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SPECIAL ARTICLE

Advances in clinical genetics and its current challenges

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Abstract The great advances in the development of genomic technologies and their incorporation into routine clinical practice is bringing about a change in which an individual's genetic information is becoming increasingly relevant to their medical care. This is known as genomic medicine. Its implementation is not without barriers, including difficulties in the assessment and interpretation of genomic data, deficient training of professionals and patients in this field, unequal access to units with expertise, and a lack of professional profiles and infrastructures necessary for the incorporation of genomic technologies into routine clinical practice. This article reviews the advances and challenges of genomic medicine.

PALABRAS CLAVE
Genética;
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Avances en genética clínica y sus retos actuales

Resumen Los grandes avances en el desarrollo de las tecnologías genómicas y su incorporación a la práctica clínica habitual, está suponiendo un cambio en el que la información genética de un individuo tiene cada vez mayor relevancia en su atención médica. Esto es lo que se conoce como medicina genómica. Su implementación no está exenta de barreras entre la cuales se encuentran las dificultades en el asesoramiento e interpretación de los datos genómicos, una formación deficiente de los profesionales y los pacientes en este campo, un acceso desigual a unidades con experiencia y una falta de perfiles profesionales e infraestructuras necesarias para la incorporación de las tecnologías genómicas en la práctica clínica habitual. En este artículo se revisan los avances y retos de la medicina genómica.

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Introduction

Genetic diseases (a majority of which are rare), while individually infrequent, are collectively estimated to affect 4%–8% of the population.[1] The Online Mendelian Inheritance in Man (OMIM) database includes approximately 7000 diseases, most of which affect the paediatric population.[2] Generally, they are multisystemic diseases associated with significant morbidity and mortality in the paediatric age group. It is estimated that up to one fourth of paediatric deaths are attributable to genetic diseases, and that approximately 30% of children affected by these disorders do not live past age 5 years. Genetic diseases are the leading cause of death in neonatal intensive care units and up to 70% of paediatric intensive care unit admissions may be entirely due or related to a genetic disease.[3–5] While our knowledge of the human genome is still very limited, there already are numerous applications of genome sequencing in clinical practice, such as the characterization of genetic diseases and improved diagnosis of rare diseases, cancer type classification, targeted therapies or the prediction of an individual's response to a given treatment.[6] The current barriers to the effective application of genomic medicine include the deficient education of both professionals and patients on the subject, unequal access to experienced units and a lack of the necessary professional roles and infrastructures to integrate genomic technologies in everyday clinical practice.[7] Genomic or precision medicine is driving a shift in medical practice and poses a series of challenges that health care systems, facilities and professionals involved will need to address in upcoming years.

Emerging genomic technologies

Traditionally, the evaluation of a patient with a suspected genetic disease was guided by clinical suspicion following an exhaustive anamnesis and examination and included a variable number of diagnostic tests, with the possibility to analyse a limited number of genes or chromosomal anomalies. This approach may still be valid in the case of diseases with limited genetic heterogeneity, such as achondroplasia,[8] but it offers a very low diagnostic yield in rare or low-prevalence diseases or diseases with less specific manifestations or with substantial genetic heterogeneity, such as intellectual disability, in which more than 1000 genes are involved.[9,10] In recent years, there has been a paradigm shift due to the introduction of genomic techniques, arrays and above all next generation sequencing (NGS). NGS allows different approaches ranging from sequencing the entire genome (whole genome sequencing [WGS]), to sequencing the coding regions of the approximately 20 000 genes in human DNA, which accounts for 1.5%–2% of the genome (whole exome sequencing [WES]), to the simultaneous analysis of sets of genes associated with a given disease (gene panels, for instance, for skeletal dysplasias or arrhythmias). The diagnostic yield of NGS varies based on the disease under study and the selected approach (panels, WES or WGS, with only proband or trio samples [proband and parents]), and ranges from 25% to 50% in diseases such as intellectual disability, ocular diseases and select patients admitted to paediatric intensive care units.[11] On the other hand, 2 or more different genetic disorders are identified in approximately 4% of patients evaluated with WES or WGS.[12] It is estimated that it takes around 5–7 years for patients with rare or orphan diseases to receive a diagnosis, something that is known as the ''diagnostic odyssey''.[13] The routine use of these emerging genomic techniques could significantly reduce these time frames.

