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Absence of *DICER1*, *CTCF*, *RPL22*, *DNMT3A*, *TRRAP*, *IDH1* and *IDH2* hotspot mutations in patients with various subtypes of ovarian carcinomas

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Abstract. Cancer is caused by multiple genetic alterations within cells. Recently, large-scale sequencing has identified frequent ribonuclease type III (*DICER1*), CCCTC-binding factor (*CTCF*), ribosomal protein L22 (*RPL22*), DNA (cytosine-5-)-methyltransferase 3α (*DNMT3A*), transformation/transcription domain-associated protein (*TRRAP*), isocitrate dehydrogenase (*IDH*)1 and *IDH2* hotspot mutations in diverse types of cancer. However, it remains largely unknown whether these mutations also exist in ovarian carcinomas. In the present study, a collection of 251 patients with distinct subtypes of ovarian carcinomas were recruited and sequenced for the presence of these hotspot mutations. However, no mutations in the seven genes were detected in the samples. These negative results, together with certain recent reports, indicate that the hotspot mutations in the *CTCF*, *RPL22*, *DNMT3A*, *TRRAP*, *IDH1* and *IDH2* genes may not be actively involved in the carcinogenesis of ovarian carcinoma. Of note, the *DICER1* mutation frequency in Sertoli-Leydig cell tumor in the present study was significantly lower compared to prior observation, and therefore, it is speculated that this discrepancy may be mainly due to the small sample size analyzed in the study. In addition, among these samples, frequent polymerase (DNA directed) ε, catalytic subunit (*POLE1*) and ring finger protein 43 (*RNF43*) mutations were identified in endometrioid and mucinous ovarian carcinomas, respectively; thus *DICER1*, *CTCF*, *RPL22*, *DNMT3A*, *TRRAP*, *IDH1* and *IDH2* hotspot mutations may not play synergistic roles with *POLE1* or *RNF43* mutations in the carcinogenesis of endometrioid or mucinous ovarian carcinomas.

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Introduction

The current understanding of human malignancy is that it mainly arises due to the accumulation of multiple genetic alterations, transforming normal cells into malignant cells (1,2). Of these genetic alterations, a myriad of genomic mutation data derived from a high-throughput DNA sequencing technique provided a unique opportunity to profile the mutation spectra underlying human cancers and a large number of significant functional mutations in multiple genes were identified in diverse types of cancer (1,3,4). These genes can be defined as oncogenes or tumor suppressor genes and are being used as molecular markers for diagnosis, staging and prognosis of human cancers (5,6).

Ovarian carcinoma constitutes a heterogeneous group of malignancies with significantly different clinical expression, pathological characteristics and genetic etiology (7,8). However, the majority of ovarian carcinomas shared certain common genetic alterations, such as frequent tumor protein p53 (*TP53*) and PIK3CA, catalytic subunit α mutations (9,10), and patients also exhibited subtype-specific mutations (11-13), which are possibly essential for the differential clinical expression and molecular-targeted therapy in ovarian carcinomas (14,15). These observations emphasized the requirement to identify novel subtype-specific molecular genetic aberrations in ovarian carcinomas.

Recently, large-scale sequencing has identified frequent mutations of the ribonuclease type III (*DICER1*) gene in Sertoli-Leydig cell tumors of the ovary (3), CCCTC-binding factor (*CTCF*) gene in transient abnormal myelopoiesis (16) and

Table I. Mutation frequencies of ribonuclease type III (*DICER1*), CCCTC-binding factor (*CTCF*), ribosomal protein L22 (*RPL22*), DNA (cytosine-5-)-methyltransferase 3α (*DNMT3A*), transformation/transcription domain-associated protein (*TRRAP*), isocitrate dehydrogenase (*IDH*)1 and *IDH2* hotspot mutations in 251 Chinese patients with ovarian carcinomas.

