Analysis of CARD10 and CARD11 somatic mutations in patients with ovarian endometriosis

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Abstract. Endometriosis is a complex and heterogeneous pre-malignant inflammatory disease harboring multiple gene mutations. Previous studies have suggested that caspase recruitment domain family member (CARD)10 and CARD11 mutations may exist in endometriosis. In the present study, a collection of endometriotic lesions and paired peripheral blood from 101 patients with ovarian endometriosis were obtained, and the entire coding sequences of the CARD10 and CARD11 genes were sequenced. Evolutionary conservation analysis and online prediction programs were applied to analyze the disease-causing potential of the identified mutations. A total of 4 novel somatic mutations were identified in 4 out of the 101 (4.0%) samples: 2 in-frame deletions in CARD10 (c.785_790delAGGAGA, p.K272_E273delKE; c.785_802delAGGAGAAGGAGAAGGAGA, p.K272_V277delKEPDNV) and 2 heterozygous missense mutations in CARD11 (c.49G>T, p.D17Y; c.160G>C, p.E54Q). The sample with CARD10 p.K272_E273delKE deletion was obtained from a 47-year-old patient who was also diagnosed with uterine leiomyoma, while the CARD10 p.K272_V277delKEPDNV-mutated sample was from a 43-year-old patient exhibiting a decreased blood eosinophil granulocyte ratio (0.3%) and an elevated serum creatine kinase level (314 U/l). The patient with the CARD11 p.D17Y mutation was 38 years old and exhibited an increased level of cancer antigen 125 (45.4 U/ml), while the patient with the CARD11 p.E54Q mutation was 46 years old and exhibited no other gynecological conditions. Evolutionary conservation analysis and online prediction programs suggested that these mutations may be disease-causing. In summary, 4 novel somatic mutations in the CARD10 and CARD11 genes were identified from amongst 101 cases of ovarian endometriosis for the first time, these mutations may serve active roles in the development of ovarian endometriosis.

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Introduction

Endometriosis is a heterogeneous estrogen-dependent chronic gynecological disease in women of reproductive age (1-3). The condition is characterized by endometrial tissues ectopically implanting outside the uterine cavity, and is subdivided mainly into ovarian, peritoneal and deep infiltrating endometriosis according to the different implant locations (4,5). The most common clinical symptoms of endometriosis include dysmenorrhea, chronic pelvic pain and diminished fertility potential, which greatly influence the quality of life of affected individuals (6). Despite numerous studies being performed on this research field, the molecular etiology of endometriosis is not yet fully understood (7,8).

It has long been accepted that endometriosis is actually an inflammatory disease (9,10), with cytokine levels that are elevated in the peritoneal fluid, serum and endometriotic lesion tissues (11-13). Based on these observations, certain researchers formulated the inflammation hypothesis that leukocytes are recruited by the endometrial stromal cells within endometriotic lesions, and that proinflammatory cytokines are then secreted from these leukocytes, which will facilitate the progression of endometriosis (14,15). Furthermore, it has also been proposed that the changed progesterone responsiveness may be the main reason for the elevated production of cytokines in endometriosis (16-18). However, in spite of advances (1,19), there have not been any therapeutic strategies targeting inflammatory factors in endometriosis that have been successfully applied to samples with endometriosis, implying a great underappreciation of the role of inflammation in endometriosis (20,21).

Caspase recruitment domain family member 11 (CARD11) belongs to the CARD protein family; it can bind with B-cell CLL/lymphoma 10 and activate the inflammation-associated nuclear factor κB (NF-κB) signaling pathway (22). Furthermore, CARD11 also acts as a scaffold protein to assist the assembly of multiprotein signaling molecules in the plasma membrane (23). Previous studies showed that CARD11 somatic mutations were detected frequently in multiple human cancer types, including hematological malignancies, colorectal cancer and malignant

melanoma; the mutations were distributed along the CARD11 coding sequence while being mainly clustered within the coiled-coil domain (24-28). Most recently, a somatic mutation in the CARD11 gene (p.R30W, c.C88T) was identified in the endometriotic lesion of 1 out of 16 samples with ovarian endometriosis. Considering the fact that endometriosis is a potential premalignant disorder and the endometriotic lesions harbored certain genetic alterations in tumor-associated genes (29-33), and furthermore that mutations in the paralogous genes usually occurred in the same cancer types (34,35), we thus hypothesized that mutations in the paralogous CARD10 and CARD11 may exist in ovarian endometriosis.

