Knowledge-Driven Mechanism Enrichment of the Preeclampsia Ignorome

Tiffany J. Callahan MPH, PhD[1,2]; Adrianne L. Stefanski PhD[2]; Jin-Dong Kim PhD[3]; William A. Baumgartner Jr. PhD[2]; Jordan M. Wyrwa DO[4]; Lawrence E. Hunter PhD[2]

[1]Department of Biomedical Informatics, Columbia University, New York, NY USA
[2]Computational Bioscience Program, University of Colorado Anschutz Medical Campus, Aurora, CO USA
[3]Database Center for Life Science, Research Organization of Information and Systems, Kashiwa, Japan
[4]Department of Physical Medicine and Rehabilitation, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO USA

SUPPLEMENTAL MATERIAL

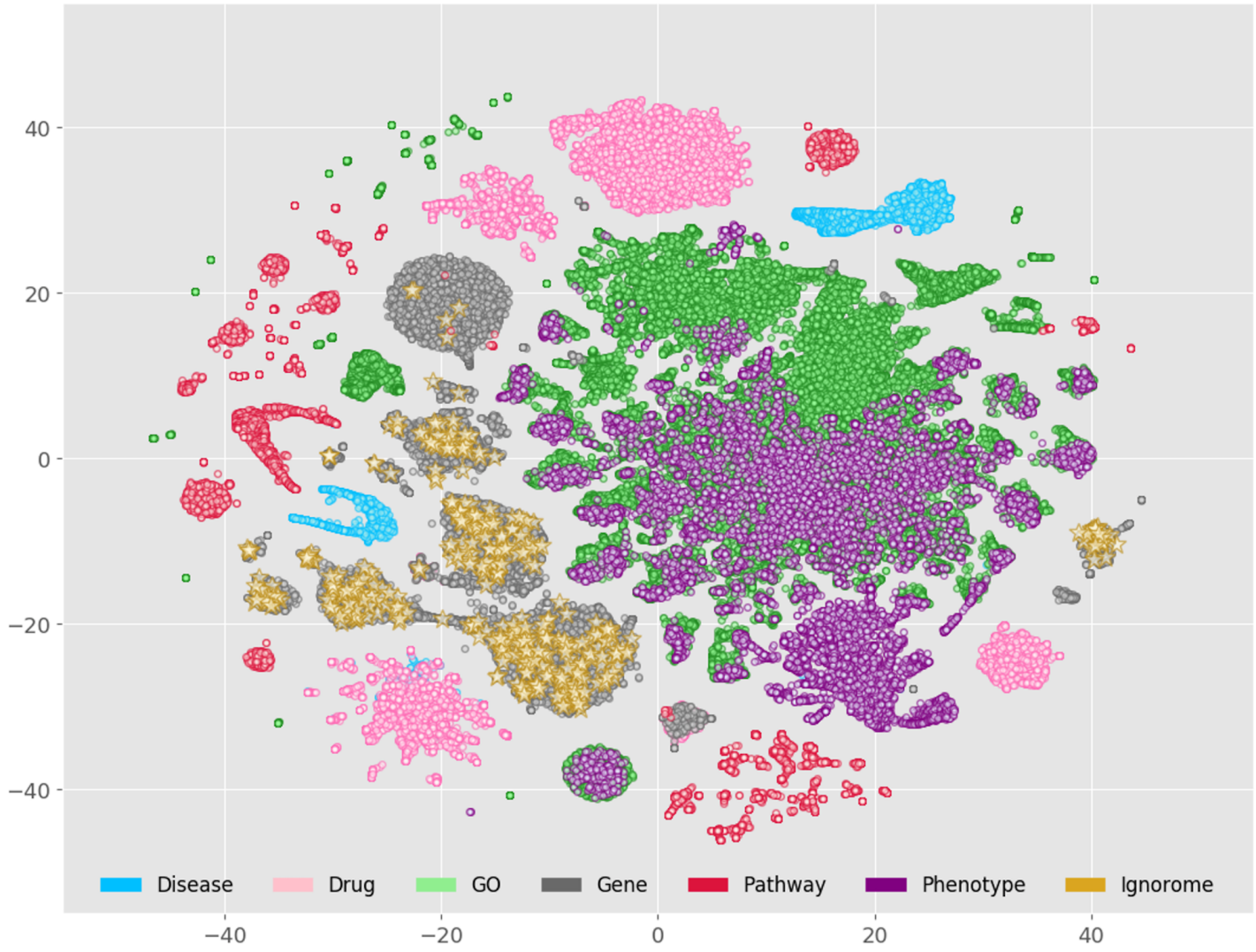
This section provides additional information on the preeclampsia ignorome studies obtained from the Gene Expression Omnibus that were examined as part of our meta-analysis.

