IVI Foundation

Functional genomic meta-analysis identifies similarities between endometrial-related subfertilities

Devesa-Peiró A. [1, 2], Sebastián-León P. [1], García F. [3], Arnau V. [4, 5], Pellicer A. [1,6], Díaz-Gimeno P.[1]

[1] Department of Pediatry, Obstetrics & Gynaecology - School of Medicine, Valencia University, Spain. [2] IVI RMA Fundación IVI / INCLIVA, Valencia, Spain. [3] Unit of Bioinformatics and Biostatistics, Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain. [4] Escuela Técnica Superior de Ingenierías, Valencia University, Spain. [5] Institute for Integrative Systems Biology (I2SysBio), Valencia University - CSIC, Paterna, Spain. [6] IVI RMA Rome, Italy.

BACKGROUND

Endometrial-related subfertilites are complex and multifactorial conditions affecting female fertility. Prior studies described **endometrial adenocarcinoma (ADC), endometriosis, recurrent implantation failure (RIF), and recurrent pregnancy loss (RPL)** through case vs control transcriptomic analysis to identify altered genes and functions. However, the underlying functional mechanisms linking between them and their association to implantation problems remain to be elucidated. The objective of this research is to identify shared functions **within and between these endometrial-related subfertilities**, and to describe their potential effect on endometrial function.