Subtype/gene	No.	*DICER1* p.1705-1709	*DICER1* p.1810-1813	*CTCF* p.T204fs*	*RPL22* c.43delA	*DNMT3A* p.R882	*TRRAP* p.S722	*IDH1* p.R132	*IDH2* p.R140	*IDH2* p.R172	*RNF43* p.I48V and p.R40fs*11[a]	*POLE1* p.S297F[b]
Epithelial												
Serous	76	0/76	0/76	0/72	0/75	0/74	0/75	0/73	0/74	0/74	0/74	0/74
Clear cell	43	0/43	0/43	0/42	0/43	0/43	0/43	0/42	0/41	0/41	0/41	0/41
Endometrioid	37	0/37	0/37	0/35	0/35	0/36	0/37	0/35	0/37	0/37	0/37	3/37
Mucinous	15	0/15	0/15	0/14	0/15	0/15	0/15	0/14	0/15	0/15	2/15	0/15
Undifferentiated	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Unclassified	4	0/4	0/4	0/3	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
Transitional cell	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Mixed	2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Non-epithelial												
Germ cell tumor												
Yolk sac	11	0/11	0/11	0/10	0/11	0/11	0/10	0/11	0/11	0/11	0/11	0/11
Dysgerminoma	7	0/7	0/7	0/7	0/7	0/7	0/7	0/6	0/6	0/6	0/6	0/6
Teratoma	9	0/9	0/9	0/8	0/9	0/9	0/9	0/8	0/9	0/9	0/9	0/9
Mixed	6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Sex cord-stromal tumor												
Granulosa cell	16	0/16	0/16	0/14	0/16	0/16	0/16	0/15	0/16	0/16	0/16	0/16
Sertoli-Leydig	2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Krukenberg tumors	17	0/17	0/17	0/16	0/16	0/17	0/17	0/15	0/17	0/17	0/17	0/17

[a,b]As per references (25,26); *POLE1*, polymerase (DNA directed) ε, catalytic subunit; *RNF43*, ring finger protein 43.

endometrial cancer (17), ribosomal protein L22 (*RPL22*) gene in endometrial cancer (18), DNA (cytosine-5-)-methyltransferase 3α (*DNMT3A*) gene in hematological malignancies (4), the transformation/transcription domain-associated protein (*TRRAP*) gene in melanoma (19) and isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) genes in gliomas (1,20) and acute myeloid leukemia (AML) (21), respectively. Some of these mutations were closely associated with cancer progression (22) and prognosis (23,24).

Thus far, the mutation statuses of *DICER1*, *CTCF*, *RPL22*, *DNMT3A*, *TRRAP*, *IDH1* and *IDH2* mutational hotspots in ovarian carcinomas remain largely unknown. One critical concern in cancer genetics is whether those cancer-associated mutations identified in one type of cancer are also common in other types of cancer. Therefore, a cohort of 251 Chinese patients with distinct subtypes of ovarian carcinomas was recruited in the present study to examine whether the hotspot mutations in these genes also existed in these samples.

Materials and methods

Sample collection. The study included 251 archival formalin-fixed, paraffin-embedded (FFPE) tissues with various subtypes of ovarian carcinoma recruited from the Jiangxi Provincial Maternal and Child Health Hospital (Nanchang, Jiangxi, China). Only those patients with >70% of neoplastic cells were recruited in the study. The sample cohort contained 76 ovarian serous carcinoma, 43 ovarian clear cell carcinoma, 37 ovarian endometrioid carcinoma, 33 ovarian germ cell tumor, 15 mucinous ovarian carcinoma, 18 ovarian sex cord-stromal tumor, 12 other rare subtypes and 17 Krukenberg tumor, and the available clinical data was as described previously (25,26) and in Table I. Informed consent conforming to the tenets of the Declaration of Helsinki was obtained from each patient prior to the study. The Institutional Review Boards of the Jiangxi Provincial Maternal and Child Health Hospital approved the study.

Mutation analysis of the DICER1, CTCF, RPL22, DNMT3A, TRRAP, IDH1 and IDH2 genes. The Omega FFPE DNA kit (Omega Bio-tek Inc., Doraville, GA, USA) was used to isolate the DNA from the FFPE tissues. The polymerase chain reaction (PCR) primers were as summarized previously (25,27) and are shown in Table II. PCR reactions were performed in a total volume of 25 μl, containing 50 ng genomic DNA, 2 units of LA Taq DNA Polymerase (Takara Biotechnology Dalian Co. Ltd., Liaoning, China), 300 μM of each dNTP and 0.2 μM of each primer. The amplification reaction was performed in a Thermal Cycler 2720 (Applied Biosystems, Foster City, CA, USA) and employed one denaturation cycle of 94˚C for 3 min, 35 amplification cycles of 94˚C for 30 sec, 50-60˚C (Table II) (25,27) for 20 sec and 72˚C for 30 sec,

Table II. Primers for the mutational analysis of the ribonuclease type III (*DICER1*), CCCTC-binding factor (*CTCF*), ribosomal protein L22 (*RPL22*), DNA (cytosine-5-)-methyltransferase 3α (*DNMT3A*), transformation/transcription domain-associated protein (*TRRAP*), isocitrate dehydrogenase (*IDH*)1 and *IDH2* genes.

