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Genetic risk factors for ovarian cancer and their role for endometriosis risk

Stefanie Burghaus [a], Peter A. Fasching [a,b,*], Lothar Häberle [c], Matthias Rübner [a], Kathrin Büchner [a], Simon Blum [a], Anne Engel [c], Arif B. Ekici [d], Arndt Hartmann [e], Alexander Hein [a], Matthias W. Beckmann [a], Stefan P. Renner [a]

[a] Department of Gynecology and Obstetrics, University Endometriosis Center for Franconia, Erlangen University Hospital, Friedrich-Alexander University of Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany
[b] Division of Hematology and Oncology, Department of Medicine, University of California at Los Angeles, David Geffen School of Medicine, Los Angeles, USA
[c] Biostatistics Unit, Department of Gynecology and Obstetrics, Erlangen University Hospital, Erlangen, Germany
[d] Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany
[e] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany

HIGHLIGHTS

- A common genetic variant in *HNF1B* (rs11651755) was associated with endometriosis risk.
- rs11651755 has been previously described as risk factor for clear cell ovarian cancer.
- Endometriosis and clear cell ovarian cancer might share a common genetic etiology.

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ABSTRACT

Objective. Several genetic variants have been validated as risk factors for ovarian cancer. Endometriosis has also been described as a risk factor for ovarian cancer. Identifying genetic risk factors that are common to the two diseases might help improve our understanding of the molecular pathogenesis potentially linking the two conditions.

Methods. In a hospital-based case–control analysis, 12 single nucleotide polymorphisms (SNPs), validated by the Ovarian Cancer Association Consortium (OCAC) and the Collaborative Oncological Gene-environment Study (COGS) project, were genotyped using TaqMan® OpenArray™ analysis. The cases consisted of patients with endometriosis, and the controls were healthy individuals without endometriosis. A total of 385 cases and 484 controls were analyzed. Odds ratios and *P* values were obtained using simple logistic regression models, as well as from multiple logistic regression models with adjustment for clinical predictors.

Results. rs11651755 in *HNF1B* was found to be associated with endometriosis in this case–control study. The OR was 0.66 (95% CI, 0.51 to 0.84) and the *P* value after correction for multiple testing was 0.01. None of the other genotypes was associated with a risk for endometriosis.

Conclusions. As rs11651755 in *HNF1B* modified both the ovarian cancer risk and also the risk for endometriosis, *HNF1B* may be causally involved in the pathogenetic pathway leading from endometriosis to ovarian cancer.

1. Introduction

Endometriosis affects approximately 10% of all women of reproductive age [1]. The pathogenesis of the condition is largely unknown. A familial risk has been reported, and this supports the view that the disease may have a genetic background [2]. Recent genome-wide association studies have identified several genetic variants as risk factors for endometriosis [3–5]. In clinical practice, endometriosis is usually a concern

Abbreviations: CPDA, citrate-phosphate-dextrose-adenine; MAF, minor allele frequency; SNP, single nucleotide polymorphism.

* Corresponding author at: Department of Gynecology and Obstetrics, Erlangen University Hospital, Friedrich Alexander University of Erlangen–Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Universitätsstrasse 21–23, 91054 Erlangen, Germany.
E-mail address: peter.fasching@uk-erlangen.de (P.A. Fasching).

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when patients present with pelvic pain syndromes and also subfertility [6].

However, increasing evidence has recently been emerging to suggest that endometriosis is a risk factor for ovarian cancer [7,8]. The genetic background of ovarian cancer has been quite extensively investigated, and several validated genetic risk factors have been described [9–15]. Endometriosis is also one of the clinical and epidemiological risk factors that has been included in a risk prediction model for ovarian cancer [16]. However, these considerations have not taken into account the possibility that some genetic risk factors may cause endometriosis first, which then later develops into an ovarian cancer.

Identifying overlapping genetic risk factors for endometriosis and ovarian cancer might be able to provide evidence of which molecular pathways are involved not only in the etiology, but also in the pathogenetic pathway leading from endometriosis to ovarian cancer. The aim of the present study was therefore to test, in an endometriosis case–control study, whether validated genetic risk variants for ovarian cancer are also predictive for endometriosis risk.

2. Material and methods

2.1. Study population

From 2002 to January 2014, endometriosis patients and healthy control individuals were recruited for a case–control study at Erlangen University Hospital. The cases included in the study consisted of patients with histologically or clinically confirmed current or former endometriosis. The corresponding control individuals were recruited using local newspaper advertisements inviting participation by self-reported healthy women or self-reported healthy women who were attending for a regular annual gynecological examination, without history of endometriosis and with no previous abdominal surgery and no pelvic pain syndrome, like dysmenorrhea, lower abdominal pain in general, dyspareunia, dysuria and dyschezia. All of the participants provided written informed consent and the medical faculty's ethics committee approved the study.