MATERIALS AND METHODS

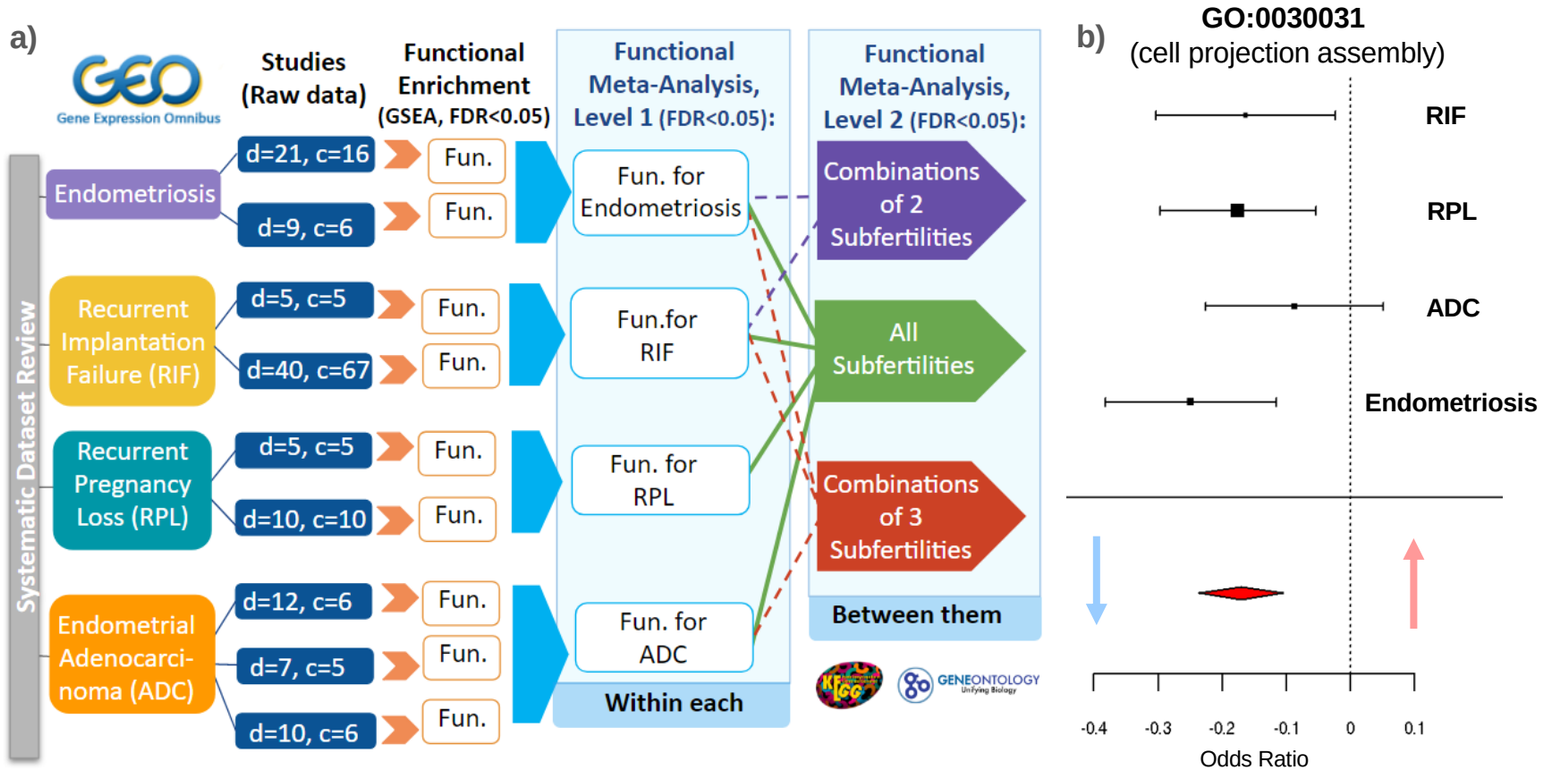

FIGURE 1. Workflow diagram. a) A systematic review was performed at Gene Expression Omnibus (GEO) public data repository to obtain transcriptomic datasets for each of the studied endometrial-related subfertilities (RIF, ADC, RPL, Endometriosis). After this dataset review, a total of 8 primary studies were included. For each of them, raw data were pre-processed and Gene Set Enrichment Analysis (GSEA) were applied to differential expression analysis results. Functional Meta-Analysis (DerSimonian & Laird random effects model, using Odds Ratio and Standard Deviation for each function) used GSEA results as input to integrate the primary studies related to each subfertility separately (Level 1). Level 1 results were then employed in Level 2 to identify shared functions between all endometrial-related subfertilities and different subgroups of them. Functional databases consulted were KEGG Pathways and Gene Ontology.(GO) d = sample size of the disease group. c = sample size of the control group. b) Forest plot of GO:003001 with the Odds Ratio (OR) and 95% Confidence Intervals (CI) for each of the 4 integrated endometrial-related subfertilities (squares are proportional to weights used in the functional meta-analysis). The red diamond represents the OR summary measure and its 95% CI obtained in the functional meta-analysis. ↑ Over-represented. ↓ Under-represented.

RESULTS

Functional Meta-Analysis Level 1: **Which are the most relevant functions shared within the primary studies of each endometrial-related subfertility?**

