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Research Report

Tumor *BRCA* testing can reveal a high tumor mutational burden related to *POLE* pathogenic variants

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ABSTRACT

Objective: Tumors harboring a *POLE* pathogenic variant, associated with high tumor mutational burden, are good candidates for immunotherapy. However, *POLE* pathogenic variants are not currently screened in routine clinical practice. Can these tumors be identified by means of an already available test?
Methods: We describe seven tumors harboring a *POLE* pathogenic variant, among eight patients with tumors harboring multiple *BRCA1/2* variants (from 4 to 20). All patients were managed at Institut Curie, Paris. Five patients were selected because of unexpected tumor *BRCA* testing results with multiple variants and another three patients were selected because of a *POLE* pathogenic variant detected by large tumor testing. We looked for other tumor variants by Next-Generation Sequencing in tumors harboring multiple *BRCA1/2* variants, and for multiple *BRCA1/2* variants in tumors harboring a *POLE* pathogenic variant.
Results: Four of the five tumors selected because of multiple *BRCA1/2* variants exhibited a *POLE* pathogenic variant, and all three tumors selected for *POLE* pathogenic variants exhibited multiple *BRCA1/2* variants.
Conclusions: Tumor *BRCA* testing could be a way to detect tumors harboring a highly mutagenic *POLE* pathogenic variant.

1. Introduction

Tumor genetic testing, allowing personalized treatment, is a rapidly growing field. Tumor *BRCA* testing is already performed routinely, especially in high-grade ovarian cancers, as identification of a pathogenic variant (PV) of *BRCA1/2* genes may guide treatment towards PARP inhibitors. (Konstantinopoulos et al., 2020) Tumors usually harbor no more than one *BRCA1/2* variant.

POLE and *POLD1* genes both code for DNA polymerases involved in DNA proofreading and repair. Some PV in the exonuclease domain have been described as drivers in various types of ultramutated tumors. (Campbell et al., 2017; Kandoth et al., 2013; Network, 2012; Briggs and Tomlinson, 2013) These tumors exhibit a specific molecular signature: tumors with *POLE* PV are enriched in [TCT → A] and [TCG → T] and tumors with *POLD1* PV are enriched in [TCT → A] and [TCA → A]. Their high tumor mutational burden (TMB) makes them good candidates for immunotherapy. (Alexandrov et al., 2013; Mehnert et al., 2016) They may also be associated with a better prognosis. (Van Gool et al., 2018; Domingo et al., 2016; Hoang et al., 2015) Identification of these tumors therefore has prognostic and therapeutic implications. Families with germline *POLE* PV, responsible for predisposition to various types of cancers, including colorectal and gynecologic tumors, have also been described. (Briggs and Tomlinson, 2013; Hansen et al., 2015) However, most tumor *POLE* PV are detected in the context of research studies, as they are not currently screened in routine clinical practice, but what if these tumors could be identified by means of an already available test: tumor *BRCA* testing? For the first time, we describe seven tumors with multiple *BRCA1/2* variants associated with a *POLE* PV.

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2. Materials and methods

Patient selection:

Patients were identified in two different ways.

First, we selected patients with more than 4 *BRCA1/2* gene variants from a group composed of 1300 patients who underwent routine tumor *BRCA* testing at Institut Curie between December 2017 and July 2020 (mainly for ovarian cancers). We subsequentially looked for other variants in their tumors using a large Next-Generation Sequencing (NGS) panel.

Second, we selected patients with a *POLE* or *POLD1* PV from a group composed of 1009 patients with different types of cancer who underwent large NGS tumor analysis between July 2019 and July 2020 and reviewed their *BRCA1/2* results.

All patients included in this study were managed at Institut Curie and provided written consent for research including genetic analysis. This project was approved by the local IRB.

Tumor analysis:

Tumor DNA was extracted from formalin-fixed and paraffin-embedded (FFPE) tumor tissue.

Tumor *BRCA* testing was performed by targeted NGS encompassing the full coding sequences of *BRCA1/2* genes. All variants with depth $\geq$ 300X and variant allelic frequency (VAF) $\geq$ 5% were retained, regardless of the ACMG class, as we wanted to detect passenger variants reflecting TMB and mutagenesis (excluding polymorphisms which can be germline variants).

