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Underrepresentation of Diverse Ancestries Drives Uncertainty in Genetic Variants Found in Cardiomyopathy-Associated Genes

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Abstract

BACKGROUND—Thousands of genetic variants have been identified in cardiomyopathy-associated genes. Diagnostic genetic testing is key for evaluation of individuals with suspected cardiomyopathy. While accurate variant pathogenicity assignment is important for diagnosis, the frequency of and factors associated with clinically relevant assessment changes are unclear.

OBJECTIVES—The authors aimed to characterize pathogenicity assignment change in cardiomyopathy-associated genes and to identify factors associated with this change.

METHODS—We identified 10 sarcomeric and 6 desmosomal genetic cardiomyopathy-associated genes along with comparison gene sets. We analyzed clinically meaningful changes in pathogenicity assignment between any of the following: pathogenic/likely pathogenic (P/LP), conflicting interpretations of pathogenicity or variant of unknown significance (C/VUS), and benign/likely benign. We explored association of minor allele frequency (MAF) differences between well, and traditionally poorly, represented ancestries in genetic studies with assessment stability. Analyses were performed using ClinVar and GnomAD data.

RESULTS—Of the 30,975 cardiomyopathy-associated gene variants in ClinVar, 2,276 of them (7.3%) had a clinically meaningful change in pathogenicity assignment over the study period, 2011 to 2021. Sixty-seven percent of variants that underwent a clinically significant change moved from P/LP or benign/likely benign to C/VUS. Among cardiomyopathy variants downgraded from P/LP, 35% had a MAF above 1×10^{-4} in non-Europeans and below 1×10^{-4} in Europeans.

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APPENDIX For supplemental methods, results, tables, and figures, please see the online version of this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

CONCLUSIONS—Over the past 10 years, 7.3% of cardiomyopathy gene variants underwent a clinically meaningful change in pathogenicity assignment. Over 30% of downgrades from P/LP may be attributable to higher MAF in Non-Europeans than Europeans. This finding suggests that low ancestral diversity in genetic studies has increased diagnostic uncertainty in cardiomyopathy gene variants.

Keywords

ancestry; cardiomyopathy; diversity; genetic testing; variant

Cardiomyopathy is a heterogeneous group of diseases defined by primary disease of the heart myocardium. Among United States cardiomyopathy cases, 20 to 35% are estimated to be congenital.[1,2] Congenital cardiomyopathy represents a substantial, continuing health burden in the United States, and is the third most common cause of cardiac-related death in children.[3–5] Congenital cardiomyopathy has a strong genetic association. In the 30 years since the discovery of the association between *MYH7*-encoded beta myosin heavy chain and the development of hypertrophic cardiomyopathy, there have been thousands of genetic variants discovered in dozens of cardiomyopathy-associated genes. While there are distinct cardiomyopathy phenotypes, including hypertrophic, dilated, and arrhythmogenic cardiomyopathy, there are overlapping genetic causes involving the cardiac sarcomere and desmosome.[6–8] Diagnostic testing for variants in cardiomyopathy-associated genes is standard of care in the evaluation of patients with suspected genetic cardiomyopathy and contributes to diagnosis, management, and cascade testing of family members.[9–12] Accurate, stable variant pathogenicity assessment is essential in allowing clinicians to make informed genetic diagnoses, which guides management and genetic counseling.

One prominent resource used by clinicians and researchers to evaluate genetic variants is ClinVar.[13] This is an open-access database that compiles variant evaluations from multiple private and academic submitters, including review committees made up of volunteers, to arrive at a pathogenicity assignment. Gene variant reclassification data from ClinVar in the field of oncology have revealed that patients with a hereditary cancer diagnosis have diagnostically relevant variants reclassified 7.7% of the time leading to significant challenges in diagnosis and management.[14,15] From the field of cardiology, recent evidence suggests instability in cardiac gene variant pathogenicity assignment, with many variants undergoing clinically relevant changes in assessment over time.[16–18] This instability highlights growing calls for continued clinical follow-up of patients with genetic diagnoses.[16,19] In parallel, there is evidence of limited ancestral diversity in many genetic studies, which diminishes accuracy of diagnostic genetic testing result interpretation primarily among individuals of non-European ancestry.[20] For example, polygenic risk scores for several diseases are less interpretable in Black Americans due to low representation of individuals with African ancestry in the genetic studies which generated the risk scores, exacerbating existing health disparities.[21,22] While existing studies have begun to explore the relationship between cardiac variant reclassification, ancestry, and health disparities, there has been a paucity of large, systematic studies quantifying differences in stability of variant evaluation across ancestries.[23] This need has been directly highlighted by recent guidance from the American Society of Human Genetics, which identified how increased

inclusion of individuals of diverse ancestries within genetic studies has the potential to increase our understanding of genetic diversity as well as improve individual patient outcomes and inform therapeutic development.[24]

In this study, we sought to determine the frequency and directionality of variant pathogenicity assignment changes in cardiomyopathy-associated genes over the last 10 years using the ClinVar database. Furthermore, we sought to identify factors associated with variant assessment instability, including the impact of lack of genetic diversity in genetic studies on variant pathogenicity assignment. We find that nearly 1 in 10 variants in cardiomyopathy-associated genes have undergone a clinically significant change in pathogenicity assessment in ClinVar over the last 10 years and that there is a higher instability in variants that are more frequent in people of non-European ancestries. These findings emphasize a need for continued follow-up of patients with genetic diagnoses of cardiomyopathy, expansion of efforts to recruit diverse participants in genetic studies, and continued expansion of genetic variants from diverse ancestries to guide diagnostic genetic testing interpretation.

