

Authors:

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Title (maximum 25 words):

Discovery of novel loci for endometriosis in genome-wide association analysis of 63K cases and 700K controls

Study question (maximum 25 words):

What common genetic variants and corresponding functional mechanisms, underlie endometriosis, and its surgical sub-types (ASRM-stages), clinical sub-types (Infertile-endometriosis) and symptom-based sub-types (Severe pelvic-pain with endometriosis)?

Summary answer (maximum 25 words):

With the largest sample size to date for endometriosis genome-wide-association-study (GWAS) meta-analysis, we expect to identify many novel susceptibility loci for this debilitating condition.

What is known already (maximum 100 words):

Endometriosis has an estimated heritability of ~ 50%, with ~26% estimated to be related to common genetic variation. To date, meta-analysis of endometriosis GWAS (17K cases and 191K controls) have robustly identified 19 variants explaining 5.2% of disease variance. Previous GWAS analyses also highlighted that the signals for most of the genome-wide significant loci are driven by ASRM stage III/IV disease, highlighting the need for further phenotype-stratified analyses.

Study design, size, duration (maximum 75 words):

IEGC consists of 25-centres, in total contributing 63K endometriosis cases, 7800 stage III/IV, and 700K controls to the GWAS meta-analysis. Some of these are population-based cohorts such as the UK Biobank, and also clinical-investigations such as ENDOX, which is a prospective study recruiting women undergoing laparoscopy, that has dense clinical phenotype data. Some of the centres have expression and eQTL datasets for endometrium, fat and ectopic-disease-tissue, allowing for evaluation of functional mechanisms of the identified genetic variants.

Participants/materials, setting, methods (maximum 75 words):

Each GWAS was imputed up to reference panels from the Haplotype Reference Consortium or 1000 Genomes Project. Association testing by each centre was conducted in a regression framework under an additive genetic model, with adjustment for confounding due to population structure. Association testing was conducted for overall, stage I/II, stage III/IV and infertile endometriosis groups. Association summary statistics were aggregated across GWAS via fixed-effects meta-analysis.

Main results and the role of chance (maximum 200 words):

The GWAS meta-analysis is on-going, and results will be presented at the meeting. Preliminary results from the UK Biobank (n=8,190 cases) identified two novel associations at near genome-wide significance ($p < 5 \times 10^{-8}$) that map outside previously reported loci. The first maps to *IGF2BP3* (rs550554633, $p = 4.4 \times 10^{-8}$), which is involved in regulation of metabolism and adiposity, supporting the genetic link between endometriosis and fat distribution. The second maps to *GDAP1* (rs554964149, $p = 7.2 \times 10^{-8}$), which is involved in neuronal development that may play a role in endometriosis-associated pain, and previously has been associated with pain severity in dysmenorrhea. Moreover, a further 18 loci with nominal significance ($p < 5 \times 10^{-6}$) were identified, many of which are expected to increase in association strength in the complete IEGC meta-analysis

Limitations, reasons for caution (maximum 50 words):

For phenotype-stratified analysis we are limited by the datasets with dense phenotypic data (i.e. infertility, pelvic pain severity).

Wider implications of the findings (maximum 50 words)

The identified genetic variants shed light on the underlying pathogenesis of endometriosis and may point to novel therapeutic interventions.