

## Introduction

Pediatric cardiomyopathy (CM) is a heterogeneous disease that may be idiopathic or familial, occur as a result of the same pathogenic variants that cause adult CM, or be the primary presenting feature of an underlying syndromic, neuromuscular, or metabolic condition [1]. Although studies have evaluated the proportions of CM attributed to inherited cardiac conditions, the study population characteristics and outcomes have varied widely. The purpose of this study was to evaluate the outcomes of genetic testing for a diverse population of pediatric CM patients and indications.

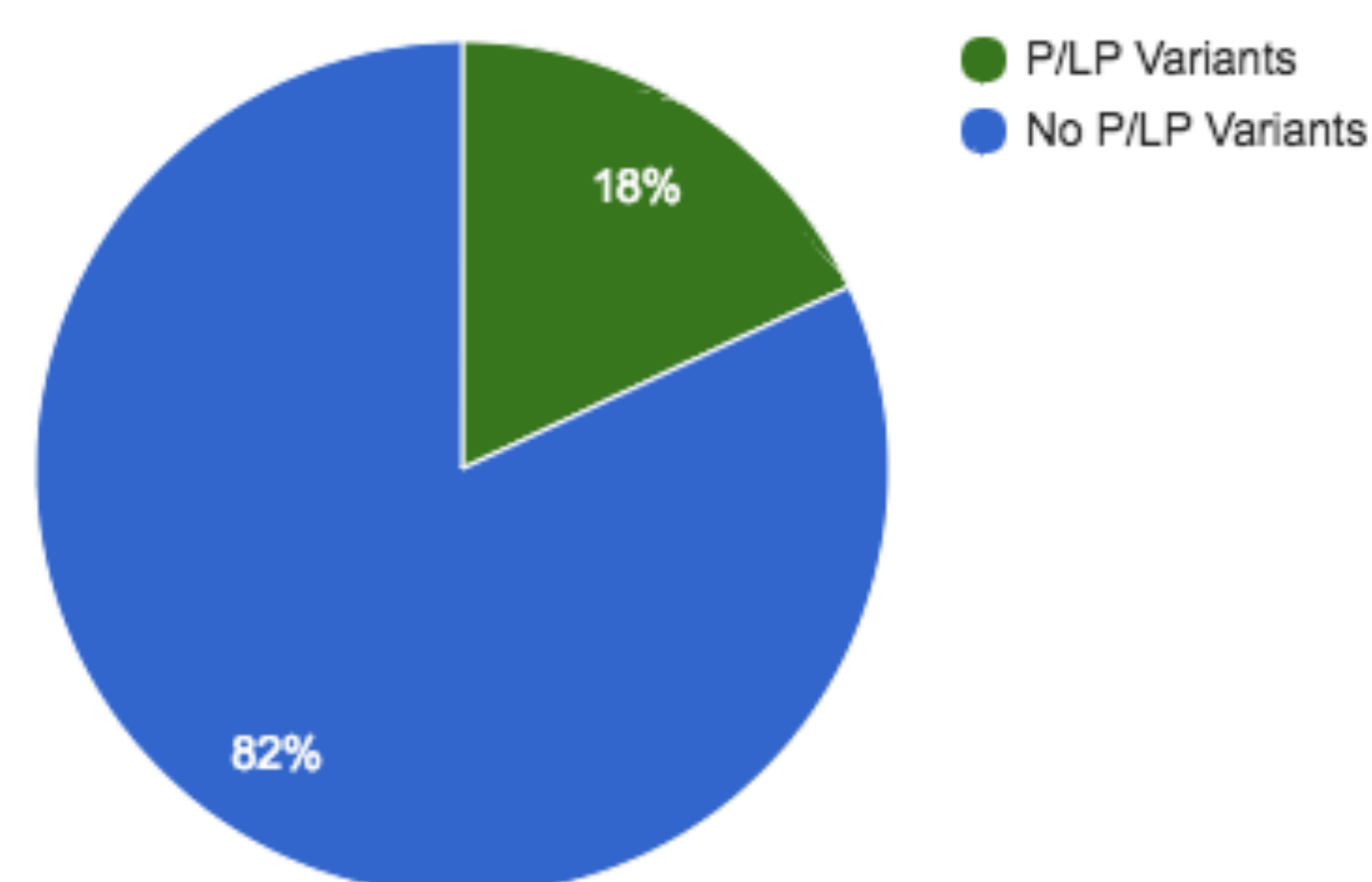
## Methods

This study analyzed the results of 179 sequential orders for CM panels in a pediatric population of patients aged 18 years or younger.

