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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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DNA was extracted up to 2006 using a standard salting-out procedure as previously described [17], and since 2006 using an automated chemagic MSM I system (Perkin Elmer, Baesweiler, Germany). Genotyping was performed using TaqMan Open Array Genotyping Plates (as part of one 32-plex panel) in accordance with the manufacturer's instructions.

2.5. Statistical methods

Primary study aim was to explore the associations between selected SNPs and endometriosis. For each SNP, a simple logistic regression model was fitted using case–control status as the outcome and the genotype of each SNP (ordinal; 0, 1, or 2 minor alleles) as predictor. The odds ratio (OR) per minor allele with confidence interval was calculated and the corresponding Wald test was performed. The *P*-values (one per SNP) were corrected for multiple testing using the Bonferroni-Holm method.

For each SNP, a multiple logistic regression model was fitted to investigate the effect of the SNP on endometriosis in addition to several well-known clinical predictors (age, body mass index, menarche, cycle length, bleeding time, number of pregnancies, number of births: each continuous and ordinal, respectively; use of oral contraceptives and smoking: both yes versus no). Odds ratios per minor allele and confidence intervals were calculated, and the *P* values were corrected for multiple testing using the Bonferroni–Holm method. Patients for whom clinical predictor variables were missing were excluded.

All of the tests were two-sided, and a *P* value of <0.05 was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (version 3.01; R Development Core Team, Vienna, Austria, 2013).

3. Results

3.1. Patient characteristics

A total of 1375 subjects (749 patients with endometriosis and 626 controls) were recruited; 390 individuals had to be excluded because sufficient germline DNA was not available. There seemed to be no differences between all recruited patients and the study population (Supplementary Tables 1 and 2). Genotyping was carried out in a total of 960 individuals overall. Clinical data were available for 899 of the 960 individuals in whom genotyping was performed. Genotyping of all SNPs was not possible in 30 of these patients, representing a total of 385 patients with endometriosis and 484 controls with clinical data and complete genotyping. The percentage of missing values in each variable was below 5% except for cycle length (16.3%) and bleeding time (8.5%).

The participants' average age was 35.9 years and their mean body mass index was 23.4 kg/m^2. There was a nominal difference in age between the cases and controls. While the cases had an average age of 37.7, the controls were on average 34.5 years old. Additional patient characteristics are listed in Table 2.

Table 2
Patient characteristics relative to case–control status, showing means and standard deviation (SD) for continuous characteristics and frequencies and percentages for categorical characteristics.

Clinical predictor		Cases (n = 385) Mean (SD) or n (%)	Controls (n = 484) Mean (SD) or n (%)
Age [years]		37.7 (9.9)	34.5 (10.3)
Menarche [age]		12.8 (1.4)	13.0 (1.5)
Cycle length [days]		27.7 (4.3)	27.8 (4.6)
Bleeding time [days]		5.6 (1.7)	5.1 (1.1)
Number of pregnancies (n)	0	189 (49.3)	214 (44.4)
	1	92 (24)	80 (16.6)
	2	59 (15.4)	102 (21.2)
	3	29 (7.6)	45 (9.3)
	4+	14 (3.7)	41 (8.5)
Number of births (n)	0	225 (58.9)	248 (51.5)
	1	78 (20.4)	86 (17.8)
	2	62 (16.2)	103 (21.4)
	3	15 (3.9)	35 (7.3)
	4+	2 (0.5)	10 (2.1)
BMI [kg/m^2]		23.7 (4.6)	23.2 (4.0)
Use of oral contraceptives (ever)			
No		44 (11.8)	44 (9.1)
Yes		329 (88.2)	438 (90.9)
Smoking (ever)			
No		178 (51.1)	268 (56.1)
Yes		170 (48.9)	210 (43.9)

3.2. Genotyping results

Genotyping results are shown in Table 3. Lowest minor allele frequencies were seen for rs2665390 (*TIPARP*), rs11782652 (*CHM4PC*), rs10088218 (*LINC00824*), and rs8170 (*BABAM1*), at 7.61%, 6.4%, 12.94%, and 17.34%, respectively. One SNP, rs3814113, was excluded because genotyping failed. All minor alleles were the same as in the ovarian cancer studies, and the odds ratios are thus comparable with regard to the direction of effect. All genotyped SNPs were within the Hardy–Weinberg equilibrium (Table 3).