Table of Contents

Keyword lists

Literature-Driven Keywords: “Preeclampsia”, “HELLP Syndrome”, “Severe Preeclampsia”, and “Placenta Disease”

Gene-Driven Keywords: "HELLP Syndrome", "gestational hypertension", "hypertensive disorders of pregnancy", "pre-eclampsia", "pre-eclamptic patient", "pre-eclamptic toxaemia", "pre-eclamptic toxemia", "preeclampsia", "preeclamptic toxaemia", "preeclamptic toxemia", "pregnancy hypertension", "pregnancy-related hypertensive disorder", "toxaemia of pregnancy", "toxaemic mother", "toxaemic pregnancy", "toxemia of pregnancy", "toxemic mother", "toxemic pregnancy"



Supplemental Figure 1. t-SNE plot of PheKnowLator Node Embeddings with Preeclampsia Ignorome Genes.
The nodes are colored by biological type (i.e., disease [blue], drugs [pink], gene ontology concepts [green], genes [gray], pathways [red], and phenotypes [purple]) and ignorome genes indicated with gold stars.

Supplemental Table 1. Status of Reviewed Preeclampsia GEO Studies.

Source	GSE	Decision	Exclusion Reason
GEO	GSE10588	Include	
GEO	GSE24129	Include	
GEO	GSE73374	Include	
GEO	GSE14722	Include	
GEO	GSE4707	Include	
GEO	GSE74341	Include	
GEO	GSE25906	Include	
GEO	GSE35574	Include	
GEO	GSE30186	Include	
GEO	GSE44711	Include	
GEO	GSE60438	Include	
GEO	GSE43942	Include	
GEO	GSE75010	Exclude	May help with post hoc interpretation
GEO	GSE12767	Exclude	May help with post hoc interpretation
GEO	GSE85307	Exclude	May help with post hoc interpretation
GEO	GSE91189	Exclude	Laser microdissection of cell types
GEO	GSE93839	Exclude	Laser microdissection of cell types
GEO	GSE94643	Exclude	Laser microdissection of cell types
GEO	GSE94644	Exclude	Laser microdissection of cell types
GEO	GSE6573	Exclude	Only 2 samples in the placenta condition
GEO	GSE47187	Exclude	Control and case occur on the same probe, but in different channels
GEO	GSE12216	Exclude	Not preeclampsia
GEO	GSE13155	Exclude	Not preeclampsia
GEO	GSE41681	Exclude	Not placenta biopsy; cultured HUVECs
GEO	GSE13475	Exclude	Not placenta biopsy; cell culture
GEO	GSE4100	Exclude	Not placenta biopsy; cell culture
GEO	GSE54400	Exclude	Not placenta biopsy
GEO	GSE86200	Exclude	Not placenta biopsy
GEO	GSE48424	Exclude	Not placenta biopsy
GEO	GSE91077	Exclude	Not placenta biopsy
GEO	GSE79782	Exclude	Not placenta biopsy

Source	GSE	Decision	Exclusion Reason
GEO	GSE79781	Exclude	Not placenta biopsy
GEO	GSE79783	Exclude	Not placenta biopsy
GEO	GSE99007	Exclude	May help cell type contribution of DEG signature
GEO	GSE38747	Exclude	May help cell type contribution of DEG signature
GEO	GSE93020	Exclude	Not gene expression; not transcriptome
GEO	GSE49343	Exclude	Not gene expression; not transcriptome
GEO	GSE84260	Exclude	Not gene expression; not transcriptome
GEO	GSE69452	Exclude	Not gene expression; not transcriptome
GEO	GSE63743	Exclude	Not gene expression; not transcriptome
GEO	GSE57767	Exclude	Not gene expression; not transcriptome
GEO	GSE73375	Exclude	Not gene expression; not transcriptome
GEO	GSE75196	Exclude	Not gene expression; not transcriptome
GEO	GSE44667	Exclude	Not gene expression; not transcriptome
GEO	GSE59274	Exclude	Not gene expression; not transcriptome
GEO	GSE75941	Exclude	Not gene expression; not transcriptome
GEO	GSE41336	Exclude	Not gene expression; not transcriptome
GEO	GSE63999	Exclude	Not gene expression; not transcriptome
GEO	GSE50783	Exclude	Not gene expression; not transcriptome
GEO	GSE98938	Exclude	Not gene expression; not transcriptome
GEO	GSE97898	Exclude	Not gene expression; not transcriptome
GEO	GSE15789	Exclude	Not gene expression; not transcriptome
GEO	GSE65271	Exclude	In vitro HTR8svneo
GEO	GSE37901	Exclude	Gestational age inconsistent with study design
GEO	GSE36083	Exclude	First trimester explants
GEO	GSE59686	Exclude	Fetal membranes; not true placental biopsy
GEO	GSE74446	Exclude	Ex vivo cultured placental explants
GEO	GSE40182	Exclude	Ex vivo cultured placental cells
GEO	GSE41331	Exclude	Ex vivo cultured placental cells
GEO	GSE73377	Exclude	Contains GSE73375 and GSE73374 (used GSE73374 for expression)
GEO	GSE44712	Exclude	Contains GSE4467 and GSE44711 (used GSE44711 for expression)
GEO	GSE31679	Exclude	Cells cultures in vitro
GEO	GSE64272	Exclude	In vitro hESCs and iPSCs