Large tumor analysis was performed with an in-house NGS panel, which allows molecular analysis of tumors for microsatellite instability, TMB and mutational signatures. (Alexandrov, 2020) All variants with depth $\geq$ 200X, VAF $\geq$ 5% and population frequency less than 0.5% in gnomAD were validated.

Methods are described in detail in the supplementary material (s1).

3. Results

In the first group (1300 patients with routine tumor *BRCA* testing), we identified 5 tumors with more than 4 different *BRCA1/2* variants. Use of the large NGS panel detected a *POLE* PV in 4 of these 5 tumors. No *POLD1* PV was detected.

In the second group (1009 patients with large NGS panel analysis), we identified 3 tumors with a *POLE* PV, all of which exhibited at least 4 *BRCA1/2* variants. No *POLD1* PV was detected.

We therefore report a total of 7 tumors (6 gynecologic and 1 colorectal) with co-occurrence of a *POLE* PV and multiple *BRCA1/2* variants. Patient characteristics are shown in Table 1 and described in detail in supplementary material (s2).

Molecular results are shown in Table 2. The 7 tumors harbored multiple *BRCA1/2* variants (from 4 to 20) with a mean of 8.4 variants per tumor, mostly corresponding to variants of uncertain significance (78%). All tumors harbored a *POLE* PV with a VAF ranging from 25% to 39%. All tumors but two (unavailable signature) had an Alexandrov mutational signature 10, corresponding to the *POLE* signature (Fig. 1) and all had a high TMB (from 92 to 841 variants/Mb) with a mean of 312 variants/Mb per tumor (greater than 15 variants/Mb cut-off).

Three different *POLE* variants were identified in these 7 tumors: c.890C > T, p.(Ser297Phe), c.857C > G, p.(Pro286Arg) and c.1231G > T, p.(Val411Leu). These variants have already been classified as drivers in ultramutated tumors. The c.857C > G, p.(Pro286Arg) variant was found in 5 different tumors, which is not surprising as it is a known hotspot variant. (Campbell et al., 2017)

All gynecologic tumors were of the endometrioid subtype (or mixed with a predominant endometrioid subtype). Pathology review of all cases failed to identify any characteristic pathologic features for these *POLE*-associated tumors.

Five of the 7 patients also underwent germline analysis, which did

Table 1
Main patient and tumor characteristics at diagnosis.

Patient	Sex	Cancer site (age)	Cancer type	Cancer grade	Cancer stage	MMR IHC	Unstable markers[a]	Other significant medical history[b] (age)	Family history of cancer (age)
1	F	Ovary (53)	Endometrioid	2	FIGO IA	No loss	NA	No	Maternal grandfather: lung cancer (55), maternal uncle: prostate cancer (60), maternal niece: borderline ovarian cancer (47), maternal niece: renal cancer (35)
2	F	Ovary (43)	Endometrioid	3	FIGO IA	No loss	0/5	No	Paternal grandfather: colorectal cancer, paternal uncle: lymphoma, paternal uncle: gastric cancer
3	F	Endometrium (52)	Mixed, predominantly endometrioid	NA	FIGO IA	NA	NA	G0P0, hypertension, type 2 diabetes, overweight	Sister: lung cancer
4	F	Endometrium (65)	Endometrioid	2	FIGO IIIC1	No loss	0/5	G0P0, hypertension, smoking, invasive ductal breast carcinoma (65), small-cell lung carcinoma (71)	No
5	F	Endometrium (51)	Endometrioid	3	FIGO IIIC2	Loss of MSH6	2/5	No	Maternal uncle: pancreas cancer (68), paternal uncle: chronic lymphocytic leukemia (61) + vesical cancer (63)
6	F	Endometrium + ovary (54)	Mixed, predominantly endometrioid	3	FIGO IA + FIGOA IA	No loss	0/5	G0P0	Father: colorectal cancer (67), paternal uncle: prostate cancer (74), maternal grandmother: endometrial cancer (74), maternal aunt: endometrial cancer (80)
7	M	Rectum (31)	Adenocarcinoma	1	T4N0M0	No loss	0/5	No	No

F: female, M: male, MMR IHC: Mismatch repair immunohistochemistry, NA: not available
BRCA testing was performed first in patients 1, 2, 4 and 6 and large NGS tumor analysis was performed first in patients 3,5 and 7.
[a] by Pentaplex analysis
[b] only other cancers and risk factors for the cancer studied are reported here

Table 2
Molecular results of *BRCA1/2* and *POLE* testing.

