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Genomic landscape of ovarian clear cell carcinoma via whole exome sequencing

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HIGHLIGHTS

- 14 genes, including PIK3CA, ARID1A and KRAS, were mutated in multiple Korean OCCCs.
- 53 somatic mutations (27 novel) were identified in fresh Korean OCCC tissue.
- Genomic landscape (somatic mutations and CNVs) expands our understanding of OCCCs.
- Genetic alteration frequencies were similar in OCCCs with or without endometriosis.

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ABSTRACT

Objective. To analyze whole exome sequencing (WES) data on ovarian clear cell carcinoma (OCCC) in Korean patients via the technique of next generation sequencing (NGS). Genomic profiles were compared between endometriosis-associated OCCC (EMS-OCCC) and Non-EMS-OCCC.

Methods. We used serum samples and cancer tissues, stored at the Seoul National University Hospital Human Biobank, that were initially collected from women diagnosed with OCCC between 2012 and 2016. In total, 15 patients were enrolled: 5 with pathologically confirmed EMS-OCCC and 10 with Non-EMS-OCCC. We performed NGS WES on 15 fresh frozen OCCC tissues and matched serum samples, enabling comprehensive genomic characterization of OCCC.

Results. OCCC was characterized by complex genomic alterations, with a median of 178 exonic mutations (range, 111-25,798) and a median of 343 somatic copy number variations (range, 43-1,820) per tumor sample. In all, 54 somatic mutations were discovered across 14 genes, including *PIK3CA* (40%), *ARID1A* (40%), and *KRAS* (20%) in the 15 Korean OCCCs. Copy number gains in *NTRK1* (33%), *MYC* (40%), and *GNAS* (47%) and copy number losses in *TET2* (73%), *TSC1* (67%), *BRCA2* (60%), and *SMAD4* (47%) were frequent. The significantly altered pathways were associated with proliferation and survival (including the PI3K/AKT, TP53, and ERBB2 pathways) in 87% of OCCCs and with chromatin remodeling in 47% of OCCCs. No significant differences in frequencies of genetic alterations were detected between EMS-OCCC and Non-EMS-OCCC groups.

Conclusion. We successfully characterized the genomic landscape of 15 Korean patients with OCCC. We identified potential therapeutic targets for the treatment of this malignancy.

1. Introduction

Ovarian cancer, the most lethal gynecologic malignancy, imposes a global burden in both developed and developing countries [1]. In Korea, the incidence of ovarian cancer has been gradually increasing and is expected to reach 2.5% (2,618) of new cancer cases and 3.8% (1,168) of all cancer deaths among women in 2017 [2,3]. Of the histologic types, the majority (90%) of ovarian cancers are epithelial ovarian cancers (EOCs), which are further grouped into different histologic subtypes [4].

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Ovarian clear cell carcinoma (OCCC), a subtype of EOC, is known to be less sensitive to chemotherapy and has a poorer prognosis than other histologic EOC subtypes, such as serous or endometrioid adenocarcinomas [5]. OCCC is associated with endometriosis (EMS), which is a common benign condition in reproductive-age women [6,7]. Interestingly, OCCC is more common in East Asian women than in Western women: it accounts for 24% of EOCs in Japan but only a small portion of EOCs in Western countries [8]. In Korea, OCCC is the fourth most common histologic subtype, which accounts for 10.3% of EOCs, and the incidence of OCCC has increased markedly across all age groups since 1999 [9].

In accordance with the era of precision medicine, it is obvious that reliable genetic diagnosis is essential for providing individualized treatment for patients with OCCC. In OCCC, both a clinical approach, considering the presence of underlying EMS, and a genomic approach, such as those conducted by The Cancer Genome Analysis (TCGA) Group, may be necessary [10]. However, the low incidence of OCCC hinders such integrative genomic analyses. To date, only small genomic studies of OCCC have been reported from some East Asian countries; the genomic landscape of Korean OCCC has not yet been investigated.

The aim of this study was to obtain whole exome sequencing (WES) data of Korean OCCC via the next generation sequencing (NGS) technique. Genomic profiles were compared between EMS-associated OCCC (EMS-OCCC) and Non-EMS-OCCC.

2. Materials and methods

This retrospective case-control study, using genomic analyses, was conducted after obtaining approval from the Institutional Review Board of Seoul National University Hospital (IRB No. 1609-081-792).

