Laboratório de Citogenômica

Cytogenomic alterations in postmortem patients with congenital heart defects: Insights into syndromic etiologies

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INTRODUCTION AND OBJECTIVES

Congenital heart defects (CHDs) are the most common birth anomalies and a leading cause of neonatal morbidity and mortality. Advances in cytogenomic testing have significantly improved our ability to uncover the genetic basis of CHDs, including in challenging postmortem investigations, where clinical and phenotypic data may be limited or incomplete. This study aimed to investigate pathogenic genomic alterations, such as copy number variations (CNVs) and other chromosomal anomalies, in postmortem samples from stillbirths and neonates with CHDs, and to evaluate their contribution to disease etiology. The study also aimed to identify other congenital anomalies frequently associated with CHDs.

METHODS

This study analyzed 42 cases referred to the Death Verification Service of the Faculty of Medicine, University of São Paulo (FMUSP). DNA was extracted from heart tissue, and the samples was assessed using the AmpFlSTR® MiniFiler™ PCR Amplification Kit (Life Technologies™, CA, USA) and Multiplex Ligation-dependent Probe Amplification (MLPA - MRC-Holland, Amsterdam, NL) with various probe sets. Fluorescence in situ hybridization (FISH) was performed to validate selected findings.

RESULTS

Pathogenic or likely pathogenic genomic alterations were identified in 15 of the 42 cases. These included trisomies of chromosomes 13, 18, and 21, monosomy X, and a duplication at 22q11 involving the *ZNF74* gene. CHDs frequently co-occurred with additional congenital anomalies, particularly severe malformations linked to chromosomal syndromes (13 cases), as well as musculoskeletal and limb anomalies. Septal defects (atrial and ventricular) were notably associated with the detected genomic alterations.

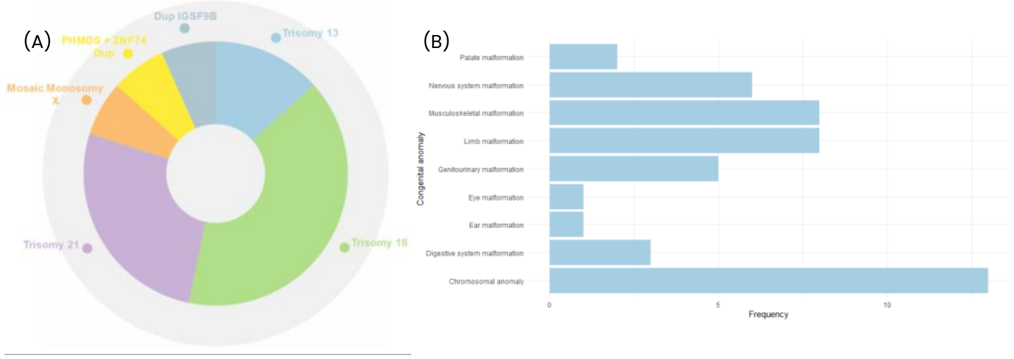

Figure 1 – (A) Proportion of genomics events. **(B)** Proportion of additional congenital anomaly.

DISCUSSION AND CONCLUSION

Duplications of the 22q11 region including *ZNF74* have been described in patients with CHDs, supporting a possible role of *ZNF74* dosage imbalance in cardiac morphogenesis. Aneuploidies such as T21, T18, T13, and monosomy X are also well-established genetic causes of CHDs, each with characteristic cardiac phenotypes. Together, these alterations illustrate how both single-gene copy number variants and chromosomal abnormalities contribute to cardiac malformations, supporting the use of integrated cytogenomic approaches and molecular testing in postmortem protocols to improve diagnosis, counseling, and reproductive planning.

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