2.2. Data acquisition

A standardized questionnaire including modules on pregnancy history, previous use of hormonal contraceptives, medical history, family history, and lifestyle was filled out by the patients and healthy control individuals, and was completed in a structured interview with trained medical personnel if any questions had not been fully answered. This questionnaire included a dedicated set of questions with regard to endometriosis history (information about previous surgeries, therapies and symptoms). Additional information for patients was obtained from the patient charts, such as information about medical procedures, tumor histology, and concomitant medication. Although ethnicity was not assessed, the population was predominantly Caucasian with an estimated non-Caucasian fraction of clearly under 5%.

2.3. Selection of SNPs

Thirteen validated single nucleotide polymorphisms (SNPs) from case–control studies conducted by the Ovarian Cancer Association Consortium (OCAC) and the Collaborative Oncological Gene-environment Study (COGS) project were originally planned for inclusion, which were well known at the time when the study was being planned (Table 1).

The study included three *HNF1B* SNPs (rs7405776, rs757210 and rs11651755). This gene encodes a member of the homeodomain-containing superfamily of transcription factors. Expression of this gene is altered in some types of cancer. The SNP rs8170 localizes to C19orf62, also known as *BABAM1*, and appears to regulate the retention of *BRCA1* at double-strand DNA breaks and maintain stability of this complex at sites of DNA damage. Also activated during tumor development is *ANKLE1* with SNP rs2363956. *TIPARP* encodes a member of the poly(ADP-ribose) polymerase superfamily. rs2665390 at 3q25 is intronic to *TIPARP* and results in a transcript variant. *BRCA1/2*-deficient cells survive by using *PARP1* as an alternative DNA repair mechanism. rs11782652 associated in the first intron of *CHMP4C*. *CHMP4C* is involved in the final steps of cell division, coordinating midbody resolution with the abscission checkpoint, and is frequently overexpressed in ovarian tumor tissues. The risk-associated SNP rs2072590 lies in *HAGLR*. The protein encoded by this gene may play a role in the regulation of cell adhesion processes. The minor allele of rs10088218 has been found to be associated with a decreased risk of ovarian cancer and is a noncoding RNA of *LINC00824*. *MLLT10* encodes a transcription factor and has been identified as a partner gene involved in several chromosomal rearrangements. Multiple transcript variants encoding different isoforms have been found for this gene, such as SNP rs1243180. 17q21.31 contains rs9303542, which is located in the intron of *SKAP1*. *SKAP1* regulates mitotic progression and expression and increases with neoplastic development. rs10069690 in *TERT* influences reverse transcriptase activity. It plays a role in cellular senescence and deregulation and may be involved in oncogenesis.

2.4. DNA extraction and genotyping

Blood samples were collected in citrate-phosphate-dextrose-adenine (CPDA) tubes (Sarstedt AG, Numbrecht, Germany). Germline

Table 1
Selected SNPs for analysis. MAF is measured in all subjects.

SNP	Gene	Chromosome	Position[a]	Reference/alternate allele for ovarian cancer studies	MAF (%)	Per-allele OR (95% CI) for ovarian cancer risk	Reference
rs2072590	*HAGLROS,HAGLR*	2	176,177,905	T/A	18.25	1.20 (1.14–1.25)	[12]
rs2665390	*TIPARP*	3	156,679,960	T/C	6.69	1.24 (1.15–1.34)	[12]
rs10069690	*TERT*	5	1,279,675	C/T	34.76	1.15 (1.11–1.20)	[37]
rs11782652	*CHMP4C*	8	81,741,409	A/G	5.45	1.19 (1.12–1.26)	[15]
rs10088218	*LINC00824*	8	128,531,703	G/A	8.67	0.76 (0.70–0.81)	[12]
rs3814113[b]	*BNC2*	9	16,915,023	T/C	44.39	0.82 (0.79–0.86)	[40]
rs1243180	*MLLT10*	10	21,626,690	T/A	15.95	1.10 (1.06–1.13)	[15]
rs7405776	*HNF1B*	17	37,733,029	G/A	36.18	1.13 (1.09–1.17)	[25]
rs757210	*HNF1B*	17	37,736,525	C/T	36.22	1.05 (1.02–1.09)	[15]
rs11651755	*HNF1B*	17	37,739,849	T/C	46.73	0.77 (0.70–0.84)[c]	[25]
rs9303542	*SKAP1*	17	48,334,138	A/G	31.51	1.14 (1.09–1.20)	[12]
rs8170	*BABAM1*	19	17,278,895	G/A	11.24	1.12 (1.07–1.17)	[9]
rs2363956	*ANKLE1*	19	17,283,315	T/G	46.07	1.16 (1.11–1.21)	[9]

MAF, minor allele frequency.
[a] According to assembly GRCh38.p2.
[b] Failed genotyping.
[c] Genome-wide significance was only reached for clear cell ovarian cancer.

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