Patient	*POLE* pathogenic variant (NM_006231.2)			TMB (variants/Mb)	*BRCA1* variants (NM_007294.3)				*BRCA2* variants (NM_000059.3)			
	Variant		VAF (%)		Variant		VAF (%)	Class[a]	Variant		VAF (%)	Class[a]
1	c.890C>T	p.(Ser297Phe)	25	841	c.5338C>A	p.(Leu1780Met)	6.8	3	c.1475C>T	p.(Ser492Phe)	13.7	3
					c.4485-31G>A	p.?	36.3	3	c.2046C>A	p.(=)	33.8	3
					c.3890C>A	p.(Ser1297Tyr)	19.4	3	c.2246G>T	p.(Ser749Ile)	7.6	3
									c.2432A>C	p.(Lys811Thr)	40.7	3
									c.3364G>T	p.(Gly1122*)	15.3	5
									c.3614C>A	p.(Ser1205Tyr)	5.1	3
									c.5362T>A	p.(Ser1788Thr)	34.9	3
									c.6430G>T	p.(Glu2144*)	16.2	5
									c.7987G>T	p.(Glu2663*)	19.0	5
									c.8360G>A	p.(Arg2787His)	33.6	2
									c.9132T>G	p.(Ile3044Met)	18.6	3
									c.9239C>T	p.(Ser3080Phe)	6.3	3
2	c.857C>G	p.(Pro286Arg)	36	566	c.5468-25C>T	p.?	11.8	3	c.632-16A>C	p.?	39.6	3
					c.5280C>A	p.(=)	6.0	3	c.2458G>T	p.(Asp820Tyr)	12.8	2
					c.5238C>A	p.(His1746Gln)	15.3	3	c.3337G>T	p.(Glu1113*)	16.7	5
					c.2961G>T	p.(Lys987Asn)	12.7	3	c.3912T>G	p.(=)	18.5	3
					c.2162T>G	p.(Phe721Cys)	15.3	3	c.4219G>T	p.(Glu1407*)	16.9	5
					c.2152C>A	p.(Leu718Ile)	15.8	3	c.4939A>G	p.(Thr1647Ala)	35.4	3
					c.1788C>T	p.(=)	15.1	3	c.5071A>C	p.(Lys1691Gln)	12.7	3
									c.5228G>A	p.(Ser1743Asn)	16.9	3
									c.5634C>T	p.(=)	13.5	3
									c.5801A>C	p.(Gln1934Pro)	17.4	3
									c.6952C>T	p.(Arg2318*)	18.2	5
									c.8009C>T	p.(Ser2670Leu)	17.4	5
									c.9625C>A	p.(Pro3209Thr)	18.7	3
3	c.857C>G	p.(Pro286Arg)	27	170	c.3798C>T	p.(=)	33.1	2				
					c.2286A>G	p.(=)	29.5	3				
					c.1934C>T	p.(Ser645Phe)	7.2	3				
					c.842G>T	p.(Ser281Ile)	6.0	3				
4	c.857C>G	p.(Pro286Arg)	39	106	c.1342C>A	p.(His448Asn)	24.1	3	c.4790C>A	p.(Ser1597Tyr)	8.4	3
									c.5719T>G	p.(Ser1907Ala)	8.1	3
									c.8524C>T	p.(Arg2842Cys)	32.8	3
5	c.1231G>T	p.(Val411Leu)	34	283	c.4358-2782C>T	p.?	32.3	2	c.2841G>A	p.(Leu947=)	32.2	3
									c.426-82G>T	p.?	24.9	2
									c.5602G>T	p.(Asp1868Tyr)	36.8	3
									c.2191G>T	p.(Glu731Ter)	33.7	3
									c.5982A>C	p.(Gln1994His)	31.8	3
6	c.857C>G	p.(Pro286Arg)	30	92					c.2451G>T	p.(Lys817Asn)	25.6	3
									c.3662C>T	p.(Ser1221Phe)	24.2	3
									c.5550A>C	p.(Lys1850Asn)	12.0	3
									c.7850G>T	p.(Arg2617Ile)	27.5	3
7	c.857C>G	p.(Pro286Arg)	26	128	c.2586G>T	p.(Lys862Asn)	29.2	3	c.7008-63C>T	p.?	5.1	2
					c.1762A>C	p.(Ser588Arg)	12.9	3	c.4177G>A		6.8	3