In the present study, a total of 101 patients with ovarian endometriosis were recruited and analyzed for the presence of CARD10 and CARD11 mutations, with the aim of exploring the potential involvement of mutations in these two genes in the pathogenesis of ovarian endometriosis.

Materials and methods

Samples. The endometriotic lesions of the ovaries and paired peripheral blood samples were obtained immediately following surgical resection from a total of 142 patients with ovarian endometriosis who were treated in the Department of Gynecology, Jiangxi Provincial Maternal and Child Health Hospital (Nanchang, Jiangxi, China), between July 2015 and January 2018. All samples were diagnosed pathologically by two experienced pathologists, and the 101 cases with an ectopic endometrium purity of >30% were included in the present study. The study was approved by the Institutional Review Board of Jiangxi Provincial Maternal and Child Health Hospital, and the detailed protocol was conducted according to the Declaration of Helsinki and the Jiangxi Provincial Maternal and Child Health Hospital. Written informed consent was obtained from all patients prior to the study.

Mutational analysis of the CARD10 and CARD11 genes. The genomic DNA was isolated from the endometriotic lesions and paired peripheral blood samples using the DNeasy Blood and Tissue kit (catalog no. 69504; Qiagen, Inc., Valencia, CA, USA) according to the manufacturer's protocols. The entire coding region of the CARD10 and CARD11 genes in the endometriotic lesions of patients with ovarian endometriosis were amplified by polymerase chain reaction (PCR) with sets of primer pairs (Table I). In brief, for each PCR amplification reaction, ~50 ng total DNA was used in a final volume of 30 μl, with the following amplification protocols: An initial pre-denaturation step at 94˚C for 3 min, followed by 35 cycles of denaturation at 94˚C for 30 sec, annealing at different temperatures (52-60˚C; Table I) for 30 sec and extension at 72˚C for 30 sec, with a final extension at 72˚C for 7 min. PCR was performed in a Thermal Cycler 2720 (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The PCR amplification products were then purified and sequenced on an ABI Prism 3730 DNA sequencer (Applied Biosystems; Thermo Fisher Scientific, Inc.). An additional independent PCR amplification and DNA sequencing was performed in the endometriotic lesions for samples harboring potential CARD10 or CARD11 mutations. The statuses of the potential somatic mutations were verified by sequencing the DNA sequences of the paired peripheral blood in the same patients. The procedure of PCR amplification and DNA sequencing was performed as described above.

Evolutionary conservation analysis. The protein sequences from 21 vertebrate species from GenBank (https://www.ncbi.nlm.nih.gov/genbank/) were used to analyze the evolutionary conservation status of the identified CARD11 mutations, including *Homo sapiens* (NP_115791), *Macaca mulatta* (XP_014988691), *Rattus norvegicus* (XP_017454079), *Mus musculus* (NP_780571), *Dipodomys ordii* (XP_012878958), *Bos taurus* (NP_001103266), *Microcebus murinus* (XP_012614839), *Equus asinus* (XP_014702187), *Pan paniscus* (XP_008971413), *Cavia porcellus* (XP_013008240), *Camelus ferus* (XP_014412591), *Ovis aries* (XP_014959439), *Mustela putorius furo* (XP_0129032), *Canis lupus familiaris* (XP_005621), *Gallus gallus* (NP_001006161), *Calidris pugnax* (XP_014801661), *Ficedula albicollis* (XP_005054487), *Lipotes vexillifer* (XP_007467483), *Apteryx australis mantelli* (XP_013797455), *Stegastes partitus* (XP_008283939) and *Ictalurus punctatus* (XP_017310081). Multiple sequence alignment was performed using the 'ClustalW' tool of the alignment function in the Molecular Evolutionary Genetics Analysis software (MEGA, version 4.0) which was created and developed by Kumar *et al* (36).