3.3. Association with endometriosis case–control status

Odds ratios and *P* values for successfully genotyped SNPs are shown in Table 4. None of the SNPs showed statistical significance after multiple testing, with the exception of one in *HNF1B* — namely rs11651755, with an adjusted OR of 0.66 (95% CI, 0.51 to 0.84). Two further SNPs in *HNF1B* were genotyped (rs7405776 and rs757210). Although neither of these SNPs achieved statistical significance after correction for multiple testing, both SNPs together with rs11651755 were among the three SNPs with the lowest *P* values in the multiple logistic regression models.

4. Discussion

In this case–control study, validated ovarian cancer SNPs were tested in patients with endometriosis. The validated ovarian cancer risk SNP rs11651755 in *HNF1B* was identified as a susceptibility locus for endometriosis. This could be an indication that *HNF1B* plays a role in the pathogenesis and possibly in the progression of endometriosis to ovarian cancer.

Until now, the common molecular pathway for the pathogenesis of endometriosis and ovarian cancer has been poorly understood [18]. Recent molecular studies have sought to link the two conditions via pathways related to oxidative stress, inflammation, and estrogen exposure. As a result of repetitive hemorrhage, with an accumulation of heme and free iron in endometriotic lesions, reactive oxygen species are produced and might play a role in the development of ovarian carcinoma [19]. Activation of oncogenic *KRAS* and *PI3K* pathways and inactivation of tumor suppressor genes *PTEN* and *ARID1A* are suggested as major pathogenic mechanisms for endometriosis associated clear-cell and endometrioid ovarian cancer [20]. Similarly, cytokines and mediators are responsible for the microenvironment of endometriosis and endometriosis-associated ovarian carcinoma. The current finding might help develop current hypotheses in a different direction.

HNF1B has been discussed in connection with in a variety of diseases and molecular processes. It has been described as a member of the homeodomain-containing superfamily of transcription factors [21]. Clinical phenotypes that have been reported, with either genetic changes or altered tissue expression, include renal malformations, early-onset diabetes, malformations of female and male genitalia, and other dysfunctions involving the pancreas, liver, and genitourinary system [22]. Genetic variants have been described as altering the risk for serous and clear cell ovarian cancer, endometrial cancer, and prostate cancer [23–26].

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Table 3
Genotyping results. Minor and major alleles and Hardy–Weinberg equilibrium calculations. MAF is measured in all subjects.

SNP	Gene	Alleles[a]	MAF (%)	Homozygous common[b]	Heterozygous[b]	Homozygous rare[b]	*P* value HWE
rs2072590	*HAGLROS,HAGLR*	C/A	31.9%	424 (45.6%)	418 (45.0%)	88 (9.5%)	0.68
rs2665390	*TIPARP*	T/C	7.6%	786 (84.9%)	139 (15.0%)	1 (0.1%)	0.92
rs10069690	*TERT*	C/T	25.6%	522 (56.6%)	328 (35.6%)	72 (7.8%)	0.74
rs11782652	*CHMP4C*	A/G	6.4%	818 (87.2%)	120 (12.8%)	0 (0.0%)	0.94
rs10088218	*LINC00824*	G/A	12.9%	691 (75.8%)	206 (22.6%)	15 (1.6%)	0.87
rs1243180	*MLLT10*	T/A	31.7%	453 (48.2%)	377 (40.2%)	109 (11.6%)	0.68
rs7405776	*HNF1B*	G/A	39.0%	336 (36.3%)	457 (49.6%)	133 (14.4%)	0.39
rs757210	*HNF1B*	C/T	40.7%	308 (34.9%)	432 (48.9%)	143 (16.2%)	0.59
rs11651755	*HNF1B*	T/C	48.6%	238 (25.7%)	477 (51.5%)	212 (22.9%)	0.51
rs9303542	*SKAP1*	A/G	26.2%	507 (54.2%)	367 (39.2%)	62 (6.6%)	0.74
rs8170	*BABAM1*	G/A	17.3%	636 (67.7%)	282 (30.0%)	22 (2.3%)	0.83
rs2363956	*ANKLE1*	G/T	48.4%	252 (27.2%)	449 (48.6%)	223 (24.1%)	0.52

HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.
[a] Minor/major allele.
[b] Values are rounded and need not add up exactly to 100%.