METHODS

GENE SELECTION AND GENE SETS.

Clinical Genomics Resource-established genes associated with hypertrophic, dilated, or arrhythmogenic cardiomyopathy were included.[6–8] A set of 10 sarcomeric (*TTN*, *MYH7*, *MYBPC3*, *MYL2*, *MYL3*, *ACTC1*, *TPM1*, *TNNT2*, *TNNI3*, and *TNNC1*) and 6 desmosomal protein genes (*PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, and *TMEM43*) were selected as the primary, cardiomyopathy-associated gene set for this study. All selected cardiomyopathy genes have an autosomal dominant inheritance pattern.[25] Three comparison gene sets were generated consisting of non-cardiomyopathy-associated autosomal dominant and autosomal recessive genes from the American College of Medical Genetics (ACMG) list of clinically actionable genes.[26,27] A list of genes in comparison sets can be found in the Supplemental Appendix. Finally, the set of all ClinVar genes was generated for comparison.

DATA ACQUISITION.

Data on variant pathogenicity assignment was acquired from the open-access ClinVar archive with archival sampling from the first available data set, January 2015, through November 2021 in 3-month intervals over this period.[28] Archival files contain variant evaluation submissions from previous years dating back to 2011 were included in our analyses. Additional information on variant evaluations, including strength of data supporting each evaluation, was obtained from the ClinVar archive over the same period. Minor allele frequency (MAF) by ancestry for each variant was derived from the GnomAD database.[29] Files from ClinVar and GnomAD were imported into RStudio for analysis. Variants in GnomAD were linked to corresponding ClinVar variants based on the common ClinVar Variation ID. Variant inclusion and exclusion criteria, evaluation reconciliation, and information on classification of evidence quality can be found in the Supplemental Appendix.

STATISTICAL ANALYSIS AND VISUALIZATION.

Analyses were performed on variant pathogenicity assignments from the cardiomyopathy-associated gene set compared to autosomal dominant, autosomal recessive, and all ClinVar gene sets. Unless otherwise noted, descriptive values are shown as mean or percentage (95% CI). A clinically meaningful change in variant pathogenicity assignment was defined as any change over the study period between any 2 of the following 3 categories: pathogenic or likely pathogenic (P/LP), conflicting interpretations of pathogenicity or variant of unknown significance (C/VUS), and benign or likely benign. Clinically meaningful changes in pathogenicity assignment from variant entry into ClinVar were visualized using alluvial plots. A visual aid for interpretation of alluvial plot can be found in Supplemental Figure 1. Diagnostic confidence of variant assessments over time for cardiomyopathy-associated genes and all ClinVar were visualized using a previously described diagnostic confidence score, with details in the Supplemental Methods.[19] The mean confidence score and standard error should be interpreted as descriptive given that they use ordinal, categorical data rather than continuous data. Factors potentially associated with pathogenicity assignment stability were analyzed including variant MAF in people with European vs non-European ancestry, quality of evidence before re-evaluation, and initial pathogenicity assignment. An MAF threshold of 1×10^{-4} defined rare vs common variants. Additional details regarding analysis of variables potentially associated with pathogenicity assignment stability can be found in the Supplemental Methods. All analyses were performed in RStudio. Analysis code is publicly available and can be found at GitHub under “Landstrom Lab” (APLandstromLab).

RESULTS

CLINICALLY MEANINGFUL CHANGE IN CARDIOMYOPATHY-ASSOCIATED GENES VARIANTS PATHOGENICITY ASSIGNMENTS.

To describe general characteristics of the primary, cardiomyopathy-associated gene set, we first determined the breakdown of initial pathogenicity assignment, reevaluation frequency, and change in variant count over time. The mean number of times a variant in the cardiomyopathy-associated gene set was reevaluated was 2.34 times/10 y (95% CI: 2.32–2.37) (Figure 1A). This value was slightly higher than the mean in all of ClinVar (2.03 times/10 y [95% CI: 2.03–2.03]). Most variants, 58.6%, were initially entered into ClinVar as conflicting interpretations of pathogenicity or variant of unknown significance (C/VUS) (Figure 1B). As expected, there was a consistent increase in the total number of reported variants in cardiomyopathy-associated genes each year, with an increase from 1,024 in 2011 to 30,975 in 2021 (Figure 1C).

To determine the frequency of clinically significant changes in variant pathogenicity evaluations, we identified the number of variants in each gene and gene set that underwent a clinically significant change over the study period. Overall, 7.3% (95% CI: 7.0%–7.6%) of cardiomyopathy-associated gene variants underwent at least one clinically meaningful change in pathogenicity assignment from 2011 to 2021 (Table 1). This total included 7.9% (95% CI: 7.6%–8.2%) of sarcomeric gene variants and 5.2% (95% CI: 4.7%–5.7%) of desmosomal gene variants. The cardiomyopathy-associated genes with the

highest proportion of variants undergoing a clinically meaningful change in pathogenicity assignment were *MYH7* (12.0%), *TNNI3* (11.5%), and *TTN* (7.0%). Variants in other ACMG-identified genes had a similarly high proportion of change. In contrast, only 4.4% (95% CI: 4.4%–4.4%) of variants across all genes in ClinVar underwent a clinically meaningful change in pathogenicity assignment which was significantly less than the proportion of cardiomyopathy gene variants ($P < 0.001$). On average, the cardiomyopathy-associated set had a proportion of variants undergoing change in the 86th percentile of all genes in ClinVar (Supplemental Figure 2). Taken together, these data show that 7.3% of cardiomyopathy-associated gene variants have undergone a clinically meaningful change in pathogenicity assignment in ClinVar which is ~1.7-fold higher than the average gene in ClinVar.

