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Minireview

Genetic Counseling System for Multi-Gene Panel Testing

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Introduction

The advent of next-generation sequencing has revolutionized the clinical approach to genetic testing across many areas of medicine [1]. Especially after US Supreme Court judged that a naturally occurring DNA segment is a product of nature and is not patent eligible merely because it has been isolated [2-4], some panels for multiple gene testing have been developed in several companies, and come to utilized in clinical scenes. Furthermore, items about multiple gene testing have been added on NCCN Guideline 2014 (ver. 2) [5], and it has been recommended in several scientific meetings that the degree of the risk in hereditary cancer syndromes are from moderate to high risk, and triage tools based on several guidelines are available [6-9].

Instead of single gene testing, multigene panel testing (MGP) provides clinicians information about one or more gene variants in a single test. Multiple genes can be analyzed at a lower cost than before, and MGP are becoming widespread.

The clinical validity and utility of MGP is getting better characterized as more data on the significance of moderate-penetrance genes are collected from large, cancer genetic testing studies.

Single Gene Testing

Clients and patients with clinical symptoms or family history suspecting a single hereditary tumor syndrome may only need to be tested for the causative gene of that particular syndrome and may not even need MGP. For example, if the medical history or family history includes adrenocortical cancer or osteosarcoma at a young age, the analysis of TP53, the causative gene of Li-Fraumeni syndrome [10], will be analyzed. If there is a macrocephaly or an esophageal hamartoma, a genetic testing for PTEN, the causative gene of PTEN Hamartoma Tumor Syndrome (PHTS) [11], will be performed.

There is a characteristic phenotype of the syndrome in this way, but in real world it is not always the case. Especially in breast cancer, multiple genes may be differentiated. Breast cancer is a related cancer in Li-Fraumeni syndrome [10] an Cowden syndrome, which is a representative of PHTS [11], but Hereditary Breast and Ovarian Cancer (HBOC) [12, 13] is the most common hereditary breast cancer.

Prior to the spread of MGP, BRCA1/2 genetic testing was first performed in patients with juvenile, bilateral, or strong family history, and if the result was negative (or VUS: variant of uncertain significant), other hereditary tumors were examined. Nowadays, NCCN Guideline shows MGP is required when a client has a possibility of hereditary tumor judging from clinical findings and family history, even if the result of single gene test is negative [14].

On the other hand, even in MGP that tests multiple genes at the same time there is a possibility of mental burden. Patients may have to be prepared for multiple hereditary tumor syndromes at the same time before testing. It is not possible to conclude which method is less psychologically burdensome.

Multigene Panel Testing

There are various types of tests in MGP. Some genes have already been determined to be analyzed, and some genes are individually combined considering from causes of hereditary tumor syndromes suspected from family history or medical history.

In addition, among the MGPs for which analysis genes have already been determined, there are MGPs that include the causative genes of diseases necessary for differential diagnosis and MGPs that comprehensively include the causative genes of he-

reditary tumors [15].

Yoshihama et al. reported a case in Japan where HBOC could not be diagnosed without MGP [16]. On the other hand, according to a paper by Yurgelun MB [17], 37% of the cases in which a pathological variant was found as a result of performing MGP in suspected Lynch syndrome cases showed a pathological variant other than the Lynch syndrome-related gene [18]. BRCA1/2 was the second most common variant other than Lynch syndrome-related genes. The NCCN guidelines indicate that MGP is useful in cases where it is not possible to diagnose by performing a conventional single genetic test based only on the person's clinical symptoms and family history, or when clinical findings overlap.

There are cases where it is better to consider MGP. For example, the paternal family has a large family history of colon cancer and the maternal family has a large family history of breast cancer. MGP is likely to be useful when multiple hereditary tumor syndromes are possible at the same time.

It should be noted that MGP has different types of genes to be examined and different evaluations of variants depending on the testing company. The gene content of MGP offered by testing laboratories vary significantly, and data on mutation detection rates by gene and by the panel is limited, causing confusion among clinicians on which test to order.

Heald B et al. reported that CGA-IGC has published a paper on the selection criteria of the gene panel [19]. In genetic counseling, you may think that there is no big difference between MGP that combines the genes to be analyzed and conventional single genetic testing. However, MGP contains a gene that is said to be at moderate risk, and the client's clinical symptoms may diagnose hereditary tumor syndrome that was unexpected.

Heald B et al. also state that performing MGP increases the identification of clinically responsive Pathogenic Variants (PV), but also increases the proportion of VUS [19]. Because the clinical significance of VUS has not been clarified yet, we should not use the result of VUS for the determination of clinical strategies, but the clinical importance of VUS is supposed to be re-evaluated by interpreting its sequence thereafter.

An MGP study of colorectal cancer stated that the percentage of VUS was 20-30%. Regarding HBOC, Catana also reported that 0.6-88% of VUS was recognized [20]. In addition to the client's wishes, factors that influence the choice of MGP or other genetic testing include the awareness and knowledge of the medical practitioner and client in genetic medicine, and the health insurance system of the country.

