

**Supplementary information: Genetic and epigenetic changes in the eutopic endometrium of women with endometriosis: association with decreased endometrial  $\alpha_v\beta_3$  integrin expression.**

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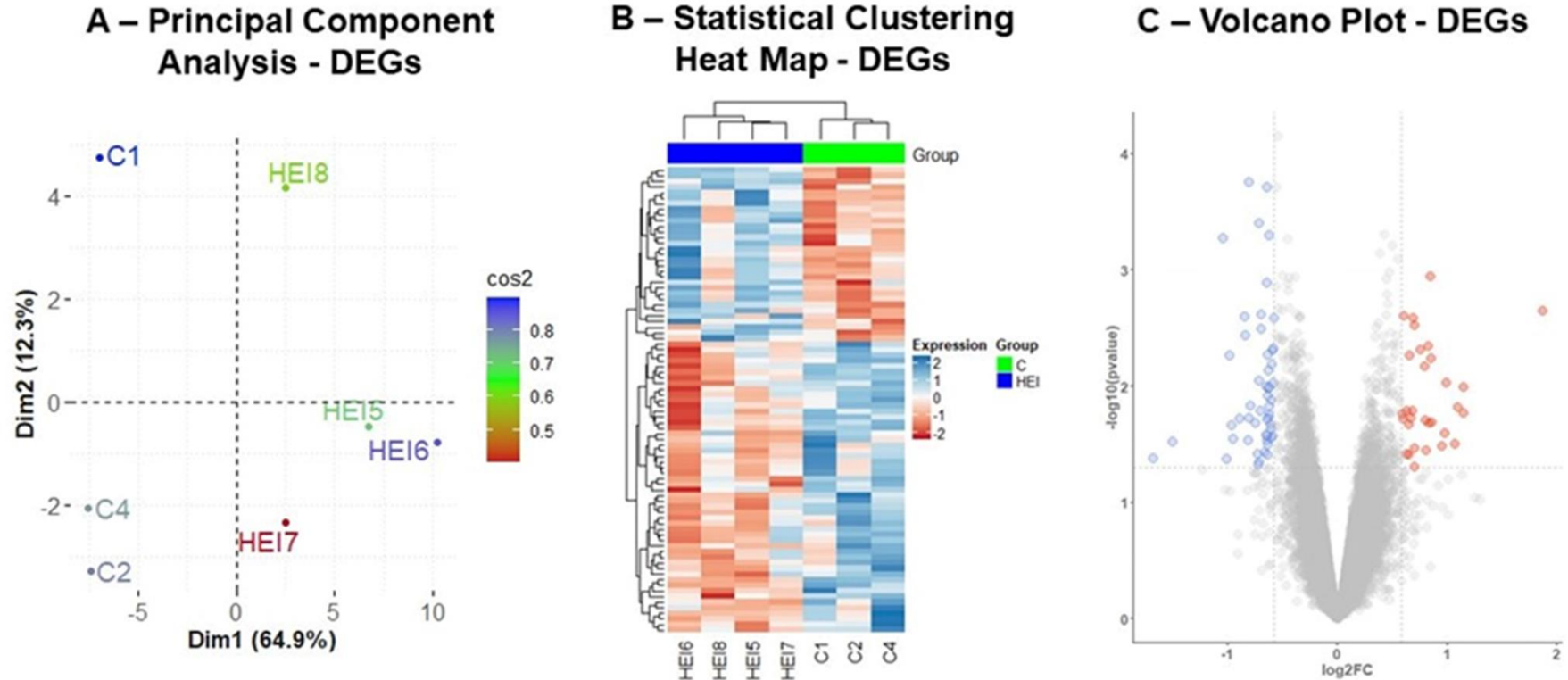
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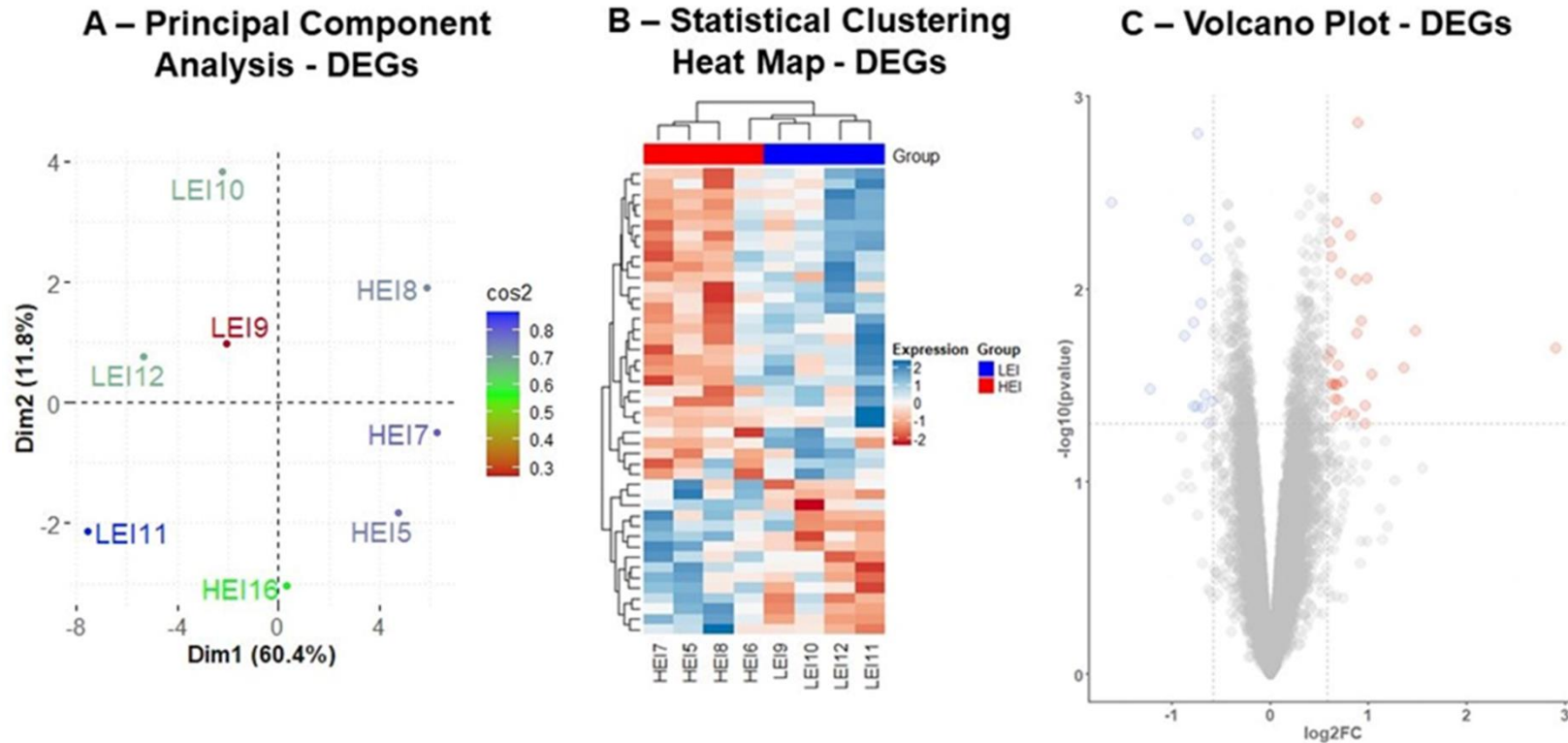
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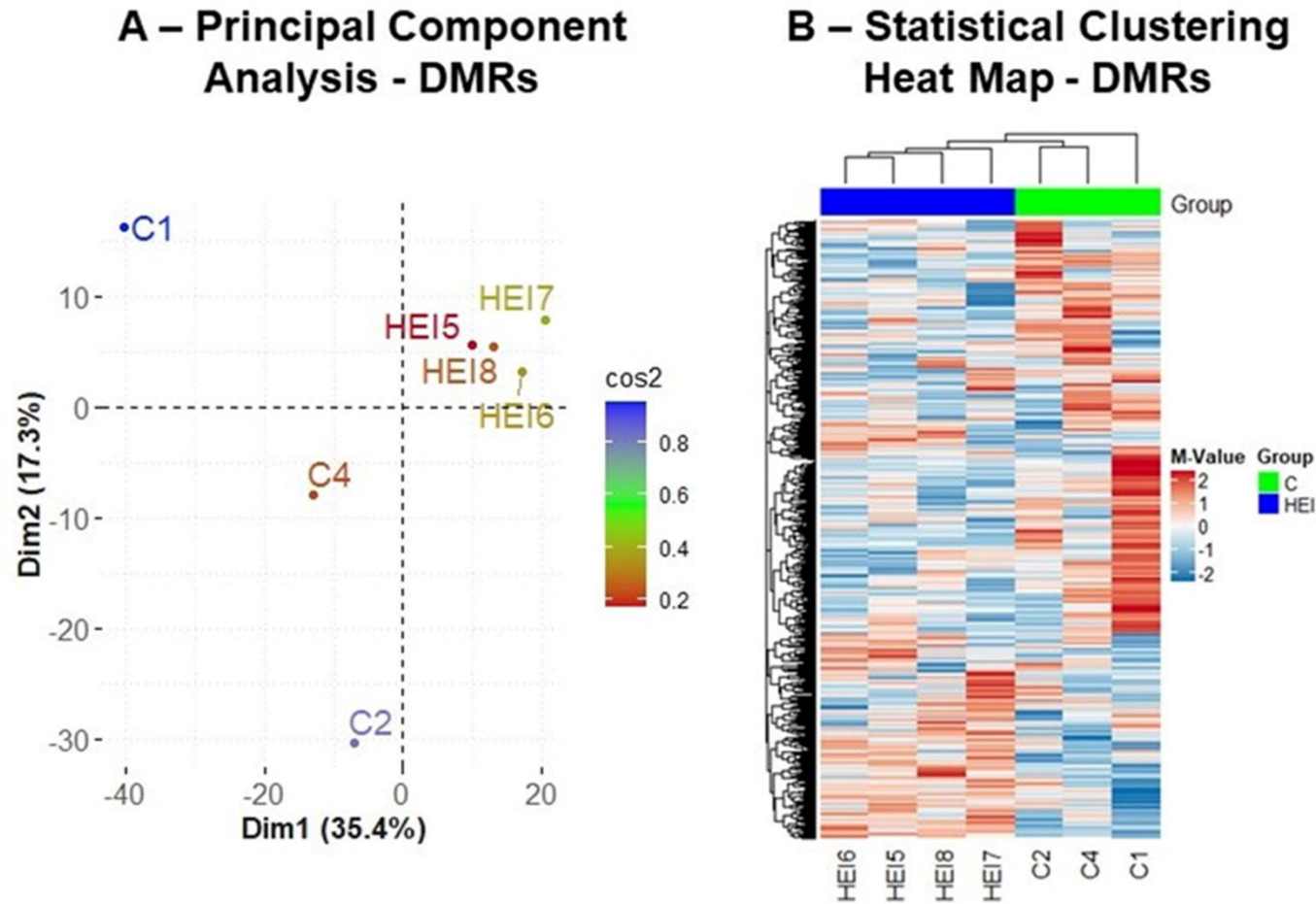
**Supplemental Figure-1:** Principal Component Analysis for 83 DEGs identified in the HEI vs. C comparisons (A). Heatmap of differentially expressed genes the two groups (HEI and C) that cluster separately. Each column represents the individual sample, and each row represents the individual DEG in the HEI vs. C comparisons (B). The volcano plot shows the statistical significance (Y-Axis) against the fold change (X-Axis) between the HEI and C groups (C). Each blue dot represents the significantly decreased expression of an individual gene, and each red dot represents the significantly increased expression of a gene on the Volcano Plot. Dotted horizontal and vertical lines represent the cut-off fold change ( $\pm 1.5$  folds) and statistical significance ( $p < 0.05$ ), respectively.