Genomic techniques have allowed the identification of a large number of genes responsible for known genetic diseases as well as the identification of a growing number of genes associated with different diseases and the description of a large number of formerly unidentified specific genetic disorders. All of it has contributed to improving our knowledge of different diseases, their main clinical features and the underlying biological processes and their molecular basis, which has resulted in improvements in diagnosis, treatment and patient outcomes. Despite the scarce data available on the prognosis of many genetic disorders or the absence of specific treatment for them, a study in parents of children diagnosed with a newly described genetic condition, revealed that most felt relief and had a positive perception of the value of the diagnosis and having an explanation of the cause of the disease, in addition to the benefit of getting in touch with other families with children with the same genetic disorder.[14]

Next generation sequencing has also transformed our understanding of cancer and, in many cases, tumour genomic profiling is now a routine diagnostic procedure used to predict the response to different drugs, select targeted therapies and give information on disease prognosis.[15] Until now, the field of pharmacogenomics has focused on a limited number of common variants with a known functional impact. Future advances in genomics will allow to assess the effect of groups of variants that have no effect in isolation but that combined may influence the response to a drug and specifically its potential adverse effects.[16] In addition, improvements in the knowledge of the molecular basis of diseases will facilitate the development of targeted therapies.[17]

Interpretation of genomic tests

At present, the traditional terms ''mutation'' or ''polymorphism'' are being replaced by the term ''variant''. Sequencing a genome, which comprises approximately 3300 millions of nucleotides, may lead to the identification of about 6 million variants, of which 600 000 may be rare and 2800 may affect protein function. Of all these variants, usually only 1 or 2 are responsible for the phenotype of the patient.[18] The interpretation of this information is still a challenge, as it continues to largely be a subjective and manual process. In an attempt to standardise the interpretation of variants, the American College of Medical Genetics and Genomics (ACMG) has developed guidelines for interpreting sequence variants based on multiple criteria, such as the allele frequency, functional data, in silico prediction data or segregation data. The classification includes 5 categories: benign (class I), likely benign (class II), variant of unknown significance (VUS, class III), likely pathogenic (class IV) or pathogenic (class V). The only ones that are considered diagnostic and medically actionable

are class IV and V variants.[19] Despite the attempts to homogenise and standardise the interpretation of variants, there are discrepancies in the classification of the same variants by different laboratories.[20,21] This can be explained by the relative subjectivity involved in the application of many ACMG criteria and the fact that most of the allele frequency data available in reference databases were obtained in the Caucasian population, which complicates the interpretation of certain variants in other ethnic groups or minorities. Furthermore, it must be taken into account that this classification is not useful for the interpretation of somatic variants in cancer tissues or pharmacogenetic variants, which have to be interpreted using the guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC).[22]

On the other hand, access to genetic testing has been generalised, and is no longer restricted to clinical genetics units, as it is increasingly ordered by different specialists with varying degrees of training in genetics. This increments discrepancies regarding the already existing heterogeneity in the indication of genetic tests, the interpretation of its results and their impact on medical management, in some cases leading to misdiagnosis, and unwarranted diagnostic investigations and management.[23,24]