Source	GSE	Decision	Exclusion Reason
GEO	GSE72712	Exclude	In vitro hESCs
GEO	GSE22526	Exclude	No control samples; may help with post hoc interpretation
GEO	GSE13299	Exclude	No control samples; may help with post hoc interpretation
GEO	GSE9984	Exclude	May help with post hoc interpretation
GEO	GSE25861	Exclude	May help cell type contribution of DEG signature
GEO	GSE54618	Exclude	Questionable, recommend excluding

Supplemental Table 2. Final Set of GEO Studies and Differentially Expressed Gene Count by Study.

GSE ID	PMID	Date	Platform Details	Study Groups	Analysis Groups	Sample	DEGs
GSE4707	16860862	2006	Agilent-012391 G4112A	Control (n=4) EO (n=5) LO (n=5)	Control vs. EO Control vs. LO	Placenta	EO: 4091 LO: 2075
GSE10588	19249095	2008	ABI Human Genome V2.0	Control (n=26) SPE (n=17)	Control vs. SEP	Placenta	5049
GSE25906	21183218	2010	Illumina Human-6 v2.0	Control (n=37) PE (n=23)	Control vs. PE	Placenta	2616
GSE14722	18818296	2009	Affymetrix U133A/U133B	PT Basal Plate (n=11) PE Basal Plate (n=12)	Control vs. PE	Basal plate	551
GSE24129	21810232	2010	Affymetrix HG 1.0	Control (n=8) FGR (n=8) PE (n=8)	Control vs. FGR Control vs. PE	Placenta	FGR: 0 PE: 981
GSE30186	22702245	2011	Illumina HumanHT-12 V4.0	Control (n=6) PE (n=6)	Control vs. PE	Placenta	201
GSE43942*	23544093	2013	NimbleGen HG18	Control (n=12) PE (n=12)	Control vs. PE	placenta	1411
GSE74341	27016783	2015	Agilent SurePrint G3	AT (n=5) EO (n=7) PT (n=5) LO (n=8)	PT vs. EO AT vs. LO	Placenta	EO: 9627 LO: 6589
GSE35574	23639576	2012	Illumina Human-6 v2.0	Control (n=40) IUGR (n=35) PE (n=19)	Control vs. IUGR Control vs. PE	Placenta	IUGR: 0 PE: 4519
GSE44711	23770704	2013	Illumina HumanHT-12 V4.0	Control (n=8) EO PE (n=8)	Control vs. EO	Chorionic villi	500
GSE60438	26010865	2014	Illumina HumanWG-6 v3.0	Control (n=23) PE (n=25)	Control vs. PE	Decidua basalis	7228
GSE73374	26510177	2015	Affymetrix HG 2.0	Control (n=17) PE (n=19)	Control vs. PE	Placenta	2678

Acronyms - AT: At Term; DEGs: Differentially Expressed Genes ($p < 0.05$); EO: Early Onset; FGR: Fetal Growth Restriction; IUGR: Intrauterine Growth Restriction; LO: Late Onset; PE: Preeclampsia; PT: Preterm; SEP: Severe Preeclampsia.
*Downloaded differentially expressed gene list directly from authors.

Supplemental Table 3. Gene Symbols by Preeclampsia-Annotated Article Count.

