Whole exome sequencing identifies hemizygous deletions in the *UGT2B28* and *USP17L2* genes in a three-generation family with endometriosis

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Abstract. Endometriosis is an enigmatic condition with an unknown etiology and a poorly understood pathogenesis. It is considered to appear from the interplay of many genetic and environmental factors, affecting up to 10% of women and represents a major cause of pain and infertility. The familial association of endometriosis, as demonstrated through monozygotic twin and family studies suggests a genetic contribution to the disease, with further case-control and genome-wide association studies (GWAS) detecting various endometriosis risk factors. In a recent study, we described a unique, three-generation family of Cretan origin (Greece) with 7 females with surgically confirmed endometriosis (grandmother, 3 daughters and 3 granddaughters). All the affected members of this family displayed a variety of clinical manifestations and complications. In the present study, to further analyze the genetic variants conferring the risk of developing endometriosis, whole exome sequencing (WES) was performed, using the AmpliSeq technology on the Ion Proton platform. An initial analysis of 64 variants that were detected across the 14 genes previously confirmed to be associated with endometriosis, did not identify any deleterious exonic variants in these genes. However, further analysis revealed 2 hemizygous deletions in the grandmother that segregate in several of her affected offspring. The first deletion was found in the *UGT2B28* locus, spanning 7 informative sequence variants across at least 14 kb. The second deletion, located in *USP17L2*, spans 3 informative variants across at least 2 kb. On the whole, the findings of the presents study implicate 2 additional genes in the pathogenesis of endometriosis, apart from those already identified by GWAS.

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Introduction

Endometriosis is a benign, common gynecologic disorder, affecting 6-10% of women during their reproductive years (1). Chronic pelvic pain, dyspareunia, dysmenorrhea and infertility represent the main manifestations (2). The absence of a timely and non-invasive diagnostic tool is presently the greatest barrier to the identification and treatment of endometriosis.

Endometriosis is characterized by a multifactorial pattern of inheritance, influenced by multiple genetic and environmental factors, as documented initially by the elevated incidence of severe endometriosis in the first-degree relatives of affected women compared to women lacking a positive family history (3,4). Furthermore, two monozygotic twin-based and family studies have demonstrated an approximately 50% heritability for endometriosis (5,6). Case-control studies, genome-wide association studies (GWAS) and meta-analyses have led to the identification of disease-risk loci that alter a woman's risk of developing the disorder and provide new insight into potential pathways leading to endometriosis. Particularly, GWAS in several series of samples have identified single nucleotide polymorphisms (SNPs) that are either directly or indirectly implicated in matrix remodeling, cell cycle regulation and signaling, cell adhesion, hormone receptors and metabolism, transcription regulation and inflammation, as well as immune and oxidative stress processes (7). However, all these data only account for approximately 5% of the disease variance (8). It is possible that rare and recent familial mutations, not detectable by GWAS, are responsible for part of the missing heritability. Thus, recent findings have suggested an increased burden of rare coding variants in genes

involved in the development of complex diseases, apart from the established common variants identified by GWAS (9). Despite the continued progress being made in resolving the genetic underpinnings of endometriosis, a comprehensive list of genetic loci is far from being completed, and the functional role of causal variants remain poorly understood.

Recent progress in next generation sequencing provides us with the opportunity to search for less common variants with significant effects. In line with the aforementioned assumptions, whole exome sequencing (WES) provides a hypothesis-neutral approach. Accordingly, WES is a procedure that allows for the purification by sequence capture of all exonic regions of a genome and their further processing by next-generation sequencing (NGS) (10). Thus, prompted by the data collected by an initial genetic analysis (11) of a three-generation family of 7 affected women with surgically confirmed endometriosis and aiming to explore the contribution of functional coding variants to this disease, in the present study, we used WES to identify inherited rare, endometriosis-associated exonic variants in the patients of this family.

Patients and methods

Patients and study design. A three-generation family with 7 affected members is shown in Fig. 1. Case no. 1 was the first individual in the family to be diagnosed with endometriosis and underwent surgical hysterectomy at the age of 32 due to stage IV bilateral ovarian endometriosis. Her mother (not shown in the pedigree) had 4 children with no gynecological problems. However, her 3 daughters (case nos. 2-4) and 3 granddaughters (case nos. 5-7) have all been surgically diagnosed with endometriosis (11,12). Further clinical details regarding the disease severity of the affected members of the family have been previously reported in the study by Matalliotakis *et al* (11). In addition to endometriosis, case no. 1 has been diagnosed with 14 other morbidities, including Crohn's disease, interstitial cystitis, bronchial asthma, cardiovascular diseases, lupus erythematosus and multiple sclerosis (12).

