

FIRST IMPRESSION OF BLENDED PHENOTYPES IN BRAZILIAN PATIENTS UNDER MOLECULAR INVESTIGATION OF PRIMARY CARDIOVASCULAR CONDITIONS

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INTRODUCTION

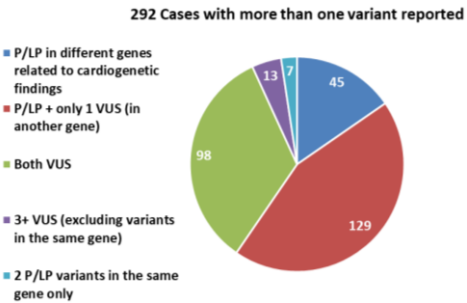
The recent use in clinical practice of broad-range next-generation sequencing (NGS) tests, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), has revealed not only various rare conditions, but also the existence of individuals expressing the so-called “blended phenotypes” due to the presence of variants of clinical significance (VCS) in more than one single gene. Focusing in the cardiovascular aspect, here we analyzed the prevalence and nuances of blended phenotypes in a large cohort of individuals submitted to comprehensive genetic testing.

OBJECTIVES

To investigate the prevalence and clinical impact of blended phenotypes in patients with cardiovascular disease enrolled in the MAPA Genoma Brasil study.

METHODS

From January 2021 to November 2024, 3541 individuals with clinical suspicion of genetic cardiovascular conditions, including cardiomyopathies, arrhythmias, dyslipidemias, aortopathies and congenital heart diseases, underwent WES or WGS. Prior negative testing for Chagas disease was mandatory for all patients. Variant interpretation followed ACMG guidelines and was conducted by clinical geneticists, with all results subsequently reviewed by fellow cardiologists. Genetic counseling was provided both before and after testing, and family screening was offered when appropriate.



RESULTS

A retrospective analysis of 3541 results identified 292 cases with more than one VCS. Most (129) involved patients carrying at least 1 variant of uncertain significance (VUS); in 98 both VCS were VUS and in another 13 patients three or more VUS were reported, yet all had only one or none confirmed molecular diagnosis to date. Seven patients each carrying two pathogenic or likely pathogenic (P/LP) variants in the same gene, consistent with a potential biallelic disease (compound heterozygosity) were excluded from further analysis. Among the remaining cases, 15% (45/292) harbored multiple P/LP in different genes related to cardiogenetic findings, most commonly hypertrophic cardiomyopathy. Finally, at least 3% (9/292) exhibited blended phenotypes with extracardiac findings such as developmental delay, muscle weakness and facial dysmorphism.

Primary cardiac condition	Variants detected	Secondary condition
Hypertrophic cardiomyopathy	LP variant in <i>TPM1</i> + P/LP compound heterozygous variants in <i>PYGM</i>	Increased creatine kinase (CPK) and exercise intolerance (McArdle disease)
Hypertrophic cardiomyopathy	P variant in <i>MYH7</i> + P/LP compound heterozygous variants in <i>PYGM</i>	Increased creatine kinase (CPK) and exercise intolerance (McArdle disease)
Congenital heart defect / Hypertrophic cardiomyopathy	Deletion in 16p11.2 (641kb) + Homozygous P variant in <i>ALDH3A2</i>	Ichthyosis, impaired intellectual development and spasticity (Sjogren-Larsson syndrome)
Congenital heart defect (Noonan syndrome)	P variant in <i>RAF1</i> + LP variant in <i>DSG2</i>	Arrhythmogenic cardiomyopathy
Hypertrophic cardiomyopathy	P variant in <i>MYBPC3</i> + Deletion in 7q11.23 (1,7Mb)	Mild developmental delay and typical facial dysmorphism (Williams-Beuren syndrome)
Hypertrophic cardiomyopathy	LP variant in <i>NAA15</i> + LP variant in <i>SALL1</i>	Autism, developmental delay and facial dysmorphism
Congenital heart defect	LP variant in <i>TBX20</i> + P variant in <i>DDX3X</i>	Mild developmental delay and facial dysmorphism
Hypertrophic cardiomyopathy	P variant in <i>MYBPC3</i> + Deletion in 4q13.3 (75kb)	Keratoconus (proximal renal tubular acidosis-ocular anomaly syndrome)
Amyloidosis	Homozygous P variant in <i>TTR</i> + Deletion in 1q21 (1,6Mb)	Myrocephaly, developmental delay and facial dysmorphism

CONCLUSIONS

The co-occurrence of rare genetic disorders is estimated around 2%–7.5% in different studies both in Brazil and around the world. In several of our cases, one diagnosis was known before investigation but the second would likely have remained undetected without broad-range genetic testing. Although not the primary aim of our study, we identified a meaningful subset of probands carrying multiple genetic diagnoses and presenting blended phenotypes. These findings underscore that comprehensive genetic testing not only reveals and the full complexity of such cases, helping clinicians recognize and manage them, but also enables a more accurate and personalized approach to patient care.

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