- In a healthy population: from 1:2500 to 1:5000

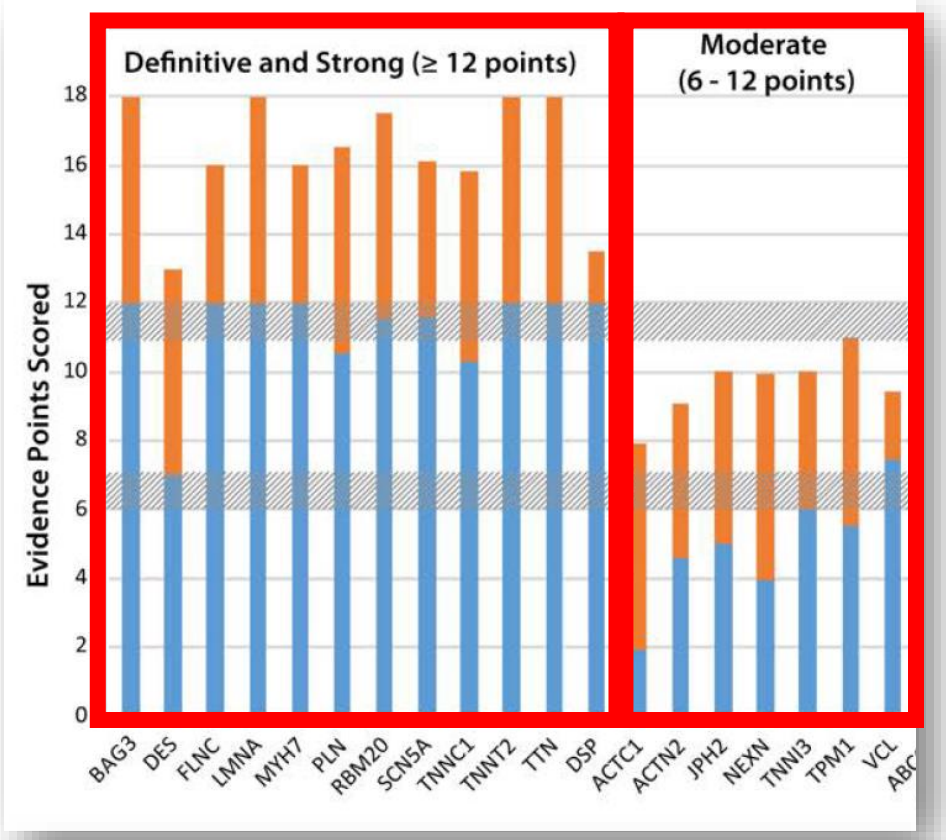
Etiology of dilated cardiomyopathy

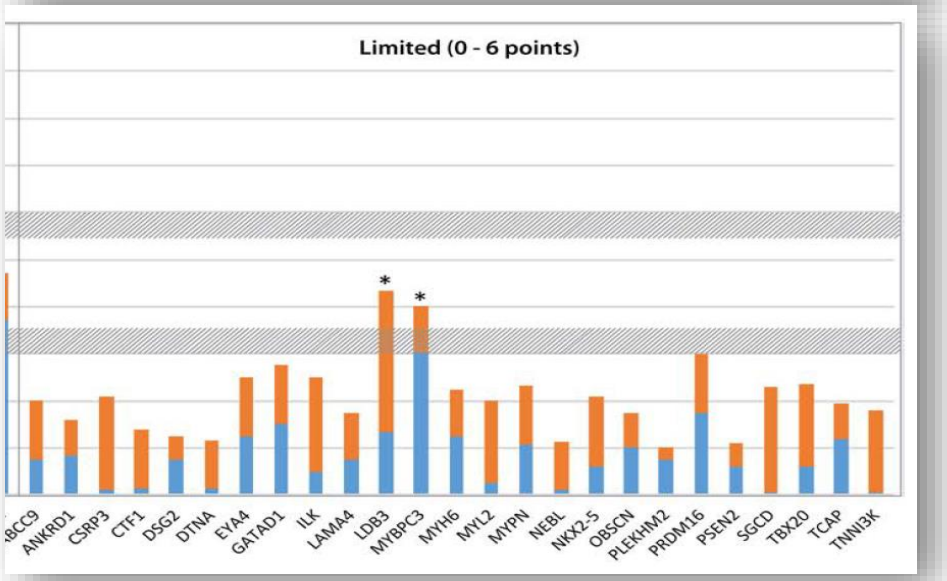
1. Genetic factors (25%)
    - 1.1 Autosomal dominant and recessive forms
    - 1.2 Neuromuscular diseases
    - 1.3 Syndrome associated diseases
2. Drugs, toxic agents
    - 2.1 Anti-neoplastic agents
    - 2.2 Psychiatric drugs
    - 2.3 Other drugs
    - 2.4 Toxic agents
3. Nutritional factors
4. Electrolyte abnormalities
5. Endocrinological causes
6. Infection
7. Autoimmune origin
    - 7.1 Organ specific
    - 7.2 Non organ specific
8. Peripartum


