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Significance of the Multi-gene Panel myRisk in Japan

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Abstract. *Background/Aim: Hereditary tumors are estimated to account for approximately 5-10% of all tumors. In Europe and the United States, multi-gene panel testing (MGPT) is the standard method used for identifying potential causative genes. However, MGPT it is still not widely used in Japan. The aim of this study was to assess the risk of hereditary tumors in Japanese cancer patients using germline MGPT and provide an overview of MGPT in the Japanese medical system. Patients and Methods: We used the myRiskTM, a 35-gene panel that determines the risk for eight hereditary cancers: breast, ovarian, gastric, colorectal, prostate, pancreatic, malignant melanoma, and endometrial cancers. Results: From June 2019 to March 2020, 21 patients who were suspected to have hereditary tumors were included, based on their family or medical history. Pathogenic variants were found in 7 patients [BRCA1 (5), MSH6 (1), TP 53 (1)]. Conclusion: In this study, despite the small number of participants, we were able to show the significance of MGPT in Japan. Therefore, MGPT should be used for evaluating hereditary tumors in clinical practice.*

Hereditary tumors account for approximately 5%-10% of all tumors (1, 2). Studies have identified many genes conferring a predisposition to inherited tumors with high penetrance, such as *BRCA1*, *BRCA2* (hereditary breast and ovarian cancer: HBOC), *APC* (familial adenomatous polyposis: FAP) (3), *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM* (Lynch syndrome) (4), and *RB1* (retinoblastoma). Advances in next-generation sequencing (NGS) have made it possible to perform genome analysis efficiently and at low cost. As a result, panel tests that analyze multiple genes at once have emerged. There are two types of panel tests used for different purposes: comprehensive cancer genome profiling (CGP) to search for therapeutic agents and biomarkers based on somatic mutations detected in cancer tissues and blood (5), and multi-gene panel testing (MGPT) to identify germline mutations (6).

In Japan, two CGP tools, FoundationOne® CDx (Chugai Pharmaceutical Co., Ltd. Tokyo, Japan) and NCC Oncopanel (Sysmex Corporation, Kobe, Japan), were approved for coverage under the national health insurance system in September 2019 (7, 8) and are becoming widely used in clinical practice. CGP is used to assess biomarkers for therapeutic drugs and resistance, but because this approach involves the simultaneous analysis of many genes at once, it may occasionally find germline pathogenic variants (secondary findings; SFs) (9, 10). Indeed, studies have reported that a SF occurred in approximately 4%-15.7% (5, 11) of patients who underwent CGP.

Over the last 20 years (6), germline genetic testing has become widespread. In the past, when a hereditary tumor was suspected, candidate genes predicted from the medical and family history were clinically tested one by one, but this can now be simplified through the availability of MGPT (2). Although MGPT is not currently covered under the national health insurance system in Japan, it is highly anticipated to become widely used in the future. However, most information obtained about MGPT in recent years has been based on the results of research in Western countries (6), and no substantial data on MGPT in the Japanese population are available.

Even in patients with suspected hereditary tumors based on family and past medical history, detection of the causative gene is sometimes difficult when testing genes individually. In such cases, MGPT is beneficial because it can investigate

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many genes in a single procedure and thus reduces the economic and psychological burden on the patient.

The aim of this study was to assess the risk of hereditary tumors in Japanese cancer patients and their family members to provide appropriate information on mutation and risk management using a germline MGPT, to comprehensively evaluate genes and parameters associated with hereditary tumors and to develop a system to carry out MGPT in our institute.

Patients and Methods

From March 2019 to March 2020, patients suspected of having hereditary tumors in Kyushu University Hospital were enrolled for clinical research. A family history of cancer was surveyed from first- to third-degree relatives with reference to the National Comprehensive Cancer Network (NCCN) guidelines for Genetic/Familial High Risk Assessment, Version 1, 2021 (12). Patients who provided written informed consent were included in the study, and clinical information, such as age, sex, height, weight, family history, blood test results (WBC, RBC, Hb, Ht, Plt, tumor markers), operative procedure, histopathology, perioperative chemotherapy, history of radiation and drug therapy, and prognosis, was collected from the clinical records. Patients recruited for this study were able to receive genetic counseling if they wished. The study conformed to the principles of the Declaration of Helsinki and was approved by the genome-related Institutional Review Board (IRB) of Kyushu University Hospital (No. 768-00). All patients had the option of confirming their desire to continue with the study or could choose to withdraw from it at any time. The IRB approved this consent procedure.

Multi-gene panel. In this study, we used the Myriad myRisk™ Hereditary Cancer test (Myriad Genetics, Inc., Salt Lake City, UT, USA) to analyse germline mutations. The myRisk™ is a 35-gene panel (*BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC*, *MUTYH*, *CDKN2A*, *CDK4*, *TP53*, *PTEN*, *STK11*, *CDH1*, *BMPR1A*, *SMAD4*, *PALB2*, *CHEK2*, *ATM*, *NBN*, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*, *POLD1*, *POLE*, *GREM1*, *HOXB13*, *AXIN2*, *GALNT12*, *RPS20*, *RNF43*, *NTHL1*, and *MSH3)* that determines the risk for eight hereditary cancers: breast, ovarian, gastric, colorectal, prostate, pancreatic, malignant melanoma, and endometrial cancers. Samples of peripheral blood (7 ml) were collected and transported *via* FALCO Biosystems Ltd. (Kyoto, Japan) to Myriad Genetics, Inc. (MGI), in the United States, where DNA was extracted and analyzed using NGS. The results were evaluated and reported based on the MGI database.