Bioinformatics programs prediction of the CARD10 and CARD11 mutations. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) (37) and MutationTaster (http://mutationtaster.org/) (38) software were used to analyze the disease-causing potential for the identified missense mutations, while the SIFT (http://sift.jcvi.org/) program (39) was used to predict the potential pathogenicity of the in-frame deletions. All bioinformatic analysis was performed on February 6th, 2018. Together, the software automatically assessed each mutation as either pathogenic or benign.

Statistical analysis. The frequency difference of CARD11 mutation in the current study and the previous study (29) was analyzed by two-tailed Fisher's exact test using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

CARD10 and CARD11 mutations in ovarian endometriosis. The median age of the sample cohort was 43 years (range, 21-56 years). A total of 4 somatic mutations in CARD10 or CARD11 genes were identified in 4 out of 101 endometriotic lesions from the patients with ovarian endometriosis, with the somatic status confirmed compared with that of the paired peripheral blood (Fig. 1). The 2 mutations in CARD10 (c.785_790delAGGAGA, p.K272_E273delKE; c.785_802delAGGAGAAGGAGAAGGAGA, p.K272_V277delKEPDNV) caused in-frame deletions, while the 2 mutations in CARD11 (c.49G>T, p.D17Y; c.160G>C, p.E54Q) were missense and heterozygous. It should be noted that a previous study identified a CARD11 somatic mutation (p.R30W) in 1 out of 16 (6.3%) patients with ovarian endometriosis, but no CARD10 mutations (29). In the present study, the sample with the CARD10 p.K272_E273delKE deletion

Table I. Polymerase chain reaction primers for the amplification of the CARD10 and CARD11 genes.