**Supplemental Figure-2:** Principal Component Analysis for 45 DEGs identified in the LEI vs. HEI comparisons (A). Heatmap of the differentially expressed genes in the two groups (LEI vs. HEI) that cluster separately. Each column represents the individual sample, and each row represents the individual DEG in the LEI vs. HEI comparison (B). The volcano plot shows the statistical significance (Y-Axis) against the fold change (X-Axis) between the LEI and HEI groups (C). Each blue dot represents the significantly decreased expression of an individual gene, and each red dot the significantly increased expression of a gene on the Volcano Plot. The dotted horizontal and vertical line represents the cut-off fold change ( $\pm 1.5$  folds) and statistical significance ( $p < 0.05$ ), respectively.

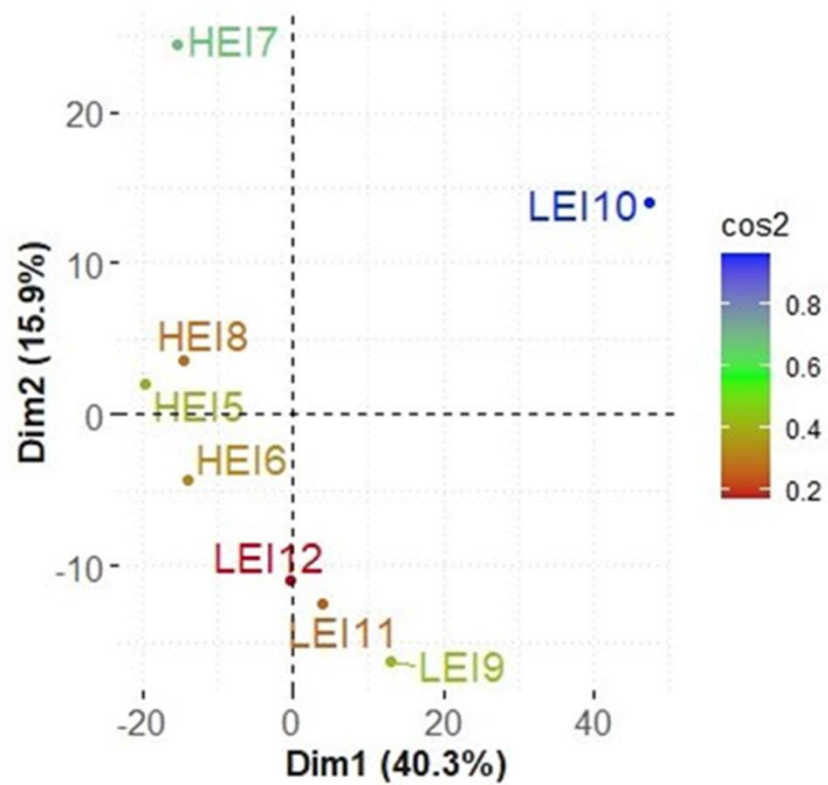


**Supplemental Figure-3:** Principal Component Analysis for 1325 DMRs identified in the HEI vs. C comparisons (A). Heatmap of differentially methylated genes demonstrates that the two groups (HEI and C) cluster separately. Each column represents the individual sample, and each row represents the unique DMR in the HEI vs. C comparisons (B).