Article Count	Gene Symbols
0	PRRG1, ZFPL1, ZNF84, ZNF646, TM9SF1, LMAN2, ILVBL, SMG5, NIPSNAP3A, ZNF330, CCDC59, SCCPDH, NIN, MBIP, KLHL28, EPS8L1, MRPS18A, LRRC1, ZNF83, CCDC47, PRRG4, RPAP3, SFXN3, RPF2, MIDN, ZNF439, TIGD7, SNX29, RDH13, LENG8, LRRC56, PUSL1, HINT3, ZNF555, CRYGN, CXorf38, ZNF114, LONRF2, DCP2, C6orf89, EP400NL, RNF222
1	ACTR3B, ADAMTSL3, AGFG1, ANXA7, ARHGAP9, ATXN7L2, BZW1, CHKA, CNOT3, CRIM1, DNAJB2, DNAJC1, DOK3, DOK6, ECM2, ENTPD4, ERRFI1, FAM120A, FBXO9, FRMD3, FXYD3, GART, HDGF, HERC4, HPCAL1, IL1RAP, IREB2, KTN1, LEO1, MAGT1, MBNL1, MFAP5, MRPL18, NFIA, NKTR, NRP2, OLFML3, ORMDL1, OSTF1, PAM, PCYOX1, PHYHIPL, POLR2H, PPP1R14B, PRKD3, PSPC1, RAPGEF3, RASGRP2, RBPMS, RFK, RGL1, RHOQ, RHPN1, SH3BGRL, SH3KBP1, SHPRH, SLC35F2, SNX3, SRP9, TARBP1, TBC1D22A, TBL1XR1, TCF7, TCP1, TGOLN2, TMEM136, TUBB, UBE2H, UPF3A, WDFY3, XPOT, YPEL4, ZFAND5, ZNF440, ZNF473
2	APLP2, BIN2, ELL2, ENTPD1, KIAA0753, KLHL7, LASP1, MICAL1, MRPL3, NAALAD2, POGZ, PPP6R3, SCP2, SDF2L1, SNAPC4, SSFA2, STK11IP, THAP5, TMEM30A, TRIM14, WBP2, ZBTB48, ZCCHC2, ZFAND2B, ZNF7, CUL2, DST, HOXB5, MBD2, MPHOSPH8, MPPE1, PTP4A1, RARRES1, SLC28A1, SLC2A3, SLC2A5, SLC9A9, TPR, ANAPC4
3	AP3S1, ATP11B, CLIC4, CSNK1G3, DSCC1, EEF1A1, GON4L, GOSR2, GPR155, HIGD1A, LIMCH1, MPHOSPH10, PNCK, PSMA2, RNF13, RPL18, SPTLC3, SSNA1, TAOK1, UGP2, CDH15, GGA1, NSF, PTGDS, TPT1, ANTXR1, LONP1, NECTIN4, PROCR, SETD1A, TRAF3, TRIM24
4-5	CLASP2, EFHD1, HMGCS1, KCNMB4, KIF2A, MARCH6, PDZRN3, GFPT1, H3F3B, QPCT, HIP1, NAIP, RNF123, APMAP, ARHGEF4, COBLL1, HIPK3, NOC3L, RGS11, SLC30A5, NDFIP1, NEBL, MARS, PHF10, STX1A, IQGAP1
6-10	BRWD1, COPS8, DNAJC10, LYPLA1, METAP1, NR2C1, PDE4DIP, TMEM45A, TRAK1, MAN1A1, PARP6, ZNF644, SLC35A2, STX16, TSPAN7, ACSS1, ALDH9A1, ARL6IP1, GDPD5, NFYC, RPS2, SLBP, TBCD, WTAP, FRMD4B, NEK11, PPM1K, SPATA13, BCAS4, KCTD11, BMP6, NDUFS7, TAF15, LRPPRC, DNAJC3, ERGIC1, GREM2, OMA1, PGLYRP1, PKP4, SPON1, YME1L1, YWHAB, DMTF1, IFITM2, ME2, MYO1B, ALDOA, HERC2, ACO2, ARRDC3, DDR1, HBD, ATXN10, ANKRD26, PBX2, RNF8, ACTR3, PPP2R5C, RASEF, USP10, JUP, CRIP2, NFIX, SCARB1, SLCO2A1, ASCC3, HIF3A, IGSF8, ARHGAP21, BAIAP2, MYT1, PDXK, LAMB1, MCFD2, MME, TFAM
11-20	BASP1, CEP72, CSNK2B, FASTK, USP11, CD164, ETNK1, TMED5, UCHL5, KRT19, MNT, NUS1, CCND2, QKI, SPG7, MXI1, TSNAX, PCBP2, STK38, E2F5, CETN2, STK17B, SEC63, RASSF8, DERL3, OLFM1, ZNF185, ANXA4, TPI1, PLOD1, CCAR1, RPS6KA5, BTF3, SSR1, STK24, PLA2G16, CFLAR, NCOA1, CTTN, SEMA7A, LRRFIP1, TLE4, GSR, HNMT, HDAC9, LMAN1, GALE, TAOK2, ATRN, FAM107B, TMED1, TMED10, RPN2, MGAT3, MKNK1, SLC27A2, NUDT6, CCNC, CSNK1A1, BCORL1, RAB6B, MATR3, PIK3CB
21-30	ARID3A, CD37, SLC44A1, PAQR3, ACSL3, RAP1GDS1, POLR3A, RHEB, ECD, DVL2, HILPDA, FOXF1, NEDD4L, BCAT1, CDO1, EXOSC6, CHD8, DYRK1A, ELL, RBBP4, PPP1R15A, ING5, CXXC1, PRPS1
31-50	TRIM29, PSMC6, CALM1, KDM3A, YES1, CSNK2A2, DNM2, FBLN5, C2, ANGPTL1, ITPR1, SNAI2, KLF10, TUG1, CTSZ, CDH23, VPS35, PSME3, NPL, CTSK, SMG1, YWHAE, VPS13A, AGL, AMD1, GLUL, HEXB, BSG
51-100	LSP1, NUCB2, CEBPZ, SLC16A3, SLC6A8, PICALM, RASSF7, CSTB, SREBF1, MKKS, LPIN1, TRAF2, TPP1, PTPRU, BACH1, RNPC3, FHIT, LGALS3, AKAP12, EDNRB, BMP1, DCK
>100	STS, SET, GHR, NDRG2, CLN3, ATXN2, KHDRBS1, SPP1, PDXP, DMPK, NPEPPS, GBA, CIB1, PMP22, IDH1, TARDBP, BRAF

Supplemental Table 4. PheKnowLator-Derived Novel Phenotype Associations.

