Untangling Genetic Signature Underlying Endometriosis and Adenomyosis in European and Eastern Mediterranean Populations

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Introduction

Endometriosis and adenomyosis are thought to be two etiologically different but related conditions that are highly co-morbid. Endometriosis is growth of endometrial-like tissue in places outside the uterus and adenomyosis is growth of endometrial-like tissue into the uterine muscle. The mechanisms contributing to the development of endometriosis and adenomyosis have not yet been elucidated (1). So far, most genetic studies have evaluated both diseases together under the label of endometriosis and they estimated a heritability of ~50% with ~26% risk attributed to common genetic variants (2,3). Genome-wide association studies (GWAS) have revealed a total of 42 genome-wide significant disease-associated loci (4). To date, no GWAS for mapping variants that maybe associated with adenomyosis development has been conducted.

Aim: To evaluate the genetic basis of adenomyosis and endometriosis independently in European populations utilising large-scale data sources including UK Biobank, FinnGen and All of Us and to expand analysis to Eastern Mediterranean Populations utilising regional datasets.

Methods

Definition of Adenomyosis cases and controls in UK Biobank. Adenomyosis case group was identified utilising two different definitions: (1) Any females with ICD9/10 codes 617.0 and N80.0 respectively (Figure 1), (2) Any females with ICD9/10 codes 617.0 and N80.0 and a history of gynaecological operation involving the uterus as a proxy for surgical diagnosis of adenomyosis (Table 1). Control group was defined as women who without endometriosis and adenomyosis according to both clinical and self-reported data.

GWAS analysis in UK Biobank. Two GWAS analyses including 1,764 adeno cases vs. controls and 804 adeno cases with surgical history vs. 106,763 controls was conducting including 19,971,374 variants across the genome using linear mixed model (LMM) in BOLT. The lead SNPs were functionally annotated utilising eQTL maps from GTEx tissues.

Defining the genetic differences in Eastern Mediterranean datasets: COHERE is 775, TROX is 741, Crete dataset is 519 (Table 2). All were genotyped using the Infinium Global Screening Array-24 BeadChip (GSA). Principal Component Analysis was conducted to identify ancestral structure of these populations on comparison to each other.

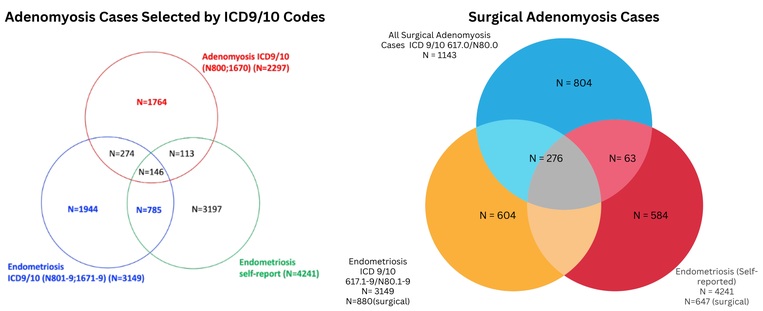

Figure 1. Defining adenomyosis cases and controls in UKBB.

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Table 1. Operations involving the uterus and breakdown of adenomyosis cases for each operation.

Operation Types	Case Numbers (N)	Operation Types	Case Numbers (N)
Hysterectomy w/o Oophorectomy	737	Excision of Lesion of Uterus	1
Myomectomy	9	Abdominal Excision of Uterus	4
Diagnostic/therapeutic Endoscopic Surgery on Uterus	35	Gynaecological Surgery	4
Operation on Uterus	4	Laparoscopy	10

Table 2: Defining Eastern Mediterranean Populations

Study	No Adenomyosis Cases	No Endometriosis Cases	No Controls
COHERE/Northern Cyprus	-	101	674
TROX/Turkiye	260	245	236
Crete, Greece	-	131	388