Gene and exon	Forward primer (5'-3')	Reverse primer (5'-3')	Annealing, ˚C	Amplicon, bp
CARD10				
1	ACATCTAGCCCTAGGGAGCC	CCCACTCTACTGATGCGGAG	52	433
2	CCCCTAGACCCTGGGTACAT	CTTCAGCCTCTCCATGCCTC	52	288
3	GAGCTGCCTATTCTGTCCCC	CGTCAAAGAGCCAGCAATGG	52	468
4	GCTTCGGCTTCTCTGGGAAT	CCACAAGCCCCAGTACCTG	58	405
5-6	CTGGTCAGGTGGGTTTGGAG	GTCCTAACCCAACAGGGAGC	52	1,088
7	TAATTTAGCTCAGGGCCCGG	CTCCACAATCTTGACCCGCT	56	358
8-9	CACATGGCAGGTGCTCAGTA	GCTATCCCCAGCCATCTCAC	52	687
10-11	CTTGGGGGCTGTGAGACATT	TAAAACAGGGGCGAGGCAAT	60	815
12-13	AGGCCTGGGGGTGGGAGTCA	CAGGAGAAGGGCAATTGG	55	976
14-15	GAAGGTCGGGTCCTGGGAA	TGGGCACATAGTAGATGACCA	52	756
16	AGGCTCTTCTGGCAAGCCT	AGCATGACCCCCACTCCTGT	56	372
17-19	TGGGGTATCGACGAGCTG	AGAGAGGCATCCTCAAGGA	60	1,189
20	ATCTTCTCTCTCTGACTCT	TGAGGAGAGTGATGGGGAC	58	1,192
CARD11				
3	GCTGTTCCAGTGAGACTGCT	GACTGCGGACCCCAGTTTAA	54	394
4	TGAGACCAGCCACAGAGACT	GTGGTTGACAGACCCCAGTT	56	366
5	CTGCGTCTGGAACCTCCTTT	CCTGCACCTGCTTTATGGGA	56	482
6	GGGAAGCGTTGCCTTTTCTG	CAGGTTCATCGTTTCCCCCA	54	326
7-8	CCAGGCACAAAACCTTCTGC	AAACACTCTGAAGGAGCCGG	60	1,132
9	GATGATGCCTGTCCCTGGG	CTTCAGGCGTGGGGTCCT	52	314
10	CCATCAGCCCAGCCATCTT	CCAAGACCCACCCAGAAGC	52	371
11	AAGCCCCAGTGACATGTGTC	CGCAGGATTGTTCGTTACAG	52	226
12	CTCCCCTCTCTCTCTTCCA	GCTGGGTCCCTGGATGGCA	60	324
13	TGCCGCCTGAGTAGGAGGC	GAGGACAGCTGGGTCAGCA	55	305
14	CCTCTCAGAAGCAAGGCCAC	AGGCTTATCTTTTGTGTTC	57	312
15	GACCAGCCCAGCAGGTCCC	CCAGGAAGTGATTTCTGACT	55	369
16-17	CACCCAGGCGCCTGATGAC	GCCTTCCACTGAACAGACGA	52	950
18-19	CTAAGAGCAGCATATTGCACA	GAATTCATCATCCCAATACGG	52	1,363
20	CTAAGAAAGCGTTAGCAT	CACTGTGAAGAGTTGCAAGT	58	351
21	TGCCGGGTTGAGGGCAGCA	GACCGATGTTCCTCCAGGT	52	299
22-23	ACACTGACGGTGGCTTCCA	TTGTCCCTGGCCCAGGTG	58	1,477
24	CCTGCATCCAGGCCCCGCT	GGTCAGTCCCGTACTTGGTG	54	336
25	TGGTGCCACACCAGCGCCA	AGCGTCTGCTGGGGCAGCTC	52	391

CARD, caspase recruitment domain family member.

was from a 47-year-old woman who was also diagnosed with uterine leiomyoma, while the sample with the CARD10 p.K272_V277delKEPDNV mutation was from a 43-year-old patient exhibiting a decreased blood eosinophil granulocyte ratio (0.3%) (normal range: 0.4-8%) and elevated serum creatine kinase level (314 U/l) (normal range for women: 96-140 U/l). The patient with the CARD11 p.D17Y mutation was 38 years old and exhibited an increased level of cancer antigen 125 (45.4 U/ml) (normal range: 0-35 U/ml), while the patient with the CARD11 p.E54Q mutation was 46 years old and exhibited no other apparent gynecological conditions.

Evolutionary conservation analysis of CARD11 missense mutations. The evolutionary conservation analysis of CARD11 in 21 vertebrate species ranging from *Homo sapiens* to *Ictalurus punctatus* showed that the two mutated amino acid residues (p.D17, p.E54) were highly conserved (Fig. 2).

Causative potential of CARD10 and CARD11 mutations. The PolyPhen-2 and MutationTaster online prediction programs were used to predict the disease-causing potentials of the detected missense mutations. The CARD11 p.D17Y (c.49G>T) and p.E54Q (c.160G>C) mutations were predicted to be possibly damaging with a score of >0.77 by Polyphen-2 software, while predicted to be disease-causing with a score of >29 and a probability of >0.99999 by MutationTaster. For the two in-frame deletions in CARD10, p.K272_V277delKEPDNV was predicted to be disease-causing, while