DIAGNOSTIC UNCERTAINTY IN CARDIOMYOPATHY-ASSOCIATED GENE VARIANTS.

To provide a clearer picture of how cardiomyopathy-associated gene variants change pathogenicity status over time, we analyzed directionality of these changes. We visualized changes in pathogenicity assignment from variant entry into ClinVar until the end of the study period using alluvial plots for each cardiomyopathy-associated gene and comparison gene set (Figures 2A to 2D). These plots demonstrate a clear trend toward diagnostic uncertainty, defined as movement from a more diagnostically confident assignment (eg, pathogenic) to a less confident one (eg, VUS). This trend toward a C/VUS assignment was present for nearly every cardiomyopathy-associated gene, as well as all comparison sets. In cardiomyopathy-associated genes, 22.5% of initially P/LP variants were downgraded to C/VUS, while only 1.4% change assignment in the reverse direction. The proportion of variants changing pathogenicity assignment in each alluvial is quantified in Supplemental Table 1. Overall, variants in cardiomyopathy-associated genes were 3.0 times as likely to be re-evaluated from B/LP or P/LP to C/VUS as compared with the converse.

To further quantify the trend in diagnostic certainty, we created a diagnostic certainty score comprised of the aggregate of all variant evaluations by year for the cardiomyopathy-associated gene set and all of ClinVar. Throughout the study period, there was a consistently lower diagnostic certainty score in cardiomyopathy-associated gene variants compared to all ClinVar variants with a mean of 0.69 and 1.05, respectively. In both cardiomyopathy-associated gene variants and all ClinVar variants, there was an initial decline in diagnostic certainty until 2016. After that point, the certainty score plateaued for ClinVar variants overall, while it continued to decline in cardiomyopathy-associated gene variants (Figure 3). This figure is also visualized as a segmented bar plot given the fact that confidence score was based on a categorical variable (Supplemental Figure 3). Taken together, these data show that changes in pathogenicity assignments of cardiomyopathy-associated gene variants are trending toward diagnostic uncertainty to a greater extent than other ClinVar gene variants.

IMPACT OF SUBJECT ANCESTRY ON VARIANT ASSIGNMENT UNCERTAINTY.

To explore factors associated with instability of variant pathogenicity assignment, we examined MAF by ancestry using GnomAD. We found 187 cardiomyopathy-associated gene variants in GnomAD that were downgraded from P/LP to C/VUS over the study period.

Remarkably, among these, 67 variants (35% [95% CI: 29%–43%]) had an MAF above 1×10^{-4} in people of non-European ancestries. Conversely, only 3 (1.6% [95% CI: 0%–3.4%]) downgraded variants had a MAF $>1 \times 10^{-4}$ in individuals of European ancestry (Figure 4A). Moreover, of the 421 cardiomyopathy gene variants initially labeled P/LP in ClinVar and present in GnomAD, 124 variants (29% [95% CI: 25%–34%]) had an MAF $>1 \times 10^{-4}$ among individuals of non-European ancestry. On the other hand, there were only 6 variants (1.4% [95% CI: 0.3%–2.5%]) which had an MAF $>1 \times 10^{-4}$ in people of European ancestry (Figure 4B). In summary, variants with a relatively high MAF in people of European ancestry are very unlikely to be labeled P/LP. Conversely, variants with high MAF among non-European ancestries were frequently labeled as P/LP yet many have been downgraded to C/VUS since initial entry into ClinVar. This influence of non-European ancestries on variant assignments was greater than both the quality of evidence and research bias based on initial pathogenicity assignment of a variant (Supplemental Figures 4 and 5). Due to the lack of literature consensus on what MAF would cause a variant to be considered “rare,” this analysis was validated using MAF as a continuous variable (Supplemental Methods and Results). Overall, these findings show that more than a third of all P/LP variants that have been downgraded in pathogenicity to VUS were common among individuals of non-European ancestry. This suggests that lack of ancestral diversity in early genetic studies impaired correct assignment of disease pathogenicity which is now being recognized as more genetic uncertainty (Central Illustration).

Other factors potentially associated with clinically significant changes in pathogenicity were also explored, including the impact of evidence quality on assessment stability. Variants in cardiomyopathy-associated genes had, on average, higher quality of evidence ratings than variants in ClinVar overall (Supplemental Figure 6). Furthermore, variants in cardiomyopathy-associated genes at every level of quality of evidence had a higher likelihood of undergoing a clinically meaningful change than variants in ClinVar overall (Supplemental Figure 7). These findings demonstrate that quality of evidence does not explain the higher level of instability in cardiomyopathy-associated gene variants supporting ancestry as a major force in driving variant demotion of diagnostic to uncertain.

