

VARIANT CLASSIFICATION HCM CardioChip and DCM Panel A

PATHOGENIC

- Functional evidence (e.g. mouse models, in vitro studies)
- Segregation w/ disease (min 5 informative meioses*) and <0.5% freq in healthy chromosomes (<1/100 individuals)
 - Note: HCM probands can be used to assess frequency if variant is rare. For common variants, healthy controls must be screened (i.e. R502W)

PRESUMED PATHOGENIC

- Missense (MYBPC3, MYH7, TNNT3, TNNT2, TPM1, ACTC, MYL2, MYL3)
 - Present in <0.5% of ethnically matched chromosomes but no segregation data, or
 - Insufficient allele frequency data but segregation with disease in family (min 5 informative meioses*)
- Nonsense
- Frameshift
- +/- 1,2 splice site
- *De novo* variants in proband with *de novo* disease

UNKNOWN SIGNIFICANCE

- Missense changes in PRKAG2, LAMP2, GLA
- Population data unavailable to determine frequency (e.g. novel variant in Hispanic proband)
- Any novel silent variants in MYBPC3 or LAMP2 (studies have shown that many silent variants can affect splicing through altering ESEs/ESSs)
- Novel/rare splice outside +/-1,2
 - Splice donor region: +3 → +6
 - Splice acceptor region: -3, -5 → -10
 - Silent variants affecting 1st and last 3 bases of exon
- Conflicting data reported or observed

PRESUMED BENIGN

- Any silent variants in genes other than MYBPC3 or LAMP2
- Any intronic variant at +7 → +10 or -4
- Any variant present in 1-5% of the general population (or a specific racial population), at least 100 individuals studied

BENIGN

- Any variant present with >5% frequency (at least 100 individuals studied)