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Investigação citogenômica em pacientes com
cardiopatias congênitas

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**BOTUCATU – SP
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UNIVERSIDADE ESTADUAL PAULISTA
“Júlio de Mesquita Filho”

INSTITUTO DE BIOCÊNCIAS DE BOTUCATU

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Palavras-chave: Anomalias congênitas; Coração; Desequilíbrios citogenômicos; Etiologia genética; Malformações cardíacas congênitas.

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*“Talvez não tenha conseguido fazer o melhor, mas lutei para que o melhor fosse
feito [...]”*

- Martin Luther King Jr.

*“Não sou quem eu gostaria de ser.
Não sou quem eu deveria ser.
Ainda não sou quem poderia ser.
Mas, graças a Deus, não sou mais quem eu era.”*

- Martin Luther King Jr.

RESUMO

GOMES, TG. **Investigação citogenômica em pacientes com cardiopatias congênitas.** 2018, 129 p. Dissertação de mestrado – Instituto de Biociências de Botucatu, Universidade Estadual Paulista “Júlio de Mesquita Filho”.

As cardiopatias congênitas (CCs) podem ser definidas como qualquer anormalidade na estrutura e/ou na função cardiocirculatória presente ao nascimento. Constituem as malformações congênitas mais comuns entre recém-nascidos vivos, podendo se apresentar de duas formas: isoladas (ou não sindrômicas) e sindrômicas. De caráter multifatorial, o surgimento de CCs envolve fatores ambientais, genéticos e epigenéticos. A etiologia genética de CCs ainda é pouco conhecida. Entre as causas genéticas conhecidas, podemos destacar: aneuploidias, alterações na estrutura dos cromossomos, desequilíbrios citogenômicos (perdas e ganhos genômicos ou variações no número de cópias genômicas – CNVs), mutações pontuais, variações em um único nucleotídeo, entre outras. Dentre essas, as CNVs contribuem com aproximadamente 10% na etiologia genética de CCs não sindrômicas, e cerca de 20% entre as sindrômicas. O objetivo deste trabalho foi investigar possíveis desequilíbrios citogenômicos em pacientes diagnosticados com CCs sindrômicas e não sindrômicas idiopáticas. Foram recrutados 31 pacientes, sendo 13 sindrômicos e 18 não sindrômicos. Todos foram submetidos à avaliação genético-clínica. As amostras foram coletadas a partir do sangue periférico, e realizou-se o cariótipo convencional para todos os sindrômicos. A análise por MLPA foi realizada em 27 pacientes. O DNA genômico dos pacientes sindrômicos selecionados foi submetido a duas plataformas de CMA (*array-CGH/SNP arrays*): *SNP-array 850K HumanCytoSNP* (Illumina®) e *SurePrint G3 Human CGH Microarray Kit, 4x180K* (Agilent Technologies®). Os resultados foram analisados através de bancos de dados *online*. A análise pela MLPA na região cromossômica 22q11.2 não evidenciou alterações, exceto para uma paciente não sindrômica que apresentou duplicação envolvendo o gene *TOP3B*, uma alteração sem relevância clínica até o momento. Dos 6 pacientes analisados pela CMA, 4 foram normais e 2 apresentaram alterações (pacientes 8325 e 8362). O paciente 8325 apresentou uma deleção de 159,11 kb em 1p36.11 envolvendo 4 genes, e uma ausência de heterozigossidade (AOH) em 2p13.2p12, abrangendo 45 genes e indicando uma dissomia uniparental. A deleção encontrada é benigna, enquanto a AOH possui genes que, quando em presença de mutações recessivas, podem ser causais. Já o paciente 8362 apresentou trissomia parcial de 15q25.2q26.3 (tamanho de 18,4 Mb e envolvendo 124 genes) e simultânea monossomia parcial de 18p11.32p11.22 (tamanho de 8,7 Mb, contendo 40 genes). Na região de 15q25.2q26.3 foram identificados 12 genes possivelmente candidatos à CC encontrada no paciente, entre eles *ADAMTSL3*, *MCTP2*, *MESF2A*, *MESP1*, *MESP2* e *NTRK3*. Outros 6 genes nessa região podem estar associados às alterações neurológicas encontradas no paciente. Em relação à perda genômica em 18p11.32p11.22, apenas um gene (*TYMS*) parece estar relacionado à CC, enquanto outros 10 genes apresentam relação com algumas alterações extracardíacas. Os resultados evidenciam a contribuição de fatores genéticos na gênese das anomalias congênitas observadas. Entretanto, não explicam todas as alterações de forma holística, havendo a necessidade de mais investigações para a definição de uma correlação genótipo-fenótipo mais robusta e mais sinérgica.

Palavras-chave: desequilíbrios citogenômicos; malformações cardíacas congênitas; etiologia genética; coração; anomalias congênitas; alterações cromossômicas.

