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Integrative transcriptome analysis reveals dysregulation of canonical cancer molecular pathways in placenta leading to preeclampsia

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Figure S1. Study Design Flow Chart

Our integrative analysis involved interrogating a preeclampsia-specific gene list obtained from meta-analysis of case-control studies in several relevant data sources, which included expression arrays of normal and time-course placentas (i.e., placenta from first, second and third trimester pregnancies), hypoxic trophoblasts, and *XPD*^{TTD} fibroblasts (i.e., cells predisposed to preeclampsia). These data sources were specifically chosen in order to filter the differentially-expressed genes and pathways to select those which preceded the development of the clinical symptoms of preeclampsia.

Figure S2. **Protein-level expression of selected preeclampsia genes in normal placenta**

Protein level expression analysis of selected genes found to be differentially-expressed in preeclamptic placentas from meta-analysis of preeclampsia case-control studies, using a protein atlas database (proteinatlas.org). Selected genes included secreted factors (FLT1, LEP, CRH, GH1), membrane-bound molecules (ENG, ADAM12, EGFR), nuclear (ATF3) and stromal (FBN2) proteins. Localization of all examined proteins was noted in trophoblasts except for FBN2, which was found expressed in extracellular matrix.

Figure S3. Comparison of preeclampsia gene signature with that of cells treated with shATF3.

Panel a. Venn diagram showing shared genes between preeclampsia and ATF3 deficient cells (shATF3). **Panel b.** Heatmap showing fold changes in the respective datasets of common genes identified in **Panel a**. Red arrows show that FLT1, ENG and INHBA are downregulated after treatment of K562 cells with shATF3. **Panel c.** Visualization of ATF3 binding to promoter region (approximately 1kb from transcription start site of Flt1 gene) in mouse dendritic cells(GSM881126[31]**).**