Co-chap HSP
BAG3
RNA-binding
SCN5A
SCN5A
Ion channel
MYH7
TNNC1
TTN
Sarcomer
TNNT2
ACTC1
TNNC3
TPM1
LMNA
Nuclear membrane
Genetic background of DCM
Membrane junction
JPH2
VLC
Cytoskeleton
FLNC
DES
Z-band
NEXN
ACTN2
DSP
Desmosome
SR
PLN
HCM
ARVC
Long QT
Brugada sy

Frequency and distribution of pathogenic DCM genes







Definitive/strong evidence
BAG3
DES
FLNC
LMNA
MYH7
PLN
RBM20
SCN5A
TNNC1
TNNT2
TTN
DSP

Moderate evidence
ACTC1
ACTN2
JPH2
NEXN
TNNI3
TPM1
VCL

source of figure?

diagnostics

MDPI

Article

The Genetic Architecture of Hypertrophic Cardiomyopathy in Hungary: Analysis of 242 Patients with a Panel of 98 Genes

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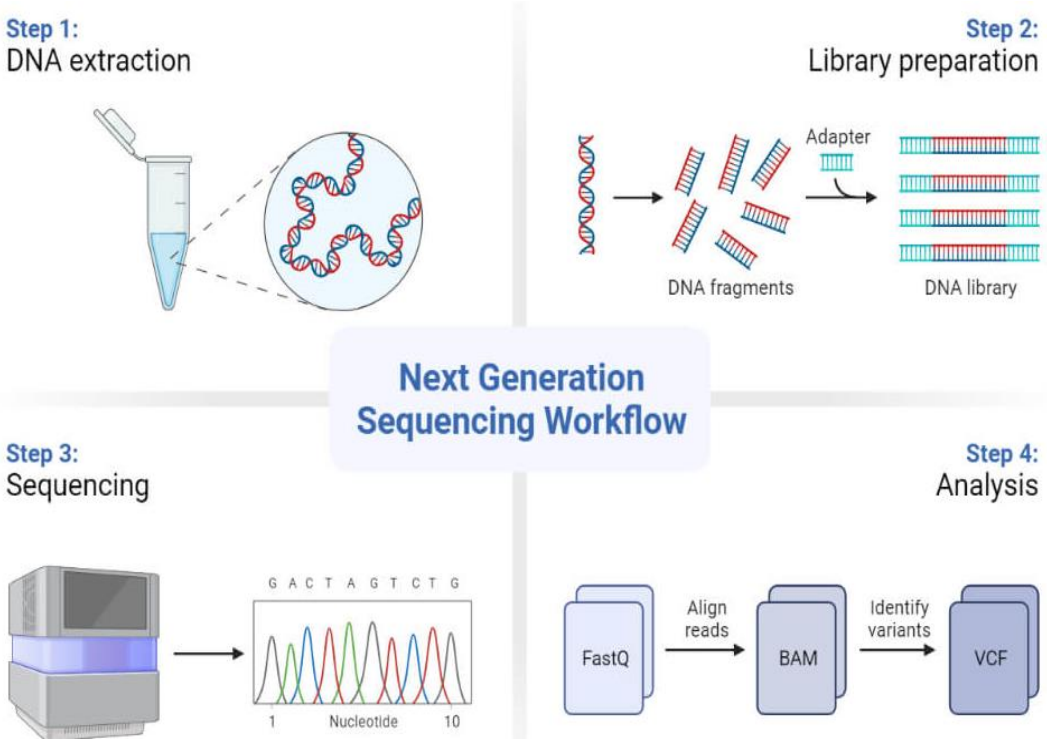
AIM

In our study, we aimed to determine the mutation spectrum of a large number of Hungarian DCM patient population using next-generation sequencing (NGS).

