Identification of Genetic risk factors for Endometriosis

Fei Yang[1], Sally Mortlock[1], Yeda Wu[1], Matthew Law[2], Stuart MacGregor[2] and Grant W. Montgomery[1]

1 The Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD 4072, Australia 2 QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia

Background: Epidemiological evidence

Endometriosis is a disease characterised by the presence of endometriotic lesions outside of the uterus and affects 11% of reproductive aged women. Epidemiological studies have reported several potentials risk factors for endometriosis. For example it has been observed that risk of endometriosis is associated with history of melanoma and vice versa. Extensive epidemiological evidence has also indicated the co-existence of endometriosis and gastrointestinal symptoms. Identification of risk factors for endometriosis can help in the development of new prevention, diagnosis and treatment strategies.

Objective: Identify potential risk factors for endometriosis and investigate shared genetic mechanisms

Methods: Apply statistical genetic tools to investigate the genetic overlap between endometriosis and risk factors using large scale GWAS datasets (Table 1).

Table 1. Description of genome-wide association study (GWAS) datasets for endometriosis and investigated risk factors.

	Endometriosis	Melanoma	Melanoma in Female	Melanoma in Male	GORD	PUD	GPM	IBS	IBD
NO.case	17,405	35,848	13,364	12,232	54,854	16,666	90,175	28,518	7,045
NO.control	191,858	371,141	24,110	20,566	401,473	439,661	366,152	426,803	449,282
Data resource	Sapkota Y et al, Nat Com. 2017	Landi et al, Nat genet.2020			Yeda Wu et al, BioRxiv.2019				

Note: Irritable Bowel Syndrome (**IBS**); Inflammatory bowel disease (**IBD**); Gastroesophageal reflux disease (**GORD**); Peptic ulcer disease (**PUD**); **GPM** represents a combination of disease-diagnosis of GORD and PUD and corresponding medication-use.

LDSC : Estimate genetic correlation between two traits from GWAS summary statistics using LD score regression (LDSC).
GSMR : A method performing a multi-SNP Mendelian randomization analysis using summary statistics to test the putative causal associations between exposures and risk factors.
GWAS-PW : A tool for jointly analyzing two GWAS studies to identify loci that influence both traits.

Results

1. Genetic overlap with melanoma

No genetic correlation (rg) was observed between endometriosis and melanoma using the full dataset. We estimated a small but significant rg with melanoma in females (rg=0.14, se=0.08, p=0.03), and there was some evidence that melanoma in females had a causal effect on endometriosis (Figure 1).

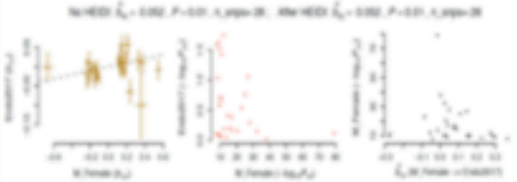

Figure 1. GSMR results for endometriosis and melanoma in females. nSNPs: Number of instruments SNPs; bxy: estimated effect of the exposure on outcome (bxy=bzy/bzx).

2. Genetic overlap with Gastrointestinal disorders (GD)

2.1 A strong genetic correlation was observed between endometriosis and GD (Figure 2).

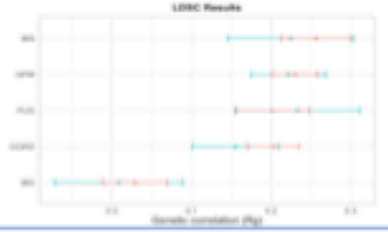

Figure 2. Results of genetic correlation between endometriosis and GD.

2.2 GSMR provided evidence of a causal relationship between GD and endometriosis (Figure 3).

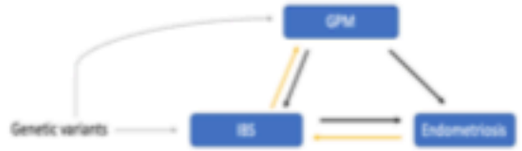

Figure 3. Simplified causal relationship identified by GSMR. Black and yellow arrows point direction of causal relationship.

2.3 Nine genomic regions with the same causal variant were shared between GD and endometriosis (Table 2).

Chr	Start	End	PPA-3
Endo & IBS			
2	215573795	217715180	0.818
1	58865399	59889341	0.766
6	30798252	31565648	0.532
Endo & GPM			
2	67227143	68009259	0.983
12	53039757	54777633	0.932
12	15248516	16309290	0.755
3	47729665	49314960	0.628
1	76729016	79660928	0.618
10	19717815	22772115	0.551

Table 2. Genomic regions that contain a same causal variant jointly influencing endometriosis with IBS and GPM respectively. PPA-3 represents posterior probability of such association.

Summary and future work: No genetic correlation (rg) with melanoma, but a strong rg with gastrointestinal disorders and the potential causality. Several genomic regions containing the same causal variant for both endometriosis and IBS/GPM were also identified. In the future, functional annotation for those regions will be conducted to further identify the shared genetic mechanisms.