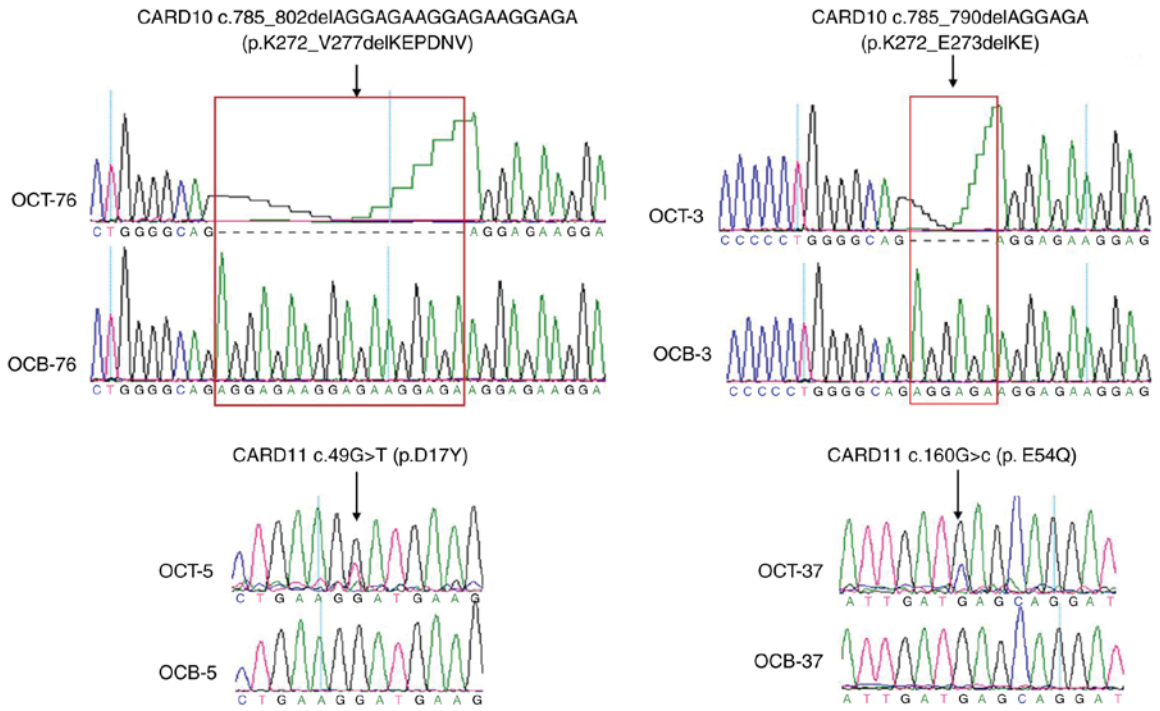

Figure 1. Sequencing electropherograms of CARD10 and CARD11 mutations. The arrows indicate the locations of the identified mutations. OCT, ovarian endometriotic lesions; OCB, paired peripheral blood from ovarian endometriosis samples; CARD, caspase recruitment domain family member.

Figure 2. Evolutionary conservation analyses of the CARD11 missense mutations. The CARD11 protein sequences of 21 vertebrate species from the GenBank database were adopted to perform the evolutionary conservation analysis. The p.D17Y and p.E54Q mutations in CARD11 were highly conserved among these vertebrates. CARD, caspase recruitment domain family member.

p.K272_E273delKE may be benign, according to the results predicted by the SIFT program. None of the mutations were found in the dbSNP (https://www.ncbi.nlm.nih.gov/snp), ExAC (http://exac.broadinstitute.org/) or 1000 Genomes Project (http://www.internationalgenome.org/) databases.

Discussion

Previous studies revealed that CARD10 and CARD11 served as scaffold proteins to regulate the activation of the NF-κB signaling pathway under different cellular contexts, by recruiting and activating the NF-κB repressor IκB kinase (22,40). When considering that i) endometriosis is an inflammation-related premalignant disease harboring somatic mutations in multiple genes (9,10), ii) CARD11 somatic mutations exist in ovarian endometriosis (29) and iii) mutations in the paralogous genes occur frequently in multiple human malignancies (34,35), the present study thus attempted to investigate the potential mutational spectra of the paralogous CARD10 and CARD11 genes in patients with ovarian endometriosis.