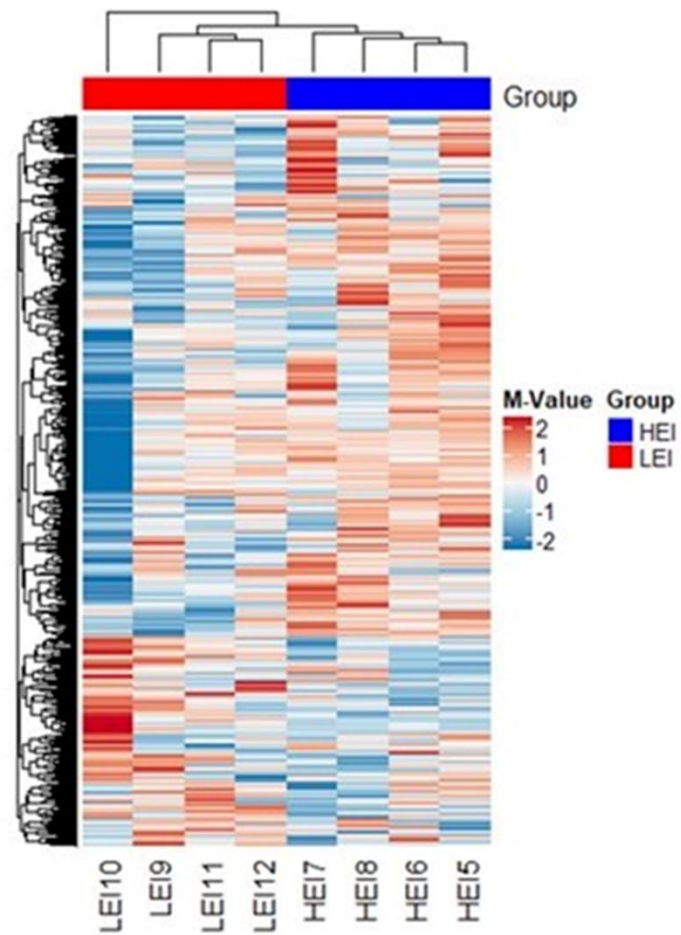


**Supplemental Figure-4:** Principal Component Analysis for 1233 DMRs identified in the LEI vs. HEI comparisons (A). Heatmap of differentially methylated genes demonstrating that the two groups (LEI vs. HEI) cluster separately. Each column represents the individual sample, and the row represents the unique DMR in LEI vs. HEI comparisons (B).

### A – Principal Component Analysis - DMRs



### B – Statistical Clustering Heat Map - DMRs



**Supplementary Table SI** Subject details for the eutopic endometrial biopsies obtained from women with and without endometriosis and used for gene expression array, methylation array, and quantitative RT-PCR analysis.

<b>Sample Id</b>	<b>Disease Status</b>	<b>Integrin <math>\alpha_v\beta_3</math> H-Score</b>	<b>Menstrual Cycle Day</b>	<b>Laparoscopic Evaluation</b>
G212A	Control	3.2	Secretory	No
G422A	Control	2.1	Secretory	Yes
G214A	Control	2.0	Secretory	No
R01c	Endometriosis - III	3.6	Secretory	Yes - 1/19/10
M102c	Endometriosis - III	1	Secretory	Yes - 7/29/10
G448B	Endometriosis - II	2.1	Secretory	Yes - 10/2007
G416A	Endometriosis	3.2	Secretory	Yes - 2002 & 2005
R03c	Endometriosis - III	0	Secretory	yes - 3/8/07 & 4/13/10
R07c	Endometriosis - I	0.5	Secretory	yes - 9/11/08 & 2/23/10
R08c	Endometriosis - Mild	0	Secretory	yes - 2/10/10
G418A	Endometriosis - II	0.0	Secretory	yes - 8/31/07

**Supplementary Table SII** Subject details for the sample used for western blot analysis.

<b>Western Blot Lane</b>	<b>Sample ID</b>	<b>Stage of Menstrual Cycle</b>	<b>Diagnosis</b>
2	H1224	Proliferative	No Endometriosis
3	H1257	Proliferative	No Endometriosis
4	H1281	Proliferative	No Endometriosis
5	N081	Proliferative	No Endometriosis
6	N099	Proliferative	No Endometriosis
7	N057	Proliferative	No Endometriosis
8	G486B	Proliferative	Endometriosis
9	G490C	Proliferative	Endometriosis
10	G492A	Proliferative	Endometriosis
12	H1200	Secretory	No Endometriosis
13	H1235	Secretory	No Endometriosis
14	H1240	Secretory	No Endometriosis
15	N065	Secretory	No Endometriosis
16	N106	Secretory	No Endometriosis
17	N080	Secretory	No Endometriosis
18	I18B	Secretory	Endometriosis
19	I06A	Secretory	Endometriosis
20	G483C	Secretory	Endometriosis