The Ethics Committee of Venizeleio General Hospital of Heraklion (Heraklion, Greece) (ECHR no. 46/6686) approved the overall study and written informed consent was obtained from all the patients. The medical records were collected by the clinicians and pathologists, including surgical procedures and findings.

WES. Venous blood samples (5 ml per patient) were collected from the family members and stored at -20˚C. Genomic DNA was isolated from peripheral blood leukocytes by using a commercial kit (PureLink® Genomic DNA mini kit; Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) according to the manufacturer's instructions. Exome sequencing was conducted using the AmpliSeq technology on Ion Proton platform (Thermo Fisher Scientific, Inc.). A series of filters was applied in order to reduce sequencing artifacts. Following sequence assembly using Torrent software, variant annotation was performed using ANNOVAR (hg19 reference; http://annovar.openbioinformatics.org/en/latest/). Variants were determined using Ion Proton protocol and confirmed using the Genome Analysis Toolkit pipeline. Identity-by-descent (IBD) was calculated using PLINK (1.07) (13) and compared to the expected values for all relative-pairs in the pedigree.

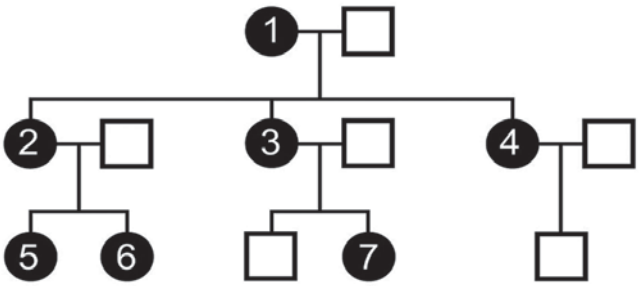

Figure 1. The three-generation family with 7 women affected with endometriosis, which was analyzed by whole exome sequencing. Filled circles represent women with endometriosis and open squares represent males. The available family members studied are indicated as case nos. 1-7. The figure has been adapted from a previous study (11).

Results

Common endometriosis-associated genetic variants. In the framework of a preliminary analysis conducted (data not shown), we first detected 64 variants across the 14 genes confirmed thus far to be associated with endometriosis (8). However, the vast majority of these variants were common in the population [minor allele frequency (MAF) >1%)] and, as a consequence, are not considered to be disease-causing. Moreover, we did not find any evidence of any deletions in these well-analyzed 14 genes.

Two rare variants (rs763439987 and rs139078629) were observed in the *FN1* gene (MAF <1%), with each of the variants present in a single member of the family. Segregation analysis revealed that both variants appeared to be paternally inherited and in linkage disequilibrium (LD) (detailed data not shown).

Novel genetic variants. In a further in-depth analysis of normally segregating rare variants, we identified approximately 20,000 exonic variants in each of the 7 individuals, and almost 34,000 variants combined across the pedigree, which was in line with our expectations. IBD and segregation analysis confirmed all individual associations and the overall pedigree structure. We identified 2 hemizygous deletions segregating in this three-generation family (Fig. 2). A deletion was found in UDP glucuronosyltransferase family 2 member B28 (*UGT2B28*) genomic region, spanning 7 informative sequence variants across at least 14 kb, as well as a deletion in ubiquitin specific peptidase 17-like family member 2 (*USP17L2*) genomic region spanning 3 informative variants across at least 2 kb. Both deletions were present in the affected grandmother and segregated in as many as 4 and 5 of her descendants, respectively.