Results

Adenomyosis GWAS Results in UK Biobank

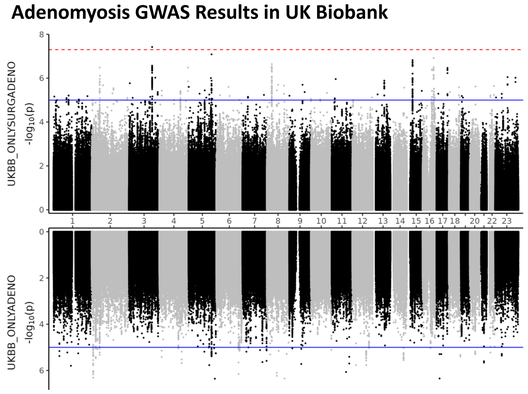

Figure 2. ICD-based adenomyosis (1,764 cases vs. 106,763 controls) GWAS results vs. adenomyosis cases with gyneacological surgical history (804 cases vs. 106,763 controls) GWAS results.

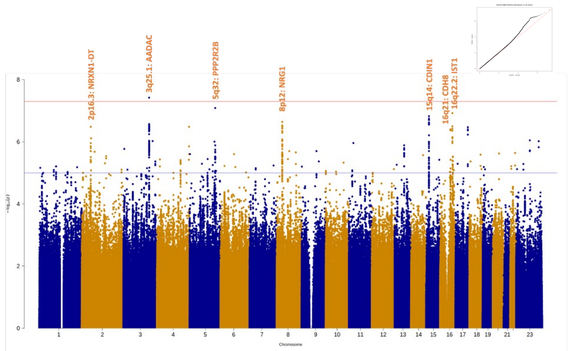

Figure 3. Annotation of adenomyosis (with surgical history) GWAS results (804 cases vs. 106,763 controls).

Table 3. Functional annotation of nominal lead SNPs (p<5x10-7) in eQTL maps from GTEx.

SNP	RA (RAF)	OR (95% CI)	P-value	Nearest Gene	eQTL Gene	eQTLs in GTEx Tissues
rs2883780	A(0.99)	0.36(0.24-0.53)	3.3X10-7	*NRXN1-DT*	-	-
rs116344065	G(0.93)	0.61(0.51-0.72)	3.8X10-8	*AADAC*	*AADAC*	Adrenal gland, adipose tissue, breast
rs188450498	G(0.99)	0.35(0.23-0.54)	9.9X10-7	*PPP2R2B*		-
rs12680129	A(0.98)	0.38(0.27-0.55)	2.3X10-7	*NRG1*	*NRG1*	Uterus, vagina, testis, bladder, brain tissue
rs2014875	C(0.83)	0.73(0.65-0.82)	1.5X10-7	*CDIN1*	*C15orf41*	Uterus, vagina, bladder, vascular tissue
rs113025560	A(0.91)	0.67(0.58-0.78)	4X10-7	*CDH8*		-
rs146497333	C(0.99)	0.29(0.18-0.46)	1.2X10-7	*IST1*		-

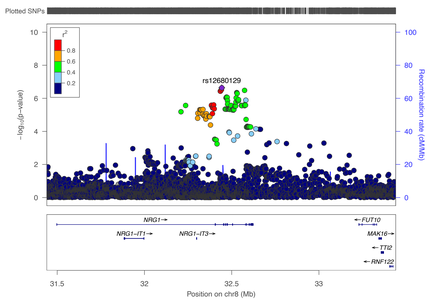

Figure 4. Regional association plot of *8p12/NRG1* from adenomyosis GWAS of surgically selected cases.

Table 4. Evaluating 42 endometriosis associated loci in adenomyosis GWAS data.