Patients and methods



Next Generation Sequencing – Definition, Types August 5, 2022 Sagal Aryal

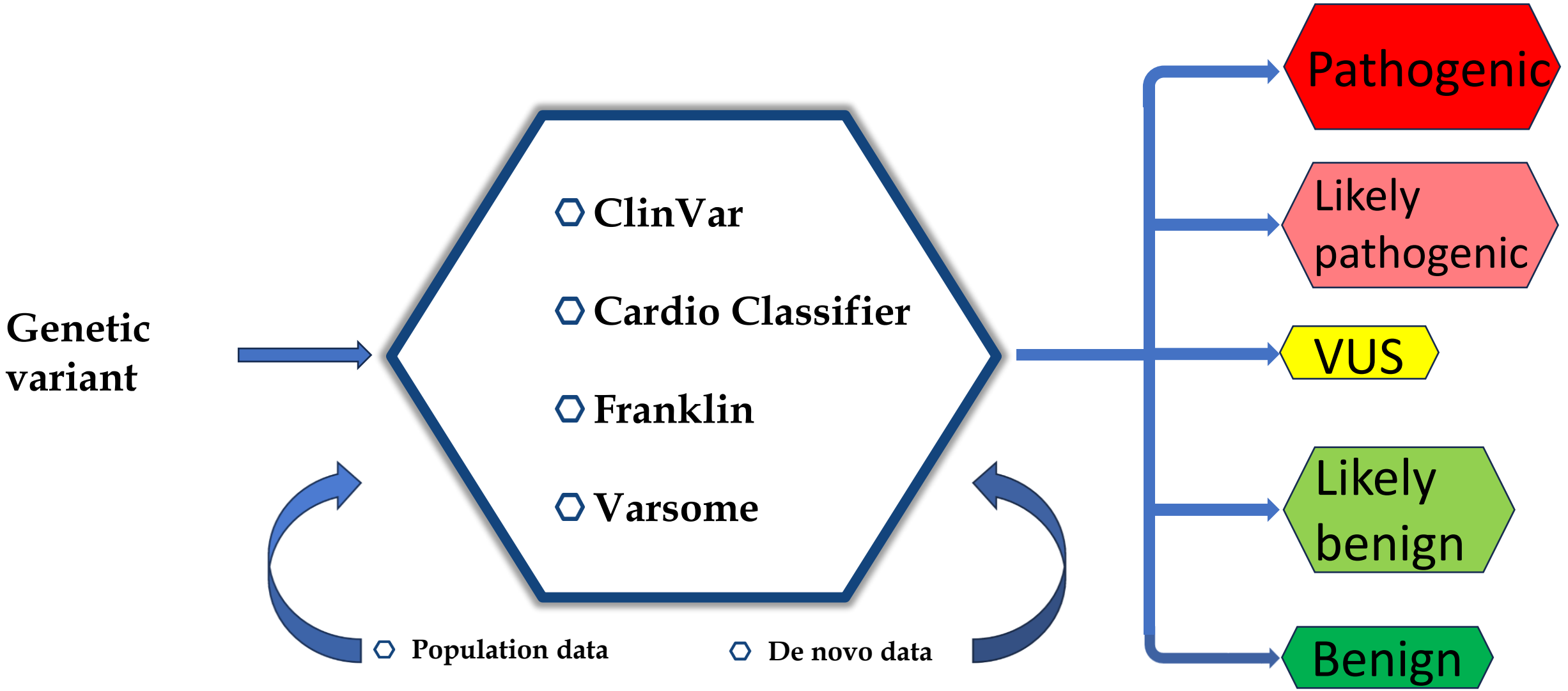
Number of patients: 135 (86 men, 49 women)