**Supplementary Table SIII** Sequence of primers used for quantitative PCR analysis.

<b>Gene</b>	<b>Gene Name</b>	<b>Forward Primer 5' to 3'</b>	<b>Reverse Primer 5' to 3'</b>
CCDC146	coiled-coil domain containing 146	TGCCATAGTGCCACAAATTAAC	TTGGCTTTTAACGCTGCCATT
PGK2	phosphoglycerate kinase 2	AAACTGGATGTTAGAGGGAAGCG	GGCCGACCTAGATGACTCATAAG
PLEKHF2	pleckstrin homology and FYVE domain containing 2	CAAAGCAAGGCAGTTTTTCTTGT	TGGTGTCTTGATTAGCCATCCA
HIST1H4F	H4 clustered histone 6	AAAGTGCTGCGTGACAACATA	AGGCCCCGAAATGCGTTTCA
ANXA3	annexin A3	TTAGCCCATCAGTGGATGCTG	CTGTGCATTTGACCTCTCAGT
PGLYRP2	peptidoglycan recognition protein 2	GGACCTTTACGCTTTTGGACC	GAGTCCGGCTCAGGTAGTCT
SLC18A2	solute carrier family 18 member A2	CGGAAGCTCATCCTGTTTCATC	CCTGGCCGTCTGGATTTCTG
RNPC3	RNA binding region (RNP1, RRM) containing 3	GTGCGGGTCCTGTCAGATAAG	TGAACTCGATCTTGCTCTTTTGC
AHR	aryl hydrocarbon receptor	GTGCACAGCTCTGCTTCAGT	CTACTCCACTTCAGCCACCA
18s	RNA, 18S ribosomal N5	TGATTAAGTCCCTGCCCTTTGT	TCAAGTTGCACCGTCTTCTCAG



**Supplementary Table SIV** List of the top 10 Biological Processes of differentially expressed genes in the eutopic endometrium of low endometrial integrin expression (LEI) patients.

GO ID	Description	GeneRatio	pvalue	Gene symbols
GO:0043062	extracellular structure organization	20/331	6.05E-05	FMOD; <b>P4HA1</b> ; SERPINH1; EFEMP2; LUM; <b>ERO1A</b> ; MFAP4; <b>ABCA5</b> ; P4HB; COMP; <b>ITGA6</b> ; <b>CFLAR</b> ; COL6A3; PLTP; COL6A1; <b>ITGA2</b> ; HAPLN1; <b>PLA2G7</b> ; TIMP1; <b>GPM6B</b>
GO:0043087	regulation of GTPase activity	18/331	0.004	<b>ERRFI1</b> ; THY1; <b>ARHGAP32</b> ; <b>FGD4</b> ; <b>RGS6</b> ; <b>RANBP2</b> ; <b>ITGA6</b> ; <b>RALGAPA2</b> ; <b>RASA2</b> ; <b>CPEB2</b> ; <b>CXCL13</b> ; <b>FAM13A</b> ; <b>RICTOR</b> ; <b>EFNA5</b> ; <b>FAM13B</b> ; <b>STXBP5</b> ; <b>BVES</b> ; <b>NTRK2</b>
GO:0003012	muscle system process	17/331	0.005	<b>MIR30E</b> ; <b>ATP1A1</b> ; <b>ERRFI1</b> ; ACTA2; <b>DSG2</b> ; <b>DSC2</b> ; CNN1; <b>CFLAR</b> ; MYL9; <b>CAMK2D</b> ; <b>ITGA2</b> ; <b>DSP</b> ; <b>DOCK5</b> ; <b>STC1</b> ; <b>TMOD1</b> ; TPM2; FLNA
GO:0042391	regulation of membrane potential	16/331	0.008	<b>ATP1A1</b> ; KCNH1; <b>DSG2</b> ; <b>DSC2</b> ; <b>CXADR</b> ; <b>USP53</b> ; <b>CAMK2D</b> ; <b>SLC26A2</b> ; <b>GABRP</b> ; <b>DSP</b> ; <b>GCLC</b> ; <b>BVES</b> ; <b>PPP1R9A</b> ; <b>PTPN3</b> ; <b>GABRQ</b> ; FLNA
GO:0032970	regulation of actin filament-based process	16/331	0.002	<b>ATP1A1</b> ; RHOC; <b>DSG2</b> ; <b>DSC2</b> ; MYADM; SYNPO2; <b>CAMK2D</b> ; <b>RICTOR</b> ; <b>EFNA5</b> ; <b>DSP</b> ; <b>PPP1R9A</b> ; <b>STC1</b> ; <b>TMOD1</b> ; <b>C9orf72</b> ; <b>GPM6B</b> ; FLNA
GO:0030198	extracellular matrix organization	16/331	0.0007	FMOD; <b>P4HA1</b> ; SERPINH1; EFEMP2; LUM; <b>ERO1A</b> ; MFAP4; COMP; <b>ITGA6</b> ; <b>CFLAR</b> ; COL6A3; COL6A1; <b>ITGA2</b> ; HAPLN1; TIMP1; <b>GPM6B</b>
GO:0006936	muscle contraction	15/331	0.002	<b>MIR30E</b> ; <b>ATP1A1</b> ; ACTA2; <b>DSG2</b> ; <b>DSC2</b> ; CNN1; MYL9; <b>CAMK2D</b> ; <b>ITGA2</b> ; <b>DSP</b> ; <b>DOCK5</b> ; <b>STC1</b> ; <b>TMOD1</b> ; TPM2; FLNA
GO:0031589	cell-substrate adhesion	14/331	0.002	THY1; PPFIA2; MYADM; <b>EPB41L5</b> ; <b>ITGA6</b> ; LGALS1; <b>PIK3CB</b> ; <b>ITGA2</b> ; <b>EFNA5</b> ; <b>BVES</b> ; <b>DOCK5</b> ; <b>PRKX</b> ; <b>GPM6B</b> ; FLNA
GO:0090257	regulation of muscle system process	13/331	0.000	<b>MIR30E</b> ; <b>ATP1A1</b> ; <b>ERRFI1</b> ; <b>DSG2</b> ; <b>DSC2</b> ; CNN1; MYL9; <b>CAMK2D</b> ; <b>ITGA2</b> ; <b>DSP</b> ; <b>DOCK5</b> ; <b>STC1</b> ; FLNA
GO:0030048	actin filament-based movement	12/331	8.43E-06	<b>FBNP1L</b> ; <b>ATP1A1</b> ; <b>DSG2</b> ; <b>DSC2</b> ; <b>EPB41L5</b> ; <b>CAMK2D</b> ; <b>DSP</b> ; <b>MYO6</b> ; <b>STC1</b> ; <b>TMOD1</b> ; TPM2; FLNA