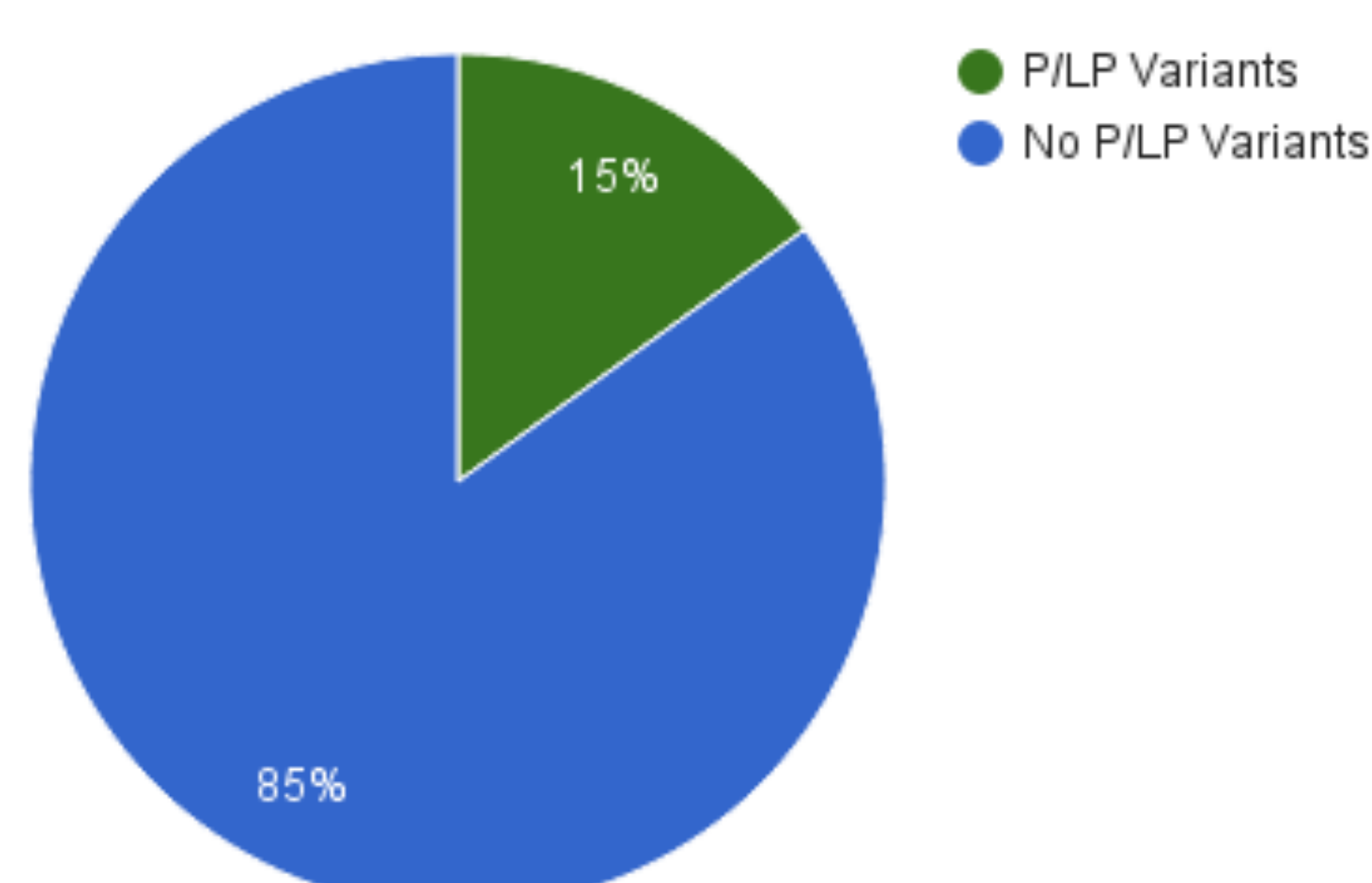
## Results

Among the 179 patients, 33 (18%) harbored a pathogenic or likely pathogenic (P/LP) variant thought to explain the phenotype, including single heterozygous variants in MYH7 (8), MYBPC3 (3), PKP2 (2), SCN5A (2), TNNT2 (2), TTN (2), CACNA1C (1), CALM3 (1), DMD (1), DSP (1), KCNH2 (1), LAMP2 (1), PTPN11 (1), RAF1 (1), RBM20 (1), and TPM1 (1) and a hemizygous variant in TAZ (1). Two patients harbored multiple P/LP variants, one with two variants in TTN (phase unknown) and one with variants in BAG3 and LMNA. One patient harbored a homozygous PLN deletion identified as part of a larger, complex event. Of note, five of these variants (MYH7, PTPN11, RAF1, TAZ, TTN) were found among the 34 patients in the study population aged 1 year or younger.