Figure S1

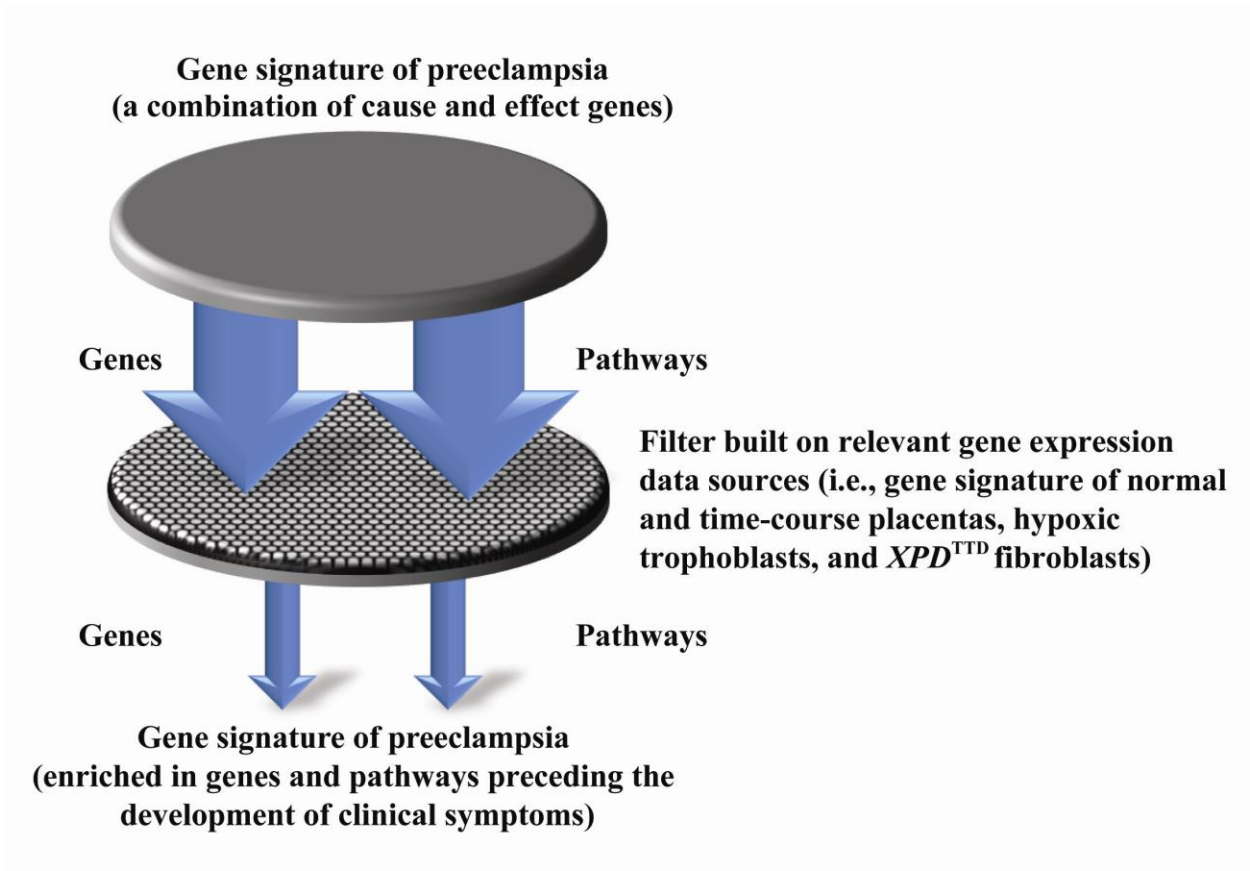

Gene signature of preeclampsia
(a combination of cause and effect genes)
Genes
Pathways
Filter built on relevant gene expression data sources (i.e., gene signature of normal and time-course placentas, hypoxic trophoblasts, and XPD^TTD fibroblasts)
Genes
Pathways
Gene signature of preeclampsia
(enriched in genes and pathways preceding the development of clinical symptoms)

