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.