Average age at diagnosis: 52±16 years

Examination of 98 known CMP-causing genes

NGS

Validation: Sanger


Genetic variant
ClinVar
Cardio Classifier
Franklin
Varsome
Population data
Bioinformatics data and predictions
Functional data
Segregation data
De novo data
Allele data
Other databases
Other data
Pathogenic
Likely pathogenic
VUS
Likely benign
Benign

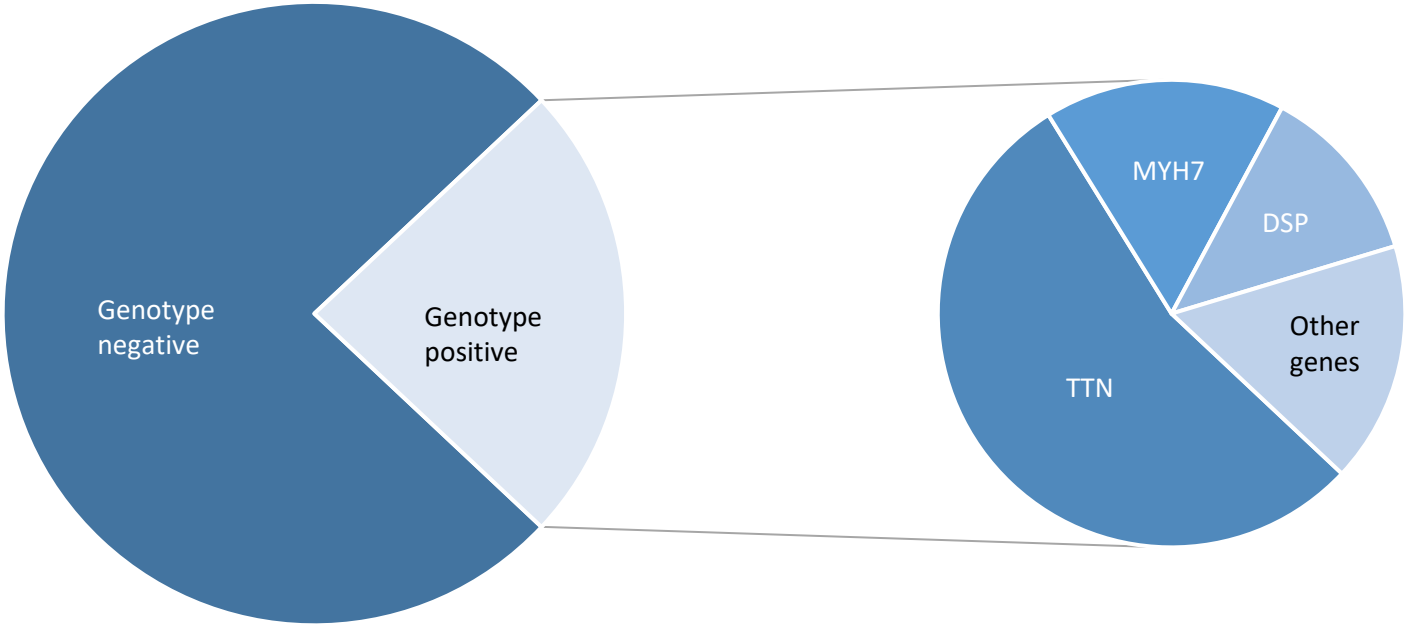
Results

D422	0	1999.01.30	3519,352	JPH2 p.Lys383_Glu385del	TTN p.His14196Arg			
D423	0	1987.03.08	3544,3545	RBM20x9 p.Arg634Trp				
D424	0	1987.05.06	3546,3547	TTN p.Val18540Ala				
D426	0	1958.05.11	3576,3577	TTN Arg27688His				
D428	0	1974.06.17	3584	TTN p.Arg19287His	TTN p.Arg15731Cys	TTN p.Pro10875Leu		
D429	0	1953.05.19	3588,3589	TTN p.Glu31896Lys				
D430	0	1992.08.31	3597,3598	TTN p.Ser10702Cys	TTN p.Arg5538His	TTN p.Val34854Leu	TTN p.Lys15136Asn	
D433	1	1984.07.07	3632,3633	MYH7 Lys1617del	NEXN p.Glu59Lys	TTN Arg3120Gln	TTN Arg32748Cys	TTN p.His10092Tyr
D435	0	1975.02.04	,3616	TTN p.Pro21891Leu				
D437	0	1942.10.23	,3732	DSP p.Arg1537Cys	TTN p.Val23549Ile			
D440	0	1995.09.27	3761,3762	TTN p.Arg17618Cys	TTN p.Val4250Met			
D441	0	1971.07.27	3763,3764	TTN x 326 (Arg25084Ter)	TTN p.Ile4327Val			
