

APPENDIX 2

ESC 2023 Guidelines on Cardiomyopathies

Overview of genes associated with monogenic, non-syndromic cardiomyopathies, and their relative contributions to different cardiomyopathic phenotypes

Gene	Cardiomyopathy phenotype					Associated phenotype
	HCM	DCM	NDLVC	ARVC	RCM	
ABCC9	● ^a	○				^a Cantu syndrome
ACTA1	○					
ACTC1	●	●	●	○	●	
ACTN2 ^b	●	●	●			
ALPK3	●					
ANKRD1	○	○				
BAG3	● ^a	●●			●	^a Myofibrillar myopathy
CACNA1C	● ^c					^c Timothy syndrome
CACNB2	○					
CALR3	○					
CASQ2	○					
CAV3	● ^a					^a Caveolinopathy
CDH2				○		
COX15	● ^a					^a Leigh syndrome
CRYAB	● ^a					^a Alpha-B crystallinopathy
CSRP3	●	○				
CTF1		○				
CTNNA3				○		
DES	● ^c	●	●	●	●	^c Desminopathy
DMD		● ^c	●			^c X-linked progressive MD
DMPK			●			
DSC2				●●		
DSG2		○		●●		
DSP	○	●●	●	●		
DTNA		○	●			
EYA4		○				
FHL1	● ^c					^c Emery-Dreifuss MD
FLNC	● ^c	●●	●	●	●	^c Myofibrillar myopathy
FHOD3	●					
FXN	● ^a					^a Friedreich ataxia
GAA	● ^a					^a Pompe disease

GATA4						
GATAD1						
GLA	● ^c	○				^c Anderson-Fabry disease
HCN4						
ILK		○	●			
JPH2	●	●				
JUP				● ^a		Naxos disease (cardiocutaneous syndrome)
KCNQ1	○					
KLF10	○					
LAMA4		○				
LAMP2	● ^c					^c Danon disease
LDB3	● ^a	○	●	○		^a Myofibrillar myopathy
LMNA		●●	●	○		
LRRC10		○				
MIB1		○	●			
MYBPC3	●●●	○	●	○	●	
MYH6	○	○				
MYH7	●●●●	●●	●	○	●	
MYL2	●●	○	●	○	●	
MYL3	●●	○	●	○	●	
MYLJ2	○					
MYOM1	○					
MYOZ2	○					
MYPN	○	○			●	
NEBL		○				
NEXN	○	●				
NOC2-5		○	●			
NNT			●			
NONO			●			
NPPA		○				
OBSCN	○	○	●			
PDLIM3	○	○				
PKP2		○		●●●		
PLEKHA2		○				
PLN ^b	●	●	●	●		

PRDM16			o	o			
PRKAG2	• ^c						^c PRKAG2 cardiomyopathy
PSEN1			o				
PSEN2			o				
PTPN11	• ^c						^c Noonan syndrome
RAF1	• ^c						^c Noonan syndrome
RBM20		••		o			
RIT1	• ^c						^c Noonan syndrome
RYR2	o			o		o	
SCN5A		•		o		o	
SGCD			o				
SLC25A4	• ^a						^a Mitochondrial disease
TAZ				o			
TBX5				o			
TBX20			o	o			
TCAP	o		o				
TGFB3						o	
TJP1						o	
TMEM43			o	o		• ^a	
TMEM70				o			
TMPO	o		o				
TNNC1	•		•			o	
TNNI3	••		•			o	o
TNNI3K			o				
TNNI2	••••	••		o		o	
TPM1	•	•		o		o	
TRIM63	•						
TTN	o	••••		o		o	
TTR	• ^c						^c Transthyretin amyloidosis
VCL	o	•					

Based on ClinGen gene validation efforts; ooo: very common (>10% of tested cases); oo: common (1–10% of tested cases); o: less common (<1% of tested cases); blue circle: definitive/strong evidence; light blue circle: moderate evidence; white circle: limited, no association or refuted/dispute evidence; blank cells: not classified; grey circle: has been described (generally rare, sporadic cases), yet not classified/evaluated by ClinGen. The yield may be higher in subgroups with more specific phenotypes, e.g. the yield of testing LMNA is higher in groups with DCM and conduction disease. As NDLVC is a new phenotypic description, genes have not been formally curated for associations with this phenotype. Values shown are based on curations for related cardiomyopathies where the phenotypic spectrum is understood to include NDLVC.