Identifier	Ignorome Hits	Domain Expert-Derived Evidence
Abnormal Mitochondria in Muscle Tissue (HP:0008316)	NDUFS7 (ncbigene:374291)	Mitochondrial dysfunction is central to the pathophysiology of preeclampsia (PMID: 33417666). Trophoblast mitochondrial function is impaired in preeclampsia (PMID: 27939475).
Systemic Lupus Erythematosus (HP:0002725)	C2 (ncbigene:717)	Women diagnosed with systemic lupus erythematosus are at increased risk of preeclampsia (PMID: 31754886).
Persistence of Hemoglobin F (HP:0011904)	HBD (ncbigene:3045)	Increased fetal hemoglobin accumulation in the placenta is associated with preeclampsia (PMID: 25628568; PMID: 24185004).
Elevated Plasma Branched Chain Amino Acids (HP:0008344)	PPM1K (ncbigene:152926)	Plasma branched chain amino acids were higher in women with gestational diabetes mellitus than control (PMID: 31497040). Gestational diabetes mellitus increases preeclampsia risk (PMID: 25644816).
Microcytic Anemia (HP:0001935)	HBD (ncbigene:3045)	Severe anemia is associated with higher risk of preeclampsia (PMID: 21867566).

Acronyms - HP: Human Phenotype Ontology; NCBIGene: National Center for Biotechnology Information Entrez gene identifier.

Supplemental Table 5. PheKnowLator-Derived Novel Pathway Associations.

Identifier	Ignorome Hits	Domain Expert-Derived Mechanism(s)
Complex I Biogenesis (R-HSA-6799198)	NDUFS7 (ncbigene:374291)	Trophoblasts cultured under hypoxic conditions have decreased Complex I respiration rate (PMID: 23383105). Hypoxia is thought to be central to the pathophysiology of preeclampsia (PMID: 30968806).
Mitochondrial Translation Termination (R-HSA-5419276)	MRPL3 (ncbigene:11222), MRPS18A (ncbigene:55168), MRPL18 (ncbigene:29074)	Mitochondrial dysfunction is central to the pathophysiology of preeclampsia (PMID: 33417666). Trophoblast mitochondrial function is impaired in preeclampsia (PMID: 27939475).
Respiratory Electron Transport (R-HSA-611105)	NDUFS7 (ncbigene:374291), LRPPRC (ncbigene:10128)	Placentas from preeclamptic pregnancies had decreased expression of essential electron transport chain proteins (PMID: 32916282). Abnormal electron transport is associated with early-onset preeclampsia (PMID: 29676857).
Elastic Fibre Formation (R-HSA-1566948)	MFAP5 (ncbigene:8076), FBLN5 (ncbigene:10516)	The elastic fibre system is altered in umbilical cord vessels from pregnancies complicated by preeclampsia (PMID: 10794169).
Diseases Associated with O-glycosylation of Proteins (R-HSA-3906995)	ADAMTSL3 (ncbigene:57188), SPON1 (ncbigene:10418)	Altered o-glycosylation is associated with aberrant immune cell dynamics at the maternal-fetal interface (PMID: 32760395). In severe preeclampsia, altered glycosylation of maternal plasma proteins is associated with increased monocyte adhesion (PMID: 23757314).
Rho GTPase Cycle (R-HSA-194840)	RHOQ (ncbigene:23433), RHPN1 (ncbigene:114822), ARHGEF4 (ncbigene:50649), ARHGAP9 (ncbigene:64333), ARHGAP21 (ncbigene:57584)	Human trophoblast migration is modulated by Rho GTPases (PMID: 21940708). Rho GTPases, RAC1 and CDC42, are required for prostaglandin E2-mediated human trophoblast migration (PMID: 18235104).
Protein Folding (R-HSA-391251)	TCP1 (ncbigene:6950), RGS11 (ncbigene:8786), TBCD (ncbigene:6904)	Protein misfolding and protein aggregation are associated with preeclampsia (PMID:31817906).
Resolution of Sister Chromatid Cohesion (R-HSA-2500257)	TAOK1 (ncbigene:57551), CLASP2 (ncbigene:23122)	TAOK1 negatively regulates IL-17 signaling (PMID: 29400705). In preeclampsia, IL-17 is increased in maternal serum and placentas (PMID: 32416889). Human extravillous trophoblasts undergo endoreduplication (PMID: 22877079). Abnormalities of extravillous trophoblasts have been extensively described in preeclampsia (PMID: 29701150).
Interferon Signaling (R-HSA-913531)	TRIM29 (ncbigene:23650), IFITM2 (ncbigene:10581), TRIM14 (ncbigene:9830)	Alterations in placental expression of IFN-gamma and its receptor are associated with preeclampsia pathophysiology (PMID: 15585559). Increased expression IFN-gamma is associated with impaired trophoblast invasion and migration *in vitro* (PMID: 33335575).
Epigenetic Regulation of Gene Expression (R-HSA-212165)	MBD2 (ncbigene:8932)	Placentas from pregnancies complicated by preeclampsia exhibit alterations in methylation and gene expression (PMID: 31212604).