(*continued on next page*)

Table 2 (*continued*)

Patient	*POLE* pathogenic variant (NM_006231.2)		TMB (variants/Mb)	*BRCA1* variants (NM_007294.3)			*BRCA2* variants (NM_000059.3)		
	Variant	VAF (%)		Variant	VAF (%)	Class[a]	Variant	VAF (%)	Class[a]
							p.(Ala1393Thr)		
							c.2419G>A p.(Val807Ile)	6.7	3
							c.6755C>A p.(Ser2252Tyr)	5.8	3

VAF: variant allelic frequency

[a] variants are classified according to ACMG guidelines: class 1 = benign, class 2 = likely benign, class 3 = uncertain significance, class 4 = likely pathogenic, class 5 = pathogenic

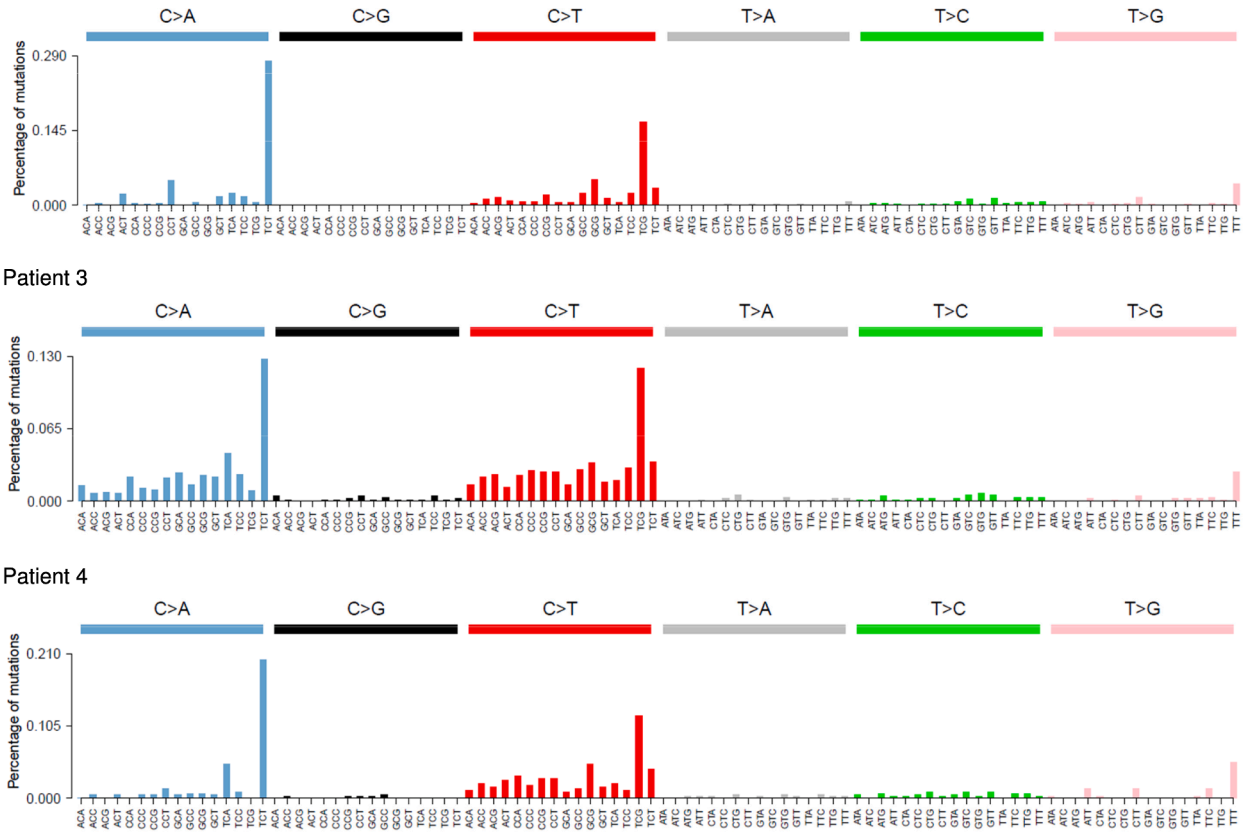

Fig. 1. Tumor signatures. All five signatures exhibit a peak in [TCT → A] and [TCG → T], corresponding to the POLE signature. Signatures could not be computed for 2 patients, i.e. patients 1 and 7. Patient 2 had ovarian cancer, patients 3, 4 and 5 had endometrial cancers, patient 6 had ovarian and endometrial cancer.

not reveal any *POLE* or *BRCA1/2* variants. Moreover, the breast tumor of patient 4, who developed multiple cancers, was also analyzed by the large NGS panel and no *POLE* PVs, *BRCA1/2* variants or high TMB were detected.