A total of 21 patients were tested with myRisk™. Sixteen patients (76%) were suspected of having hereditary tumors based on past and family history. The other five patients (24%) had undergone CGP in which a suggestive SF had been obtained before they entered this study.

The genetic team of our institution has identified 42 genes associated with a SF according to the American College of Medical Genetics (ACMG) (13), the European Society for Medical Oncology (ESMO) Recommendations (10), or the NCCN guidelines (12, 14).

Results

The characteristics of the 21 patients who underwent myRisk™ analysis are shown in Table I. They included 20 female patients and one male patient. The ages of the patients ranged from 30 to 87 years. Breast cancer was the most common tumor type in this study, affecting a total of 19 individuals. Of these 19 patients, 6 had bilateral breast cancer and 6 had a combination of breast cancer and other tumors, which included pancreatic cancer (#2), gastric cancer (#7), thyroid cancer (#8), endometrial cancer (#11), malignant lymphoma and SCC (#14), and ovarian cancer (#21) (Table II). The other three patients had pancreatic cancer (#3 and #12) and one had colorectal cancer (#4).

Table I. *Clinical characteristics*.

Age at testing (years), median (range)	64 (30-87)		
Sex			
Female	20		
Male	1		
Tumor type			
BC	13	Bilateral BC	6
Pancreatic cancer	1		
CRC	1		
BC and pancreatic cancer	1		
BC and gastric cancer	1		
BC and ovarian cancer	1		
BC and thyroid cancer	1		
BC and endometrial cancer	1		
BC, ML, CRC, and SCC	1		
Cancer genome profiling			
Yes (FoundationOne® CDx)	5		
No	16		

BC: Breast cancer; CRC: colorectal cancer; ML: malignant lymphoma; SCC: squamous cell carcinoma.

Of the 21 patients, seven had pathogenic variants (PVs) and 16 had variants of uncertain significance (VUS). Three patients had neither PV nor VUS. The seven PVs included five in *BRCA1*, one in *MSH6*, and one in *TP53* (Table II). As shown in Table II, 13 genes (*AXIN2*, *MSH3*, *BRIP1*, *NBN*, *BARD1*, *BRCA2*, *MSH6*, *MLH1*, *CDH1*, *NTHL1*, *GALNT12*, *RNF43,* and *STK11*) were identified to feature VUS in 16 patients. All patients with a PV detected with myRisk™ underwent genetic counseling.

Discussion

Approximately 10 years after the emergence of MGPT, various commercial panels are being developed and others are widely used in clinical practice (15), especially in the United States. Regarding genetic medicine in Japan, BRACAnalysis was indicated for patients with breast and ovarian cancer who met certain criteria in 2020 (16). However, the cost of MGPT for patients is not covered by the Japanese national health insurance and remains expensive.

In Japan, there are no established indications for MGPT. Therefore, MGPT has been performed in only a limited number of institutions and data on MGPT in Japan remain

Table II. *Clinical characteristics and genetic findings of all 21 patients.*

No.	Age	Sex	Tumor type	PV				VUS											
				Gene	Cording DNA	Protein	Protein change	*AXIN2*	*MSH3*	*BRIP1*	*NBN*	*BARD1*	*BRCA2*	*MSH6*	*MLH1*	*CDH1*	*NTHL1*	*GALNT12*	*RNF43*	*STK11*
1	37	F	BC	*BRCA1*	c.190T>C	p.Cys64Arg	Missense	Ms												
2	67	F	BC, pancreatic cancer	*BRCA1*	c.188T>A	p.Leu63*	Nonsense		Ms											
3	42	F	BC							Ms	D									
4	68	M	CRC								Ms									
5	81	F	BC (metachronous bilateral)							Ms										
6	72	F	BC (metachronous bilateral)										Ms							
7	64	F	BC, gastric cancer	*BRCA1*	c.81-1G>A	-	Splice acceptor													
8	72	F	BC, thyroid cancer											Ms						Ms
9	45	F	BC (metachronous bilateral)												Ms					
10	35	F	BC (metachronous bilateral)	*BRCA1*	c.2679_2682del	p.Lys893Asnfs*106	Frameshift									Mic				
11	71	F	BC, endometrial cancer	*MSH6*	c.3404dup	p.Asn11236Lysfs*28	Frameshift													
12	50	F	Pancreatic cancer	*BRCA1*	c.5154G>T	p.Trp1718Cys	Missense											Ms		Ms
13	55	F	BC															Ms	Ms	
14	87	F	BC, ML, colon cancer, SCC										Ms							
15	42	F	BC																	
16	48	F	BC																	
17	30	F	BC (metachronous bilateral)	*TP53*	c.613T>C	p.Tyr205His	Missense	D			Ms									Ms
18	43	F	BC																	
19	71	F	BC											Ms						
20	66	F	BC (metachronous bilateral)										Ms							
21	70	F	BC, ovarian cancer					Ms	Ms										Ms	Ms

PV: Pathogenic variant; F: female; M: male; VUS: variant of uncertain significance; BC: breast cancer; CRC: colorectal cancer; ML: malignant lymphoma; SCC: squamous cell carcinoma; Ms, Missense; D, Duplication; Mic, Microsatellite.