ABSTRACT

GOMES, TG. **Cytogenomic investigation in patients with congenital heart defects.** 2018, 129p. Master's degree in Science – Instituto de Biociências de Botucatu, Universidade Estadual Paulista “Júlio de Mesquita Filho”.

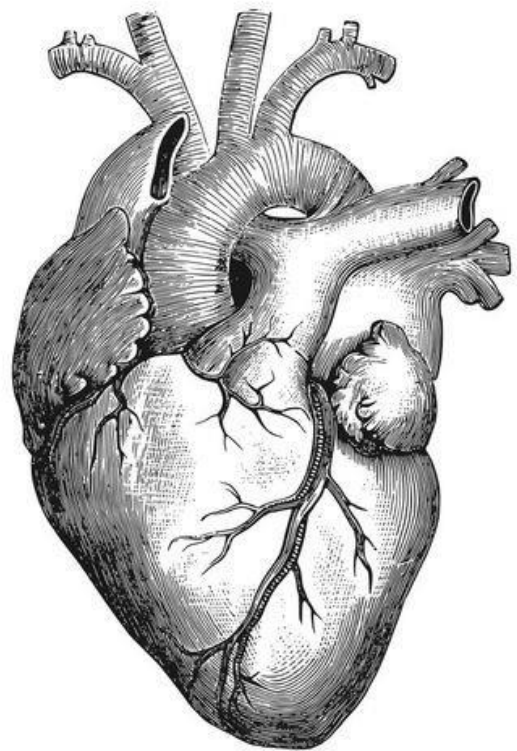
Congenital heart defects (CHD) can be defined as any abnormality in the structure and /or cardiocirculatory function present at birth. Congenital malformations are more common among live newborns. CHD can be presented at two forms: isolated (or non syndromic) and syndromic ones. Of multifactorial spectrum, the emergence of CHD involves environmental, genetic and epigenetic factors. The genetic etiology of CHD is still poorly understood. Among the known genetic causes, we can highlight: aneuploidies, changes in chromosome structure, cytogenetic imbalances (losses and genomic gains, can be also called copy number variations - CNVs), point mutations, variants in a single nucleotide, among others. Among these, CNVs contribute to approximately 10% in the genetic etiology of non-syndromic CHD, and about 20% among syndromic ones. The aim of this study was to investigate possible cytogenetic imbalances in patients diagnosed with idiopathic syndromic and non-syndromic CHD. Thirty one patients were recruited, of which 13 syndromic and 18 non-syndromic. Each patient were submitted to genetic-clinical evaluation. Only patients with an undefined syndromic condition were included in cytogenetic investigations. Samples were collected from the peripheral blood, and the conventional karyotype was performed for all syndromic patients. MLPA analysis was performed in 27 patients. The genomic DNA of the selected patients was analyzed into two CMA (array-CGH / SNP arrays) platforms: SNP-array 850K HumanCytoSNP (Illumina®) and SurePrint G3 Human CGH Microarray Kit, 4x180K (Agilent Technologies®). All results were analyzed through online databases. The MLPA analysis in the 22q11.2 chromosomal region did not show alterations, except for a non-syndromic patient who presented a duplication involving the *TOP3B* gene, an alteration with no known clinical relevance. Of the 6 patients analyzed by CMA, 4 were normal and 2 presented alterations (patients 8325 and 8362). Patient 8325 had a deletion of 159.11 kb in 1p3611 involving 4 genes, and an absence of heterozygosity (AOH) in 2p13.2p12, spanning 45 genes and indicating an uniparental disomy (UPD). The deletion found is benign, whereas AOH has genes that, if they are carriers of recessive mutations, may be causal. Patient 8362 presented partial trisomy of 15q25.2q26.3 (size of 18.4 Mb and involving 124 genes) and simultaneous partial monosomy of 18p11.32p11.22 (size of 8.7 Mb, containing 40 genes). In the region of 15q25.2q26.3 we identified 12 possibly candidate CHD genes in the patient, among them we can highlight: *ADAMTSL3*, *MCTP2*, *MESF2A*, *MESPI1*, *MESP2* and *NTRK3*. Another 6 genes in this region may be associated with the neurological changes found in the patient. Regarding genomic loss in 18p11.32p11.22, only one gene (*TYMS*) appears to be related to CHD, while another 10 genes are related to some extracardiac features. Results evidenced the contribution of genetic factors (in this case, cytogenetic imbalances) in the genesis of the observed congenital anomalies. However, they do not fully explain all the clinical phenotype. It is necessary to perform further investigations to define a more robust and synergistic genotype-phenotype correlation.

Keywords: cytogenomic imbalances; congenital cardiac malformations; genetic etiology; heart; congenital anomalies; chromosomal alterations.

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