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Modern Medical Genetics and Genomics in the Era of Personalized/Precision Medicine

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1. Introduction

Modern medical genetics as a well-defined field of medicine has developed so fast since its origins half a century ago that we cannot bear in mind how long time ago its roots and beginnings came from.

It can be argued that genetics overall was based on measuring the problems of human hereditary features and inherited diseases, since before the twentieth-century acceptance of Mendelian laws of heredity. Thus, medical genetics, viewed from its broadest perspective, is perhaps the oldest area of genetics and not a recent area that it is sometimes believed.

2. Modern genomics in medicine

During the years, with developments in cellular and molecular biology, the field of medical genetics expanded from a small clinical subspecialty focused at describing a few rare hereditary disorders to a recognized medical specialty whose principles and approaches are essential parts of the diagnosis and management of many disorders, both common and rare. These genetic concepts and approaches are not restricted to any one medical specialty or subspecialty, as they permeate many, and perhaps all areas of medicine.

The medical geneticist is usually a physician who works as part of a team of clinical providers, including many other physicians, nurses, and genetic counselors, to evaluate patients and their relatives for possible hereditary diseases. They characterize the patient (or proband) through analyses of personal and family history and physical examination; assess risk and possible modes of inheritance; indicate diagnostic testing; manage prevention, treatment, and surveillance; and participate in communicating to other family members at risk for the disorder.

During the twentieth century, it gradually became clear that hereditary factors were implicated in many conditions and that different genetic mechanisms were involved. Virtually, any disease is the result of the interaction of genes and environment, but the relative influence of the genetic component may be large or small. Traditionally, genetic conditions have been classified into three categories: monogenic, chromosomal, and multifactorial disorders. However, it is becoming increasingly evident that the interplay of different genes (polygenic inheritance) is essential in disease and that an additional category—acquired somatic genetic disease—should also be included.

Improvements in all areas of medicine, mainly public health and therapeutics, resulted in modifying patterns of diseases, with improving recognition of the role

of genetic factors for most of common disorders or even for the susceptibility to infectious diseases. For complex chronic degenerative diseases of adult onset, their overall contribution of heritability has been identified, as life expectancy increases and high-throughput technologies improve. These provide the opportunity for understanding the interactions between the genetic and environmental factors of diseases such as cancer, Alzheimer's disease, diabetes mellitus, macular degeneration, and cardiomyopathy.

In recent years, we have been facing the applications of modern genomics to the practice of medicine. With robust molecular biology technologies, one can identify the actionable mutations present in a tumor and establish the profile of its pattern of RNA expression, which are currently being used for determining prognosis and choosing appropriate targeted therapies for individual cancer patients. Another application is how modern genomic approaches are increasing our abilities in risk assessment and helping provide more accurate genetic counseling to patients and families affected with hereditary diseases as well as advances in prenatal diagnosis.

There are further examples of applications of genomics to individualized health care: screening asymptomatic individuals for genetic predisposition to various diseases in order to improve health care, population-based newborn screening for preventable and treatable genetic diseases, identifying couples that are carriers for autosomal recessive or X-linked diseases that could affect their children before conception, prenatal screening of the fetus for aneuploidy by maternal cell-free DNA, and applications of pharmacogenomics on the detection of individual variation affecting drug therapy, which can be used to improve therapeutic efficacy and reduce adverse events.

At the beginning of the twenty-first century, the Human Genome Project (HGP) provided a virtually complete sequence of human genome from which now derives the efforts to catalog all human genes, understand their structure and regulation, determine the extent of their variation in different populations, and uncover how genetic variation contributes to susceptibility. The whole genome of any individual can now be sequenced rather than sequencing one gene at a time. These achievements are making possible the practice of genomic medicine, which aims at applying a wide analysis of the human genome and its products, including the epigenetic regulation of gene expression, gene variation, and their interactions with the environment, to medical care.