2.1. Study population

At our institution, Seoul National University Hospital (SNUH), patients scheduled to undergo surgery for gynecologic cancer have been routinely asked whether they will donate their biological samples (e.g., blood samples, cancer tissue samples) for research purposes since June 2012. Blood samples and cancer tissues are obtained before surgery and at the time of surgery, respectively, from those patients who provide informed consent. The cancer tissues undergo gross examination and frozen section procedures. In this step, the pathologists ascertain necrotic portions of the tumor, which are ruled out from banking. Only viable portions of the tumor are selected and cut in the form of a 1 cm^3 sized cube. These biospecimens are then stored at the SNUH Human Biobank.

For the present study, we searched relevant patients from the SNUH Ovarian Cancer Cohort to identify those who met the following inclusion criteria: 1) older than 18 years; 2) diagnosed with OCCC between June 2012 and December 2016; 3) underwent primary debulking surgery (PDS); 4) agreed to donate their biological samples and provided informed consent; and 5) blood and cancer tissue samples were stored simultaneously at the SNUH Human Biobank. Patients with following conditions were excluded: 1) diagnosis of any malignancy other than ovarian cancer; 2) neoadjuvant chemotherapy or targeted therapy before surgery; 3) insufficient clinical data or lost to follow-up; and 4) severe co-morbidities, such as end-stage renal disease, uncontrolled diabetes mellitus, or long-term corticosteroid use.

Of the 15 patients with OCCC who met these criteria, 5 were pathologically diagnosed with OCCC arising in EMS (EMS-OCCC group) and the other 10 were pathologically diagnosed with OCCC that did not arise in EMS (Non-EMS-OCCC group) [11,12]. By reviewing their

Table 1
Clinicopathologic characteristics of the patients.

Characteristics	All ($n = 15$)	EMS-OCCC ($n = 5$)	Non-EMS-OCCC ($n = 10$)	P
Age at diagnosis, years				
Median (range)	51.1 (28.9–71.4)	51.3 (42.7–55.5)	49.8 (28.9–71.4)	0.953
BMI, kg/m^2				
Median (range)	21.5 (16.9–28.3)	21.5 (19.5–23.1)	21.6 (17.0–28.3)	0.513
Parity				
Mean ± SD	1.3 ± 0.9	1.2 ± 0.8	1.4 ± 1.0	0.594
Menopause	10 (66.7)	4 (80.0)	6 (60.0)	0.600
Comorbidities				
Hypertension	1 (6.7)	0	1 (10.0)	1.000
Diabetes	2 (13.3)	0	2 (20.0)	0.524
Dyslipidemia	2 (13.3)	0	2 (20.0)	0.524
Alcohol intake	3 (20.0)	0	3 (30.0)	0.505
Smoking	0	0	0	N/A
CA-125 at diagnosis, IU/ml				
Median (range)	79.9 (7.7–1067.0)	447.5 (15.5–1067.0)	63.7 (7.7–269.8)	0.165
FIGO stage				0.839
I	9 (60.0)	3 (60.0)	6 (60.0)	
II	2 (13.3)	1 (20.0)	1 (10.0)	
III	4 (26.7)	1 (20.0)	3 (30.0)	
Residual tumor at PDS				0.333
None	14 (93.3)	4 (80.0)	10 (100.0)	
RT < 1 cm	1 (6.7)	1 (20.0)	0	
Adjuvant chemotherapy				
None	2 (13.3)	0	2 (20.0)	0.524
Paclitaxel-carboplatin	12 (80.0)	5 (100.0)	7 (70.0)	
Irinotecan-cisplatin	1 (6.7)	0	1 (10.0)	
Observation period, months				0.440
Median	23.4	48.9	20.3	
Recurrence	2 (13.3)	1 (20.0)	1 (10.0)	1.000
Progression free survival, months				
Median	23.4	30.1	19.4	0.808[a]
Death	1 (6.7)	0	1 (10.0)	1.000
Survival, months			19.0	

Values are n (%) unless otherwise specified.
EMS, endometriosis; EMS-OCCC, endometriosis associated ovarian clear cell carcinoma; BMI, body mass index; CA-125; cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics 2014; N/A, not applicable; PDS, primary debulking surgery; RT, residual tumor; SD, standard deviation.
[a] Log-rank test.

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