Clinical utility of high-throughput sequencing for the diagnosis of hereditary hemolytic anemia

Myungshin Kim

Department of Laboratory Medicine & Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Hereditary hemolytic anemias (HHAs) are genetic diseases that present with anemia due to the increased destruction of circulating abnormal RBCs. The RBC abnormalities are classified into the three major disorders of membranopathies, hemoglobinopathies, and enzymopathies. Traditional diagnosis of HHA has been performed via a step-wise process combining clinical and laboratory findings. Nowadays, the etiology of IHA accounts for germline mutations of the responsible genes coding for the structural components of RBCs. Genetic testing has been used for the confirmatory diagnosis of HHA. Sanger sequencing is primarily performed in order to identify the causative mutations in single gene disorders. It is very lucky to identify mutation(s) in the disease-associated gene in the initial trial. If not, a gene-by-gene approach is required. In these cases, patients may undergo multiple rounds of testing for different genes, a pathway to diagnosis, which can be costly and time-consuming. Additionally, the usefulness of Sanger sequencing is limited for the diagnoses of complex, multi-gene disorders or those with locus heterogeneity. Recent advances in molecular technologies, including next-generation sequencing (NGS), inspire us to apply these technologies as a first-line approach for the identification of potential mutations and to determine the novel causative genes in patients with HHAs. NGS panels consisting of common disease-causing genes have been developed and applied to routine molecular diagnosis for undiagnosed IHA patients and their families. In particular, patients with the co-presence of membranopathy, enzymopathy, and/or hemoglobinopathy can be effectively diagnosed using this new technology. Causal gene identification can be deduced through an efficient and reliable strategy to impute and analyze NGS data. The expanded implementation of the new technology will increase our knowledge of the genetic and genomic differences among individuals, gradually leading to a shift in the clinical management and the therapeutic plan from a population-based approach to a personalized therapy for individual patients. In this talk, I review the concept and strategy for the genetic diagnosis of HHAs and provide an overview of the preparations for clinical applications of the new molecular technologies.

References

1. Kim Y, Park J, Kim M. Diagnostic approaches for inherited hemolytic anemia in the genetic era. Blood Res 2017;52:84-94.
2. Haley K. Congenital hemolytic anemia. Med Clin North Am 2017;101:361-74.
3. Park J, Deong DC, Yoo J *et al*. Mutational characteristics of ANK1 and SPTB genes in hereditary spherocytosis. Clin Genet 2016;90:69-78.
4. Agarwal AM, Nussenzveig RH, Reading NS *et al*. Clinical utility of next-generation sequencing in the diagnosis of hereditary haemolytic anemias. Br J Haematol 2016;174:806-14.

5. Lin PC, Chiou SS, Lin CY *et al*. Whole-exome sequencing for the genetic diagnosis of congenital red blood cell membrane disorders in Taiwan. Clin Chem Acta 2018;487:311-17.