Frequent CARD11 mutations were detected first in diffuse large B cell lymphoma (41) and then also identified in melanoma, colorectal and endometrial cancer (26-28). Besides

being found in these different cancer types, a previous study also identified a CARD11 somatic mutation (p.R30W) in 1 out of 16 (6.3%) patients with ovarian endometriosis (29). In the present study, 2 novel CARD11 somatic mutations (p.D17Y and p.E54Q) were detected in 2 out of 101 (2.0%) ovarian endometriosis cases; the observed frequency in the current study did not reach a statistically significant level when compared with that in the prior study (P=0.40) (29). All the identified mutations in the present study were somatic and not found in the dbSNP, 1000 Genome Project or ExAC databases. The evolutionary conservation analysis showed that the mutated amino acids in CARD11 (p.D17Y and p.E54Q) were highly conserved in 21 vertebrate species. Furthermore, these mutations were predicted to be disease-causing by Polyphen-2 and MutationTaster. It should be mentioned that a somatic mutation in the 54th codon of CARD11, p.E54V (c.161A>T), was previously identified in a patient with hepatocellular carcinoma (42). Taken together, these results indicated that these somatic mutations in CARD11 may serve active roles in the development of ovarian endometriosis.

Besides CARD11 mutations, 2 somatic in-frame deletions in CARD10 were also identified in 2 out of 101 (2.0%) cases of ovarian endometriosis. Since the indel mutations could be predicted by SIFT, but not by Polyphen-2 and MutationTaster, the p.K272_V277delKEPDNV deletion was predicted to be disease-causing, while the p.K272_E273delKE deletion was predicted to be benign by SIFT only. By contrast, Li *et al* (29) did not identify any CARD10 mutations in 16 cases with ovarian endometriosis, and we speculate that the relatively small sample size may be a main reason for this discrepancy. To the best of our knowledge, the present study is the first to reveal that CARD10 somatic mutations also exist in ovarian endometriosis. It should be noted that the p.K272_E273delKE somatic deletion has also previously been identified in a cancerous tissue from renal cell carcinoma (43) (http://cancer.sanger.ac.uk/cosmic). These results indicated that CARD10 p.K272_V277delKEPDNV deletion may facilitate the progression of ovarian endometriosis, while the role of the p.K272_E273delKE deletion requires further elucidation.

In the present study, the 4 somatic mutations in CARD10 and CARD11 were identified in 4 different individuals; this is consistent with previous observations that mutations in the paralogous genes are usually exhibited in a mutually exclusive manner (34,35). The present study had several limitations. Firstly, the sample size was small, which may affect the mutation frequencies of the CARD10 and CARD11 genes, and the identified mutations should be verified in a larger sample size. Secondly, the study failed to obtain the clinical data showing whether samples with CARD10 or CARD11 mutations will display higher inflammation levels (such as interleukins) within the local endometriotic lesions or serum. Finally, further investigation is required to determine whether mutations would promote ovarian endometriosis via enhanced inflammation.

In summary, the present study identified 4 novel somatic mutations in CARD10 and CARD11 in 4.0% (4/101) of patients with ovarian endometriosis for the first time. The results indicated that these mutations existed in a mutually exclusive manner and may serve a positive role in the pathogenesis of ovarian endometriosis.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YZ performed mutation detection and manuscript preparation. JYZ and FW performed experiments. ZYZ performed conservation analysis. FYL and JT performed data analysis. YL performed mutation analysis. XZ and XDW performed sample collection. OPH performed study design and manuscript revision.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Jiangxi Provincial Maternal and Child Health Hospital, and the detailed protocol was conducted according to the Declaration of Helsinki and the Jiangxi Provincial Maternal and Child Health Hospital. Written informed consent was obtained from all patients prior to the study.

Consent for publication

All the sample donors gave permission for the publication of their data prior to the study.

Competing interests

The authors declare that they have no competing interests.

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