Upregulated genes are shown in bold font and the down-regulated genes in a standard font.

**Supplementary Table SV** List of the top 10 Cellular Components of differentially expressed genes in the eutopic endometrium of LEI patients.

GO ID	Description	GeneRatio	pvalue	Gene symbols
GO:0031012	extracellular matrix	21/347	0.0002	FMOD; <b>MMP26</b> ; EFEMP2; CD248; LUM; MFAP4; <b>OMG</b> ; COMP; <b>ITGA6</b> ; COL6A3; COL6A1; TIMP3; LGALS1; P3H2; ADAMTS6; HAPLN1; <b>EFNA5</b> ; <b>SERPINB1</b> ; PCOLCE; ASPN; TIMP1
GO:0005578	proteinaceous extracellular matrix	19/347	8.10E-05	FMOD; <b>MMP26</b> ; EFEMP2; CD248; LUM; MFAP4; <b>OMG</b> ; COMP; <b>ITGA6</b> ; COL6A3; COL6A1; TIMP3; LGALS1; P3H2; ADAMTS6; HAPLN1; <b>EFNA5</b> ; ASPN; TIMP1
GO:0098589	membrane region	13/347	0.006	<b>ATP1A1</b> ; SERPINH1; CAVIN3; <b>PPP2R1B</b> ; THY1; MYADM; <b>RANBP2</b> ; <b>CFLAR</b> ; <b>CXADR</b> ; <b>TLR2</b> ; <b>EFNA5</b> ; <b>BVES</b> ; <b>GPM6B</b>
GO:0005788	endoplasmic reticulum lumen	12/347	0.009	<b>P4HA1</b> ; SERPINH1; <b>TXNDC16</b> ; <b>ERO1A</b> ; PPIB; P4HB; COL6A3; COL6A1; LGALS1; P3H2; <b>RNASET2</b> ; TIMP1
GO:0098858	actin-based cell projection	12/347	0.0003	RHOC; ACTA2; <b>FGD4</b> ; <b>ITGA6</b> ; <b>CXADR</b> ; <b>ACPP</b> ; MUC20; <b>SLC4A7</b> ; <b>S100P</b> ; <b>SLC26A2</b> ; <b>MYO6</b> ; <b>PPP1R9A</b>
GO:0030427	site of polarized growth	8/347	0.009	THY1; <b>CXADR</b> ; <b>FRYL</b> ; DBN1; <b>PPP1R9A</b> ; STMN2; <b>C9orf72</b> ; <b>USP9X</b>
GO:0044420	extracellular matrix component	8/347	0.001	EFEMP2; LUM; MFAP4; <b>ITGA6</b> ; TIMP3; P3H2; <b>EFNA5</b> ; TIMP1
GO:1990204	oxidoreductase complex	7/347	0.004	<b>SDHD</b> ; <b>DBT</b> ; <b>P4HA1</b> ; P4HB; NDUFA13; <b>GPD2</b> ; <b>BCKDHB</b>
GO:0030175	filopodium	6/347	0.009	ACTA2; <b>FGD4</b> ; <b>ITGA6</b> ; <b>CXADR</b> ; <b>ACPP</b> ; <b>PPP1R9A</b>
GO:0005604	basement membrane	6/347	0.007	EFEMP2; <b>ITGA6</b> ; TIMP3; P3H2; <b>EFNA5</b> ; TIMP1

Upregulated genes are shown in bold font and down-regulated genes in normal font.

