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EDITORIAL

The human genome and medicine☆

Genoma humano y medicina

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The analysis of the human genome and the use of genetic tests in medicine can be traced back to the late 1950s. Karyotyping (cytogenetic analysis) has been the traditional approach to the study of chromosomes, and, at a resolution of 400–550 bands, allowed the detection of chromosomal rearrangements and abnormalities larger than 5–10 Mb anywhere in the genome. Karyotyping made possible the diagnosis of disorders such as Down syndrome (trisomy 21) or cri du chat syndrome (chromosome 5p deletion syndrome). Conventional karyotyping brought the genome into medical knowledge, clinical practice and medical laboratories. However, despite encompassing the entire genome, the microscopic resolution of cytogenetic analysis does not reach the molecular level of the DNA sequence, which places significant limitations on its overall capacity for diagnosing genetic diseases and syndromes. In the past 10 years, the reach of genetic and genomic analysis has advanced spectacularly, going from the analysis of chromosome and subchromosomal regions to determining the molecular sequence of DNA fragments through Sanger sequencing or larger pieces of DNA through massively parallel or next generation sequencing (NGS). The introduction of chromosomal microarrays, or molecular karyotyping, into genomic analysis and clinical practice has allowed investigation of gene number copy variations through the comparison of a patient DNA sample with reference DNA. This allows the rapid and efficient detection of deletions and duplications.[1] These variants or abnormalities may be the cause of neurodevelopmental or psychiatric disorders, for example, autism spectrum disorder, as well as various genetic syndromes, such as 22q11 deletion syndrome, Smith-Magenis syndrome, Williams syndrome or 16p11.2 deletion/duplication syndrome, among others. The use of molecular karyotype analysis increases the yield of diagnostic testing in intellectual disability, genetic/chromosomal disorders and in the aetiologic investigation of congenital malformations in general, from 3% to 5% with conventional G-banded chromosome analysis to approximately 12–16% with molecular cytogenetic technologies.

In this issue of *Anales de Pediatría*, Castells-Sarret et al.[2] present the results of using molecular karyotype analysis (more specifically, comparative genomic hybridisation array [aCGH]) in 1000 patients with global developmental delay/intellectual disability, autism spectrum disorder, congenital malformations and other clinical indications such as epilepsy or short stature. Their results confirmed the

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findings of other studies: chromosomal imbalances were found in 140 patients (14%) out of the total 1000. These results stood in contrast with the detection rate obtained with other genomic techniques, such as conventional karyotype analysis and multiplex ligation-dependent probe amplification, with which the authors only succeeded in detecting chromosomal rearrangements or imbalances in 43 patients. The diagnostic yield of aCGH is, therefore, significantly higher, especially in the assessment of global developmental delay/intellectual disability (18.9%), autism spectrum disorder (14.8%) and congenital malformations (13.7%). An interesting finding was the detection of genetic abnormalities in 13.3% of patients with short stature, something that will need to be confirmed by future studies to determine the usefulness of molecular chromosomal analysis in the aetiological investigation of short stature. Although the diagnostic yield was not as high, the detection of abnormalities in 7% of patients with epilepsy was also relevant. These results led the authors to assert that molecular chromosome analysis, in this case aCGH, should be the first-line test for genetic diagnosis of patients with suspected genetic imbalances.

There are many patients with undiagnosed developmental delay. In the case series published by Castells-Sarret et al.,[2] the use of genomic analysis techniques quadrupled the detection rate, from an estimated 4.3% with the combination of conventional karyotype analysis and multiplex ligation-dependent probe amplification to 14% with aCGH. The advances in medical diagnosis brought on by genomic technologies have been considerable, and in addition, the authors of this study demonstrated that using aCGH compared to the approach of combining conventional karyotype analysis with multiplex ligation-dependent probe amplification is more cost-effective, cutting the cost of diagnostic evaluation by around 50%. Given the improved effectiveness and efficiency of molecular karyotype analysis as one of the genetic tests available for diagnosis of patients with neurologic or systemic developmental disorders, it is important to consider the usefulness of our current capabilities in genomic analysis in ''undiagnosed patients.''[3] Our capabilities have increased with the analysis of DNA sequences by means of massively parallel NGS. Analysis of exon genes and adjacent introns, either by disease-targeted panels for analysis of the clinical exome (the set comprehending most of the genes associated with a given disease) or whole-exome sequencing, has further increased our diagnostic capacity and yield, especially in the evaluation of patients with suspected monogenic disorders.[3] In studies published only a few years ago, the molecular diagnosis rate in ''undiagnosed patients'' overall using clinical exome sequencing ranged between 26% when only the patient was analysed and 31% when exome sequencing was performed in the patient-parents trio.[4] In 2017, in the Hospital Sant Joan de Déu, the addition of clinical exome sequencing to the diagnostic evaluation (first with a panel of 4813 genes, and later with a panel of 6710 genes) allowed us to detect genetic mutations and make a molecular diagnosis in 54.4% of the 362 probands under study (Armstrong et al., data not published, https://www.sjdhospitalbarcelona.org/es/ninos/genetica).

Knowledge of the aetiology of a disease may allow its prognosis, guide functional diagnostic evaluations and inform its treatment and rehabilitation, and allows us to anticipate and provide prophylactic treatment for problems associated with the disease and potential comorbidities. Specific diagnosis is also essential for genetic counselling of families. These data compels us to seriously consider the ethical dilemma posed by ''diagnostic effort'' in individuals with an ''undiagnosed'' disease that have been managed correctly and received all the necessary care required of health professionals.[5] Thus, the question we may want to address is: how far do we need to push our ''diagnostic efforts'' when the relevant evaluations based on current medical knowledge and technical resources have already been performed? Today, we can reply that pursuing all diagnostic options is a moral imperative for physicians as well as the health care system. In addition to the right to health of each individual or citizen, there are two other powerful reasons to do so: first, to further our understanding of disease and its pathophysiology in the context of the technological advances achieved in biomedicine, and second, to establish the necessary structure and material and human resources in the health care system. While the public health system may not yet offer this as a service for the general population, the results obtained by Castells-Sarret et al.[2] outline the current situation and the path to follow in the progressive integration of genomic analysis in the everyday practice of contemporary medicine, and, as far as we are concerned, in the specific field of paediatrics.

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