Figure S2

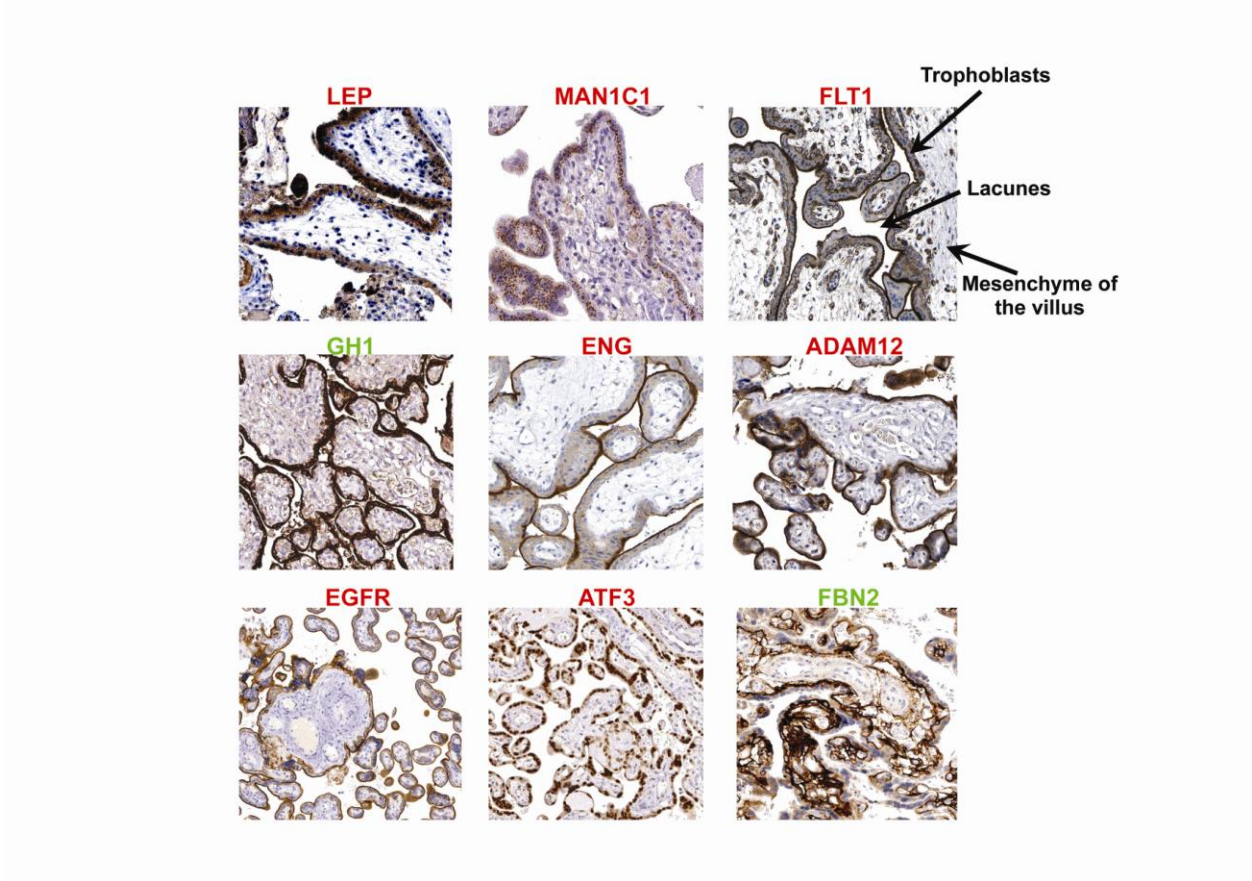
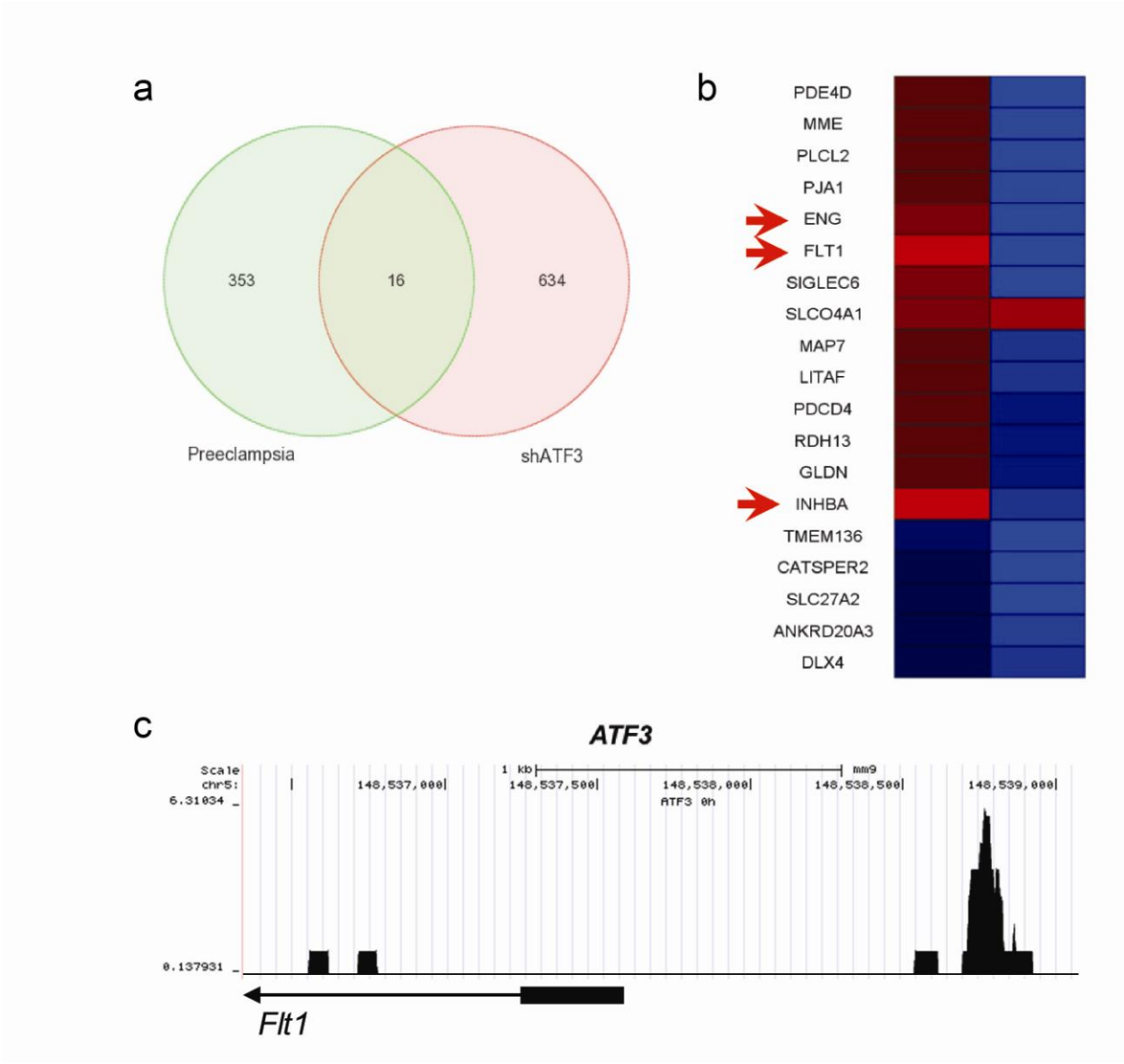

LEP
MAN1C1
FLT1
Trophoblasts
Lacunes
Mesenchyme of the villus
GH1
ENG
ADAM12
EGFR
ATF3
FBN2

Figure S3


a
353
16
634
Preeclampsia
shATF3
b
PDE4D
MME
PLCL2
PJA1
ENG
FLT1
SIGLEC6
SLCO4A1
MAP7
LITAF
PDCD4
RDH13
GLDN
INHBA
TMEM136
CATSPER2
SLC27A2
ANKRD20A3
DLX4
c
ATF3
Scale
chr5:
6.31034
0.137931
148,537,000
148,537,500
148,538,000
148,538,500
148,539,000
ATF3 0h
Flt1