Gene	Target regions	Amplicon, bp	Sample detected	Annealing, ˚C	Forward primer (5'-3')	Reverse primer (5'-3')
DICER1	p.E1705-D1709	159	251/251	55	CGGATCCCCTCAGATTGTTA	CGATGCAAAGATGGTGTTGT
DICER1	p.D1810-E1813	171	251/251	55	TGGCCTTTTTGCTTACAAGTC	TGCCAGACTGTCTCCAGTGA
CTCF	p.T204fs*	212	237/251	56	GTTAAAGTGGGGGCCAATG	AGCAGACCCTCCTGCTGTT
RPL22	c.43delA	190	247/251	60	TCTTGTTTTTCCGACTGACTGA	CCGAGTGGCAATAAGGATGT
DNMT3A	p.R882	177	248/251	52	TGCCCTCTCTGCCTTTTCT	CCATGTCCCTTACACACACG
TRRAP	p.S722	183	249/251	52	TCTGCTCTGTTTGCTACGAT	GCACTACTTAGATTAAATGGAC
IDH1	p.R132	269	239/251	50	TGCTGCAGAAGCTATAAAGAAG	GCAAAATCACATTATTGCCAAC
IDH2	p.R140 and p.R172	209	246/251	50	GCTGCAGTGGGACCACTATT	ACCCTGGCCTACCTGGTC

bp, base pair.

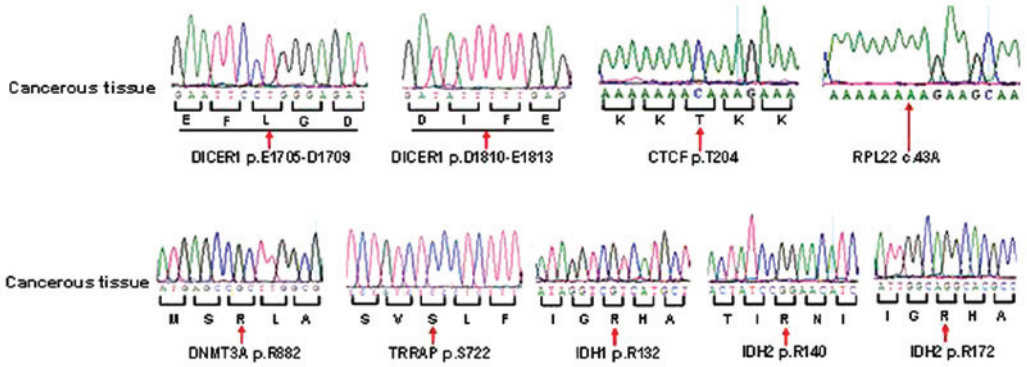

Figure 1. Representative sequencing electropherograms of the ribonuclease type III (*DICER1*), CCCTC-binding factor (*CTCF*), ribosomal protein L22 (*RPL22*), DNA (cytosine-5-)-methyltransferase 3α (*DNMT3A*), transformation/transcription domain-associated protein (*TRRAP*), isocitrate dehydrogenase (*IDH*)1 and *IDH2* genes in Chinese patients with ovarian carcinomas.

with one final extension cycle of 72˚C for 10 min. The PCR products were purified and sequenced with an ABI 3730 DNA sequencer (Applied Biosystems). DNA sequence analyses were performed with the DNASTAR package software (DNASTAR Inc., Madison, WI, USA).

Results and Discussion

The available clinical data of these patients are as described previously (25,26). In the present study, a total of 251 Chinese samples with distinct subtypes of ovarian carcinoma were screened for the presence of potential hotspot mutations in the *DICER1*, *CTCF*, *RPL22*, *DNMT3A*, *TRRAP*, *IDH1* and *IDH2* genes. However, no mutations in these genes were detected in the 251 samples (Table I and Fig. 1).

Previous studies have found frequent *DICER1* p.E1705-D1709 and p.D1810-E1813 mutations in Sertoli-Leydig cell tumors (3,28). However, no *DICER1* mutations were detected in the two patients with Sertoli-Leydig cell tumors. Therefore, it can be speculated that this discrepancy may be caused mainly by the small sample size of the Sertoli-Leydig cell tumors analyzed in the present study. In addition, *DICER1* mutations were not identified in other subtypes of ovarian carcinomas in the samples, which is consistent with previous large-scale sequencing results in which the *DICER1* hotspot mutations were absent in 12 mucinous (29) or 316 serous ovarian carcinomas (9). Collectively, these results indicated that the *DICER1* hotspot mutations may not be actively involved in the pathogenesis of ovarian carcinoma, except for Sertoli-Leydig cell tumors.

