META-SIGNATURE OF ENDOMETRIAL RECEPTIVITY GENES

S. Altmäe[1,2], M. Koel[2,3], U. Võsa[4], P. Adler[5], M. Suhorutšenko[2], T. Laisk-Podar[2], V. Kukushkina[2], K. Krjutškov[2,3], L. Aghajanova[6], P. Lalitkumar[1], K. Gemzell-Danielsson[1], L. Giudice[6], C. Simón[7], A. Salumets[2,8]

[1]*Women's and Children's Health, Karolinska Institutet, Sweden*
[2]*Competence Centre on Health Technologies, CCHT, Estonia*
[3]*Biosciences and Nutrition, Karolinska Institutet, Sweden*
[4]*Biotechnology, University of Tartu, Estonia*
[5]*Institute of Computer Sciences, University of Tartu, Estonia*
[6]*Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, USA*
[7]*Obstetrics and Gynaecology, Valencia University & INCLIVA. Igenomix & Fundación IVI, Spain*
[8]*Obstetrics and Gynecology, Helsinki University, Finland*

Background: Previous microarray-based transcriptome studies of the endometrium have revealed hundreds of simultaneously up- and down-regulated genes that are involved in endometrial receptivity. However, the overlap between the studies is relatively small, and we are still searching for potential diagnostic biomarkers.
Aim: To identify the meta-signature and putative biomarkers of receptive endometrium.
Materials and Methods: A systematic review of the literature was conducted up to March 2016 in PubMed and Scopus databases. Of the final 14 eligible studies, nine were included in the meta-analysis. The pooled dataset obtained represented 164 endometrial samples – 76 from pre-receptive- and 88 from receptive-phase endometria. The up- and down-regulated genes were ranked by their fold changes. A robust rank aggregation (RRA) algorithm was used for meta-analysis of the gene lists, followed by enrichment analysis.
Results: We identified a meta-signature of endometrial receptivity involving 57 genes as putative receptivity markers, including *ANXA4*, *APOD*, *CD55*, *CLDN4*, *COMP*, *DPP4*, *EDN3*, *GADD45A*, *GPX3*, *HABP2*, *IGFBP1*, *IL15*, *MAOA*, *MMP7*, *PAEP*, *SLC1A1*, *SPP1* and *S100P*. The meta-signature genes highlight the importance of immune responses, the complement cascade pathway and the involvement of extracellular vesicles in mid-secretory endometrial function.
Conclusions: Using a novel meta-analysis approach, we identified a meta-signature of receptive endometrium involving 57 genes. The identified meta-signature genes and pathways could serve as promising and sought-after biomarkers of endometrial receptivity and pregnancy establishment, and also markers of uterine pathologies.