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COMMENTARY

A commentary on the promise of whole-exome sequencing in medical genetics

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The dawn of next-generation sequencers (NGSs) and innovative sequencing technologies have brought a paradigm shift in medical research and clinical practice. Furthermore, the cost reduction of NGSs enables personalized medicine to come to fruition.

However, whole-genome sequencing (WGS) remains expensive when applied to personal genome analysis. WGS generates a large amount of data that requires high-performance computer processing. Targeted whole-exon capture and sequencing [whole-exome sequencing (WES)] is more cost-effective when compared with WGS because exons represent only ~1–2% of the genome and also higher sequence coverage can be achieved by NGSs. In addition, most Mendelian disorders are caused by exonic mutations or splice-junction mutations, and protein-coding genes harbor ~85% of the mutations that have large effects on disease-related traits.[1] Thus, WES will provide many advantages and lower costs than WGS when analyzing personal genomes.

WES was first successfully used in 2010 to discover the gene responsible for Miller syndrome, a Mendelian disorder.[2] Since then, WES has been increasingly used as a fast and accurate genomic discovery approach to investigate both rare genetic disorders and common diseases.

WES is widely applied across different areas of medicine, because it has the added advantage of reduced cost and requires analysis of a much smaller but essential dataset when compared with WGS. In addition, recent clinical molecular diagnostics have used WES to detect heterogeneous Mendelian diseases.[3,4]

A recent review of WES approaches in medical genetics describes the usefulness of WES in medicine and medical research and the impact of WES on clinical diagnoses.[5] WES approaches have greatly facilitated the discovery of candidate genes or gene variants in Mendelian disorders and rare variants in common diseases and genomic characterization in cancer. Currently, WES is increasingly being applied to disease gene discovery, cancer typing and molecular diagnosis.[5]

Presently, WES is an essential tool in medical genetics, especially in the research of Mendelian disorders. WES or multigene tests using NGSs are widely applied to heterogeneous disorders including deafness or ciliopathy.[5,6] WES is also being increasingly applied to genetic testing for undiagnosed patients.[4,5] Yang *et al.*[4] performed WES in undiagnosed patients whose phenotypes were suggestive of potential genetic disorders and achieved a molecular diagnosis for 62 of 250 (25%) patients.

Because WES detects individual genetic variation, it can be used to construct a variation database of anthropic and ethnic populations. At the same time, because WES can detect groups of genetic variations that are unrelated to the indication for the first diagnostic purpose but are of medical value for individual patient care, such 'incidental findings' pose potential ethical problems that should be strongly considered and discussed in clinical practice.[5,7]

WES is a widely applied technique in medical genetics that is capable of detecting variations in whole exons. However, in practical use, understanding WES methodology and limitations are important. Current WES techniques are not capable of detecting all of the variations surrounding exons. Detecting variation by WES is limited by the experimental methods, probe coverage and/or platforms used.[8–10] Hence, WES may not always detect pathogenic or causative variations in a genetic disease. In addition, because WES is a method to detect genomic sequence variations, when a candidate of causative variation in the disease is detected, it requires verification or support by secondary analyses. In particular, further functional analyses are important to confirm whether the variant is pathogenic or benign.

Nevertheless, WES enables the unprecedented low cost and highly efficient analysis of whole exons. WES can be easily used to comprehensively detect individual variations in exons. It is without doubt that WES is a powerful tool in genome analysis, and it greatly progresses medical genetics.

Although WESs' limitations need to be overcome, we anticipate that WES will be used not only in medical research but also in clinical practice for example, molecular diagnosis (whole-gene test) and personal genomics before WGS becomes a common place in medical genetics. Thus, a paradigm shift in medicine by advancement in both WES and WGS is expected to continue.

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