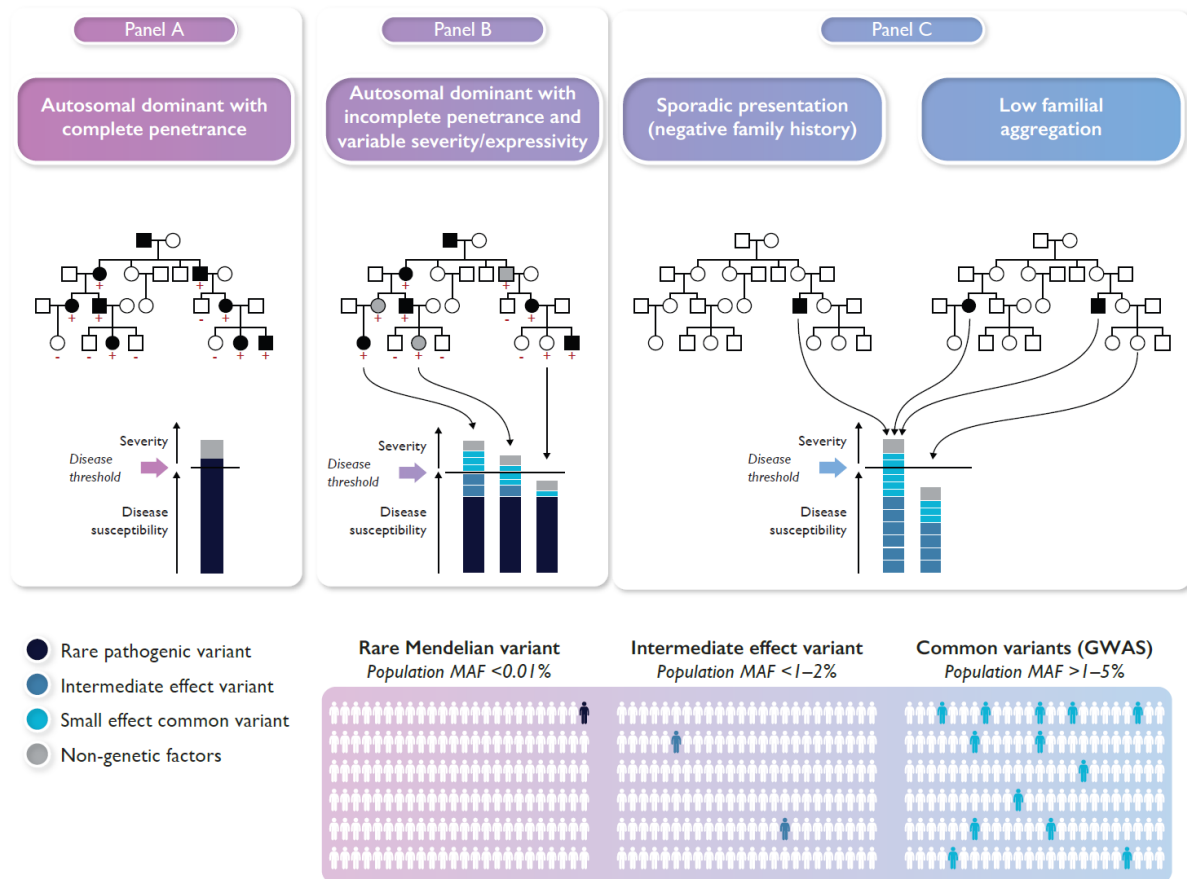
a indicates genes associated with syndromic presentations that can include cardiomyopathy as a feature, but where cardiomyopathy is not expected to occur as the only or presenting feature of the syndrome.

b ACTN2 and PLN can present a mixed phenotypic picture that may not fit into classical cardiomyopathy descriptions.

c indicates genes associated with syndromic presentations that can include cardiomyopathy as a feature, and where cardiomyopathy may be the only or presenting feature of the syndrome. These are sometimes referred to as genocopies. E.g. GLA is shown as definitive for HCM, because it causes Anderson–Fabry disease which can present with LVH fulfilling diagnostic criteria for HCM.

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; MD, muscular dystrophy; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy.

The genetic architecture of the cardiomyopathies.



GWAS, genome-wide association studies; MAF, minor allele frequency. Cardiomyopathy can be Mendelian, caused by genetic variants that are ultra-rare in the general population and have large effect sizes. Such variants can display complete penetrance; i.e. all individuals with the variant in the family manifest the disease (panel A). However, individual variants are often insufficient to yield a disease phenotype in isolation, and their effect is modulated by the co-inheritance of modulatory genetic factors and by non-genetic factors (panel B). Besides increasing disease penetrance, such modulatory variants also affect the severity of the disease (panel B). Modulatory genetic factors are thought to comprise common variants with individually small-effect sizes and intermediate-effect variants that have population frequencies and effect sizes between rare and common variants. Some patients have a more complex aetiology (non-Mendelian/polygenic inheritance) in which a substantial number of non-Mendelian genetic factors and non-genetic factors are required to reach the threshold for disease (panel C). Such patients typically have a sporadic presentation or present with a less pronounced familial clustering of the disease. Family trees demonstrate the male (square) and female (circle) family members that are affected (black filled), with incomplete phenotype (grey filled) or unaffected (white filled). The presence or absence of the variant of interest is noted with “+” or “-”, respectively.