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ORIGINAL ARTICLE

Chromosomal microarrays testing in children with developmental disabilities and congenital anomalies☆

Guillermo Lay-Son[a,b,*], Karena Espinoza[a], Cecilia Vial[a], Juan C. Rivera[a], María L. Guzmán[a,b], Gabriela M. Repetto[a,b]

[a] *Center for Human Genetics, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile*
[b] *Hospital Padre Hurtado, Santiago, Chile*

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KEYWORDS
Microarrays;
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Abstract
Objectives: Clinical use of microarray-based techniques for the analysis of many developmental disorders has emerged during the last decade. Thus, chromosomal microarray has been positioned as a first-tier test. This study reports the first experience in a Chilean cohort.
Methods: Chilean patients with developmental disabilities and congenital anomalies were studied with a high-density microarray (CytoScan™ HD Array, Affymetrix, Inc., Santa Clara, CA, USA). Patients had previous cytogenetic studies with either a normal result or a poorly characterized anomaly.
Results: This study tested 40 patients selected by two or more criteria, including: major congenital anomalies, facial dysmorphism, developmental delay, and intellectual disability. Copy number variants (CNVs) were found in 72.5% of patients, while a pathogenic CNV was found in 25% of patients and a CNV of uncertain clinical significance was found in 2.5% of patients.
Conclusion: Chromosomal microarray analysis is a useful and powerful tool for diagnosis of developmental diseases, by allowing accurate diagnosis, improving the diagnosis rate, and discovering new etiologies. The higher cost is a limitation for widespread use in this setting.

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* Corresponding author.
E-mail: glayson@udd.cl (G. Lay-Son).

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PALAVRAS-CHAVE
Microarrays;
Anomalias congênitas;
Atraso de desenvolvimento;
Variante do número de cópia;
Diagnóstico

Análise cromossômica por microarray em crianças com deficiências de desenvolvimento e anomalias congênitas

Resumo

Objetivo: O uso clínico de técnicas baseadas em microarrays para a análise de transtornos de desenvolvimento tem surgido durante a última década. Assim, o microarray cromossômico tem sido posicionado como um teste de primeiro nível clínico. Relatamos a primeira experiência em uma coorte chilena.

Métodos: Pacientes chilenos com atraso de desenvolvimento e anomalias congênitas foram estudados com um microarray de alta densidade (CytoScan™ HD Array, Affymetrix, Inc., Santa Clara, CA, EUA). Pacientes tiveram estudos citogenéticos anteriores, ou um resultado normal ou de uma anomalia não bem caracterizada.

Resultados: Foram analisados 40 pacientes selecionados por dois ou mais critérios, incluindo: anomalias congênitas maiores, dismorfismo facial, atraso de desenvolvimento e deficiência intelectual. Uma variante do número de cópia (CNV) foi encontrada em 72,5% dos pacientes, enquanto que uma CNV patogênica foi encontrada em 25% dos pacientes e uma CNV de significado clínico incerto foi encontrada em 2,5% dos pacientes.

Conclusões: A análise cromossômica microarray é uma ferramenta útil e poderosa em transtornos de desenvolvimento, permitindo um diagnóstico preciso, melhorando a taxa de diagnóstico, e descobrindo novas etiologias. O custo mais elevado é uma limitação para um uso difundido em nossa realidade.

Introduction

Major congenital anomalies affect two to three of every 100 live newborns, and are a leading cause of infant mortality and disability.[1,2] Although most are isolated and multifactorial in origin, patients with multiple abnormalities require an assessment to identify an underlying genetic cause.

In recent years, the etiological study of developmental disorders has been enriched with the clinical use of microarray-based techniques. In developed countries, molecular karyotyping or chromosomal microarray (CMA) is considered the first-line technique for the analysis of patients with multiple congenital anomalies, nonsyndromic developmental delay/intellectual disability, and autism spectrum disorders.[3–7]

In contrast, in developing nations such as Latin American countries, detection of chromosomal anomalies is still performed mainly by conventional cytogenetic techniques. GTG (G-bands by trypsin using Giemsa) banding karyotyping in lymphocytes has been mainly used to identify chromosomal abnormalities with a resolution equal or greater than 5-10 megabases (5-10 Mb).[8–11] Fluorescent *in situ* hybridization (FISH) is available for a limited number of diseases caused by chromosomal microdeletions/microduplications and has a resolution of 2-5 Mb in metaphase and between 50-150 Kb in interphase nuclei.[8,9,11–13] Other molecular techniques have been developed to look for small microdeletions/microduplications, such as multiplex ligation-dependent probe amplification (MLPA).[14] In contrast to these conventional techniques, CMA has a higher resolution, which reaches up to 50 Kb, a ten times higher resolution than conventional karyotyping.[13,15] It seeks genetic imbalances (gains or losses of chromosomal segments) across the genome and has allowed the identification of new syndromes that are not readily detected by the methods described above.[16–18] The discovery of normal variation as copy number variations (CNVs) poses a challenge for the clinical interpretation.[15]

Whilst diagnostic studies for individuals with congenital anomalies or intellectual disability based on conventional cytogenetics have a diagnostic yield close to 3%, CMA has a yield of around 15% to 20%, over five timesgreater than G-banded karyotype,[6] justifying its use as a first line diagnostic test for patients with an unknown clinical diagnosis. It is estimated that CMA alone is capable of detecting over 99% of all karyotype abnormalities.[5]

This report presents the authors' pioneering experience in the use of CMA in a cohort of Chilean patients with multiple congenital anomalies without etiological diagnosis.

Methods

Patients

Forty patients were selected from the Genetic Clinics at Hospital Padre Hurtado (Santiago, Chile), between May of 2012 and November of 2012.

This study included patients who had at least two of the following clinical features: major congenital anomalies (MCAs), facial dysmorphism (FD), developmental delay (DD), or intellectual disability (ID). All patients lacked a definite cause for the disorder.

Of all patients, 36 had a normal karyotype, two patients had an uncharacterized small additional marker chromosome (sSMC), one had a derivative chromosome, one had an