Hospital-based NGS tend to have a better diagnostic yield, probably due to a better knowledge of the case, the additional diagnostic tests performed and the family history. In contrast, external laboratories often have limited clinical information at their disposal, which may make it more difficult to correctly establish the genotype-phenotype association. This illustrates the importance that the clinical information of the patient has in the correct interpretation of genomic data. Just as guidelines have been developed to standardise the interpretation of sequence variants, in recent years there have been initiatives to codify clinical findings with a homogeneous and structured approach. At present, the most widely used tool to codify phenotypes is the Human Phenotype Ontology (HPO), which allows integration of phenotypic and genomic data.[25] Its use is still limited because of the lack of time and training on this tool of different medical specialists. In this regard, the introduction of electronic health records (EHRs) in health care systems provides an opportunity to facilitate the integration of clinical information and genomic data. We ought to underscore that free text fields in EHRs can be used to describe relevant phenotypic characteristics that cannot be entered in the encoded structured data fields of the EHR, so that natural language processing (NLP) tools will be necessary to transform these data to ontologies.[26] On the other hand, only a small part of the genetic information obtained in a genomic test is usually applied to clinical diagnosis, so the availability of genomic data in EHRs and the possibility of sharing them, safely and following anonymization and informed consent, with national or international reference sequence databases could provide an invaluable source of information that would contribute to an improved understanding of the association between genetic variation and disease, facilitating translational research and precision medicine.

Secondary/incidental findings

The increase in the diagnostic yield of NGS has been accompanied by an increase in findings of unknown clinical significance and secondary or incidental findings (those unrelated to the reason testing was sought but that may be medically relevant for the patient and/or their family). It is estimated that secondary findings are identified in as many as 1%–6% of tests. In the paediatric population, the actionability of these variants, especially in the case of secondary findings, is particularly relevant, and is still a subject of considerable interest and debate.[27,28] The ACMG recommends offering the option of analysing a panel of 73 genes chiefly associated with a predisposition to cancer, cardiomyopathy and arrhythmias to any patient that undergoes WES or WGS, although recently the list has been expanded to include some inborn errors of metabolism and familial hypercholesterolaemia, among other diseases.[29,30] The approach in Europe is more cautious, especially when it comes to reporting secondary findings in children of variants associated with adult-onset diseases.[31] Given all of the above, it is essential that any patient undergoing genetic testing receive pre- and post-test counselling delivered by a professional well acquainted with the test, its potential findings and its limitations, followed by the signing of an informed consent by the patient and/or the relatives.[32]

New professional roles

The effective implementation of genomic medicine requires the integration of new professional roles in our health care system. On one hand, bioinformaticians, who are essential for the processing, evaluation and analysis of data generated by NGS and the integration of clinical phenotyping and genomic data.[33] On the other, genetic counsellors, who play a key role by helping patients understand the indications, potential repercussions and risks and benefits of genetic and genomic tests, as well as to interpret their results and explain how the diagnosis may affect the patient and the family.[18,34] The inclusion of these professionals in multidisciplinary genomic medicine teams is essential at this moment in which genomic medicine is already a reality and exome and genome sequencing are being integrated routinely in the diagnosis of our patients. Furthermore, as the use of genomic data is extended to more common and complex diseases, the demand of genetic counsellors and more agile models to provide information to patients outside the framework of monogenic disorders will increase substantially.

Conclusion

The introduction of genomic medicine has brought on new challenges, such as difficulties in the interpretation of genomic data and genetic counselling, the scarcity of professionals trained in this field and the paucity of technological resources allowing the processing and analysis of the generated data. Its correct implementation requires the incorporation of new professional roles in genetics teams, such as bioinformaticians or genetic counsellors, as well as

the formation of multidisciplinary teams including specialists in genetics and other fields. It is also key to promote education and training in genetics of health care professionals that are not directly involved in genetics as well as of patients, families and society overall. Lastly, technological advances are required to enable the storage, handling, exchange and mining of genomic data in the context of patient health records.

Genomic medicine is a reality that is already changing the management of rare diseases, cancer and pharmacogenetics and has an enormous potential to guide the development of new drugs, transform health care and improve population health.

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