**Supplementary Table SVI** List of the top 10 Molecular Functions of differentially expressed genes in the eutopic endometrium of LEI patients.

GO ID	Description	GeneRatio	pvalue	Gene symbols
GO:0016747	transferase activity, transferring acyl groups other than amino-acyl groups	10/328	0.008	<b>DBT</b> ; <b>ZDHHC13</b> ; <b>ESCO1</b> ; <b>MBOAT1</b> ; <b>AGPAT5</b> ; <b>ZDHHC2</b> ; <b>ELP3</b> ; <b>ZDHHC21</b> ; <b>SAT1</b> ; NAA10
GO:0061134	peptidase regulator activity	10/328	0.008	SERPINH1; BIRC5; COL6A3; <b>CST11</b> ; TIMP3; <b>PCOLCE2</b> ; PTTG1; <b>SERPINB1</b> ; PCOLCE; TIMP1
GO:0005518	collagen binding	8/328	2.17E-05	SERPINH1; LUM; PPIB; COMP; <b>PCOLCE2</b> ; <b>ITGA2</b> ; PCOLCE; ASPN
GO:0048306	calcium-dependent protein binding	6/328	0.0007	S100A4; <b>ANXA4</b> ; <b>S100P</b> ; <b>ANXA3</b> ; STMN2; <b>VLDLR</b>
GO:0098631	cell adhesion mediator activity	5/328	0.0008	<b>DSG2</b> ; <b>DSC2</b> ; <b>CXADR</b> ; <b>ITGA2</b> ; <b>DSP</b>
GO:0016706	2-oxoglutarate-dependent dioxygenase activity	4/328	0.009	<b>P4HA1</b> ; P4HB; P3H2; <b>PHF8</b>
GO:0098632	cell-cell adhesion mediator activity	4/328	0.002	<b>DSG2</b> ; <b>DSC2</b> ; <b>CXADR</b> ; <b>DSP</b>
GO:0086080	protein binding involved in heterotypic cell-cell adhesion	4/328	2.30E-05	<b>DSG2</b> ; <b>DSC2</b> ; <b>CXADR</b> ; <b>DSP</b>
GO:0008329	signaling pattern recognition receptor activity	3/328	0.003	PGLYRP2; <b>TLR2</b> ; <b>TLR4</b>
GO:0031543	peptidyl-proline dioxygenase activity	3/328	0.001	<b>P4HA1</b> ; P4HB; P3H2

Upregulated genes are shown in bold font and down-regulated genes in normal font.

**Supplementary Table SVII** Signal pathway analysis of differentially expressed genes in the eutopic endometrium of LEI patients, classified by the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

KEGG ID	Description	GeneRatio	pvalue	Gene symbols
hsa04151	PI3K-Akt signaling pathway	15/151	0.002	<b>PKN2</b> ; <b>THEM4</b> ; <b>PPP2R1B</b> ; <b>IGF1R</b> ; COMP; <b>ITGA6</b> ; COL6A3; COL6A1; <b>PIK3CB</b> ; <b>TLR2</b> ; <b>ITGA2</b> ; <b>EFNA5</b> ; NTRK2; <b>TLR4</b> ; FGF16
hsa04510	Focal adhesion	10/151	0.004	<b>IGF1R</b> ; COMP; <b>ITGA6</b> ; COL6A3; MYL9; COL6A1; <b>PIK3CB</b> ; <b>ITGA2</b> ; <b>PIP5K1B</b> ; FLNA
hsa05142	Chagas disease (American trypanosomiasis)	7/151	0.002	C1QC; <b>PPP2R1B</b> ; <b>CFLAR</b> ; <b>PIK3CB</b> ; <b>TLR2</b> ; <b>IFNGR1</b> ; <b>TLR4</b>
hsa04066	HIF-1 signaling pathway	7/151	0.004	<b>IGF1R</b> ; <b>PIK3CB</b> ; <b>CAMK2D</b> ; <b>PGK2</b> ; <b>IFNGR1</b> ; <b>TLR4</b> ; TIMP1
hsa00640	Propanoate metabolism	4/151	0.003	<b>DBT</b> ; <b>ALDH6A1</b> ; <b>SUCLG2</b> ; <b>BCKDHB</b>

Upregulated genes are shown in bold font and down-regulated genes in normal font.

**Supplementary Table SVIII** List of genes that are differentially methylated and show an altered expression in the LEI versus Control comparison.