DISCUSSION

Genetic testing is now a standard part of the diagnosis of suspected genetic cardiomyopathy.[10] Early diagnosis of genetic cardiomyopathy is associated with improved health outcomes and detection of genetic disease in family members.[30,31] However, accurate and stable variant pathogenicity assessment is essential to make the best use of genetic testing. We find that there has been considerable instability of pathogenicity assignment in cardiomyopathy-associated genes over the past 10 years with nearly 1 in 10 variants undergoing a clinically meaningful change—a rate of ~1%/variant/y. This instability of variant assessment has highly relevant implications for clinical practice. First, it provides additional evidence for the use of genetic testing as a probabilistic, rather than definitive, marker of disease.[32] In other words, diagnosis and treatment decisions must be made in the context of the greater clinical picture, in alignment with current ACMG recommendations, and comprehensive variant interpretation which can be fluid over time.[33] There are numerous examples in the literature of cases in which a diagnostically

relevant genetic finding underwent a change in variant pathogenicity leading to re-evaluation of diagnosis and treatment strategies.[23,34] For example, unfortunately, there are cases in which implantable cardiac defibrillators were incorrectly placed into family members of a proband suspected of having a cardiac channelopathy based solely on a genetic variant cascade testing that was later downgraded from P/LP.[35,36] Second, variant instability in cardiomyopathy genes adds to the body of evidence supporting periodic reassessment of genetic diagnoses as a key component of clinical follow-up.[16] We found that the level of pathogenicity assignment instability in cardiomyopathy genes is relatively unique among noncardiac diseases, with cardiomyopathy-associated gene variants nearly twice as likely to undergo a clinically meaningful change compared with ClinVar as a whole. This finding corroborates existing evidence in genetic, cardiac channelopathy-associated genes, where instability in variant pathogenicity assignments was noted to be considerably higher than the average ClinVar gene.[19]

Along with high levels of pathogenicity assignment instability, we found that assessment changes tend to decrease the diagnostic certainty of cardiomyopathy-associated gene variants. This means that variant re-evaluations tended to result in shifts from more diagnostically confident assessments (P/LP or benign or likely benign) to less confident ones (C/VUS). It has been previously shown that most variants in cardiac disease-associated genes are initially evaluated as VUS.[18] However, the contribution of reassessment toward lower diagnostic confidence has not been comprehensively demonstrated in cardiomyopathy-associated genes. While previous work has shown that the diagnostic confidence of pathogenicity assessments of ClinVar variants generally increased when variants were re-evaluated by a single submitter, our study incorporates variant calls using the contribution of multiple different submitters evaluating a single variant.[37] We find that the accumulation of varied assessments from several submitters tends to lower diagnostic confidence, unlike individual submitter re-evaluations, suggesting that one factor contributing to the observed overall decline in diagnostic confidence is heterogeneity and discordance in variant evaluation between institutions. Since many clinicians use resources that summarize multiple submitters, such as ClinVar, this heterogeneity may confound the clinical relevance of a variant.

To understand the cause of the high rate of clinically meaningful change and the trend in variant re-evaluation toward low diagnostic confidence in cardiomyopathy-associated gene variants, we explored factors associated with instability. A key factor which we found to be associated with a high probability of downgrade was differences in MAF by ancestry. The fact that a variant was far more likely to be initially labeled P/LP with a high MAF in non-Europeans, compared with Europeans, suggests underrepresentation of non-European ancestries in genetic studies may lead to increased P/LP assignment designation. This finding does not seem to be explainable by a difference in prevalence of genetic cardiomyopathy between populations which, at least in the United States, is quite minimal, or in sequencing technology applied, given that the most common ClinVar submitters primarily use next-generation sequencing.[2] Furthermore, since over 1/3 of downgraded variants in cardiomyopathy genes have a high MAF in non-Europeans and a low MAF in Europeans, there is evidence that disparities in representation have meaningfully contributed to pathogenicity assignment instability in cardiomyopathy. The

limitation of nondiverse ancestry in the field of genetics is well-documented.[38,39] Our findings indicate potential diagnostic miscues in people of non-European ancestry due to increased variant instability and higher probability of incorrect initial pathogenicity assessment of variants that are common in non-Europeans. Fortunately, recent efforts by the American Society of Human Genetics and National Human Genetics Research Institute, among other institutions, to improve diverse recruiting to genetic studies and diversity, equity, and inclusion into the genetics workforce may mitigate these disparities in the future.[40,41] In fact, the observed downgrading of variants with high MAF in people of non-European ancestries already suggests a trend toward more accurate, if more diagnostically uncertain, pathogenicity assignments. Continued commitment toward community outreach and recruitment of ancestrally[42] diverse participants to genetic studies is necessary to ensure equal access to the benefits of advances in human genetics research.

STUDY LIMITATIONS.

While ClinVar is a resource referenced by clinicians and researchers, it is not the only source of variant pathogenicity assessments and trends in ClinVar may differ from other genetic databases. This limitation is mitigated by the fact that ClinVar amalgamates variant evaluations from multiple submitters, including academic and private, who use a variety of assessment techniques. Regarding the relationship between MAF by ancestry and stability of variant pathogenicity assessment, we can only comment on association and are not able to determine, using the data available in ClinVar or GnomAD, causes of most downgrades. Additionally, there may be factors influencing variant pathogenicity evaluation stability that we were not able to analyze due to lack of data availability. One factor we were not able to directly analyze that likely contributed to variant downgrades P/LP to C/VUS was the release of new, and often more stringent ACMG criteria over the course of the study period.[26] Moreover, since individual-level sequencing data are not available through the ClinVar data set, we are unable to account for the effect of variable penetrance or multiple variants in cardiomyopathy-associated genes within one individual.