The HGP has now been succeeded by the Human Variome Project, which seeks to compile and share the huge variation in human DNA sequence worldwide. This is potentially possible since whole exome sequencing (WES) and whole genome sequencing (WGS) have been increasingly performed in several population studies. For example, the 100,000 Genomes Project in the United Kingdom have recently achieved its goal of 100,000 genomes sequenced [1].

The study of genetics and its role in causing human disease is now widely acknowledged as being among the most exciting and influential areas of medical research. Certainly, their valuable discoveries have benefited patients and families dramatically, but this achievement will be measured by translating them into both treatment and prevention of disease.

3. Diagnostic advances

Advances over the past few years in mutation identification have provided many improvements in risk assessment, carrier detection, and prenatal diagnosis, allowing the detection of particular mutations with almost 100% accuracy. Laboratory testing for pathogenic (disease-causing) mutations is available for more than 4,500 genes associated to over 11,000 genetic conditions [2]. The better knowledge of the genes involved in hereditary disease and the rapidly

cheaper cost of DNA sequencing have permitted the identification of mutations in a patient or family member, and, therefore, the molecular diagnosis has become the standard of care for many conditions. DNA samples for testing are available not only from readily accessible tissues, such as a buccal scraping or blood sample, but also from tissues obtained by more invasive testing, such as chorionic villus sampling or amniocentesis.

For many hereditary disorders (including retinal degeneration, deafness, hereditary breast and ovarian cancer, Lynch syndrome, congenital myopathy, mitochondrial disorders, and hypertrophic or dilated cardiomyopathies), there is a substantial locus heterogeneity, that is, numerous genes are known to be mutated in different families with these disorders. When a patient with one of these highly heterogeneous disorders seeks for testing, recent advances in DNA sequencing make it possible to analyze large panels of dozens to more than 100 genes simultaneously and cost-effectively for mutations in every gene in which mutations have been seen previously to cause the disorder.

In those conditions for which even a large panel of relevant genes cannot be formulated for a particular phenotypically defined disorder, or for those genetically heterogeneous entities (e.g. intellectual disability, autism spectrum disorder) genetic diagnosis still can be achieved by analyzing all the coding exons of every gene (by WES) or by sequencing the entire genome (by WGS) to identify pathogenic mutations.

The use of large gene panels and, even more so, WGS or WES raises special issues for sequence interpretation and risk assessment. As there are more genes being tested, the number of sequence differences between a patient's DNA and that of an arbitrary reference sequence also increases; consequently, many previously undescribed variants will be found whose pathogenicity is unknown. These are so-called variants of uncertain significance (VUSs). This is the case, for example, of a missense mutation that results in the substitution of one amino acid for another in the encoded protein.

Thus, the interpretation of variants is a challenging and demanding area for all professional geneticists who provide molecular diagnosis. The American College of Medical Genetics and Genomics has recommended that variants be categorized into one of five classes: pathogenic, likely pathogenic, of uncertain significance, likely benign, and benign variants [3]. Specialists in molecular diagnostics, human genomics, and bioinformatics have developed a series of criteria for addressing the mutation status. In most cases, none of these criteria is absolutely definitive but must be considered together to provide an overall assessment of the pathogenicity of a variant. Only those variants with a high probability of being pathogenic are communicated to the health professional and patient. It is arguable whether the testing laboratory should disclose all VUSs, at the same time remaining available for updating as new information allow reclassification as either benign or pathogenic.

Despite all the time and effort put into interpretation, it is still impossible to ensure any clinical significance to the vast majority of all variants found through next-generation sequencing (NGS). There is a general concern that individuals and their clinical providers, when confronted with VUSs, will require additional unnecessary testing, with the potential for finding results with even more VUSs, thereby increasing patient's uncertainty and anxiety. Moreover, there is the additional concern that even when a variant is known to be pathogenic and highly penetrant in families with multiple affected individuals, the true penetrance of a variant when it is found in individuals with a negative family history may be much lower.

Therefore, risk assessment and genetic counseling in this context are challenging processes and depend on continually addressing recently available information and communicating it properly to healthcare providers and patients.

