Editorial

The human genome and the clinic: impact of clinical genomics to patient's bedside

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Editorial

Sequencing of the individual genome provides valuable opportunities to better diagnose and treat many human diseases.[1] Over 3,000 genes are listed in the Online Mendelian Inheritance in Man (OMIM) database as disease causing.[2] Medicines based on genomics are making inroads in the fields of oncology, infection, pharmacology, and rare and undiagnosed diseases. The genetic variants in the human genome, both at the whole genome and at the exome level, if identifiable, provide a rational approach to diagnosis, therapy, and personalized medicine. The clinical applications of the genome sequencing, termed as clinical genome and exome sequencing (CGES) have already entered the clinic.[3–6] In the past, bidirectional Sanger sequencing was used to detect gene-specific mutations and small variants. With the lower cost of the whole genome sequencing technique, the CGES could readily become a tool for genetic analysis involving a large number of patients. Such a high throughput approach can help identify targets or candidate genes for Sanger sequencing verification in the future.[7–9]

Among many diseases, the CGES is well developed for cancer indications and therapy.[9,10] The clinical oncologists benefit from the high-throughput sequencing efforts for diagnosis, identification of patient cohort for targeted therapy, and in early identification of mutations for resistance to ongoing therapy. The US Federal Drug Administration (FDA) approves mutations or gene expression analysis of genes such as EGFR, KRAS, HER2/NEU, C-KIT, BRCA and BRAF for therapy of diverse cancer types. The CGES results in oncology have helped establish a new paradigm in drug development in industry whereby a co-development of a diagnostic test kit and a drug for treatment is becoming common for simultaneous submission to the FDA. The extensive experience gained with the oncology indications further provides a framework to expand the utility of CGES for non-oncology indications. Increasingly, FDA approved drugs incorporate pharmacogenomics information in their labels in diverse therapeutic areas such as analgesics, antiviral, cardiovascular drugs, and anti-cancer therapeutics.

The Next Generation Sequencing (NGS), a widely used high-throughput sequencing technology, offers powerful solutions to the CGES. The whole exome sequencing (WES) and the whole genome sequencing (WGS) provides distinct advantages for the clinicians.[11] The WES approach focuses on the coding region of the genome, is less expensive, and is currently offered by many testing laboratories. The WGS approach on the other hand, focuses on the entire genome and is more sensitive than the WES in detecting the structural variations. Furthermore, the WGS can help identify non-exonic regulatory regions encoded by the genome. This non-coding intronic and intergenic region of the genome encodes the most common complex disease risk variants and pharmacogenomics variants. The WGS, however, is not currently offered by the testing laboratories, but is likely to become an integral part of clinical testing in the next decade.

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The CGES does not detect a wide variety of variations and deletions such as repetitive DNA including tri-nucleotide repeats (Fragile X syndrome, Huntington's disease), copy-number variants (DiGeorge syndrome, Charcot-Marie-Tooth disease type 1A), long insertion-deletion variants (resistance to HIV infections), structural variants (chromosomal translocations), aneuploidy associated (Down's syndrome, Turner syndrome) and many epigenetic changes (Beckwith-Wiedermann syndrome). In these instances, the Sanger sequencing and the Polymerase Chain Reaction provides valuable alternatives.

Global measurement of the variations among the 22,000 genes can provide an attractive starting point for novel diagnosis and prediction of risk of disease development.[12] The variants are classified according to the American College of Medical Geneticists[13] into 1) Disease causing, 2) likely disease causing, 3) possibly disease causing and 4) variants of unknown clinical significance. Numerous databases are emerging to facilitate analysis of these variants including ClinGen,[14] Clinical Genomics Database-CGD,[15] ClinVar[16] Decipher,[17] and Electronic Medical Records and Genomics-eMERGE.[18]

Challenges

Despite the promise of the CGES in improving the quality of healthcare, the healthcare providers are not yet rapidly incorporating CGES into clinical practice. Various reasons including lack of knowledge and training, interpretations of big data, cost and some degree of skepticism about the validity of the tests contribute to this.[19,20] A curriculum based on the clinical genomics for the next generation of clinicians would be necessary to overcome these challenges.

Interpreting the clinical significance of mutations is complex. Over one-fourth of the mutations reported in the literature may be incorrect.[21] Clinical-quality databases of disease-associated mutations currently do not exist. Efforts are underway to establish such a database by the human variome project.[22]

The genome sequencing by CGES is likely to raise some ethical challenges including identification of variants relevant to long term medical care such as cancer, Alzheimer's disease, stroke and neurological disorders as well as risk for development for other

diseases. There are no effective guidelines to tell the clinicians as to when or whether to inform the patients of such a discovery. Issues of privacy and insurance discrimination provide another layer of challenges for the benefits of clinical genomics to reach the patient's bedside.

The future of clinical genomics

Despite these challenges, integration of the genome medicine into the clinical setting is likely to become a reality in the coming decade. Most patients entering the clinic in the future are likely to have their genome sequenced prior to the clinical evaluation. An initial focus on the Mendeliome sequencing might help transfer the research findings to the patient's bedside rapidly. The UK Genomics England's efforts to sequence 100,000 patients with rare genetic diseases and cancer are expected to establish a sound framework for translational medicine. Clinical genomics promises to change current approaches to therapeutics development, delivery of quality healthcare and population health management in the future.

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Conflict of interest

The author declares no conflict of interest.

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