Discussion

Recent advances in genome sequencing technologies provide many opportunities for the characterization of individual genomic landscapes and for the identification of mutations relevant for diagnosis and therapy. In particular, WES has become a popular approach in the human genetics community considering

Chr	Pos	Ref	Alt	Gene	Nucl	SNP	Individual ID						
							1	2	3	4	5	6	7
4	69,972,949	C	G	UGT2B7	c.C1059G	rs4292394	0/1	1/1	0/0	1/1	1/1	1/1	1/1
4	70,079,838	T	C	UGT2B11	c.A603G	rs4694697	0/1	0/0	0/1	0/0	0/0	0/0	0/0
4	70,079,963	G	A	UGT2B11	c.C478T	rs72551399	0/0	0/0	0/0	0/0	0/1	0/1	0/0
4	70,146,230	G	A	UGT2B28	c.G12A	rs13139691	1/1	0/0	1/1	0/0	0/0	0/0	0/1
4	70,146,704	G	A	UGT2B28	c.G486A	rs7689398	1/1	0/0	0/1	0/0	0/0	0/0	0/0
4	70,146,804	G	C	UGT2B28	c.G586C	rs148987832	0/0	0/0	0/1	0/0	0/0	0/0	0/0
4	70,156,392	A	G	UGT2B28	c.A1173G	rs10013145	1/1	0/0	0/0	0/0	0/0	0/0	0/0
4	70,160,277	T	G	UGT2B28	c.T1340G	rs6843900	1/1	0/0	0/1	0/0	0/0	0/0	0/0
4	70,160,309	C	G	UGT2B28	c.C1372G	rs6828191	1/1	0/0	0/1	0/0	0/0	0/0	0/0
4	70,160,338	G	C	UGT2B28	c.G1401C	rs72552703	0/0	0/0	0/1	0/0	0/0	0/0	0/1
4	70,160,342	TG	CC	UGT2B28	c.1405_1406	rs796618077	0/0	0/0	0/1	0/0	0/0	0/0	0/0
4	70,346,564	GA	TT	UGT2B4	c.1374_1375	rs67904882	0/0	0/0	0/1	0/0	0/0	0/0	0/1
4	70,355,211	T	C	UGT2B4	c.A948G	rs1845555	1/1	1/1	1/1	1/1	1/1	1/1	0/1
8	11,706,581	T	G	CTSB	c.A420C	rs13332	0/1	0/1	0/1	0/1	0/1	0/1	1/1
8	11,710,888	G	C	CTSB	c.C76G	rs12338	0/1	0/1	1/1	1/1	0/1	0/1	0/1
8	11,832,079	A	G	DEFB136	c.T30C	rs10108075	0/0	0/1	0/1	0/1	0/0	0/0	0/1
8	11,994,716	C	A	USP17L2	c.G1554T	rs199935289	1/1	0/0	0/0	0/0	0/0	0/0	0/0
8	11,994,957	T	C	USP17L2	c.A1313G	rs12543578	1/1	0/0	0/0	0/0	1/1	1/1	0/0
8	11,995,062	G	A	USP17L2	c.C1208T	rs75807755	0/0	0/0	1/1	1/1	0/0	0/0	0/1
8	12,600,720	T	A	LONRF1	c.A793T	rs1139354	0/0	0/0	0/1	0/1	0/0	0/0	0/0
8	12,878,637	A	G	KIAA1456	c.A449G	rs528255	1/1	1/1	1/1	1/1	1/1	1/1	1/1
8	12,878,677	T	C	KIAA1456	c.T489C	rs622106	0/1	0/1	0/1	0/1	0/0	0/0	1/1

Figure 2. The chromosomal position and characteristics of the genetic variants surrounding the hemizygous deletions of the *UGT2B28* and *USP17L2* genes are shown to the left, and the genotypes for each of the 7 affected women are shown to the right. Bold red boarders indicate the extent of the deletion and the individuals that carry the deletions. Thin red boarders indicate possible carriers of the deletion. The fields in the table shown with 0/0 are interpreted as wild-type homozygous, fields with 0/1 as heterozygotes (yellow), and those with 1/1 as homozygous for the alternate allele (green). SNP, single nucleotide polymorphisms.

its moderate costs, the amount of data that can be managed reasonably and the straightforward interpretation of the accumulated results upon analysis. The progress of high-throughput sequencing has led geneticists to directly perform WES for identifying the candidate variants in monogenic, as well as multifactorial diseases (14), for elucidating the genetic basis of some genetically heterogeneous disorders (15) and for an improved diagnosis of patients (16). In this framework, we hypothesized that WES of the affected members of a rare, three-generation family with 7 members with endometriosis, would be more likely to facilitate the identification of common and rare deleterious genetic variants that contribute to disease risk.