As endometriosis is associated with both a risk for endometrial cancer [27] and more clearly with a risk for clear cell ovarian cancer [7,8], molecular associations are of special interest in this context. Different SNPs within *HNF1B* have been shown to differentially influence *HNF1B* expression [25]. *HNF1B* appears to be overexpressed in clear cell tumors and silenced in serous ovarian cancers, underlining the different hypothesized pathogenesis of these two subtypes of ovarian cancer — with serous ovarian cancer most likely originating from fallopian tube cells [28] and clear cell ovarian cancer originating from uterine cells and being linked with endometriosis [7]. Our results are in line with these findings. For both diseases the C-allele was associated with a lower risk for the disease (OR for endometriosis: 0.66 in our study and OR for clear cell ovarian cancer: 0.77 in OCAC findings). This supports a common genetic etiology.

In this context, it has been shown that *HNF1B* overexpression in immortalized endometriosis epithelial cells changed the morphology of the endometriosis cells, with the formation of multinucleated cells [25], indicating that maintenance of *HNF1B* expression in endometriosis cells might play an essential role in the pathogenesis from endometriosis cells to clear cell ovarian cancer.

Ovarian endometriosis cysts have been shown to express *HNF1B* in 40% of cases. Histopathologically, these *HNF1B* overexpressing ovarian endometriosis cells have been described as displaying reactive atypia [29]. Additionally, clear cell ovarian cancer tumors are accompanied by ovarian endometriosis in more than half of the cases [30,31]. These data strengthen the hypothesis that endometriosis is part of the pathogenesis of clear cell ovarian cancer.

Although *HNF1B* has been discussed as a potential gene involved in the development of ovarian cancer from endometriosis, little is known about its role in the pathogenesis of endometriosis independently of an ovarian cancer history. The present study provides evidence that *HNF1B* SNP rs11651755 is not only involved in the pathogenesis of ovarian clear cell cancer, but is also an etiological factor for endometriosis itself. This would suggest the hypothesis that *HNF1B* is involved very early in the pathogenesis of clear cell ovarian cancer, even before the development of endometriosis.

There is also some additional information linking *HNF1B* to the pathogenesis of endometriosis. Osteopontin has been hypothesized as a direct target of *HNF1B* as a transcription factor, as osteopontin contains functional binding HNF1 sites in its promotor region [32]. The clinical relevance of this finding has been demonstrated in studies showing that endometriosis patients have higher plasma levels of osteopontin than patients without endometriosis [33,34]. The finding in the present study of a genetic variant that most likely maintains *HNF1B* expression in the pathogenesis of both endometriosis and clear cell ovarian cancer should encourage further research to explore the role of this molecular pathway in the early pathogenesis of this endometrium–endometriosis–ovarian cancer complex. Other genes (*MERIT40*, *TIPARP*, *BNC2*, *TERT*) have not shown any association with endometriosis. The involvement of these molecular pathways in the pathogenesis of both endometriosis and ovarian cancer thus appears less likely, and those ovarian cancers might be driven by a different molecular mechanism, independently of endometriosis. This is also reflected in the odds ratios that associate endometriosis with high-grade serous ovarian cancer (OR 1.13;

Table 4
SNPs with *P* values for the odds ratios (ORs) obtained using the simple logistic regression model. Unadjusted and adjusted ORs with 95% confidence intervals (in brackets) and uncorrected *P* values are shown.