MSH2 and *MSH6* PVs were also found in the tumor of patient 5 together with microsatellite instability, although germline analysis of these genes was normal. The tumor mutational signature is typical of a tumor driven by the *POLE* variant p.(Val411Leu) (i.e. signature 5; Fig. 1), but the contribution of a mutational signature associated with loss of mismatch repair cannot be excluded, as described by Haradhvala *et al.* (Haradhvala et al., 2018)

4. Discussion

We report 7 patients with ovarian, endometrial or colorectal cancer exhibiting a tumor *POLE* PV associated with multiple tumor *BRCA1/2* variants. Each tumor also harbored a high TMB, MSS status (except for one tumor) and the molecular signature associated with *POLE* exonuclease deficiency was detected in all of the 5 tumors for which this signature could be computed, confirming the role of *POLE* in the oncogenesis of these tumors.

Five out of 7 tumors presented the c.857C > G, p.(Pro286Arg) *POLE* PV. This recurrent variant is found in 122 samples in the Cosmic database, including 87 endometrial cancers.

As we did not observe any characteristic pathologic features associated with these tumors, pathologic examination does not appear to be an informative tool to distinguish these tumors. However, it could be useful to investigate a deep learning-based approach on a greater number of tumors. (Courtiol et al., 2019) It should be noted that all of the gynecologic tumors described here were of the endometrioid subtype (including the ovarian tumors).

A new classification of endometrial cancers based on immunohistochemistry and variant analysis identified four groups of patients including the group of endometrial carcinomas with *POLE* PVs,

characterized by their excellent prognosis (Alexa et al., 2021). However, they often have an aggressive presentation and patients usually receive intensive therapy based on stage and pathology. (Kandoth et al., 2013; Van Gool et al., 2018) It is therefore essential to identify these tumors in order to consider de-escalation of adjuvant therapy to avoid over-treatment. Tumor *BRCA* testing could be integrated into the new classification strategy for endometrial cancer.

POLE alterations seem to be a rare event in endometrioid ovarian cancers, but they are also suspected to be associated with a better prognosis, although this association has not been formally demonstrated. (Hoang et al., 2015) Tumor *BRCA* testing is already performed routinely and recommended for all ovarian cancers, as PARP inhibitor treatment may be indicated when a *BRCA1/2* PV is detected. (Konstantinopoulos et al., 2020) Tumors usually harbor no more than one *BRCA1/2* variant. We suggest that 4 or more *BRCA1/2* tumor variants should indicate the need for further investigations, especially screening for an associated *POLE* PV, which could allow identification of tumors that may have a better prognosis, as well as potential good candidates for immunotherapy. These analyses could be the basis for a new classification for endometrioid ovarian cancers, mimicking endometrial cancers. To the best of our knowledge, immunotherapy has never been used for ovarian cancer harboring a *POLE* PV, but could constitute a new treatment option for these patients. Moreover, a combination of immunotherapy and PARP inhibitors could be proposed in patients with a tumor harboring *BRCA1/2* PV associated with *POLE* PV.

Like endometrial carcinomas, colorectal cancers with *POLE* PVs appear to constitute an immunogenic subset of colorectal cancers characterized by a good prognosis. It may also be clinically relevant to identify these tumors. (Domingo et al., 2016)

Families with germline *POLE* PVs, responsible for a predisposition to various cancers, including colorectal and gynecologic tumors, have been described. (Briggs and Tomlinson, 2013; Hansen et al., 2015) Patients with tumors harboring a *POLE* PV should therefore have access to germline genetic testing.

In conclusion, tumor *BRCA* testing appears to be an easy, affordable and already available way to detect ultramutated tumors harboring a *POLE* PV who would be eligible for immunotherapy, as the number of *BRCA1/2* variants reflects the TMB. We believe that this approach should be considered in other tumor types, especially in endometrioid endometrial carcinomas.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2021.100855.

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