Acronyms - R-HSA: Reactome Pathway Database; NCBIGene: National Center for Biotechnology Information Entrez gene identifier.

Supplemental Table 6. PheKnowLator-Derived Novel Drug Associations.

Identifier	Ignorome Hits	Domain Expert-Derived Mechanism(s)
Flavin Mononucleotide (MeSH:D005486)	RFK (ncbigene:55312)	Riboflavin-deficient women are more likely to develop preeclampsia (PMID:10862839).
17-benzyl-5-androstane-3,17-diol (MeSH:C445526)	STS (ncbigene:412)	17-benzyl-5-androstane-3,17-diol is an inhibitor of steroid sulfatase (PMID: 11600235). Steroid sulfatase is increased during preeclampsia in both placenta and maternal blood and modulates s-Flt1 (PMID: 27871476).
Sodium Borate (MeSH:C010634)	STS (ncbigene:412)	Boron participates in Vitamin D metabolism (PMID: 29207789). Maternal Vitamin D levels are associated with preeclampsia risk (PMID: 27841759).
Estranes (MeSH:D004962)	STS (ncbigene:412)	Oral contraceptive use for 8 or more years before pregnancy is associated with increased risk of preeclampsia (PMID: 10640157).
HDL Cholesteryl Ester (MeSH:C059714)	SCARB1 (ncbigene:949)	In preeclampsia, decreased levels of HDL-c have been observed during the third trimester (PMID: 24989239). The HDL-c of women with preeclampsia exhibits oxidative damage (PMID: 28511654).
Glycogen (MeSH:D006003)	AGL (ncbigene:178)	Villous syncytiotrophoblast microvesicles isolated from placentas from pregnancies complicated by preeclampsia have increased glycogen content (PMID: 8514882).
Enrasentan (MeSH:C098288)	EDNRB (ncbigene:1910)	Enrasentan is a high-affinity antagonist of Endothelin Type A Receptor (PMID: 12595914). Endothelin Type A Receptor antagonism has been suggested as a potential therapeutic strategy for preeclampsia (PMID: 28264495, PMID: 31221823).
Anti-Asthmatic Agents (MeSH:D018927)	MME (ncbigene:4311)	Women who experience symptomatic asthma during pregnancy have an increased risk of preeclampsia (PMID: 16572909).
Magnesium Oxide (MeSH:D008277)	CFLAR (ncbigene:8837)	During a clinical trial, significantly fewer women developed hypertension during pregnancy when supplemented with magnesium oxide (PMID: 1492408).
Sitagliptin Phosphate (MeSH:D000068900)	NAALAD2 (ncbigene:10003)	In gestational diabetes mellitus, Sitagliptin Phosphate ameliorates insulin resistance (PMID: 28213841). Preeclampsia is associated with increased risk of gestational diabetes mellitus in later pregnancies (PMID: 28542483). Women who experience preeclampsia are at increased risk of developing diabetes (PMID: 27646865).

Acronyms - MeSH: Medical Subject Headings; NCBIGene: National Center for Biotechnology Information Entrez gene identifier.

Supplemental Table 7. PheKnowLator-Derived Novel Gene Associations.