The current analysis demonstrated the absence of any deleterious exonic variants in genes confirmed thus far to be associated with endometriosis (8). However, the results obtained implicate the *UGT2B28* and *USP17L2* genes in the pathogenesis of endometriosis. Neither of the genes has previously been reported to be associated with endometriosis, at least to the best of our knowledge. *UGT2B28* is a member of the UGT2B gene family, which is known to be involved in the metabolism of steroid hormones and several other xenobiotics (17) and is widely expressed in the liver, as well as extrahepatic steroid target tissues (18). Germ line copy-number variation in the *UGT2B28* gene has been associated with Addison's disease (19), while common polymorphisms and copy number variation of the gene affect steroid hormone abundance and has been implicated in the increase of prostate cancer risk (18,20). Deletions of this gene have been reported to be predictors of the prostate-specific antigen (PSA) level in clinically localized prostate cancer following surgical treatment (21). Based on the aforementioned findings, the important role of *UGT2B28* in the regulation of the hormonal exposure of steroid target cells has been suggested, and it has also been suggested that the alteration of *UGT2B28* function may affect the metabolism of sex hormones (22). However, the mechanisms through which *UGT2B28* may affect the pathogenesis of endometriosis are not yet clear.

USP17L2 (also known as DUB3, DUB-3 or USP17) is a member of the USP17 subfamily of USPs, consisted by cysteine proteases (23) regulating key cellular processes, such as cell growth and survival (24). It is transiently induced in response to cytokines and, when it is constitutively expressed, can block growth factor-dependent proliferation (24). USP17L2 has deubiquitinating activity and its overexpression leads to apoptosis and cell death (25). Ubiquitin has been found to be expressed in endometriotic cells and, as suggested, may contribute to a reduced sensitivity of ectopic endometrial tissue to apoptosis (26). Thus far, USP17L2 has been suggested to possibly be a valuable biomarker for the prediction of ovarian cancer prognosis and its inhibition may be a potential strategy for ovarian cancer treatment (27). This gene plays a central role in the regulation of the transcription factors, Slug and Twist. Particularly, it has been found that *USP17L2* interacts with and stabilizes Slug and Twist through de-ubiquitination (28). As is known, Slug, Snail and Twist are three key epithelial-to-mesenchymal transition transcription factors (EMT-TFs) that are tightly regulated via ubiquitination and degradation. Furthermore, the aberrant expression/activation of EMT-TFs can give rise to tumor angiogenesis, invasion and metastasis (29,30).

EMT can be considered as a cellular de-differentiation process providing cells with the increased plasticity required during embryonic development and tissue remodeling, due to the similarities in the migratory and invasive characteristics that the cells obtain during these processes (31,32). We have previously proposed that the pathogenesis of endometriosis involves the loss of mesothelial barrier integrity due to the activation of the EMT repair mechanism (33). As a consequence, in the absence of the mesothelial barrier, endometrial cells can more readily adhere to the underlying peritoneal stroma

and establish endometrial lesions. Thus, we speculate that the dosage-dependent loss of USP17L2 affects mesothelial integrity and increases the risk of developing endometriosis.

Furthermore, in the framework of the present WES, two rare variants (rs763439987 and rs139078629) were observed in the *FN1* gene to be paternally inherited. Although both of the hemizygous deletions clearly are inherited from the grandmother of the family under investigation, any paternally inherited risk-variants, such as the rare *FN1* haplotype, must also be considered.

In conclusion, the present study identified, for the first time, to the best of our knowledge, a role of the *UGT2B28* and *USP17L2* genes in endometriosis and underlines the power of WES to decipher complex phenotypes. However, the precise underlying mechanisms remain elusive. The present findings may enhance our biological insight of endometriosis and may contribute towards novel strategies regarding improved patient care. Further in-depth analysis of normally segregating rare variants is ongoing.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article or are available from the corresponding author on reasonable request.

Authors' contributions

HMA, RC, KW, GNG and CM conceived and designed the study and drafted the manuscript. HMA, RC, KW and MIZ performed the experiments. MM, RC, CM, GNG and MIZ searched the literature. IM, CM and MM obtained the clinical data. CM, RC, MIZ, DAS, GNG and IM analyzed and interpreted the data. DAS, HMA, MM, MIZ and IM critically revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committees of the Human Research at Venizeleio General Hospital of Heraklion (ECHR no. 46/6686) approved the overall study and written informed consent was obtained from all the patients.

