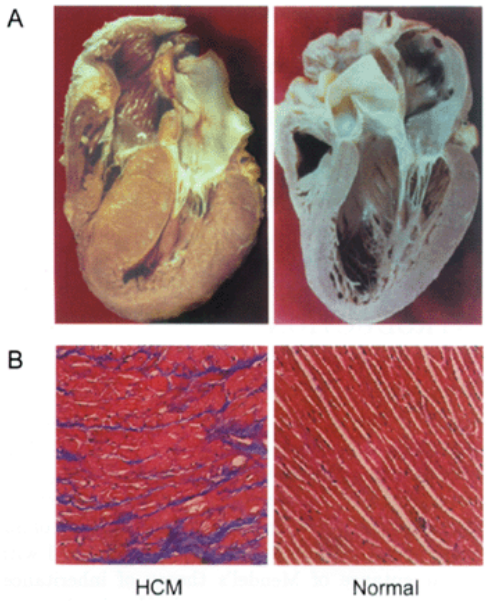
Hypertrophic cardiomyopathy (HCM)



Variants from hypertrophic cardiomyopathy (HCM)
Classify the variants into one of the 6 classification categories typically used in the clinic, which includes the following range of categories: likely benign; VUS- favor benign; VUS; VUS-favor disease-causing; Likely disease-causing; very likely disease-causing.

1. *MYH7 (*p.Gly741Arg)
c.2221G>C

2. *MYH7* (p.Asp168Asn)
c.502G>A

3. *LDLR* (p.Arg2X)
c.4C>T
Chr19:11210912C>T

4. *ASPA* p.Ala305Glu
c.914C>A

5. *MYBPC3* p.Ser236Gly
c.706A>G

6. *PKP2* p.Gln62Lys
c.184C>A

Variant curation tips

1. Variant level evidence:
- Human evidence (MAF; is this variant seen in published cases? if so, is there available segregation data..)
- Functional evidence (animal or cell model for this particular variant? Biochemical support (i.e. in silico prediction programs)?
- Conservation and genomic context

2. Gene level evidence:
- is there strong evidence linking the gene to phenotype? i.e. MYH7 is clearly implicated in HCM; encodes myosin heavy chain 7, a subunit of the cardiac sarcomere
- what types of variants in this gene are pathogenic? (i.e. if LOF, have LOF variants been implicated in disease?)

3. Phenotype level evidence:
- inheritance pattern
- estimated disease prevalence
- penetrance, variable expressivity, disease onset, etc.

Resources one might try:
- Allele frequency:
  - NHLBI Exome Sequencing Project (allele frequency)
  - dbSNP
  - 1000Genome
- Conservation, genomic context:
  - UCSC Genome Browser
- In silico predictions
  - Polyphen, Mutation Taster, SIFT
- Gene and phenotype information:
  - NCBI gene, GeneReviews, OMIM…
  - Mutation databases: HGMD, locus specific.
- primary literature search and review

PubMed, etc.