CTCF p.T204fs* and *RPL22* c.43delA mutations have been observed frequently in endometrial carcinoma in previously studies (17,18). Considering the fact that ovarian carcinoma have certain overlapped genetic aberrations with endometrial cancer, such as frequent *TP53* (9,30) and polymerase (DNA directed) ε, catalytic subunit (*POLE1*) mutations (26,30), we hypothesized that ovarian carcinomas may also harbor these mutations. However, neither *CTCF* p.T204fs* nor *RPL22* c.43delA mutations were identified in the samples in the present study. The absence of the *CTCF* and *RPL22* mutations in ovarian cancer in a previous study (29) and the present study suggested that the *CTCF* and *RPL22* hotspot mutations may play an extremely limited role in the pathogenesis of ovarian cancer.

Prevalent *TRRAP* p.S722 mutation was initially identified in melanomas in a whole-exome sequencing study (19). Subsequent extended studies failed to identify these mutations in thyroid cancer (31) or splenic marginal zone lymphoma (32). In the present study, no *TRRAP* p.S722 mutations were detected

in our ovarian cancer patients with distinct subtypes. Also, *TRRAP* p.S722 mutations were not found in 12 mucinous (29) or 316 serous ovarian carcinomas (9). These negative results led us to speculate that *TRRAP* p.S722 mutations may not play a crucial role in the malignant transformation of ovarian carcinoma.

DNMT3A p.R882 mutations were identified almost exclusively in hematological malignancies, including AML (33), acute lymphoblastic leukemia (34) and myelodysplastic syndromes (35), and are generally infrequent or absent in some solid tumors (9,29,36). *DNMT3A* p.R882 mutations were not detected in the 251 samples with distinct subtypes of ovarian carcinoma. Similarly, whole-exome sequencing studies suggested that *DNMT3A* p.R882 mutations were absent in 12 mucinous (29) or 316 serous ovarian carcinomas (9). Taken together, the absence of *DNMT3A* p.R882 mutations in ovarian carcinoma analyzed in the present study and in previous studies (9,29) indicated that *DNMT3A* p.R882 mutations may be infrequent in ovarian carcinoma.

Frequent *IDH1* p.R132, and *IDH2* p.R140 and p.R172 mutations were identified in the central nervous system tumors and AML (1,20,27). However, no *IDH1* or *IDH2* mutations were detected in the present samples. Similar results were observed in previous studies in which *IDH1* p.R132 mutations were not detected in 168 ovarian carcinomas or 8 ovarian cancer cell lines (20,37-39). In addition, *IDH1* and *IDH2* hotspot mutations were also not identified in 12 mucinous (29) or 316 serous ovarian carcinomas (9). These combined results suggested that *IDH1* and *IDH2* potential hotspot mutations may not be common in patients with ovarian carcinoma.

Among these patients, the *POLE1* mutation has been previously found to be frequent in 37 ovarian endometrioid carcinomas (26), whereas ring finger protein 43 (*RNF43*) mutations were recurrent in 15 mucinous ovarian carcinomas (25) (Table I). In the present study, neither endometrioid nor mucinous ovarian carcinomas were detected to harbor *DICER1*, *CTCF*, *RPL22*, *DNMT3A*, *TRRAP*, *IDH1* and *IDH2* hotspot mutations. These results suggested that these potential hotspot mutations observed in other (sub)types of cancer may not play synergistic roles with *POLE1* or *RNF43* mutations in the carcinogenesis of endometrioid or mucinous ovarian carcinomas, respectively.

The main limitation of the present study was that only short DNA fragments spanning the potential hotspot mutations were screened in the seven genes, and therefore, there is a possibility that mutations in other residues of these genes may exist in these samples. However, due to the shortage of DNA amounts, this hypothesis was not tested.

In conclusion, *DICER1*, *CTCF*, *RPL22*, *DNMT3A*, *TRRAP*, *IDH1* and *IDH2* hotspot mutations were not identified in 251 Chinese patients with diverse subtypes of ovarian carcinoma. These results were generally consistent with previous studies and these combined results indicated that the hotspot mutations in these genes may not be actively involved in the carcinogenesis of Chinese patients with ovarian carcinoma, except for *DICER1* mutations in Sertoli-Leydig cell tumors.

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