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Short Commentary Open Access

CHIPS to Disseminate the Genetic Testing of Rare Diseases

Yo Niida1,2*

[1]Division of Genomic Medicine, Department of Advanced Medicine, Medical Research Institute, Kanazawa Medical University, Ishikawa, Japan
[2]Center for Medical Genetics, Kanazawa Medical University Hospital, Ishikawa, Japan

Abstract

Alternative splicing is a co-transcriptional mechanism that regulates eukaryotic gene expression affecting the majority of human genes. In this mechanism, different sequences can be identified and removed from the pre-mRNA. Using alternatives splicing, multiple mRNA combinations of joined sequences can be produced from a single gene, increasing the coding potential of the genome.

Malfunctions of alternative splicing events can affect the natural expression of different transcripts. Several strategies have been developed to regulate alternative splicing and the mechanisms underlying the functional and physiological implications of these tools are diverse. Collectively, these strategies are intended to improve the treatment of human genetic diseases.

Short Communication

With the advance of molecular genetics, causative genes of about half of the estimated 7,000 Mendelian inherited diseases were identified. It becomes more important than ever before to confirm the diagnosis by genetic testing for appropriate medical care of the patient and genetic counseling to the family. However, in routine clinical practice, a smaller range of genetic tests are available. A limited number make up the most popular tests, which are easy to commercialize because the diseases have either relatively high incidence or testing procedures are simple because of existing mutational hot spot or a single mutational mechanism cause the disease. On the other hand, genetic testing for rare diseases such as malformation syndromes and genetic skeletal disorders are not provided enough. In these diseases, responsible genes are frequently large in size and have broad mutational spectrum by allelic and locus heterogeneity. Thus, molecular diagnoses of these syndromes are quite labor-intensive when using whole coding exon sequencing strategy, as gold standard method of genetic diagnosis at present, and are supplied at expensive prices. For example, GENDIA (for GENetic DIAgnostic Network, http://www.gendia.net/) provides more than 2,000 different tests including these rare diseases in average price €1,000; as high as €4,000 depending on gene size and numbers. Patients have to bear its cost, and hardly undergoing these tests without the coverage of health insurance.

There are two ways to supply the genetic tests of these orphan diseases in the general public. One way is establishing a central testing facility and collecting samples across the country. Recently, next generation sequencing (NGS) has been used to screen the mutation of single but large size gene or list of genes that cause similar phenotypes. If enough samples are gathered at once, NGS is a hopeful and fascinating strategy in near feature, because pooling of samples lowers the running cost per sample. Another way is that the local hospitals provide in-house molecular testing at low price for fulfilling local needs. To address this point, we recently developed CHIPS (CEL nuclease mediated heteroduplex incision with polyacrylamide gel electrophoresis and silver staining) technology, which uses an enzyme mismatch cleavage method finely optimized at every step to achieve maximum sensitivity and simplicity [1]. CHIPS achieve virtually 100 percent sensitivity of mutation detection, using only commercially available reagents and basic apparatus. At the same time, CHIPS offers inexpensive easy mutation screening by cutting out 90~95% cost and effort of the direct sequencing.

These two ways are not intended to be contradictory, rather use both as the situation of medical and social environment. In Japan, all citizens have a duty to join in the universal-coverage-of-health-insurance system of the government. By this insurance system, Japanese people are blessed with respect to ordinary medical care. However, most of advanced medical technology including genetic testing is not covered by this insurance. Consequently, many patients give up the genetic testing because of its high price. We can provide the same (or rather better) quality test at low cost by CHIPS. In our clinic, we provide various genetic testing on demand of our patients in $100 US per sample. Our hospital satisfies the needs of quick molecular screening and genuine genetic counseling in the Hokuriku district that is a small region of Japan with three million inhabitants and thirty thousand annual births. Since starting up this system from 2011, we can now analyze more than 130 genes and more than 100 orphan disorders, and the list is still growing [2]. I think cost reduction seems to be essential to provide genetic testing in many other countries and regions. I hope other laboratories or hospitals, elsewhere in the world where genetic diagnosis is not accessible enough, consider a similar solution and take action to satisfy the needs of genetic medicine to all patient and families suffering with rare congenital diseases.

References

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***Corresponding author:** Yo Niida, Division of Genomic Medicine, Department of Advanced Medicine, Medical Research Institute, Kanazawa Medical University, Ishikawa, Japan, Tel: +81 076-286-2211; E-mail: niida@kanazawa-med.ac.jp

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