CONCLUSIONS

We find that nearly 1 in 10 cardiomyopathy-associated gene variants have undergone a clinically meaningful change in pathogenicity assignment over the past 10 years, a rate that is nearly twice that of all of ClinVar. Changes in variant evaluations have primarily led to decreases in diagnostic certainty. Furthermore, over 1/3 of the variant downgrades from P/LP to C/VUS in cardiopathy genes can be attributed to differences in MAF between European and non-European ancestries. Our results demonstrate the need in the field of cardiac genetics for consensus-seeking approaches to variant evaluation, as well as the need for periodic reassessment of patients with genetic diagnoses of cardiomyopathy. We also demonstrate a clear example of an effect of underrepresentation of non-Europeans in genetic studies and the need for further efforts to improve diverse recruiting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ACMG	American College of Medical Genetics
C/VUS	conflicting interpretations of pathogenicity or variant of unknown significance
GnomAD	Genome Aggregation Database
MAF	minor allele frequency
P/LP	pathogenic/likely pathogenic

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

There is uniquely high pathogenicity assessment instability in cardiomyopathy-associated genes that may disproportionately impact people of non-European ancestries.

COMPETENCY IN PATIENT CARE:

Interpretation of genetic testing for cardiomyopathy must involve periodic reassessment of patients with a genetic diagnosis and decision-making based on a broader clinical picture.

TRANSLATIONAL OUTLOOK 1:

Guidelines for genetic testing in cardiomyopathy should reflect the need for reassessment.

TRANSLATIONAL OUTLOOK 2:

Continued efforts should be made to improve ancestral diversity in genetic studies. Furthermore, minor allele frequency of a variant in a given ancestry should be considered, when possible, in cases of potential genetic cardiomyopathy.

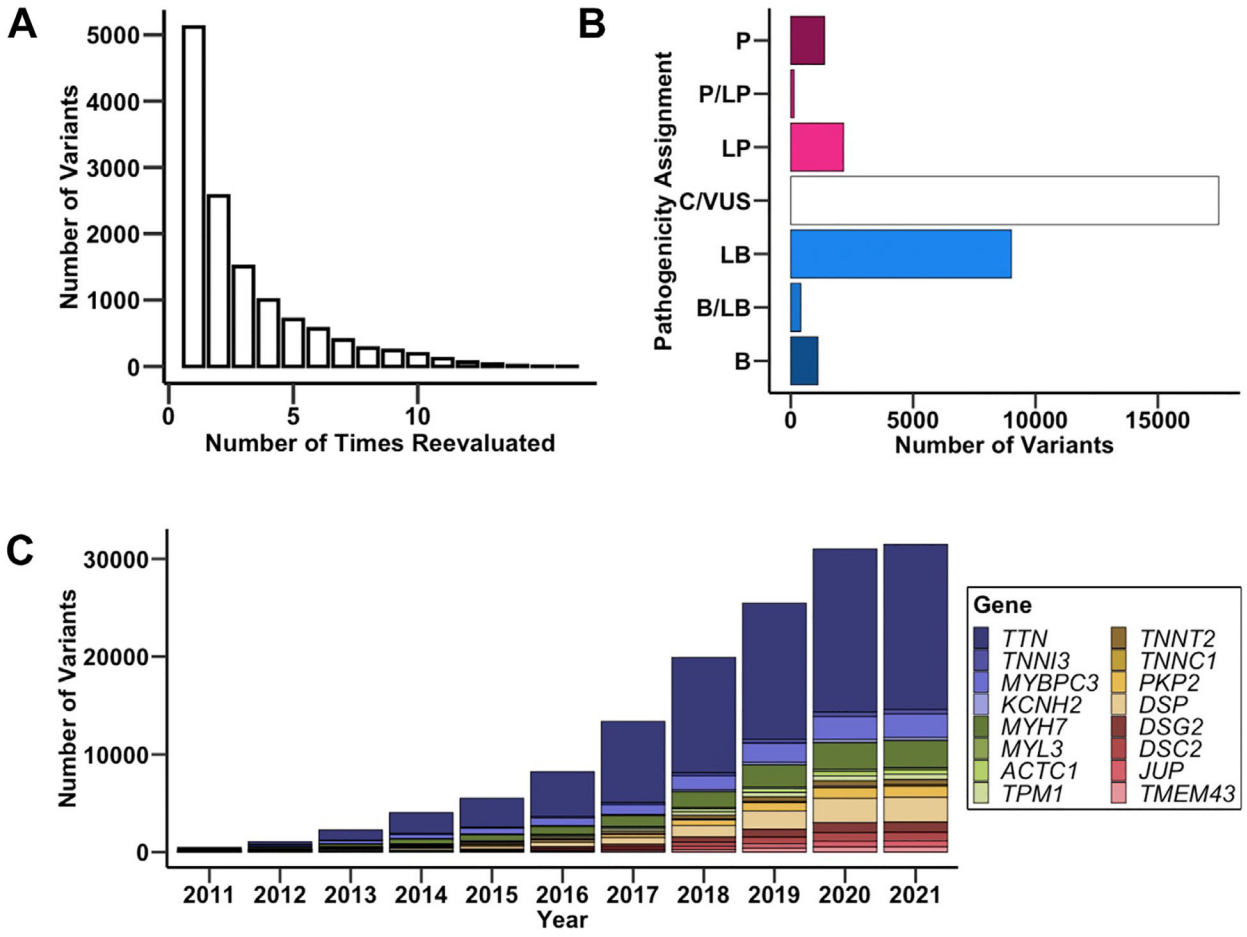


FIGURE 1.

Descriptive Analyses for Cardiomyopathy-Associated Gene Variants in ClinVar Including Bar Plots Depicting

(A) The distribution in the number of times variants are evaluated. (B) The initial pathogenicity assignment upon entry into ClinVar. (C) The total number of variants by gene over the study period from 2011 to 2021.