4. Ethical dilemmas

Each new advance in genetic technology has simultaneously brought new ethical concerns and raised new dilemmas about how science will be applied and utilized in medicine. At the center of this is the recognition that an individual's genetic background is fundamental to both their identity and possible disease susceptibility. The most controversial field is prenatal genetics and reproductive choice, though national legal frameworks and cultural practices vary widely worldwide. The debate surrounding the early ability to perform prenatal diagnosis for Down syndrome through invasive procedures in the mid-1960s is compared to the new technology that makes it possible to perform detailed genetic screening of the fetus on cell-free fetal DNA in the maternal blood or on embryos created through in vitro fertilization for preimplantation genetic diagnosis (PGD). Great controversy has taken place, and will go on, regarding the disclosure of unexpected but significant "incidental findings" from WES or WGS carried out for specific clinical purposes [4]. Furthermore today there is the technical feasibility of all newborns having their genome sequenced and screened for either childhood disorders or adult-onset conditions [5].

Advances in genetics attract great media attention, and this has brought the ethical debate to a wide public scenario. Issues about insurance, forensic science and DNA databases, patenting, gene therapy, population screening, cloning, stem cell research, and hybrids are considered to have major societal, commercial, and political importance and therefore impact clinical and laboratory practice in medical genetics. On a global scale, it is essential to safeguard fundamental principles such as privacy, confidentiality, and respect for human life at all stages and ages.

Many of the questions raised do not have easy or definitive answers, which means that there will be a great need for both public awareness and properly trained clinicians and counselors to balance the needs of their patients and families with these ethical challenges for the foreseeable future.

5. Personalized and precision medicine

The aim of personalized or individualized medicine is to use knowledge of an individual's genetic (or genomic) background relevant to the maintenance of health, prevention, and treatment of diseases as a routine part of medical care.

During the past 10 years, many examples of stratified medicine have blossomed, where the therapy of a particular disease is dependent on the germline or somatic variants patients may carry. These examples include monogenic rare diseases where a different treatment is recommended for patients with some types of germline mutations in a specific gene, such as *CFTR* gene mutations that cause cystic fibrosis, and the molecular therapy targeted on an actionable somatic mutation of a specific tumor, such as the *BRAF* V600E mutation in malignant melanoma. The genetic (or genomic) diagnosis is therefore a crucial step toward the most appropriate treatment and/or prevention, what is so-called clinical utility or actionability [6, 7]. Recent initiatives are focusing on improving health outcomes through precision medicine especially in Oncology [8] (**Table 1**). This is a multidisciplinary integrated approach that analyzes human samples and personal data to improve health care through increased precision in the knowledge of mechanisms of both disease and drug response.

Personalized genomic medicine (PGM) is only one component of precision medicine, which means, in a broadest sense, it requires clinical care providers to combine genomic information with other types of information, such as biochemical or physiological testing results, neurodevelopmental history, environmental exposures, and psychosocial experiences. The most important goal is provide more

Tumor(s)	Genes	Clinical application(s)
Melanoma	<i>BRAF, CDKN2A, KIT</i>	Therapy; risk assessment; inherited susceptibility
Breast and ovarian cancer	<i>BRCA1, BRCA2</i>	Therapy; inherited susceptibility
Colorectal cancer	<i>MLH1, MSH2, MSH6, PMS2, EPCAM, BRAF, KRAS, NRAS</i>	Therapy; inherited susceptibility
Non-small-cell lung cancer	<i>EGFR, BRAF, KRAS, ERBB2, RET, MET, ALK, ROS1</i>	Therapy
Myelodysplastic syndrome	<i>TP53, GATA2, JAK2, ASXL1, ETV6, RUNX1, SF3B1, EZH2</i>	Diagnosis; risk stratification
Acute myeloid leukemia	<i>KIT, CEBPA, FLT3, NPM1</i>	Risk stratification

Table 1.
Genetic/genomic profiling for selected malignancies (adapted from [8]).

precise diagnosis, genetic counseling, management, prevention, and therapy. This effort has already got started, but plenty of work still needs to be done before PGM becomes integrated into medicine itself.

Conflict of interest

The author declares no conflict of interest.

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