**Title**: Manrai et al. (2016)

**Background**: Hypertrophic Cardiomyopathy (HCM) has a strong genetic component and targeted genome sequencing is often used to establish diagnoses, risk stratify relatives, and sometimes, to tailor therapy. The pathogenicity of certain variants is determined based on guidelines in the Human Genome Mutation Database (HGMD) and other sources. Manrai et al. discovered overrepresented HCM-variants in large-scale control Exome Sequence Project data and reviewed patient records for variant occurrences.

**Findings**: The five “high-frequency variants” (of ninety-four total) HCM-associated variants are found in nearly 75% of all patients expressing some kind of variant. These variants were significantly more common in African-Americans than in European-Americans (P < 0.001). Manrai et al. compared sequence variation between the two groups in the 1000 Genomes Project, finding four to eight times more segregating loci in African-Americans. This suggests that ancestry-based differences may have prompted false associations with pathogenicity in the HGMD, which classifies four of these in the most pathogenic category, “Disease causing mutation,” and the fifth as “disease-causing?”. A review of the medical literature revealed that the initial studies of two of these variants, MYBPC3 G278E and TNNI3 P82S, had minimal or inadequate control sample sizes, and that neither were explicitly undertaken in African-Americans. Statistical analysis and simulation showed that diverse populations in studies can prevent misclassification. The chance of correctly ruling out pathogenicity for a benign variant was shown to increase with the number of controls and the fraction of the ancestry group in the cohort. Lastly, seven patients of African/unspecified ancestry were found to have been misclassified based on standard guidelines before the variants were reclassified as benign.

**Conclusions**: Differences in allele frequencies between populations can result in misclassifications of variant pathogenicity and patient disease risk. This illustrates the need for a diverse set of ancestry-matched controls in interpretation of variant pathogenicity and suggests that current classifications of variants be reevaluated.