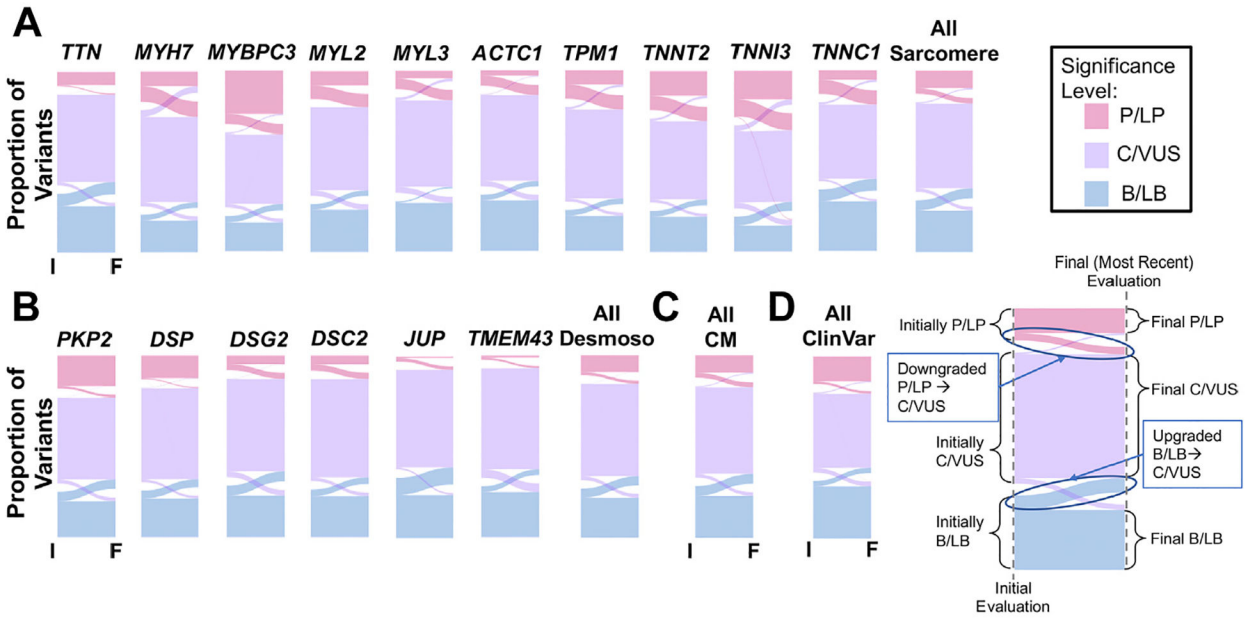


FIGURE 2.

Alluvial Plots Showing Changes in Variant Pathogenicity Assignment From Initial Evaluation in ClinVar to its Most Recent, or Final, Evaluation

These alluvial plots are divided by gene. (A) Sarcomeric gene alluvial plots. (B) Desmosomal gene alluvial plots. (C) Summative alluvial plot for all cardiomyopathy-associated gene variants. (D) Summative alluvial plot for all ClinVar variants. F = final; I = initial.