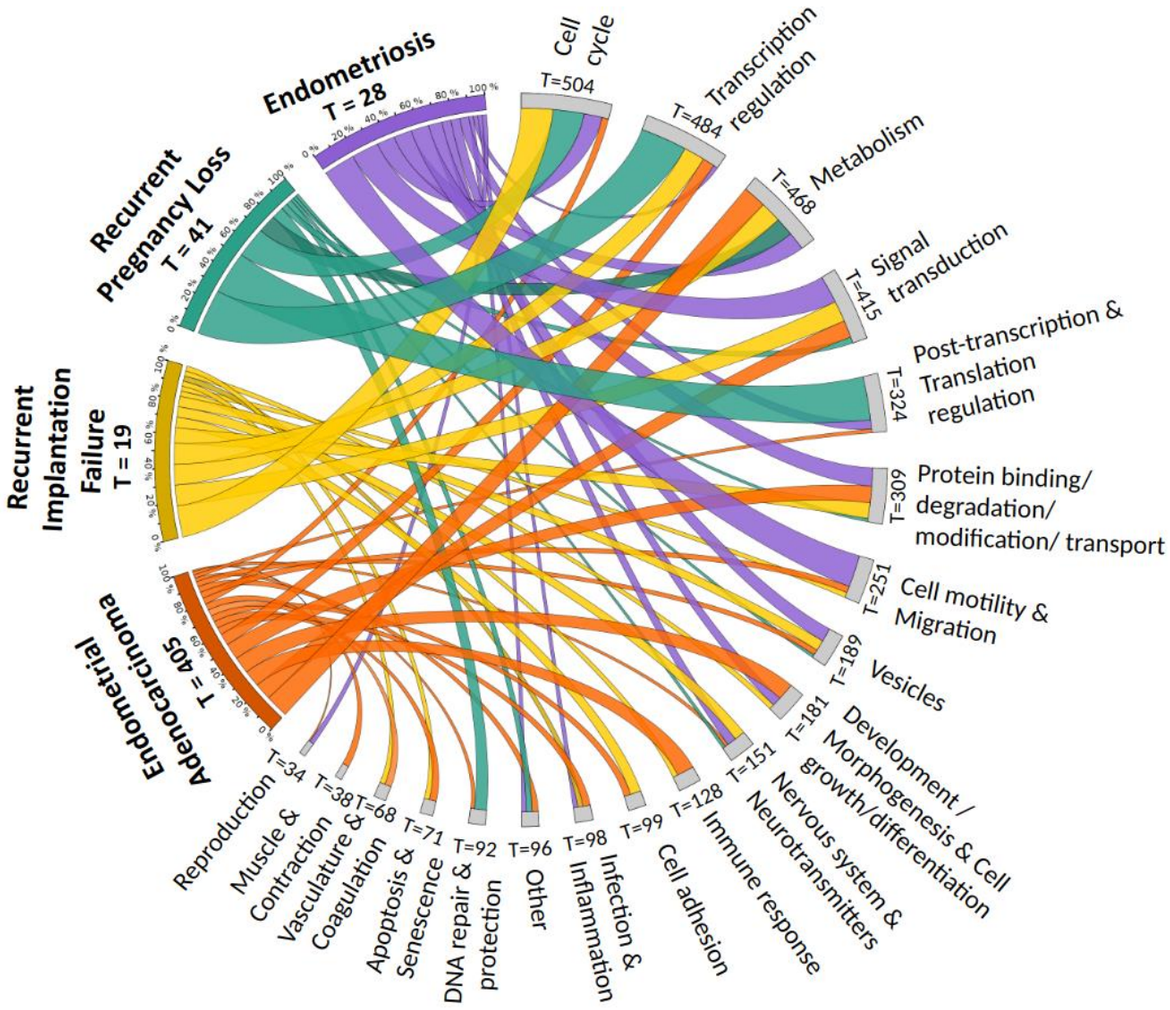

FIGURE 2. Comparative circus plot between the most relevant functions identified in the functional meta-analysis within each endometrial-related subfertility. T = Total number of significant functions (GO and KEGG term, FDR < 0.05) for each endometrial-related subfertility (in bold) or defined functional group. Ribbon width represents the % of total number of functions (T) associated to a given endometrial-related subfertility and functional group.

Functional Meta-Analysis Level 2: **Which are the most relevant functions shared between different endometrial-related subfertilities?**