D443	0	1970.05.06	3785,3786	TTN p.Glu35478Gly	TTN p.Asp21293Asn	TTN p.Gly4471Ala		
D444	0	1958.06.21	3793,3794	DSP p.Lys1288SerfsTer6	DSP p.Val495Ala			
D445	0	1996.09.09	,3850	none				
D446	0	1968.04.05	3858,3859	TTN p.Arg19576Cys				
D447	0	1953.01.20	3862,3863	none				
D448	0	1979.04.10	3701,3702	TTN p.Gly26298Arg	TTN p.Ile23902Thr			
D450	0	1964.04.27	3893,3894	TTN p.Arg28291Cys				
D451	0	1960.02.10	3895,3896	TTN p.Thr21008Ile	TTN p.Tyr5683Cys			
D452	0	1972.09.23	3901,3902	TTN p.Arg35043His	TTN p.Glu27502Lys	TTN p.Glu24609Gln	TTN p.Ile17720Thr	TTN p.Glu5963Gly
D453	0	1962.04.22	3903,3904	ACTN2 p.Arg298His	TNNT2 p.Ala38Val			
D454	0	1970.02.23	3907,3908	ACTN2 p.Arg298His	MYH7 p.Arg1897His			
D455	0	1980.01.13	3909, 3910	DSP p.Arg1537Cys	TTN p.Val5435Met	TTN p.Ala7122Thr		
D456	0	1966.01.05	3911,3912	TTN p.Lys8325Glu	TTN p.Gln5188Pro	TTN p.Ser1937Cys		
D461	0	1979.09.14	3968,3969	TTN p.Gln33928Arg	TTN p.Arg2083Ile	TTN p.Phe1466Leu	TTN p.Asp22314Tyr	TTN p.Ser29465Phe
D462	0	1964.05.10	3972,3973	none				
D464	0	1961.04.11	4053,4054	TTN p.Tyr5683Cys				

Results

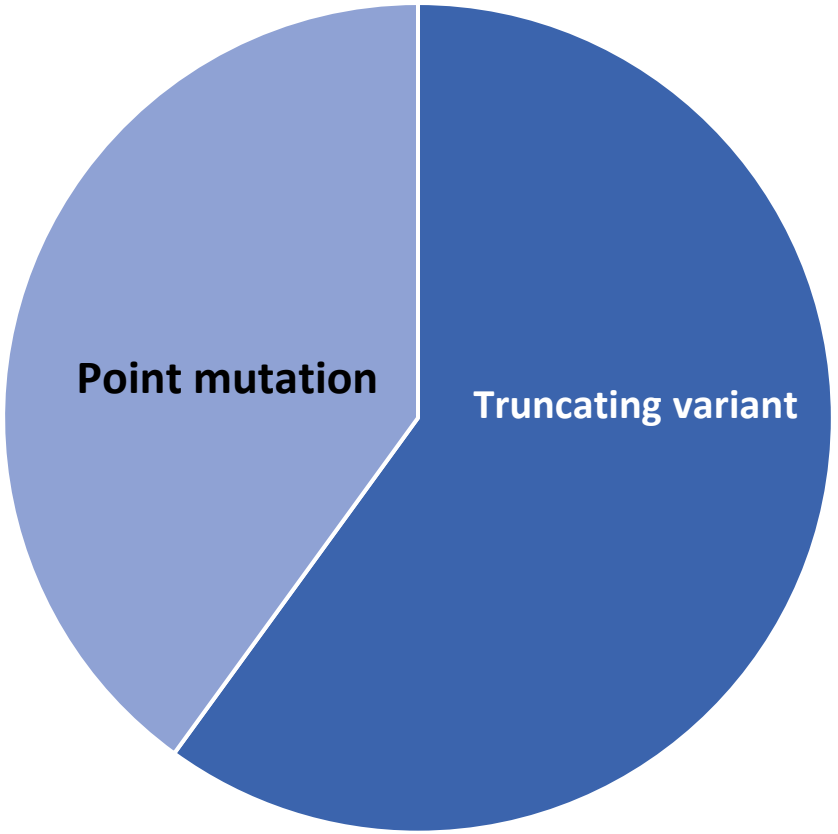
- We detected a pathogenic (P) or presumably pathogenic (LP) genetic variant in 32 of the 135 patients (24%).

