Review

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Innovations in Genetic Medicine: A Journey in Time

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Abstract

The relationships between science and technology have been disputed for almost a century now. As they appear to accelerate each other, the major effect of the technological innovation on genetic medicine has been mainly observed following the completion of the Human Genome Project. Genetic medicine, also known as medical genetics, currently focuses on many aspects of medicine including genomic analyses and clinical services, such as genetic counseling, diagnosis, and management of genetic and hereditary disorders or genetic aspects and management of neoplastic diseases. This review provides an overview of the history of genetic medicine and an insight to the current application of genomic technology into clinical practice.

Keywords: Medical genetics, innovation, technology

INTRODUCTION

Genetic analyses have become crucial in patient management as a result of advances in the field in the last two decades, following the mapping of the human genome in 2003. Since then, many disease-causing and/or related genes have been explored, and the introduction of genomic medicine, also known as personalized medicine, was an important milestone, especially for patients with cancer and their relatives. Genetic medicine, also known as medical genetics, currently focuses on many aspects of medicine including genomic analyses as well as clinical services, such as genetic counseling, diagnosis, and management of genetic and hereditary disorders or genetic aspects and management of neoplastic diseases. This review discusses the innovative genetic techniques and their use in daily routine practice.

Evolution of Clinical Cytogenetics

Cytogenetics studies the chromosomes by making their structure visible under a microscope and identifying their size, banding pattern, and centromere locations, thus demonstrating the chromosomal defects, such as deletions, translocations, or inversions. Chromosomal analysis has been widely used for prenatal diagnosis to diagnose patients with congenital anomalies and/or mental retardation (1) and diagnosis and management of patients with cancer. It can be performed on cells obtained from different tissues, including blood, fetal blood and tissues, chorionic villi, amniotic fluid cells, skin, bone marrow, tumor samples, and effusion fluid. In 1956, Tijo and Levan (2) conducted the first study on cytogenetics. They established the normal human chromosome number as 46. In the 1960s, cytogenetic studies accelerated with the discovery that fetal cells could be obtained through amniocentesis to identify chromosomal abnormalities (3). While high-resolution banding techniques improved the chromosome analysis (4), submicroscopic chromosomal alterations remained to be undetected until the discovery of fluorescence in situ hybridization (FISH) in the early 1980s, the beginning of the molecular cytogenetics era. Fluorescent DNA or RNA probes targeting specific chromosomal locations allowed the assessment of fluorescent-dyed signals to be visualized under a fluorescent microscope. FISH does not require cell culture and can directly use fresh or paraffin-embedded interphase nuclei for rapid evaluation compared with conventional cytogenetics metaphase

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karyotype analysis (5). In addition, it has become a widely used diagnostic tool in both genetic and neoplastic diseases, providing simultaneous evaluation of multiple abnormalities in multiple locations (e.g., centromeric and subtelomeric).

Fluorescence in Situ Hybridization (FISH) can also be used in preimplantation genetic diagnosis (PGD), which is a procedure that identifies embryonal genetic defects prior to implantation. It is performed in in vitro fertilization of embryos (IVF embryos) and allows for the detection of the abnormality before embryo transfer so that only unaffected embryos are transferred back (6). The indications for PGD can be divided into five categories: chromosome abnormalities, sexing for X-linked disease, single gene defects, preimplantation genetic screening, and social sexing (7). In 1990, the first PGD was performed by Handyside et al. (8) for the detection of X chromosome-linked diseases in two couples known to be at risk of transmitting adrenoleukodystrophy and X-linked mental retardation. Although they used polymerase chain reaction (PCR) to detect the defects, FISH has also been widely applied for the preimplantation detection of chromosome abnormalities, allowing the evaluation of many chromosomes at the same time, with up to 15 chromosome pairs in a single cell (9). However, FISH has several technical limitations, including hybridization failure (lack of signal), signal overlap, signal splitting, poor probe hybridization, cell loss, and variable cell fixation (10). Currently, PCR, comparative genomic hybridization (CGH), single-nucleotide polymorphism (SNP) microarray analysis (10), and next-generation sequencing (NGS) can be used for PGD.

