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Original contribution

Targeted gene sequencing of Lynch syndrome–related and sporadic endometrial carcinomas☆,☆☆

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Summary About one-third of endometrial carcinomas (ECs), mainly of endometrioid histology, harbor the mismatch repair (MMR) defects and microsatellite instability (MSI). Among these, ECs arising in women with Lynch syndrome (LS) account for a large proportion. To date, no somatic genetic analyses have been published comparing LS-ECs with sporadic ECs. In this work, we examined the mutational profiles of a well-characterized series of sporadic and LS-related ECs, performing exonic targeted sequencing of 16 genes mainly involved in MSI ECs. Next-generation sequencing analysis was performed in 35 ECs on the MiSeq platform (Illumina, San Diego, CA), and the mutational profile was analyzed integrating molecular and immunohistochemical data. *PTEN*, *ARID1A*, and *ARID2* were the most frequently mutated genes regardless of MSI status or family history. MSI ECs showed a higher mutational load than MMR-proficient cases, exhibiting an MMR-deficient mutational signature. Among MSI tumors, LS-related and sporadic ECs exhibited similar mutational profiles, with *MSH2* as the most commonly mutated gene. *KRAS* mutations seemed to be more common in sporadic MSI ECs than in LS-related ECs even if further studies are needed to confirm this finding. MMR-deficient ECs carried a higher mutational load and an excess of C>T transitions compared with MMR-proficient ECs, suggesting that the use of a small gene panel may be adequate to highlight significant differences between these 2 groups. An integrated analysis of genetic and epigenetic features of LS-related and sporadic ECs provides useful insights into disease biology and diagnostic classification of these tumors.

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1. Introduction

Endometrial cancers (ECs) are the most prevalent gynecologic malignancies in the developed world and have dramatically increased over the last decades [1]. This increase has been attributed at least in part to the global epidemic of obesity and is mainly confined to the most common histological subtype, that is, endometrioid endometrial carcinoma (EEC), the prototype of type I estrogen-dependent ECs.

EECs exhibit very different clinicopathological features and pathogenic mechanisms from type II ECs that mainly include non–estrogen-dependent serous carcinomas (SCs) and clear cell carcinomas. Recently, many efforts have been devoted to obtain a molecular classification of ECs [2-7], proving that this approach may be very useful to identify distinct EC subtypes in terms of biological and clinical features. In 2013, the Cancer Genome Atlas Network published the most comprehensive genomic, transcriptomic, and proteomic characterization ever reported on ECs [8], stratifying 232 fully evaluable cases into 4 main distinct molecular subgroups: an ultramutated/POLE mutant group (7%), a hypermutated/microsatellite-unstable (MSI) tumors group (28%), copy number–low microsatellite-stable (MSS) ECs (39%), and a copy number–high MSS tumors (26%), the latter consisting mostly of high-grade SCs or of grade 3 EECs.

Currently, a poorly investigated issue is the somatic genetic analysis of ECs arising in women with Lynch syndrome (LS), accounting for about 5% of all ECs [9,10]. To date, no studies

Table 1 Clinicopathological and molecular information of 35 ECs

Group	ID	Subsite	Age	Histotype	pT	pN	G	MSI test	MMR IHC defect	MLH1 methylation	Germline variant
LS	1	C/F	55	E	1a	0	1	H	MLH1-PMS2	M	MLH1
	2	C/F	46	E	1a	0	1	H	MLH1-PMS2	M	MLH1
	3	C/F	67	E	1a	0	1	H	MLH1-PMS2	U	MLH1
	4	C/F	46	E	1a	0	2	H	MSH2-MSH6	–	MSH2
	5	C/F	64	E	1a	0	1	H	MLH1-PMS2	M	MLH1
	6	C/F	63	E	1a	0	2	H	MSH2-MSH6	–	MSH6
	7	C/F	31	E/CC	1b	1	3	H	MSH2-MSH6	–	MSH2
	8	C/F	33	E	1a	1	3	H	MSH2-MSH6	–	MSH2
	9	C/F	42	E	1a	0	2	H	MLH1-PMS2	–	PMS2
	10	C/F	58	E	–	–	3	H	MSH2-MSH6	–	MSH2
	11	C/F	55	E	1a	0	2	H	MSH2-MSH6	–	MSH2
	12	C/F	51	E	1b	X	1	H	MSH2-MSH6	–	MSH2
	13	I	41	E	–	–	3	H	MSH2-MSH6	–	MSH6
	14	C/F	54	E	–	–	2	H	MLH1-PMS2	U	MLH1
	15	C/F	37	E/S	–	–	3	H	MSH2-MSH6	–	MSH6
	16	C/F	45	E	1b	0	1	MSS	MSH6	–	MSH6
	17	C/F	65	E	–	–	3	MSS	MSH6	–	MSH6
	18	C/F	61	E	1a	0	2	H	Pro-MMR	U	MLH1
	19[a]	C/F	69	E	1a	0	2	H	MLH1-PMS2	U	Not found
	20[a]	C/F	56	E	–	–	3	H	MSH2-MSH6	–	Not found
Sporadic MSI	21	C/F	64	E	1a	0	1	H	MLH1-PMS2	M	–
	22	C/F	71	E	1a	0	2	H	MLH1-PMS2	M	–
	23	C/F	54	E	1b	0	3	H	MLH1-PMS2	M	–
	24	C/F	62	E	1a	0	1	H	MLH1-PMS2	M	–
	25	C/F	68	E	3a	0	2	H	MLH1-PMS2	M	–
Sporadic MSS	26	C/F	48	E	1a	0	1	MSS	Pro-MMR	–	–
	27	C/F	67	E	1a	0	2	MSS	Pro-MMR	–	–
	28	C/F	55	E	1b	0	2	MSS	Pro-MMR	–	–
	29	C/F	52	E	2	0	2	MSS	Pro-MMR	–	–
	30	C/F	60	E	1a	–	1	MSS	Pro-MMR	–	–
	31	C/F	70	E	1a	0	2	MSS	Pro-MMR	–	–
	32	C/F	57	E/Muc/S	–	1	3	MSS	Pro-MMR	–	–
	33	C/F	72	E	1a	0	2	MSS	Pro-MMR	–	–
	34	C/F	53	E	1a	–	1	MSS	Pro-MMR	–	–
	35	C/F	56	E	1a	–	1	MSS	Pro-MMR	–	–

NOTE. No metastatic cases were observed. All these data have been collected in our previous works as detailed in the text.
Abbreviations: C/F, corpus/fundus; I, isthmus; E, endometrioid histotype; CC, clear cell histotype; S, serous histotype; Muc, mucinous histotype; H, microsatellite unstable; MSS, microsatellite stable; Pro-MMR, MMR proficient; U, *MLH1* promoter unmethylated; M, *MLH1* promoter methylated; –, not examined.
[a] LS-related EC according to clinical criteria.