Gene Symbol	Name	Functions	Dataset	Expression Pattern	Reference
PLEKHF2	pleckstrin homology and FYVE domain containing 2	Involved in induction of Autophagy	-		-
SNORD82	small nucleolar RNA, C/D box 82	The majority of small nucleolar RNAs (snoRNAs) function as guide RNAs in the nucleotide modification of preribosomal RNA (pre-rRNA). C/D box snoRNAs, like SNORD82, are involved in site-specific 2-prime-O-ribose methylation of pre-rRNA	-		-
<b><u>HIST1H3I</u></b> #	H3 clustered histone 11	-	-		(Mortlock <i>et al.</i> , 2019)
<b><u>RNPC3</u></b>	RNA binding region (RNP1, RRM) containing 3	This gene encodes a 65K protein that is a component of the U12-type spliceosome. This protein contains two RNA recognition motifs (RRMs), suggesting that it may contact one of the small nuclear RNAs of the minor spliceosome.	GDS2835	Upregulated in ovarian endometriosis	(Hever <i>et al.</i> , 2007)
<b><u>SLC18A2</u></b> x	solute carrier family 18 member A2	This gene encodes a transmembrane protein that functions as an ATP-dependent transporter of monoamines, such as dopamine, norepinephrine, serotonin, and histamine. This protein transports amine neurotransmitters into synaptic vesicles.	GDS2737	Upregulated in mid secretory phase in both control and endometriosis cases	(Burney <i>et al.</i> , 2007; Mortlock <i>et al.</i> , 2020)
<b><u>SMCHD1</u></b> x	structural maintenance of chromosomes flexible hinge domain containing 1	his gene encodes a protein which contains a hinge region domain found in members of the SMC (structural maintenance of chromosomes) protein family.	GDS2835	Upregulated in ovarian endometriosis	(Hever <i>et al.</i> , 2007; Mortlock <i>et al.</i> , 2020)
SNORD58A	small nucleolar RNA, C/D box 58A	-	-		-
<b><u>PGLYRP2</u></b> #	peptidoglycan recognition protein 2	This gene encodes a peptidoglycan recognition protein, which belongs to the N-acetylmuramoyl-L-alanine amidase 2 family. This protein hydrolyzes the link between N-acetylmuramoyl residues and L-amino acid residues in bacterial cell wall glycopeptides, and thus may play a scavenger role by digesting biologically active peptidoglycan into biologically inactive fragments	-		(Mortlock <i>et al.</i> , 2019)
<b><u>ANXA3</u></b> #	annexin A3	This protein functions in the inhibition of phospholipase A2 and cleavage of inositol 1,2-cyclic phosphate to form inositol 1-phosphate.	CDS3060 GSE87809 CDS2737	--Upregulated in eutopic endometrium of patients with endometriosis	(Mortlock <i>et al.</i> , 2019; Predeus <i>et</i>

				--Downregulated in ovarian endometriosis	<i>al.</i> , 2018; Sha <i>et al.</i> , 2007)
<b><u>HIST1H4F</u></b> <sup>X, #</sup>	H4 clustered histone 6	-	GDS2835	Downregulated in ectopic endometriosis	(Hull <i>et al.</i> , 2008; Mortlock <i>et al.</i> , 2020; Mortlock <i>et al.</i> , 2019)
<b><u>PGK2</u></b>	phosphoglycerate kinase 2	phosphoglycerate kinase that catalyzes the reversible conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate	GDS2835		(Hever <i>et al.</i> , 2007)
<b><u>AHR</u></b> <sup>X, #</sup>	aryl hydrocarbon receptor	The protein encoded by this gene is a ligand-activated helix-loop-helix transcription factor involved in the regulation of biological responses to planar aromatic hydrocarbons. This receptor has been shown to regulate xenobiotic-metabolizing enzymes such as cytochrome P450.	GDS2835 GSE11691 GSE87809	Upregulated in ectopic and eutopic endometrium of women with ovarian endometriosis	(Hever <i>et al.</i> , 2007; Hull <i>et al.</i> , 2008; Mortlock <i>et al.</i> , 2020; Mortlock <i>et al.</i> , 2019; Predeus <i>et al.</i> , 2018)
<b><u>CCDC146</u></b> <sup>X, #</sup>	coiled-coil domain containing 146	Part of the centrosome complex	GDS2835	Downregulated in ovarian endometriosis	(Hever <i>et al.</i> , 2007; Mortlock <i>et al.</i> , 2020; Mortlock <i>et al.</i> , 2019)
<b><u>AGPAT5</u></b> <sup>X, #</sup>	1-acylglycerol-3-phosphate O-acyltransferase 5	This gene encodes a member of the 1-acylglycerol-3-phosphate O-acyltransferase family. This integral membrane protein converts lysophosphatidic acid to phosphatidic acid, the second step in de novo phospholipid biosynthesis.	GDS2737	Upregulated in mid secretory phase in both normal and endometriosis cases	(Burney <i>et al.</i> , 2007; Mortlock <i>et al.</i> , 2020; Mortlock <i>et al.</i> , 2019)

Gene name and reported biological functions were obtained from the Pubmed Gene Database (<https://www.ncbi.nlm.nih.gov/gene>). The genes in **bold** and underlined fonts are also reported to be altered in the publicly available endometriosis-related datasets and/ or mentioned in the published expression quantitative trait loci (eQTLs) and methylation quantitative trait loci (mQTLs) dataset. The reported eQTLs (X) and mQTLs (#) that matched with the genes of interest are listed in the data table.

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