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ORIGINAL ARTICLE

Comparative genomic hybridisation as a first option in genetic diagnosis: 1000 cases and a cost–benefit analysis☆,☆☆

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KEYWORDS
Comparative genomic hybridisation array;
Microdeletion syndrome;
Intellectual disability;
Global developmental delay;
Autism spectrum disorders;
Congenital malformation

Abstract
Background and objective: Conventional cytogenetics diagnoses 3–5% of patients with unexplained developmental delay/intellectual disability and/or multiple congenital anomalies. The Multiplex Ligation-dependent Probe Amplification increases diagnostic rates from between 2.4 and 5.8%. Currently the comparative genomic hybridisation array or aCGH is the highest performing diagnostic tool in patients with developmental delay/intellectual disability, congenital anomalies and autism spectrum disorders. Our aim is to evaluate the efficiency of the use of aCGH as first-line test in these and other indications (epilepsy, short stature).
Patients and method: A total of 1000 patients referred due to one or more of the abovementioned disorders were analysed by aCGH.
Results: Pathogenic genomic imbalances were detected in 14% of the cases, with a variable distribution of diagnosis according to the phenotypes: 18.9% of patients with developmental delay/intellectual disability; 13.7% of multiple congenital anomalies, 9.76% of psychiatric pathologies, 7.02% of patients with epilepsy, and 13.3% of patients with short stature. Within the multiple congenital anomalies, central nervous system abnormalities and congenital heart

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☆☆ Previous presentations: part of this study has been included in the doctoral dissertation of Neus Castells Sarret, titled *Array CGH como primera opción en el diagnóstico genético postnatal*, defended on December 1, 2015 at the Hospital Universitario Vall d'Hebron, Universitat Autònoma de Barcelona. The study has also been presented as a poster titled *1.000 estudios de aCGH como técnica de primera línea: la experiencia del Hospital Vall d'Hebron* at the XXVIII Congreso Nacional de la Asociación Española de Genética Humana (AEGH); May 13–15, 2015; Palma de Majorca, Spain. Part of this study was the subject of the article titled *A novel recurrent breakpoint responsible for rearrangements in the Williams–Beuren region*; Cytogenet Genome Res. 2015;146(3):181–186.

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diseases accounted for 14.9% and 10.6% of diagnoses, respectively. Among the psychiatric disorders, patients with autism spectrum disorders accounted for 8.9% of the diagnoses.
Conclusions: Our results demonstrate the effectiveness and efficiency of the use of aCGH as the first line test in genetic diagnosis of patients suspected of genomic imbalances, supporting its inclusion within the National Health System.

PALABRAS CLAVE
Array de hibridación genómica comparada;
Síndrome de microdeleción;
Discapacidad intelectual;
Retraso global del desarrollo;
Trastornos del espectro autista;
Malformación congénita

Array CGH como primera opción en el diagnóstico genético: 1.000 casos y análisis de coste-beneficio

Resumen
Fundamento y objetivo: La citogenética convencional detecta un 3-5% de los pacientes con retraso global del desarrollo/discapacidad intelectual y/o malformaciones congénitas. La amplificación de sondas múltiples dependientes de ligación permite incrementar la tasa diagnóstica entre 2,4-5,8%. Actualmente, los arrays de hibridación genómica comparada o aCGH son la herramienta diagnóstica con mayor rendimiento en estos pacientes, en malformaciones congénitas y trastornos del espectro autista. El objetivo del presente trabajo ha sido evaluar la eficiencia del uso del aCGH como técnica de primera línea diagnóstica en estas y otras indicaciones (epilepsia, talla baja).
Pacientes y método: Se ha estudiado a 1.000 pacientes afectados por las patologías mencionadas mediante la técnica de aCGH.
Resultados: Se detectaron desequilibrios de efecto patogénico en un 14% de los pacientes (140/1.000). Según el fenotipo, se diagnosticaron un 18,9% de los pacientes afectados de retraso global del desarrollo/discapacidad intelectual; un 13,7% de las malformaciones congénitas; un 9,76% de las patologías psiquiátricas, un 7,02% de los casos con epilepsia y un 13,3% de los pacientes con talla baja. Dentro de las malformaciones congénitas destacan las del sistema nervioso central con un 14,9% y las cardiopatías congénitas con un 10,6% de diagnósticos. En las patologías psiquiátricas destacan los pacientes con trastornos del espectro autista, con un 8,9% de diagnósticos.
Conclusiones: Nuestros resultados demuestran la efectividad y la eficiencia de la utilización del aCGH como test de primera línea en el diagnóstico genético de los pacientes con sospecha de desequilibrios genómicos. Todo ello avala su inclusión dentro del Sistema Nacional de Salud.

Introduction

In the general population, the prevalence of global developmental delay/intellectual disability (GDD/ID) is estimated at 1–3%,[1] the prevalence of autism spectrum disorder (ASD) at 0.7%,[2] and the prevalence of congenital anomalies (CAs) at 2–3%,[1–3] constituting, overall, a significant health care and social burden. The genetic diagnosis of these patients is very useful in their clinical management, as it allows an accurate prognosis and, above all, is crucial to the prevention of new cases (genetic counselling for family planning). Until recently, these patients were assessed with a set of laboratory techniques, each with a low diagnostic yield in isolation. The most commonly used technique, conventional cytogenetic testing (karyotype analysis), can detect large losses or gains of genetic material and structural rearrangements in 3% to 5% of patients GDD/ID and/or CAs.[1,4–6] To improve the diagnostic yield, conventional karyotype analysis has been supplemented with fluorescent in situ hybridisation (FISH) and multiplex ligation-dependent probe amplification (MLPA) techniques. Thanks to their introduction, the detection of abnormalities in patients with unexplained GDD/ID or CAs and normal results of karyotype analysis increased by 2.4–3.7% with subtelomere analysis[7,8] and by 5.8% with screening for the most frequent microdeletion and microduplication syndromes.[9]

The recent development of arrays for the detection of changes in gene dosage (single nucleotide polymorphism arrays [aSNPs] and comparative genomic hybridisation arrays [aCGHs]) has considerably increased the number of diagnoses, allowing molecular diagnosis in 15–20% of patients with GDD/ID, CAs or ASD.[5] Single nucleotide polymorphism arrays, originally designed to genotype human DNA at thousands of SNPs across the genome, also allow the assessment of the number of copies of DNA by comparing the intensity of patient DNA hybridisation with the signal intensity of the probes immobilised in the matrix or array.