SNP	Gene	Unadjusted analysis			Analysis adjusted for clinical predictors		
		OR (CI)[a]	Unorrected *P* value[b]	Corrected *P* value[c]	OR (CI)[d]	Uncorrected *P* value[b]	Corrected *P* value[c]
rs2072590	*HAGLROS,HAGLR*	0.99 (0.80–1.22)	0.94	1.00	0.98 (0.75–1.27)	0.85	1.00
rs2665390	*TIPARP*	0.87 (0.60–1.27)	0.46	1.00	0.91 (0.56–1.47)	0.70	1.00
rs10069690	*TERT*	1.32 (1.06–1.63)	0.01	0.15	1.22 (0.94–1.59)	0.14	1.00
rs11782652	*CHMP4C*	0.93 (0.62–1.39)	0.72	1.00	0.76 (0.46–1.28)	0.31	1.00
rs10088218	*LINC00824*	1.01 (0.75–1.34)	0.97	1.00	1.08 (0.75–1.55)	0.67	1.00
rs1243180	*MLLT10*	1.02 (0.83–1.24)	0.87	1.00	0.96 (0.75–1.24)	0.76	1.00
rs7405776	*HNF1B*	0.96 (0.78–1.17)	0.65	1.00	0.72 (0.56–0.94)	0.01	0.15
rs757210	*HNF1B*	0.93 (0.76–1.13)	0.45	1.00	0.73 (0.56–0.94)	0.02	0.16
rs11651755	*HNF1B*	0.84 (0.69–1.02)	0.08	0.86	0.66 (0.51–0.84)	<0.01	0.01
rs9303542	*SKAP1*	1.19 (0.95–1.48)	0.13	1.00	1.03 (0.78–1.35)	0.86	1.00
rs8170	*BABAM1*	0.80 (0.62–1.03)	0.09	0.90	0.76 (0.55–1.06)	0.10	0.93
rs2363956	*ANKLE1*	0.97 (0.80–1.17)	0.75	1.00	0.98 (0.77–1.24)	0.86	1.00

[a] OR calculated with simple logistic regression model, one SNP per model.
[b] *P* value, uncorrected for multiple testing.
[c] *P* value, corrected for multiple testing (Bonferroni-Holm).
[d] OR calculated with multiple logistic regression model.

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95% CI, 0.97 to 1.32; $P = 0.13$) [7], which is driven by some of the DNA-related genes that were tested in the present study, for example.

There are some limitations to this study. At the time when the SNPs for ovarian cancer were selected, there were only 13 confirmed and validated ovarian cancer SNPs [35]. Furthermore the discovery and validation was done in populations consisting mainly of serous papillary ovarian cancer, although some SNPs like our top finding reached genomewide significance for clear cell ovarian cancer [25]. Additional validated SNPs have been published in the meantime that did not form part of the study presented here. There are now further SNPs in the iCOGS array that were not examined here, such as rs12942666 [36], rs7705526 and rs2242652 [37], rs56318008, rs58722170, rs17329882, rs116133110, rs635634 and rs199661266 [38], rs17041869, rs7937840, rs1469713, rs200182588 and rs8037137 [39]. Another subsequent large-scale genotyping effort will most likely reveal further genetic variants that are associated with the risk of ovarian cancer, and those SNPs have not been included in this study either. Another limitation of the study is the use of cases and controls regardless of age. However, all of the multivariate analyses were adjusted for age, and one strength of the study is its strict definition of control individuals, excluding persons with previous abdominal surgery and with abdominal pain. It has to be kept in mind that the effects of this common variant in *HNF1B* is clearly not leading to a transformation of all endometriotic lesions into an ovarian cancer. Our findings are rather hypothesis generating, which common genetic variants might contribute to the epidemiological risk of endometriosis.

In conclusion, this study supports that *HNF1B* is involved in the etiology of both endometriosis and ovarian cancer, suggesting a common genetic etiology. It can be hypothesized that *HNF1B* is involved in the very early pathogenesis of ovarian cancer including endometriosis as part of this pathway. Further studies are needed in order to confirm these results and to try to identify drivers and inhibitors of this multistep carcinogenesis through endometriosis. *HNF1B* represents a reasonably well known gene that can help promote this research in the field of endometriosis and ovarian cancer.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2017.02.022.

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