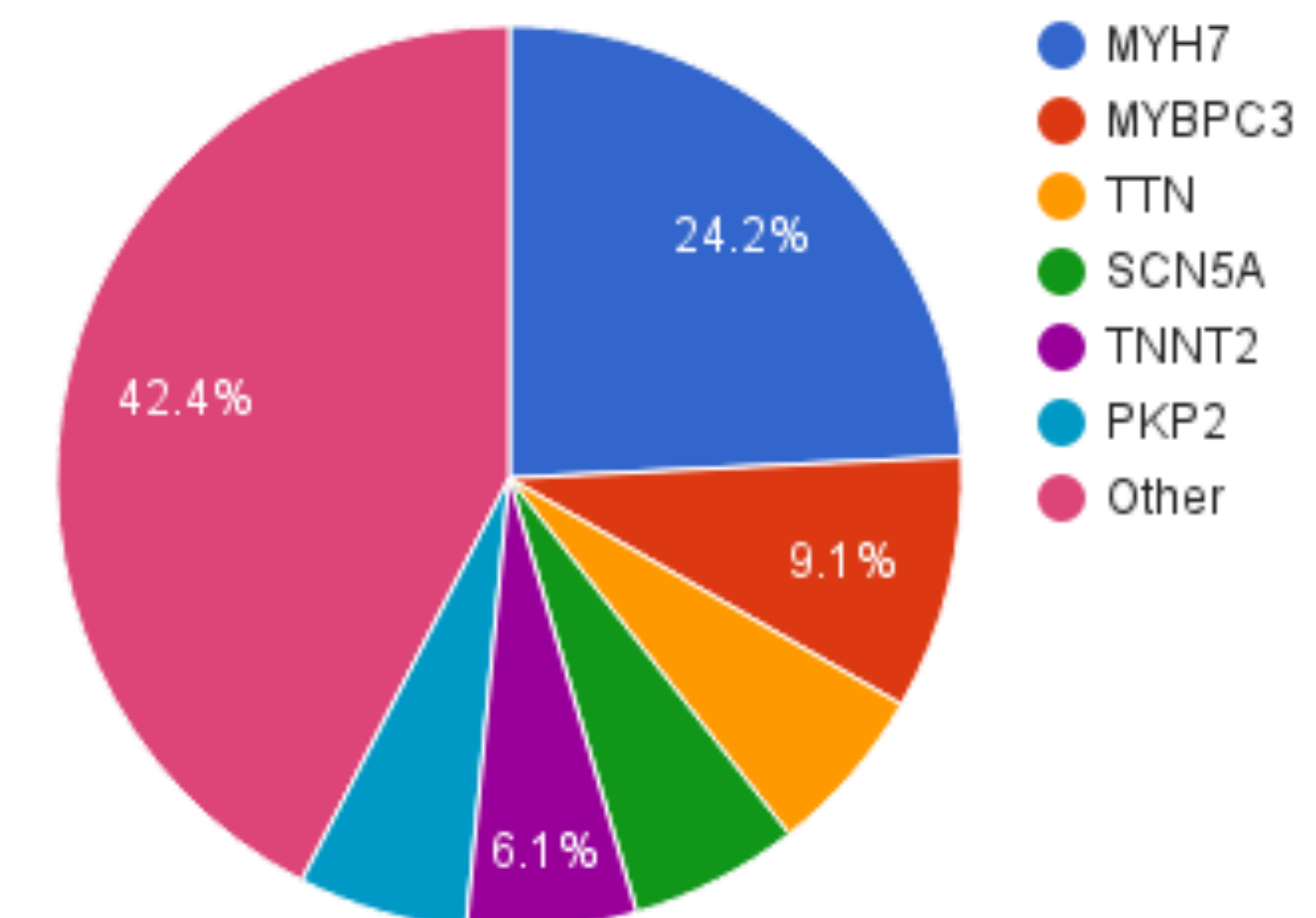
**Yield of genetic testing in overall study population**