Distribution: 1. titin gene (*TTN*, 54%)
2. beta myozin heavy chain gene (*MYH7*, 17%)
3.Desmoplakin gene (*DSP*, 12%)
4. Other : troponin T (*TNNT2*), RNA binding motif protein 20 (*RBM20*), BAG cochaperone 3 (*BAG3*), phospholamban (*PLN*), lamin A/C (*LMNA*)



P/LP variants

- *TTN*: stop codon v. frame-shift: 17/17, point mutation: 0/17
- *DSP*: stop codon v. frame-shift: 3/4, point mutation : 1/4
- *MYH7*: stop codon v. frame-shift: 0/12, point mutation : 12/12

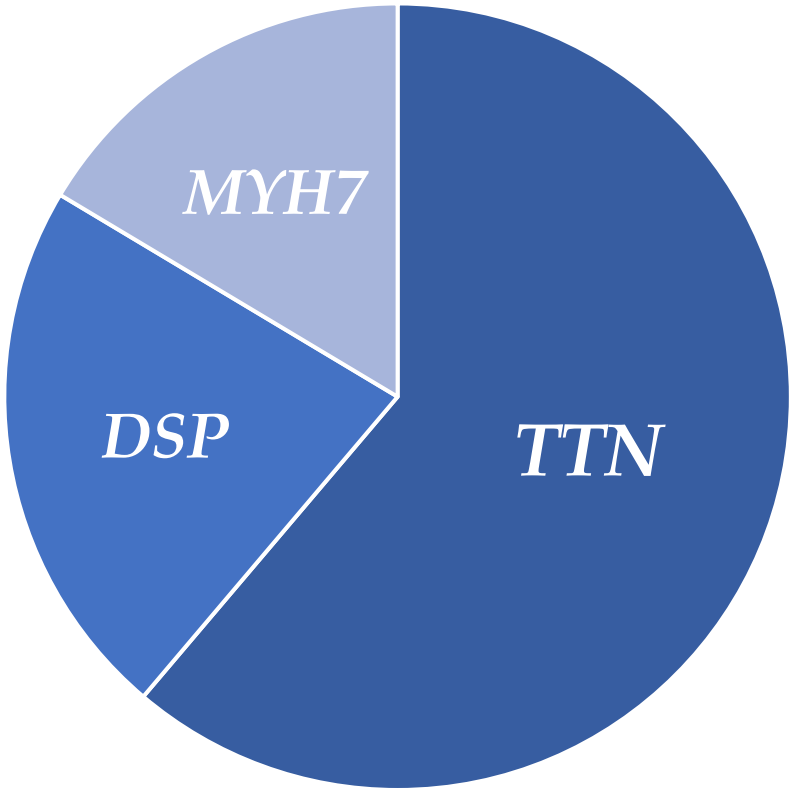


VUS variants

Among the non-P/LP carrier patients, 54 patients (40%) carried a variant of unknown significance (VUS).

Genes in which most frequently VUS occurs:

- *TTN* (41%),
- *DSP* (15%)
- *MYH7* (11%)



Conclusion

Our results suggest that genetic variants that can be considered pathological can be detected in about 25% of the Hungarian DCM patient population. The latter variants most often affect the TTN gene. The above mutation spectrum is similar to data from other European DCM patient populations.

