KEEPING THE RHYTHM: GENETIC DETERMINANTS OF ARRHYTHMIAS IN A NATIONAL COHORT STUDY FROM BRAZIL

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INTRODUCTION

Inherited arrhythmias are characterized by incomplete penetrance and variable expressivity. Advances in next-generation sequencing (NGS) have enhanced our ability to study these conditions in populations, enabling more accurate diagnoses, personalized therapies, and informed family screening.

OBJECTIVES

To characterize the genetic landscape of inherited arrhythmias in a Brazilian cohort through the MAPA Genoma Brasil initiative.

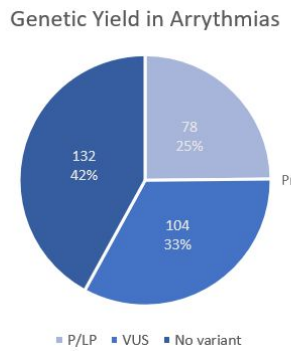
METHODS

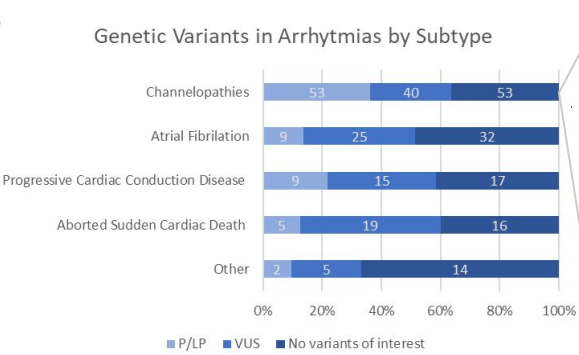
As part of a national multicenter effort, individuals with confirmed primary arrhythmias, channelopathies, isolated atrial fibrillation (AF), progressive cardiac conduction disease (PCCD), and aborted sudden cardiac death (ASCD), underwent whole exome sequencing (WES). Participants were recruited from cardiology centers across Brazil, mainly from the Heart Institute (InCor), University of São Paulo. Variant interpretation followed ACMG guidelines and was performed by clinical geneticists. Genetic counseling was provided pre- and post-testing. When indicated, family members were evaluated clinically and underwent Sanger sequencing.

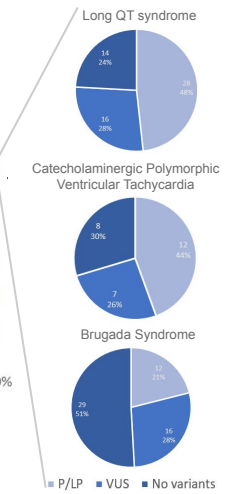
RESULTS AND DISCUSSION

Among 314 individuals analyzed, 78 (25%) had pathogenic or likely pathogenic (P/LP) variants, 104 (33%) had variants of uncertain significance (VUS), and 132 (42%) had no significant findings. Among 146 individuals with channelopathies, P/LP variants were found in 53 (36%) and VUS in 40 (27%), with yield varying by subtype: Long QT syndrome (48%), Brugada syndrome (22%), and catecholaminergic polymorphic ventricular tachycardia (44%). In AF (n=66), P/LP variants were found in 13.6% and VUS in 38%; in PCCD (n=41), 22% and 36.5%, respectively; and in ASCD (n=40), 12.5% and 47.5%.

Twenty-eight individuals carried more than one variant of interest, including two with dual P/LP variants (e.g., *TTN/TTR* and *KCNH2/ALPK3*), suggesting blended phenotypes. Four individuals had homozygous P/LP variants in genes typically linked to dominant inheritance, indicating possible modifier effects. The most frequent P/LP variants were in *SCN5A* (n=17), *KCNH2* (n=15), *KCNQ1* (n=5), and *CASQ2* (n=5). Notably, 25 individuals carried P/LP variants in cardiomyopathy-associated genes (e.g., *LMNA, FLNC, TTN, PRKAG2, DES*), highlighting the overlap between electrical and structural heart disease. Family screening was performed in 45 of 78 families (n=172 relatives), with 88 (51%) testing positive for the familial variant. Segregation analysis is ongoing to support VUS reclassification.







CONCLUSIONS

This study provides the first large-scale genomic profile of inherited arrhythmias in Brazil. The diagnostic yield is consistent with international cohorts and demonstrates the value of genomic testing. Findings emphasize the overlap between arrhythmia- and cardiomyopathy-associated genes and the importance of early detection as arrhythmias may precede structural heart disease. Family-based screening and genetic counseling are essential components of care, underscoring the clinical utility of precision medicine for inherited arrhythmias.

REFERENCES

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