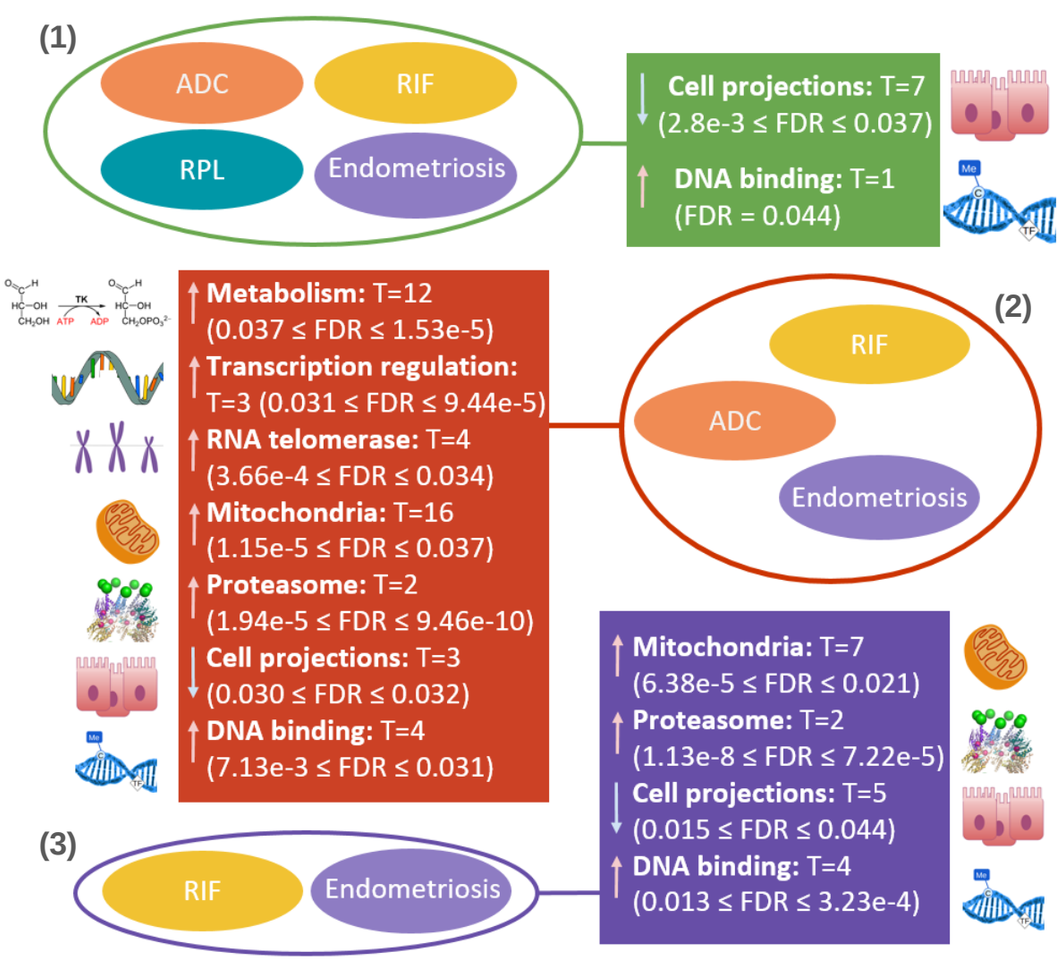

FIGURE 3. Summary outline highlighting the most relevant functions identified as shared between all endometrial-related subfertilities (1) and subgroups of three (2) and two (3) of them. T = Total number of significant functions (GO and KEGG terms, FDR < 0.05), shared between the encircled endometrial-related subfertilities. FDR = False Discovery Rate range of T. ↑ Over- and ↓ Under-represented functions.

CONCLUSIONS

- **Transcription and post-transcription regulation** were the most relevant functions **for RPL**; and **signal transduction and cell motility for endometriosis.**
- **RIF and ADC** were functionally the most **heterogeneous;** highlighting **metabolism for ADC** and **cell cycle for RIF.**
- **Chromatin binding and cell projections** were identified as **shared between endometriosis, ADC, RIF and RPL.** RPL was the least similar at functional level.
- Due to the functional similarities between endometriosis and RIF, there is evidence in our results supporting the hypothesis that **eutopic endometrium could be affected in endometriosis.**

Funded by IVI RMA Fundación IVI and the Ministry of Science and Innovation (Spanish Government – FPU Grant Program)