J Pediatr (Rio J). 2017;xxx(xx):xxx–xxx

Jornal de Pediatria
www.jped.com.br

ORIGINAL ARTICLE

Genomic imbalances in syndromic congenital heart disease☆,☆☆

Miriam C. Molck[a], Milena Simioni[a], Társis P. Vieira[a], Ilária C. Sgardioli[a], Fabíola P. Monteiro[a], Josiane Souza[b], Agnes C. Fett-Conte[c], Têmis M. Félix[d], Isabella L. Monlléo[e], Vera Lúcia Gil-da-Silva-Lopes[a,*]

[a] *Universidade Estadual de Campinas (UNICAMP), Departamento de Genética Médica, Campinas, SP, Brazil*
[b] *Centro de Atendimento Integral ao Fissurado Lábio Palatal (CAIF), Curitiba, PR, Brazil*
[c] *Faculdade de Medicina de São José do Rio Preto, Departamento de Biologia Molecular, São José do Rio Preto, SP, Brazil*
[d] *Hospital de Clínicas de Porto Alegre, Serviço de Genética Médica, Porto Alegre, RS, Brazil*
[e] *Universidade Federal de Alagoas (UFAL), Hospital Universitário, Serviço de Genética Clínica, Maceió, AL, Brazil*

Received 26 July 2016; accepted 24 November 2016

KEYWORDS
DNA copy number variations;
Congenital heart defects;
22q11 deletion syndrome;
Comparative genomic hybridization;
Chromosome aberrations

Abstract
Objective: To identify pathogenic genomic imbalances in patients presenting congenital heart disease (CHD) with extra cardiac anomalies and exclusion of 22q11.2 deletion syndrome (22q11.2 DS).
Methods: 78 patients negative for the 22q11.2 deletion, previously screened by fluorescence in situ hybridization (FISH) and/or multiplex ligation probe amplification (MLPA) were tested by chromosomal microarray analysis (CMA).
Results: Clinically significant copy number variations (CNVs ≥300 kb) were identified in 10% (8/78) of cases. In addition, potentially relevant CNVs were detected in two cases (993 kb duplication in 15q21.1 and 706 kb duplication in 2p22.3). Genes inside the CNV regions found in this study, such as IRX4, BMPR1A, SORBS2, ID2, ROCK2, E2F6, GATA4, SOX7, SEMAD6D, FBN1, and LTPB1 are known to participate in cardiac development and could be candidate genes for CHD.

☆ Please cite this article as: Molck MC, Simioni M, Vieira TP, Sgardioli IC, Monteiro FP, Souza J, et al. Genomic imbalances in syndromic congenital heart disease. J Pediatr (Rio J). 2016 http://dx.doi.org/10.1016/j.jped.2016.11.007
☆☆ Study conducted at Universidade Estadual de Campinas (UNICAMP), Departamento de Genética Médica, Campinas, SP, Brazil.
* Corresponding author.
E-mail: vlopes@fcm.unicamp.br (V.L. Gil-da-Silva-Lopes).

http://dx.doi.org/10.1016/j.jped.2016.11.007

Conclusion: These data showed that patients presenting CHD with extra cardiac anomalies and exclusion of 22q11.2 DS should be investigated by CMA. The present study emphasizes the possible role of CNVs in CHD.

PALAVRAS-CHAVE
Variações do número de cópias de DNA;
Cardiopatias congênitas;
Síndrome de deleção 22q11;
Hibridização genômica comparativa;
Aberrações cromossômicas

Desequilíbrios genômicos na cardiopatia congênita sindrômica

Resumo
Objetivo: Identificar desequilíbrios genômicos patogênicos em pacientes apresentando Cardiopatias Congênitas (CC) e anomalias extra cardíacas, e exclusão da Síndrome de Deleção 22q11.2 (SD22q11.2).
Métodos: Um total de 78 pacientes negativos para a deleção 22q11.2, previamente testados por hibridação *in situ* com fluorescência (FISH) e/ou amplificação de múltiplas sondas dependentes de ligação (MLPA), foram avaliados por *microarray* cromossômico (*CMA*).
Resultados: Foram identificadas variações do número de cópias de DNA (CNVs) clinicamente significativas (≥ 300 kb) em 10% (8/78) dos casos, além de CNVs potencialmente relevantes em dois casos (duplicação de 993 kb em 15q21.1 e duplicação de 706 kb em 2p22.3). Genes envolvidos como IRX4, BMPR1A, SORBS2, ID2, ROCK2, E2F6, GATA4, SOX7, SEMAD6D, FBN1 e LTPB1 são conhecidos por atuarem no desenvolvimento cardíaco e podem ser genes candidatos a CC.
Conclusão: Estes dados mostram que pacientes apresentando CC, com anomalias extra cardíacas e exclusão da SD22q11.2, devem ser investigados por CMA. Ainda, este estudo enfatiza a possível função das CNVs nas CC.

Introduction

Congenital heart disease (CHD) is a common malformation affecting approximately six per 1000 live births. It occurs as an isolated trait or related to multiple congenital anomalies, among which the 22q11.2 deletion syndrome is the most common.[1] CHD is the most critical manifestation and represents the major morbimortality factor in 22q11.2 deletion syndrome (22q11.2 DS), affecting between 74% and 80% of patients. Among the variety of CHDs reported, conotruncal and/or aortic arch defects are the most prevalent.[2] The cause of cardiac phenotypic heterogeneity is not known, but there is no evidence of correlation with sex, race, 22q11.2 deletion size, or parental origin of the deletion.[3]

It is recommended that all newborns or children presenting CHD and dysmorphism or other congenital anomalies be screened for 22q11.2 deletion.[4] In addition, genomic imbalances of other chromosomal regions, including 10p12-p15, 4q21-q35, 8p21-p23, 17p13, and 18q21, can be found in patients with clinical suspicion of 22q11.2 DS and without 22q11.2 deletion.[5]

Currently, the application of chromosomal microarray analysis (CMA) for clinical diagnosis allows the identification of previously undetectable submicroscopic genomic imbalances, bringing new information about the genesis of congenital defects. The current study investigated a group of individuals presenting CHD with extra cardiac anomalies and exclusion of 22q11.2 DS to identify pathogenic genomic imbalances.

Patients and methods

Patients

The Research Ethics Committee of the University of Campinas approved this study (No. 487/2009 and 433/2010). All participants or their guardians signed the written informed consent. The evaluation included a standardized protocol as part of a multicenter study of the Brazilian Craniofacial Project, and all individuals were seen by a geneticist.

Initially, a group of 108 patients having CHD with extra cardiac anomalies and clinical suspicion of 22q11.2 deletion were screened by fluorescence *in situ* hybridization (FISH) and/or multiplex ligation probe amplification (MLPA). Only 78 patients (43 males and 35 females) without 22q11.2 deletion were included in the present study.

Among the CHDs in this cohort, tetralogy of Fallot (ToF) was observed in 40%, ventricular septal defect (VSD) in 22%, and atrial septal defect (ASD) in 8% of cases. In 9% of cases, two of these three defects were observed. The remaining 21% of cases presented other cardiac defects such as truncus arteriosus (TA), bicuspid aortic valve (BAV), and patent ductus arteriosus (PDA), among others.

The main clinical features found in these patients, in addition to CHD, were: facial dysmorphisms – 96% (75/78), neurocognitive and behavioral-developmental abnormalities – 65% (51/78), skeletal abnormalities – 58% (45/78), palatal abnormalities – 43% (34/78), immunological abnormalities – 41% (32/78), growth delay and/or feeding