Locus	SNP	RA (RAF)	Only Surgical Adenomyosis GWAS (804 cases vs. 106,763 controls)		Overall Endometriosis GWAS (6,611 cases vs. 196,188 controls)	
			OR (95% CI)	P-value	OR (95% CI)	P-value
WNT4/1p36.12	rs10917151	A(0.16)	1.03(0.91-1.16)	0.63	1.16 (1.10-1.21)	2.1x10-9
NGF/1p13.2	rs12030576	G(0.67)	0.98(0.89-1.08)	0.72	1.03 (0.99-1.07)	0.11
SLC19A2/1q24.2	rs2040445	G(0.98)	0.71(0.53-0.95)	0.02	1.08 (0.96-1.21)	0.18
DNM3/1q24.3	rs2421985	C(0.48)	1.01(0.92-1.10)	0.86	1.05 (1.01-1.09)	6.1x10-3
GREB1/2p25.1	rs11674184	T(0.61)	1.11(1.02-1.22)	0.02	1.10 (1.06-1.14)	9.3x10-8
ETAA1/2p14	rs1430787	A(0.31)	1.06(0.96-1.17)	0.26	1.06 (1.02-1.10)	2.5x10-3
BMPR2/2q33.1	rs6435157	T(0.76)	1.02(0.92-1.14)	0.68	1.05 (1.01-1.10)	0.015
BSN/3p21.31	rs1352889	T(0.18)	0.96(0.85-1.08)	0.48	1.04 (1.00-1.09)	0.076
KDR/4q12	rs1903068	A(0.67)	1.00(0.91-1.10)	0.97	1.07 (1.03-1.11)	1.8x10-4
PDLIM5/4q22.3	rs2510770	A(0.33)	1.01(0.92-1.11)	0.87	1.07 (1.03-1.11)	4.6x10-4
EBF1/5q33.3	rs2946160	A(0.74)	1.17(1.06-1.29)	0.00	1.05 (1.01-1.09)	0.012
ID4/6p22.3	rs6456259	A(0.15)	1.02(0.90-1.15)	0.80	1.06 (1.01-1.11)	0.021
CD109/6q13	rs4540228	C(0.66)	1.02(0.92-1.12)	0.75	1.05 (1.01-1.09)	0.015
HEY2/6q22.31	rs2226158	G(0.45)	0.98(0.90-1.08)	0.71	1.02 (0.99-1.06)	0.23
SYNE1/6q25.1	rs71575922	G(0.84)	0.90(0.80-1.02)	0.10	1.18 (1.13-1.24)	1.5x10-11
FAM120B/6q27	rs11756073	A(0.16)	1.06(0.94-1.20)	0.31	1.06 (1.01-1.11)	0.014
7p15.2/7p15.2	rs1451383	G(0.75)	0.98(0.88-1.08)	0.64	1.04 (0.98-1.08)	0.064
HOXA10/7p15.2	rs6970537	G(0.56)	1.05(0.96-1.15)	0.28	1.05 (1.02-1.09)	4.4x10-3
7p12.3/7p12.3	rs55909142	C(0.59)	1.01(0.92-1.11)	0.84	1.08 (1.04-1.12)	1.3x10-5
KCTD9/8p21.2	rs17053711	G(0.74)	1.11(1.00-1.22)	0.05	1.07 (1.03-1.12)	4.4x10-4
GDAP1/8q21.11	rs10090060	A(0.57)	1.12(1.02-1.23)	0.01	1.10 (1.07-1.14)	6.8x10-8
VPS13B/8q22.2	rs12549438	T(0.21)	0.93(0.83-1.04)	0.18	1.05 (1.01-1.10)	0.022
CDKN2B-AS1/9p21.3	rs10122243	T(0.42)	0.97(0.87-1.06)	0.52	1.08 (1.04-1.12)	3.6x10-5
ASTN2/9q33.1	rs10983311	T(0.78)	0.97(0.87-1.08)	0.53	1.07 (1.03-1.12)	1.2x10-3
ABO/9q34.2	rs507666	A(0.19)	1.08(0.96-1.21)	0.19	1.07 (1.03-1.12)	2.3x10-3
MLLT10/10p12.31	rs10828249	A(0.34)	1.06(0.96-1.16)	0.23	1.08 (1.04-1.12)	6.x10-5
RNLS/10q23.31	rs7907732	T(0.38)	1.11(1.01-1.21)	0.03	1.09 (1.05-1.13)	4.7x10-6
FSHB/11p14.1	rs3858429	C(0.84)	1.15(1.02-1.30)	0.03	1.17 (1.11-1.22)	2.2x10-10
WT1/11p14.1	rs7924571	C(0.78)	1.08(0.97-1.20)	0.19	1.07 (1.02-1.11)	3.6x10-3
PTPRO/12p12.3	rs56090796	A(0.32)	0.94(0.85-1.03)	0.21	1.04 (1.00-1.08)	0.028
HOXC10/12p13.13	rs3803042	A(0.43)	0.93(0.85-1.02)	0.13	1.06 (1.02-1.09)	2.7x10-3
VEZT/12q22	rs12320196	G(0.47)	1.03(0.94-1.13)	0.47	1.04 (1.01-1.08)	0.021
IGF1/12q23.2	rs10860864	C(0.82)	1.04(0.92-1.17)	0.53	1.10 (1.05-1.15)	2.7x10-5
DLEU1/13q14.2	rs7334326	C(0.14)	1.14(1.00-1.30)	0.05	1.08 (1.02-1.13)	3.9x10-3
RIN3/14q32.12	rs57281976	G(0.76)	1.04(0.93-1.15)	0.52	1.04 (1.00-1.09)	0.049
SRP14-AS1/15q15.1	rs12441483	C(0.46)	1.06(0.97-1.16)	0.22	1.05 (1.01-1.09)	8.0x10-3
SKAP1/17q21.32	rs66683298	C(0.61)	1.08(0.99-1.19)	0.09	1.08 (1.04-1.12)	1.3x10-5
CEP112/17q24.1	rs7214750	C(0.93)	1.15(0.96-1.37)	0.12	1.10 (1.03-1.18)	6.7x10-3
ACTL9/19p13.2	rs2967684	A(0.15)	0.91(0.80-1.03)	0.12	1.07 (1.02-1.12)	8.3x10-3
TEX11/Xq13.1	rs13441059	G(0.64)	0.86(0.79-0.95)	0.00	1.04 (1.01-1.08)	0.022
FRMD7/Xq26.2	rs5933091	T(0.69)	1.06(0.96-1.16)	0.26	1.06 (1.02-1.10)	5.0x10-3
LINC00629/Xq26.3	rs73241342	A(0.96)	0.79(0.63-1.00)	0.05	1.23 (1.12-1.34)	8.8x10-6