Table III. *Commercial multi-gene panel tests*.

Company	Head office	Type of panel	Reference
ACTmed	Japan	ACTRisk Care (67 genes) ACTRisk (31 genes)	(24)
Labcorp	USA	VistaSeq (11 types)	(21)
Invitae	USA	Multi-Cancer Panel (84 genes)	(1)
Igenomix	Spain	Precision Panel (Maximum 174 genes, 11 types)	(25)
Ambrey Genetics	USA	CancerNext	(22)
Myriad Genetics	USA	myRisk™ (35 genes)	(16)
GeneDx	USA		(26)
Baylor	USA		(15)
Color	USA	Color Hereditary Cancer Test (30 genes)	(1)

limited. In this study, we performed myRisk™ on 21 Japanese patients with suspected hereditary tumors. Of these 21 patients, 7 (33%) had PVs and 16 (76%) had VUS. All seven patients with PVs received genetic counseling and were offered surveillance and/or preventive options depending on their clinical condition. One patient had a PV in *TP53* that had not been previously reported, thus genetic testing of her parents was also performed, which led to a diagnosis of Li-Fraumeni syndrome.

Prior to the advent of MGPT in 2013, MGI conducted several genetic tests related to HBOC (*BRCA1/2*) from 1997 and to Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*) from 2002. MGI introduced MGPT that included 25 genes in 2013 (17), to which three genes (*POLD1*, *POLE*, *GREM1*) were added in 2017. As reported by Rosenthal *et al*., of the approximately 250,000 people who have undergone genetic testing with myRisk™, 6.7% had PVs (18). In addition, 4.7% of unaffected individuals had a PV, and approximately 30% of all test results featured one or more VUS. The MGPT can identify several VUS, because it analyses many genes, with insufficient understanding of their functions. Kurian *et al*. reported that VUS rates in MGPT ranged from 33% to 40% (6). The lack of clear recommendations for patients with VUS means that their management is left up to the individual physician's judgement. Myriad continues to reclassify VUS using their system called the myVision Variant Classification program. In 2016, more than 10,000 variants were reclassified and corresponding clients were notified of this change (19). It is important to track VUS assessments and notify clients when a VUS that they possess is reclassified.

Other commercial panels for hereditary tumors in addition to myRisk™ are available, as summarized in Table III. Of the different panel tests that have been developed, each contains a different number of genes. However, since 2018, only BRACAnalysis has been accepted as a companion diagnostic for olaparib in Japan, and in this study, we chose to focus on myRisk™ , a test based on the extensive Myriad database.

One of the reasons why MGPT is not widely used is that it is considered to be expensive. In practice, however, when individual genes are tested one by one, the cost of tests regarding two to three genes is almost the same as that of MGPT. In addition, Li *et al*. (20) reported that it was cost-effective to assume that PVs are successfully identified using MGPT, based on which appropriate medical management can be selected (prophylactic resection, surveillance with magnetic resonance imaging). In 2020, BRACAnalysis began to be covered by the national health insurance for patients who have already developed primary breast or ovarian cancer, and meet certain criteria for HBOC (16). Therefore, BRACAnalysis is currently more accessible than MGPT for HBOC-suspected cancer patients. However, Castéra L *et al*. (21), focusing on HBOC for example, performed MGPT on patients with suspected hereditary breast cancer based on past and family history, and found that approximately half of patients with PVs had *BRCA1/2* variants, followed by those with variants in *CHECK2* (7.6%), *ATM* (7.0%), and *PALB2* (5.9%), which are high-to-moderate-penetrance variants in breast cancer. In other words, these genes would be missed by a single testing for *BRCA1/2* alone. Although this study included only 21 participants, which was not a large cohort, it may be representative of the Japanese population.

In conclusion, this study showed that MGPT is useful for evaluating hereditary tumors in a single process because it reduces the time and psychological burden on patients. However, the practice of managing hereditary tumors requires the involvement of various departments, such as Surgery, Oncoplastic surgery, Obstetrics and Gynaecology, Gastroenterology, Radiology, Pathology, and Diagnostics. Therefore, we should consider using MGPT for patients and their family suspected of having hereditary disease in the near future.

Conflicts of Interest

There are no conflicts of interest to declare regarding this study.

Authors' Contributions

SH and M Kubo conceived and designed the study; SH, M Kubo, SM, M Kai, TM, MY, KK, YT, AS, KN and YM analyzed the data; SH and M Kubo drafted the manuscript; MN provided intellectual input.

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