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The role of genetic counseling on cancer precision medicine

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Advance in genome analysis technology has led to the practical application of clinical sequencing that connects patient's genomic information to clinical applications. In particular, the application of genomic information in clinical medicine is advanced in the field of cancer. In June 2019, two types of gene panel tests used for precision cancer medicine were covered by medical insurance. Comprehensive genetic analysis of cancers, including gene panel testing, is expected not only to lead to selection of optimal therapeutic agents and determine treatment strategies, but also to enable various advances including new drug discovery and biomarker development. However, there are also problems. In comprehensive genetic analysis, a large amount of genetic information can be obtained at one time, and therefore secondary findings (SF) may be detected in addition to the primary findings. Furthermore, comprehensive gene analysis may increase the detection of variants with unknown clinical significance (VUS) and novel variants that have not been previously registered in the database.

In this study, we examined the frequency of VUS, novel variants, and SF obtained from a previous study on cancer precision medicine conducted at the Shizuoka Cancer Center "Project HOPE" and considered the role of genetic counseling.

Chapter 1 of Part 1 describes the frequency and pathogenicity of the mismatch repair (MMR) gene (*MLH1, MSH2, MSH6, PMS2*) variants that cause Lynch syndrome, as detected by germline whole-exon sequence (WES). Three pathogenic variants of the *MMR* gene were detected by germline WES in 1,058 solid cancer patients (about 0.3% of the total and about 0.6% of colorectal cancer cases). This frequency was comparable to those in previous studies. Two of the three pathogenic variants had no database entry. In addition, VUS of the *MMR* gene was detected in 68 of the 1,058 patients (6.4%), and the pathogenicity assessment in the ClinVar database for 16 variants in 2015 was changed in 2018. Pathogenicity assessment using the ClinVar database was consistent with microsatellite instability (MSI) analysis and MMR protein immunohistochemistry (MMR-IHC) results. MMR-IHC and MSI analysis were thought to be useful for evaluating the pathogenicity of VUS variants of the *MMR* gene. In Chapter 2 of Part 1, the novel *MLH1* gene variants detected in Chapter 1 were analyzed to evaluate pathogenicity using reverse transcription polymerase chain reaction. The novel *MLH1* gene variant was determined to be a pathogenic variant and registered in the database. To

provide useful information to clients in genetic counseling, certified genetic counselors should contribute to the construction of a Japanese variant database.

In Part 2, we disclosed SF detected in the Project HOPE study to the patients, and tried to establish SF disclosure procedures, inter-professional collaboration, and genetic counseling systems. Analysis of 1,058 germline WES detected SF in 17 patients [1.6% of the total; hereditary tumors: 11 patients (1.0% of all), non-cancer hereditary diseases according to ACMG v2.0: 6 patients (0.6% of all)]. About half of the patients (8/17 patients) with detected SF had no history of related diseases or family history. Most of the patients to whom SF were disclosed received the results positively and shared information with the relatives. To disclose SF, it is necessary for the attending physician to determine the timing, to respect the will of the patient, to introduce the genetic counseling and surveillance systems for the genetic disease, and to provide a long-term support system for patients and families as well as a consultation service.

Because current precision cancer medicine of Japan targets patients who have completed standard treatment, the patients may have more advanced cancer than those in Project HOPE. Therefore, there is a possibility that SF information may be received more negatively for patients targeted by current precision cancer medicine than for those in Project HOPE. In genetic counseling, it is necessary to explain the clinical utility of the SF and to provide psychological support so that patients and relatives can positively receive their own genetic information. If VUS are detected, certified genetic counselors should explain the possibility of changes in pathogenicity in the future and maintain contact with the patient. In addition, building a system that can share genetic information among medical staff is also required. Generally, germline genetic information should be handled with care due to its characteristics. However, especially in the field of hereditary cancer, germline genetic information can be useful, such as the selection of the way to the treatment of patients and the early detection and prevention of relatives' cancer. In genetic counseling for precision cancer medicine, certified genetic counselors, as a member of the multidisciplinary medical team, need to consider both somatic and germline genetic information collectively as patient’s information for appropriate treatment and prevention of cancer.