Eastern Mediterranean Populations

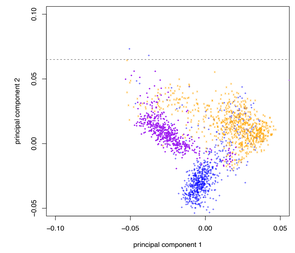

Figure 5. Principal component analysis of Turkiye, Northern Cyprus and Greek populations. Orange = Turkiye, Blue = Northern Cyprus, Purple = Greek

Conclusion and Future Work

Genetic sensitivity analyses illustrated that within UK Biobank adenomyosis cases with surgical history have different genetic basis compared to anyone with an adenomyosis ICD code – that was more similar to endometriosis genetic basis. On-going work include analysis of adenomyosis cases with surgical history in FinnGen and All of Us data resources and meta-analysis to achieve a large dataset to identification and replication of susceptibility loci.

We have genotyped data from three populations in the EM region. Initial unsupervised cluster analysis revealed that these populations although close to each other cluster separately. Next is imputation of each dataset to TOPMed reference panel followed by GWAS and meta-analysis for endometriosis and adenomyosis. The aim is to test whether susceptibility variants identified in European populations are replicable in EM populations or whether new variants gain significance.

References
1. PMID: 26209831, 2. PMID: 23193196, 3. PMID: 10202882, 4. PMID: 36914876

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