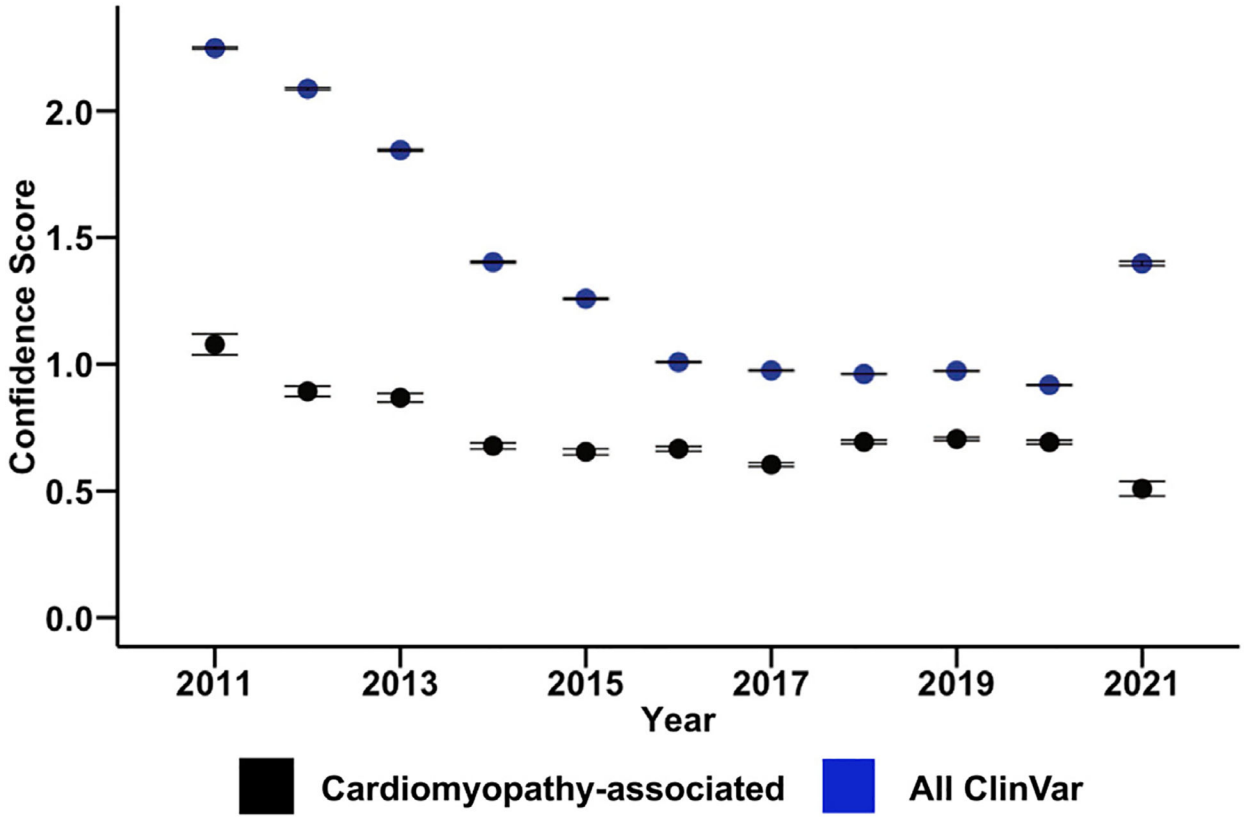


FIGURE 3.

Continued Decline in Diagnostic Certainty Score Among Cardiomyopathy-Associated Gene Variants

Plot representing the change in overall diagnostic confidence over time in cardiomyopathy-associated gene variants (black) and all ClinVar (blue) over the study period 2011 to 2021. Each point represents the mean confidence score for all evaluations in a given year (±1 standard error).

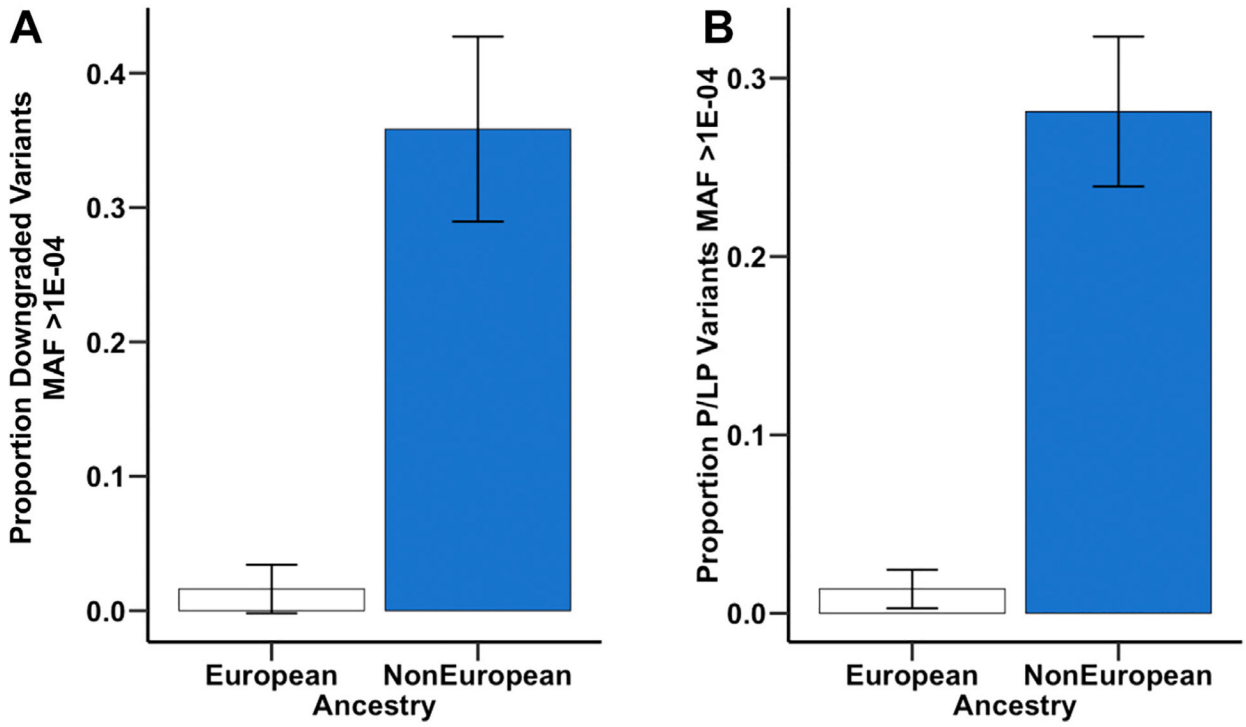
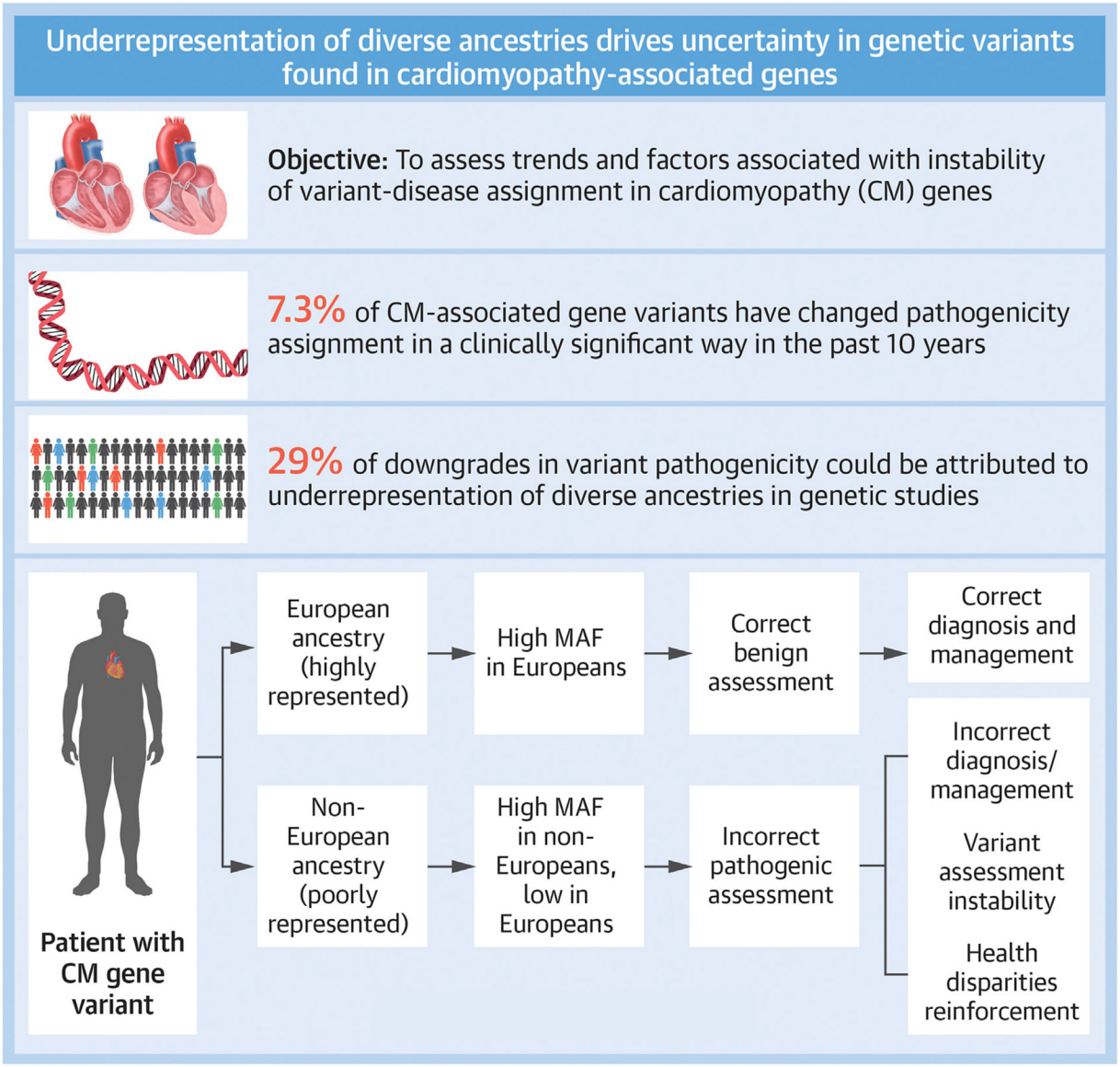