Patient consent for publication

Not applicable.

Competing interests

HMA, RC and KW are employed by Juneau Biosciences who provided salary support for the study. DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

References

1. Burney RO and Giudice LC: Pathogenesis and pathophysiology of endometriosis. Fertil Steril 98: 511-519, 2012.
2. Halis G and Arici A: Endometriosis and inflammation in infertility. Ann N Y Acad Sci 1034: 300-315, 2004.
3. Simpson JL, Elias S, Malinak LR and Buttram VC Jr: Heritable aspects of endometriosis. I. Genetic studies. Am J Obstet Gynecol 137: 327-331, 1980.
4. Hadfield RM, Mardon HJ, Barlow DH and Kennedy SH: Endometriosis in monozygotic twins. Fertil Steril 68: 941-942, 1997.
5. Treloar SA, O'Connor DT, O'Connor VM and Martin NG: Genetic influences on endometriosis in an Australian twin sample. sueT@qimr.edu.au. Fertil Steril 71: 701-710, 1999.
6. Saha R, Pettersson HJ, Svedberg P, Olovsson M, Bergqvist A, Marions L, Tornvall P and Kuja-Halkola R: Heritability of endometriosis. Fertil Steril 104: 947-952, 2015.
7. Kobayashi H, Imanaka S, Nakamura H and Tsuji A: Understanding the role of epigenomic, genomic and genetic alterations in the development of endometriosis (review). Mol Med Rep 9: 1483-1505, 2014.
8. Sapkota Y, Steinthorsdottir V, Morris AP, Fassbender A, Rahmioglu N, De Vivo I, Buring JE, Zhang F, Edwards TL, Jones S, *et al*; iPSYCH-SSI-Broad Group: Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. Nat Commun 8: 15539, 2017.
9. Gao L, Emond MJ, Louie T, Cheadle C, Berger AE, Rafaels N, Vergara C, Kim Y, Taub MA, Ruczinski I, *et al*; National Heart, Lung, and Blood Institute GO Exome Sequencing Project: Identification of rare variants in ATP8B4 as a risk factor for systemic sclerosis by whole-exome sequencing. Arthritis Rheumatol 68: 191-200, 2016.
10. Ng SB, Turner EH, Robertson PD, Flygare SD, Bigham AW, Lee C, Shaffer T, Wong M, Bhattacharjee A, Eichler EE, *et al*: Targeted capture and massively parallel sequencing of 12 human exomes. Nature 461: 272-276, 2009.
11. Matalliotakis M, Zervou MI, Matalliotaki C, Arici A, Spandidos DA, Matalliotakis I and Goulielmos GN: Genetic association study in a three-generation family with seven members with endometriosis. Mol Med Rep 16: 6077-6080, 2017.
12. Matalliotaki C, Matalliotakis M, Zervou MI, Trivli A, Matalliotakis I, Mavromatidis G, Spandidos DA, Albertsen HM, Chettier R, Ward K and Goulielmos GN: Co-existence of endometriosis with 13 non-gynecological co-morbidities: Mutation analysis by whole exome sequencing. Mol Med Rep 18: 5053-5057, 2018.
13. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ and Sham PC: PLINK: A tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81: 559-575, 2007.
14. Ng SB, Buckingham KJ, Lee C, Bigham AW, Tabor HK, Dent KM, Huff CD, Shannon PT, Jabs EW, Nickerson DA, *et al*: Exome sequencing identifies the cause of a mendelian disorder. Nat Genet 42: 30-35, 2010.
15. Girard SL, Gauthier J, Noreau A, Xiong L, Zhou S, Jouan L, Dionne-Laporte A, Spiegelman D, Henrion E, Diallo O, *et al*: Increased exonic de novo mutation rate in individuals with schizophrenia. Nat Genet 43: 860-863, 2011.
16. Choi M, Scholl UI, Ji W, Liu T, Tikhonova IR, Zumbo P, Nayir A, Bakkaloğlu A, Ozen S, Sanjad S, *et al*: Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. Proc Natl Acad Sci USA 106: 19096-19101, 2009.
17. Tephly TR and Burchell B: UDP-glucuronosyltransferases: A family of detoxifying enzymes. Trends Pharmacol Sci 11: 276-279, 1990.
18. Guillemette C, Lévesque E, Harvey M, Bellemare J and Menard V: UGT genomic diversity: Beyond gene duplication. Drug Metab Rev 42: 24-44, 2010.
19. Brønstad I, Wolff AS, Løvås K, Knappskog PM and Husebye ES: Genome-wide copy number variation (CNV) in patients with autoimmune Addison's disease. BMC Med Genet 12: 111, 2011.