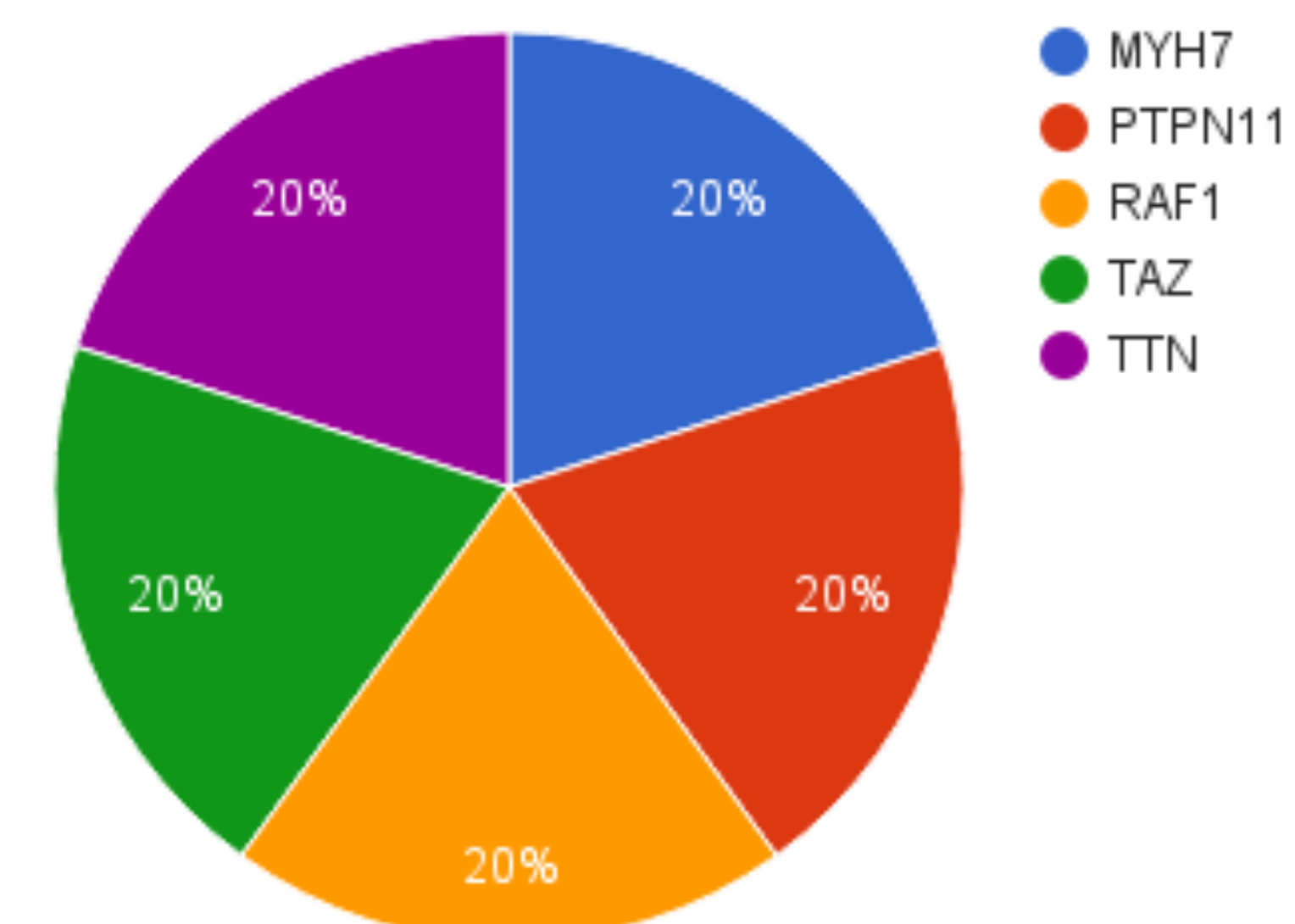
**Yield of genetic testing in patients aged 1 year or younger**



**Distribution of pathogenic or likely pathogenic variants within the study population**



**Distribution of pathogenic or likely pathogenic variants in patients aged 1 year or younger**



## Conclusion

Syndromic and neuromuscular etiologies were key causes of infantile-onset CM in this study population. Beyond infancy, pediatric patients harbored a number of P/LP variants in genes that are also associated with adult-onset CM. The overall yield of genetic testing for this study was lower than that of previous studies of dilated cardiomyopathy or hypertrophic cardiomyopathy (HCM) populations [2,3]. Factors such as the inclusion of diverse or non-specific indications, or both, within the study population likely played a role in this difference.

Interestingly, although previous studies have identified multiple mutations in up to 5% of patients with HCM [4], no instances of multiple P/LP variants were identified in any of the 47 individuals in the present study for whom at least an HCM panel was ordered. However, the sample size may be too small to accurately assess the frequency of multiple mutation carriers, or the clinical phenotypes represented in this study may differ significantly from those of previously reported populations. Previous reports may also have overestimated the frequency of multiple mutations according to classification systems used before the implementation of the 2015 ACMG/AMP guidelines [5]. Additional studies are needed to clarify this frequency.

Overall, the genetic analysis of pediatric CM patients aids in determining treatment and prognosis and provides insight into the significant clinical variability among CM patients.

## References

- Ware, SM. *Cardiol Young*. 2015; 25 (Suppl 2):43-50.
- Affares, AA, et al. *Genet Med*. 2015; 17(11):880-8.
- Fugh, T.J, et al. *Genet Med*. 2014; 16(8):601-9.
- Ingles, J, et al. *J Med Genet*. 2005; 42(10): e59.
- Richards, S, et al. *Genet Med*. 2015; 17(5):405-24.