Genetic Counseling for Single Gene Testing

Genetic counseling before a genetic testing and that after a genetic testing often differ in content. After the genetic testing, the results will be used to discuss future medical management, relative diagnosis and other genetic testing. On the other hand, before the genetic test, we mainly discuss the following contents.

1) Opportunity to visit

2) Family history

3) How much do you know about hereditary tumors and genetic tests?

4) What do you think about hereditary tumors?

5) Want to carry out a genetic test

6) What kind of measures should be taken after being diagnosed with a hereditary tumor?

7) How to share information with relatives when diagnosed as a hereditary tumor And so on.

If only the causative genes of some hereditary tumor syndromes that are differentiated from family history and clinical symptoms are tested, pre-test genetic counseling may include the types of cancers that are at increased risk, their age, and their pathology. Tell them what you can do if a pathogenic variant is found. There is also the option of not performing genetic testing, suggesting that regular screening, such as breast cancer screening and colonoscopy, can be performed as screening.

Genetic Counseling for MGP

Genetic counseling in conducting MGP requires that genetic counselors not only have a good understanding of the above benefits and problems, but also share them with their clients. For example, in pre-test genetic counseling, whether to perform BRCA1/2 genetic testing, what to do when the results are Pathogenic Variant (PV) or Likely Pathogenic Variant (LPV), and whether to perform risk-reducing surgery. We were able to discuss with the client and share their worries and anxieties.

However, in the case of MGP, it is difficult to talk about all genes or syndromes in detail before the test because the number of genes to be analyzed and the number of syndromes included in the panel are large. Therefore, we will talk about detailed risks and countermeasures after disclosing the results. Hooker, et al reported that cancer genetic counselors are adapting quickly to the changes in genetic testing considering from the results of qualitative analysis that some counselors have altered the counseling session contents, trading depth of information for breadth and spending more time for counseling about uncertainty [21].

Genetic counseling after disclosure of results in conventional genetic testing is important, but that of MGP is considered to be more important. MGP genetic counseling has something in common with traditional ones as follows.

1) Check the client's clinical symptoms and family history in detail before genetic testing (however, some have clinical diagnosis such as FAP and PHTS, and genetic testing is used as a supplement).

2) No matter how many genes are analyzed, the causative gene of an unknown hereditary tumor cannot be denied, so it cannot be said that it is not a hereditary tumor.

3) Limitations of inspection technology

4) Possibility of VUS

MGP includes moderate risk gene group other than high risk one, the former has more VUS than high risk gene group [22]. So, genetic counselors for MGP are forced to say in more uncertain tones of voice than for single gene tests. Although guidelines about moderate gene variants will be issued in future, it is one way for genetic counselors to support clients according to

guidelines for high risk gene variants as well as their preference after explaining less evidence and guidelines about actions for moderate gene group.

Most of the moderate risk genes contained in MGP are found infrequently and no guidelines have been established. The test criteria described in the NCCN guidelines are limited to genes that have long been associated with hereditary tumor syndrome, such as BRCA1/2, MMR genes, and TP53. Inspection criteria are needed to help the client make decisions. Counseling after disclosure of MGP results is more complicated than that of the single gene tests. The reasons are as follows.

1) Unlike the single gene test and single syndrome test, sufficient information and examination have not been provided when a variant is found in a related gene in advance, so genetic counselors have to consider how to support decision-makings of clients on clinical actions after the disclosure of MGP.

2) Since MGP has a large number of genes to be analyzed and also contains a large number of moderate-genes, the proportion of VUS is higher than that of high-risk genes [22].

3) The clinical actions or guidelines for moderate-gene have not been sufficiently established. In the future, as the number of cases increases and data is accumulated, medical management guidelines for moderate-gene will be established. However, now that there is no guideline, we will explain this situation to the client and decide the response according to the client's wishes. At that time, it may be one idea to refer to the management for mutation cases of high-risk gene.

Conclusion

Nowadays, we can obtain the results by NGS more rapidly and less expensively than Sanger Sequencing, and MGP makes us able to diagnose hereditary cancer syndromes that have been missed by single genetic tests for each genetic cancer syndrome. MGP can detect even moderate risk genes other than high risk ones, but with higher incidence of VUS than single gene tests such as BRCA1/2 or MMR. Furthermore, it is a subject to resolve that clinical and mental follow-up steps after diagnosis have not been established yet in the case of moderate risk genes.

Even after MGP shows negative for pathological mutations, it is not always negative for hereditary cancer syndromes. In such cases, it is necessary to respond to clients according to family/past history in the same way as the negative cases of single gene tests. Gene testing is not only for diagnosis of hereditary cancer syndromes, but also for a companion diagnostic tools to determine therapeutic drugs, namely analysis of germline mutations has neither been only for diagnosis of hereditary cancer, nor for the support planning of patients and their family. After all, it is essential to think about how clients want to live after knowing the result of MGP.

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