In 1992, CGH, also known as chromosomal microarray analysis (CMA), a technique combining cytogenetics with molecular genetics, was introduced by Kallioniemi et al. (11) to detect DNA amplification in tumor cells. CGH (or CMA) is based on competitive hybridization of tumor DNA and normal DNA using traditional metaphase chromosome preparation, and a few years after the first report, DNA microarrays replaced the traditional preparation (array CGH) (12). It is generally used for genetic testing of individuals with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorder (ASD), or multiple congenital anomalies (MCAs) (13), offering a much higher diagnostic yield (15%-20%) for genetic testing of individuals with unexplained DD/ID, ASD, or MCA than a G-banded karyotype, primarily because of its higher sensitivity for submicroscopic deletions and duplications (13). CMA is a high-resolution technique that allows the detection of microdeletions and/or duplications, which are called copy number variants (CNVs), but it is expensive to be used in routine screening and is not able to detect truly balanced chromosomal rearrangements or low-level mosaicism (1, 13). Therefore, an algorithmic approach should be employed based on the clinical indication, and it would be more appropriate to use traditional (G-banded) karyotype analysis to investigate for chromosomal syndromes, such as Down syndrome or balanced rearrangements. It is also noted that a CNV can be of no medical consequence. CGH (CMA) is also one of the most commonly used methods in PGD, and an SNP-based array has been developed to improve the resolution recently (10).

Evolution of Molecular Genetics

Molecular genetics focuses on the structure and function of genes at a molecular level. Gene amplification is the most widely used procedure for molecular analyses. In 1983, Kary Mullis developed the PCR technique, an amplification technique enabling the DNA replication many times. He was awarded the 1993 Nobel Prize in Chemistry along with Michael Smith. The automation of the PCR technique was one of the major improvements to begin the Human Genome Project, and the project also led to a significant improvement in the sequencing technology (14). First-generation sequencing (Sanger sequencing) has analyzed only individual samples of DNA, whereas NGS, also known as massively parallel sequencing or second-generation sequencing, has provided a thorough and rapid sequencing of large amounts of genetic material with reasonable costs. NGS is now widely used for both clinical and research purposes. NGS technology successfully provides a genome-wide investigation of causal variants in single gene disorders and complex genomic landscapes of many diseases (14). Whole genome sequencing (WGS) and whole exome sequencing (WES) basically use the NGS method. In WGS, the sequence of most of the DNA content comprising the entire genome of an individual can be determined, whereas exomes are sequenced in WES. Exome is the component of the genome that encodes proteins and comprises approximately 1% of the genome. Protein coding segments are referred to as exons and exomes can also include non-coding exons. Therefore, WES provides the identification of the DNA sequence of most of these protein-encoding exons and may include some DNA regions that encode RNA molecules that are not involved in protein synthesis. It is a cheaper and more effective method than WGS, considering that most disease-causing mutations are detected within the protein-encoding regions of the genome.

Noninvasive prenatal testing (NIPT), a screening method to detect fetal aneuploidy by analyzing small fragments of fetal cell-free DNA circulating in maternal blood, is another application of NGS technology. NIPT is most commonly used for prenatal diagnosis of trisomy (trisomy 21 (Down syndrome), trisomy 18, or trisomy 13) or sex chromosome abnormalities. However, NIPT is not yet recommended as a routine prenatal screening test, especially in low-risk pregnancies, due to lower positive predictive value in low-risk pregnancies/populations, being relatively expensive, and offering a limited diagnostic window. On the other hand, it is a promising prenatal diagnostic test and will probably improve with the technological advances. The utility of microRNAs in NIPT may help the improvement of NIPT, given that the increased maternal plasma levels of some microRNAs have been shown in women carrying a fetus with Down syndrome in a recent study (15).

Another recent discovery particularly affecting tumor genetics is the implementation of liquid biopsy into the clinical practice. A liquid biopsy may be defined as obtaining circulating tumor cells, tumor-derived cell-free DNA, or other compounds from body fluids, mostly from peripheral blood, and it can be used for diagnosis, follow-up, and management of diseases, with neoplasms in most cases. While it is a highly advanced non-invasive diagnostic tool using novel molecular techniques, such as PCR or NGS, there are still disadvantages and limitations, such as the fragmentation of cell-free DNA, RNA instability, the low concentrations of certain analytes in body fluids, and the confounding presence of normal and aberrant DNAs and RNAs (16).

A third-generation sequencing technique, also known as long-read sequencing, that reads nucleotide sequences at the single molecular level appears to have the potential to open a new era

in medical genetics. However, this technology still needs to be improved to be used in routine clinical practice.

CONCLUSION

Science and technology go hand in hand. Technological innovations lead to genomic discoveries, and genomic discoveries fuel more technological advancements to fulfill the need in clinical practice. While a multidisciplinary approach is of utmost importance to select the most useful genetic tests and approach in patient management, computational genomics appears to be an essential part of future research, as it is used to analyze, process, and store all the data obtained from projects by using mathematics and computer techniques to develop algorithms or models.

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