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COMMENTARY

A commentary on The diagnostic utility of exome sequencing in Joubert syndrome and related disorders

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During the past decade, remarkable advances have been made in DNA sequencing including the development of next-generation sequencing (NGS) technologies,[1] which has led to marked cost reduction in genome sequencing. The simultaneous development of high-throughput sequence capture platforms has made whole-exome sequencing technically feasible.[2]

To date, whole-exome sequencing has been mainly used for the analysis of mutations in cancer cells and more than 100 genes responsible for Mendelian disorders have been identified.[3–5] For example, whole-exome sequencing of 14 matched normal and metastatic melanoma DNAs revealed that *GRIN2A* frequently mutates in melanoma.[6] It has been increasingly reported that critical mutations can be identified in tumors by whole-exome sequencing.[5] Reports of gene discovery for Mendelian disorders using whole-exome sequencing are still increasing as well.

In addition, recent improvements in the accuracy and cost optimization of NGS and exon-capturing platforms have widened the application of whole-exome sequencing to other areas of research. These include molecular diagnostics[3] and the identification of rare variants[7,8] to explain the heritability of complex diseases and health-related traits.

Recently, Tsurusaki *et al.*[9] have identified mutations in five non-consanguineous families with Joubert syndrome or related disorders (JSRD) using whole-exome sequencing analysis as a diagnostic tool. JSRD are genetically heterogeneous, and a total of 19 responsible genes have been identified.[9–11] JSRD is sometimes clinically indistinguishable; therefore, it is necessary to examine all implicated genes to identify mutations in the affected patients. It is time consuming and costly to perform such molecular diagnoses by conventional Sanger sequencing. Whole-exome sequencing analysis is emerging as a cost-effective method for the clinical diagnosis of not only multi-gene disorders but also of single, large gene disorders.

The following three important points should be considered in the practical application of whole-exome sequencing for molecular diagnosis purposes. First, clinical diagnosis is important to identify genes for further examination. Second, it is possible that several variations may be found in the gene(s) of one patient. In such a case, it would be necessary to detect and confirm which variations are pathogenic. Tsurusaki *et al.*[9] used genomic analyses to identify a non-synonymous variation in *CEP290* of a Japanese family that was considered to be a non-pathogenic but rare variation.[9] The pathogenicity of even a single variation found in one patient should be evaluated by genetic, genomic and/or other biological means; for example, by investigating the functional relevance of the variation *in vitro* and/or *in vivo*. Third, a 100% detection rate of pathogenic mutations in patients by whole-exome sequencing analysis may not be possible because commonly used exome capture platforms are based on a hybridization method at this moment.[2]

Moreover, it is difficult to identify a pathogenic mutation when the mutation lies in a gene that has not yet been determined as a causative gene for a particular disease; however, the mutation may be identified by exome data analysis after gene discovery.

Nevertheless, there is no doubt that the diagnostic utility of exome sequencing is emerging as one of the most effective approaches for the diagnosis of genetic diseases.

Recent advances that have led to cost reductions for NGS and whole-exome capture will ensure that whole-exome sequencing will be more widely and likely used as a diagnostic tool for various diseases in the near future.

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