Identifier	Ignorome Hits	Domain Expert-Derived Mechanism(s)
PLOD2 (ncbigene:5352)	PLOD1 (ncbigene:5351), FBLN5 (ncbigene:10516), PTGDS (ncbigene:5730)	Plod2, a protein associated with extracellular matrix remodeling, is upregulated in trophoblast stem cells cultured under hypoxic conditions (PMID: 27807143). Hypoxia is thought to be central to the pathophysiology of preeclampsia (PMID: 30968806).
KCNMB3 (ncbigene:27094)	KCNMB4 (ncbigene:27345)	KCNMB3 was differentially methylated at 2 CpG sites in cord blood samples obtained from pregnancies conceived using assisted reproductive technologies (PMID: 25580569). Women who conceive using assistive reproductive technologies are at increased risk of preeclampsia (PMID: 31046710).
NDUFB3 (ncbigene:4709)	NDUFS7 (ncbigene:374291), SPG7 (ncbigene:6687), LRPPRC (ncbigene:10128), YME1L1 (ncbigene:10730)	Trophoblasts cultured under hypoxic conditions have decreased Complex I respiration rate (PMID: 23383105). Hypoxia is thought to be central to the pathophysiology of preeclampsia (PMID: 30968806).
MRPL32 (ncbigene:64983)	MRPL3 (ncbigene:11222), MRPS18A (ncbigene:55168), MRPL18 (ncbigene:29074)	Increased oxidative stress is central to preeclampsia pathogenesis (PMID: 20110125). Oxidative stress is associated with alterations in folding and degradation of MrpL32 (PMID: 21610694).
HBG1 (ncbigene:3047)	HBD (ncbigene:3045)	Increased fetal hemoglobin accumulation in the placenta is associated with preeclampsia (PMID: 25628568, PMID: 24185004).
RBBP7 (ncbigene:5931)	RBBP4 (ncbigene:5928), HDAC9 (ncbigene:9734), SETD1A (ncbigene:9739), ING5 (ncbigene:84289), CSNK2A2 (ncbigene:1459), E2F5 (ncbigene:1875), H3F3B (ncbigene:3021), KDM3A (ncbigene:55818), MPHOSPH8 (ncbigene:54737), MBD2 (ncbigene:8932), CXXC1 (ncbigene:30827), BCORL1 (ncbigene:63035)	RBBP7 was identified using co-expression network analysis as a gene to prioritize for investigation for association with preeclampsia (PMID: 24219996).
SLC30A7 (ncbigene:148867)	SLC30A5 (ncbigene:64924)	SLC30A7 is involved in regulation of cellular zinc and low levels of serum zinc are associated with preeclampsia (PMID: 26389947).
SLC44A5 (ncbigene:204962)	SLC44A1 (ncbigene:23446)	SLCA44A5 is a choline transporter, and choline supplementation down-regulates preeclampsia-associated protein sFLT1 (PMID: 23195033).

Identifier	Ignorome Hits	Domain Expert-Derived Mechanism(s)
RHOU (ncbigene:58480)	RHOQ (ncbigene:23433), RHPN1 (ncbigene:114822), BIN2 (ncbigene:51411), ARHGEF4 (ncbigene:50649), ARHGAP9 (ncbigene:64333), ARHGAP21 (ncbigene:57584), RAP1GDS1 (ncbigene:5910), SPATA13 (ncbigene:221178)	JAK/STAT signaling alters EGF-induced trophoblast invasion *in vitro* (PMID: 28542650). RhoU is downstream of the JAK/STAT signaling pathway (PMID: 29440639).
CCT2 (ncbigene:10576)	TCP1 (ncbigene:6950), STK24 (ncbigene:8428), DNAJC3 (ncbigene:5611), USP11 (ncbigene:8237), MKKS (ncbigene:8195), RGS11 (ncbigene:8786), DNAJB2 (ncbigene:3300)	Analysis of differentially expressed genes in preeclampsia reveals disruption of the CCT2-containing pathway “formation of tubulin-folding intermediates by CCT/Tric” (PMID: 30589053).

Acronyms - HP: Human Phenotype Ontology; NCBIGene: National Center for Biotechnology Information Entrez gene identifier.

Supplemental Table 8. PheKnowLator-Derived Novel Gene Ontology Associations.

Identifier	Ignorome Hits	Domain Expert-Derived Mechanism(s)
Mitochondrial Translational Elongation (GO:0070125)	MRPL3 (ncbigene:11222), MRPS18A (ncbigene:55168), MRPL18 (ncbigene:29074)	Mitochondrial dysfunction is central to the pathophysiology of preeclampsia (PMID: 33417666). Trophoblast mitochondrial function is impaired in preeclampsia (PMID: 27939475).
Cellular Zinc Ion Homeostasis (GO:0006882)	SLC30A5 (ncbigene:64924)	Preeclampsia is associated with lower levels of zinc in maternal serum (PMID: 26389947).
Mitochondrial Respiratory Chain Complex I (GO:0005747)	NDUFS7 (ncbigene:374291)	Trophoblasts cultured under hypoxic conditions have decreased Complex I respiration rate (PMID: 23383105). Hypoxia is thought to be central to the pathophysiology of preeclampsia (PMID: 30968806).
Cul2-RING Ubiquitin Ligase Complex (GO:0031462)	CUL2 (ncbigene:8453)	miRNA-584 is differentially expressed in preeclampsia and targets CUL2 (PMID: 27529341).
Hemoglobin Complex (GO:0005833)	HBD (ncbigene:3045)	Maternal hemoglobin concentration is associated with higher odds of preeclampsia (PMID: 30994929).
Calmodulin Binding (GO:0005516)	CALM1 (ncbigene:801), IQGAP1 (ncbigene:8826), BASP1 (ncbigene:10409), MYO1B (ncbigene:4430), PNCK (ncbigene:139728)	CALM1 (Calmodulin 1) is differentially expressed in severe early-onset preeclampsia (PMID: 33754042). A protein-protein interaction network identified IQGAP1 as related to preeclampsia but poorly explored or of unknown preeclampsia pathophysiology (PMID: 22873350).
Sister Chromatid Cohesion (GO:0007062)	TAOK1 (ncbigene:57551), CLASP2 (ncbigene:23122)	TAOK1 negatively regulates IL-17 signaling (PMID: 29400705). In preeclampsia, IL-17 is increased in maternal serum and placentas (PMID: 32416889). Human extravillous trophoblasts undergo endoreduplication (PMID: 22877079). Abnormalities of extravillous trophoblasts have been extensively described in preeclampsia (PMID: 29701150).
Histone Binding (GO:0042393)	H3F3B (ncbigene:3021), MPHOSPH8 (ncbigene:54737), SET (ncbigene:6418)	Human trophoblast differentiation is associated with epigenetic changes (PMID: 31294776). Preeclampsia is associated with epigenetic alterations (PMID: 31343798). H3F3B is induced in preeclampsia (PMID: 16129025).
mRNA Splicing, via Spliceosome (GO:0000398)	RNPC3 (ncbigene:55599), ECD (ncbigene:11319), CCAR1 (ncbigene:55749), PCBP2 (ncbigene:5094)	Alternative splicing affects many placental and preeclampsia-related genes (PMID: 33433680). Alternative splice variants of sFlt1 (PMID: 19147226) mineralocorticoid receptor (PMID: 31197761) are associated with preeclampsia.
Actin Filament Binding (GO:0051015)	ACTR3 (ncbigene:10096), NEBL (ncbigene:10529), ACTR3B (ncbigene:57180), MYO1B (ncbigene:4430), COBLL1 (ncbigene:22837), ZNF185 (ncbigene:7739), ITPRID2 (ncbigene:6744)	Preeclampsia is associated with altered actin polymerization via endothelial protein C receptor (PMID: 32003123).

