DECODING THE HEART: GENETIC INSIGHTS INTO CONGENITAL HEART DISEASE THROUGH WHOLE GENOME SEQUENCING

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INTRODUCTION

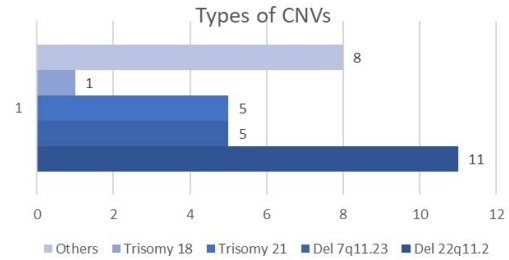
Congenital Heart Disease (CHD), affecting approximately 1% of live births worldwide, accounts for 40% of all congenital anomalies and contributes to 6% of infant mortality. Differentiation between syndromic and isolated (non-syndromic) CHD relies on clinical assessment, imaging, family history, and evaluation of extracardiac anomalies. Whole Genome Sequencing (WGS) has emerged as a transformative tool in precision medicine, offering improved diagnostic accuracy, personalized care, and informed family screening.

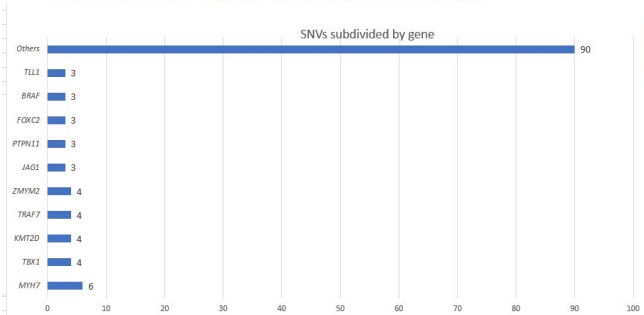
OBJECTIVES

To characterize the genetic architecture of CHD in a Brazilian cohort using WGS, as part of the multicenter MAPA Genoma Brasil initiative.

METHODS

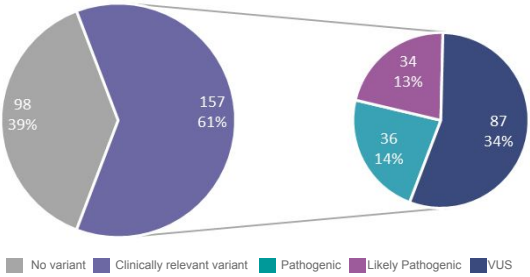
We analyzed 255 individuals with confirmed CHD through clinical and imaging evaluations. All underwent WGS to detect rare variants associated with CHD. Variant classification followed ACMG guidelines and was performed by clinical geneticists. Genetic counseling was provided pre- and post-test, and cascade testing via Sanger sequencing was offered when relevant.



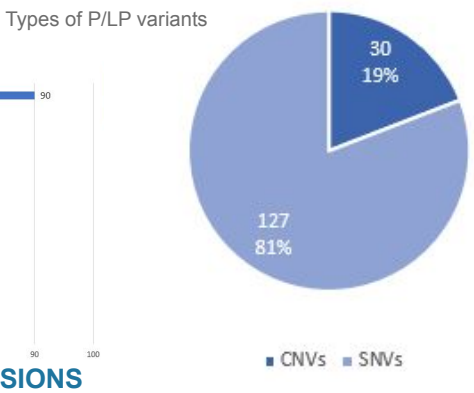


RESULTS AND DISCUSSION

Clinically relevant variants (pathogenic or likely pathogenic) were identified in 70 individuals, resulting in a diagnostic yield of 27%. Additionally, variants of uncertain significance (VUS) were found in 87 cases (34%), while 98 patients (39%) had no detectable relevant variants.



Among the 157 patients harboring potentially contributory variants: 30 individuals (19%) carried copy number variants (CNVs), including deletions at 22q11.2 (n=11) and at 7q11.23 (n=5), and full aneuploidies such as trisomy 21 (n=5) and trisomy 18 (n=1). The remaining 127 individuals (81%) had single nucleotide variants (SNVs), with recurrently affected genes including *MYH7* (4%), *TBX1* (3%), *KMT2D* (3%), *TRAF7* (3%), and *ZMYM2* (3%). WGS demonstrated a diagnostic yield of 27%, consistent with international studies from the US and Europe, reinforcing its value in CHD evaluation. The detection of both SNVs and CNVs highlights the versatility of WGS as a first-tier diagnostic tool.



CONCLUSIONS

The significant representation of syndromic cases underscores the need for integrated genetic assessment and counseling in CHD care. These findings support the implementation of genome-wide strategies to enhance diagnosis, guide treatment, and inform family planning in the context of CHD.

REFERENCES

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