Thank you for your attention!

Eredmények

- 130 betegből 104 genotípus pozitív (hordozó) és 26 genotípus negatív beteget találtunk.

- 232 genetikai variáns: 34 patogén (P), vagy feltehetően patogén (LP), 103 „ismeretlen hatású variáns” (VUS), 58 fellelhetően jóindulatú (LB) , 37 jóindulatú (B)

- 33 betegben (25%) észleltünk patogén (P), vagy feltehetően patogén (LP) genetikai variánst.
  Ezek eloszlása:

  1. titin gén (TTN, 54%)
  2. béta myozin nehéz lánc gén (MYH7, 15%)
  3. dezmoplakin gént (*DSP*, 12%)
  4. Egyéb: : troponin T (*TNNT2*), RNA binding motif protein 20 (*RBM20*), BAG cochaperone 3 (*BAG3*), foszfolambán (*PLN*), lamin A/C (*LMNA*)

- Hatás alapján: TTN és DSP → többnyire csonkoló hatású mutációk (stop kodon, frameshift), MYH7 → pontmutációk

- 55 betegben (42%) „ismeretlen hatású variáns” (VUS): *TTN* (?%), *DSP* (?%), *MYH7* (?%)

MYH7

740	MYH7 p.Arg904Cys
3,632	MYH7 Lys1617del
2803	MYH7 p.Asn1623Lys
2803	MYH7 p.Asn1623Asp
3,907	MYH7 p.Arg1897His
4,529	MYH7 p.Gly1154Ser
3,485	MYH7 p.Ala445Val
1353	MYH7 p.Asp1096Tyr

TTN

3,243	TTN p.Arg16095*
4,670	TTN p.Arg16095Ter
3,763	TTN p.Arg25084Ter
4,200	TTN p.Pro4353GlnfsTer14
1353	TTN p.Glu28720Ter
566	TTN p.Ser17459Ter
4,244	TTN x 48 p.Thr4160ProfsTer8
3,215	TTN p.Thr14780AspfsTer29
4,704	TTN p.Ser34359ArgfsTer2
4,743	TTN p.Ser25388LysfsTer2
4,212	TTN p.Glu22675Ter
4,355	TTN p.Gly23575LysfsTer4
4,216	TTN p.Ile20508ValfsTer68
1353	TTN p.Ile16687Leu
566	TTN p.Thr23453Asn
4,244	TTN p.Thr23394Met
3,215	TTN Thr12015Arg
4,704	TTN p.Ile32071Arg
4,670	TTN p.Ile30927Lys
4,670	TTN p.Thr455Ala
3,763	TTN p.Ile4327Val
4,200	TTN Asp17380Val
740	TTN p.Cys33409Tyr
740	TTN p.Thr23448Arg
3,632	TTN p.Arg3120Gln
1092	TTN p.Val9208Ile
3,243	TTN p.Val12836Met
3,485	TTN p.Val1045Met

OTHER

3,046	TNNT2 p.Glu158del
4,555	TNNT2 p.Arg151fs
3,903	TNNT2 p.Ala38Val
4,065	BAG3 p.Ala155Thr
3,113	PLNx2 p.Arg9Leu
3,485	LMNA p.Gln553fs (p.Asp553G

DSP

3,243	DSP p.Arg2284*
3,243	DSP p.Arg2284*
4,745	DSP p.His2742Leu
3,793	DSP p.Lys1288SerfsTer6
3,793	DSP p.Val495Ala
2090	DSP p.Lys2038Gln
4682	DSP p.Glu1493Ala
4,216	DSP p.Val30Met
4,722	DSP p.Val30Met
3909	DSP p.Arg1537Cys
2090	DSP p.Glu1740Lys

Moderate genes

3,632	NEXN p.Glu59Lys
4,085	NEXN p.Gly650del
4,259	NEXN p.Glu332Ala
4,733	NEXN p.Glu332Ala
3,519	JPH2 p.Lys383_Glu385del
1232	ACTN2 p.Ala52Thr
3,903	ACTN2 p.Arg298His
3,907	ACTN2 p.Arg298His