Acronyms - GO: Gene Ontology; NCBIGene: National Center for Biotechnology Information Entrez gene identifier.

Supplemental Table 9. PheKnowLator-Derived Novel Disease Associations.

Identifier	Ignorome Hits	Domain Expert-Derived Mechanism(s)
Galactosemia (DOID:9870)	GALE (ncbigene:2582)	Galactosemia is caused by mutations in one of three genes needed to metabolize galactose to glucose: GALT, GALK1, and GALE (PMID: 30451973). Hypoglycemia can present clinically as galactosemia (PMID: 9832597). Preeclampsia increases the risk of neonatal hypoglycemia (PMID: 22525036).
X-linked Ichthyosis (DOID:1700)	STS (ncbigene:412)	X-linked ichthyosis is a rare dermatological condition caused by STS deficiency (PMID: 30768640). STS expression is increased in preeclamptic placentas and maternal whole blood (PMID: 27871476).
Progressive Bulbar Palsy (DOID:681)	RFK (ncbigene:55312)	Riboflavin Kinase is an essential enzyme for catalyzing the phosphorylation of riboflavin (PMID:12623014). Progressive bulbar palsy is caused by riboflavin transporter deficiency (PMID: 26973221). Riboflavin deficiency is a known risk factor for preeclampsia (PMID: 10862839).
Amyotrophic Lateral Sclerosis (DOID:332)	TARDBP (ncbigene:23435)	TARDBP encodes the protein TDP-43 which accumulates in amyotrophic lateral sclerosis (PMID: 28476168). AhR agonists increase TDP-43 in neurons. Placentas with high AhR expression during fetal development are highly susceptible to environmental toxicants (PMID:20354149). AhR has been proposed as a mechanism for the protective effects of cigarette smoke on preeclampsia (PMID: 21864991).
Attention Deficit Hyperactivity Disorder (DOID:1094)	STS (ncbigene:412)	The association between attention deficit hyperactivity disorder and STS dysfunction has been well established (PMID: 21255266). Offspring of preeclamptic mothers are 3-fold more likely to be diagnosed with attention deficit hyperactivity disorder (PMID: 30605798).
Pleural Cancer (DOID:5158)	SPP1 (ncbigene:6696)	SPP1 (secreted) has been shown to both regulate angiogenesis and inflammation associated with tumor growth and promote cancer cell survival, elements vital to the pathogenesis of pleural cancer (PMID: 22370646). SPP1 has been to be increased in preeclamptic patients with endothelial injuries (PMID: 19943814).
Gaucher's Disease (DOID:1926)	GBA (ncbigene:2629)	Gaucher's disease is caused by mutations in GBA (PMID: 18338393). It's been hypothesized that increased GBA expression might relate to placentation through decreased BMP4 signaling or vascularization through downregulation of TFEB (PMID: 25552189).
Fatty Liver Disease (DOID:9452)	STS (ncbigene:412)	STS expression has been shown to be induced in response to inflammation-activated NF-κB, a recognized mechanism in the development of chronic inflammatory liver disease (PMID: 26220752). STS expression is increased in the placenta and maternal whole blood samples of preeclamptic patients (PMID: 27871476).

Acronyms - DOID: Human Disease Ontology; NCBIGene: National Center for Biotechnology Information Entrez gene identifier.