FIGURE 4.

Greater Uncertainty in Variant Pathogenicity Assignment Amongst Variants With High MAF in Non-Europeans

Bar graphs depicting the proportion of variants in cardiomyopathy-associated genes with a minor allele frequency (MAF) $>1 \times 10^{-4}$ in people of European ancestry (white) and non-European ancestry (blue) in A. The set of variants that were downgraded from pathogenic or likely pathogenic (P/LP) to conflicting interpretations of pathogenicity or variant of unknown significance (C/VUS). (B) The set of variants that were initially assessed as P/LP in ClinVar.

CENTRAL ILLUSTRATION



CENTRAL ILLUSTRATION.
CM = cardiomyopathy; MAF = minor allele frequency. Illustration created using BioRender.

TABLE 1

Summary of ClinVar Variants in Cardiomyopathy Genes and Comparison Gene Sets

Genes	Total Variants	Re-Evaluated Variants	Average Number of Evaluations per Variant	Variants That Changed Clinical Significance	Variants With a Clinically Meaningful Change[a]
TTN	16,587	7,080	2.22	2,887	1,169 (7.0%)
MYH7	2,725	1,451	2.69	626	327 (12.0%)
MYBPC3	2,347	1,256	2.96	494	204 (8.7%)
MYL2	305	147	2.43	56	29 (9.5%)
MYL3	225	101	2.49	39	15 (6.7%)
ACTC1	453	178	1.74	56	25 (5.5%)
TPM1	520	193	2.01	70	43 (8.3%)
TNNT2	534	245	2.64	113	49 (9.2%)
TNNI3	434	195	2.39	89	50 (11.5%)
TNNC1	158	73	2.20	28	15 (9.5%)
Total (sarcomere)	**24,288**	**10,919**	**2.35**	**4,458**	**1,926 (7.9%)**
PKP2	1,113	562	2.54	179	64 (5.8%)
DSP	2,531	1,119	2.26	284	96 (3.8%)
DSG2	1,024	450	2.30	149	67 (6.5%)
DSC2	891	391	2.22	120	48 (5.4%)
JUP	589	312	2.44	94	47 (8.0%)
TMEM43	539	228	2.29	69	28 (5.2%)
Total (desmosome)	**6,687**	**3,062**	**2.33**	**895**	**350 (5.2%)**
Total (cardiomyopathy)	**30,975**	**13,981**	**2.34**	**5,353**	**2,276 (7.3%)**
Autosomal recessive	**3,287**	**1,516**	**2.25**	**693**	**234 (7.1%)**
Autosomal dominant	**41,694**	**20,070**	**2.46**	**5,697**	**2,643 (6.3%)**
All of ClinVar	**1,016,826**	**438,105**	**2.03**	**150,533**	**44,720 (4.4%)**

[a]Defined as a change in pathogenicity assignment of a given variant between 2 of the following 3 categories: pathogenic/likely pathogenic, conflicting interpretations of pathogenicity or variant of unknown significance, and benign/likely benign. **Bold** indicates a total that is derived from summation of values from multiple genes.