20. Karypidis AH, Olsson M, Andersson S-O, Rane A and Ekström L: Deletion polymorphism of the UGT2B17 gene is associated with increased risk for prostate cancer and correlated to gene expression in the prostate. Pharmacogenomics J 8: 147-151, 2008.
21. Nadeau G, Bellemare J, Audet-Walsh É, Flageole C, Huang SP, Bao BY, Douville P, Caron P, Fradet Y, Lacombe L, *et al*: Deletions of the androgen-metabolizing UGT2B genes have an effect on circulating steroid levels and biochemical recurrence after radical prostatectomy in localized prostate cancer. J Clin Endocrinol Metab 96: E1550-E1557, 2011.
22. Belledant A, Hovington H, Garcia L, Caron P, Brisson H, Villeneuve L, Simonyan D, Têtu B, Fradet Y, Lacombe L, *et al*.: The UGT2B28 sex-steroid inactivation pathway is a regulator of steroidogenesis and modifies the risk of prostate cancer progression. Eur Urol 69: 601-609, 2016.
23. Nijman SM, Luna-Vargas MP, Velds A, Brummelkamp TR, Dirac AM, Sixma TK and Bernards R: A genomic and functional inventory of deubiquitinating enzymes. Cell 123: 773-786, 2005.
24. Burrows JF, McGrattan MJ, Rascle A, Humbert M, Baek KH and Johnston JA: DUB-3, a cytokine-inducible deubiquitinating enzyme that blocks proliferation. J Biol Chem 279: 13993-14000, 2004.
25. Shin JM, Yoo KJ, Kim MS, Kim D and Baek KH: Hyaluronan- and RNA-binding deubiquitinating enzymes of USP17 family members associated with cell viability. BMC Genomics 7: 292, 2006.
26. Ilad RS, Fleming SD, Bebington CR and Murphy CR: Ubiquitin is associated with the survival of ectopic stromal cells in endometriosis. Reprod Biol Endocrinol 2: 69, 2004.
27. Zhou B, Shu B, Xi T, Su N, Liu J: Dub3 expression correlates with tumor progression and poor prognosis in human epithelial ovarian cancer. Biomed Pharmacother 70: 84-89, 2015.
28. Lin Y, Wang Y, Shi Q, Yu Q, Liu C, Feng J, Deng J, Evers BM, Zhou BP and Wu Y: Stabilization of the transcription factors slug and twist by the deubiquitinase dub3 is a key requirement for tumor metastasis. Oncotarget 8: 75127-75140, 2017.
29. Blanco MJ, Moreno-Bueno G, Sarrio D, Locascio A, Cano A, Palacios J and Nieto MA: Correlation of Snail expression with histological grade and lymph node status in breast carcinomas. Oncogene 21: 3241-3246, 2002.
30. Zhou BP, Deng J, Xia W, Xu J, Li YM, Gunduz M and Hung MC: Dual regulation of Snail by GSK-3beta-mediated phosphorylation in control of epithelial-mesenchymal transition. Nat Cell Biol 6: 931-940, 2004.
31. Thiery JP and Sleeman JP: Complex networks orchestrate epithelial-mesenchymal transitions. Nat Rev Mol Cell Biol 7: 131-142, 2006.
32. Thiery JP, Acloque H, Huang RY and Nieto MA: Epithelial-mesenchymal transitions in development and disease. Cell 139: 871-890, 2009.
33. Albertsen HM and Ward K: Genes linked to endometriosis by GWAS are integral to cytoskeleton regulation and suggests that mesothelial barrier homeostasis is a factor in the pathogenesis of endometriosis. Reprod Sci 24: 803-811, 2017.

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