Description of Additional Supplementary Files

Supplementary Data 1: **Overview of 40 traits and GWAS consider in analysis**. The consortium, trait category, trait, URL for summary statistics, sample size, number of cases (if binary trait), SNP heritability estimate and standard error, Lambda GC, mean χ2 statistic, reference DOI for GWAS, and expression mediated heritability and standard errors (using all and all TWAS-significant genes) are provided in order.

Supplementary Data 2: Comparison of GWAS and TWAS associations. The category, trait, GWAS sample size, number of cases, number of significant GWAS SNPs (P < 5×10^{-8}), and number of significant total and GWAS-overlapping TWAS associations (P < 2.5×10^{-6}) are provided in order.

Supplementary Data 3: Genetic correlations between traits at SNP- and placenta-expression mediated levels. Genetic correlations, standard errors, two-sided Z-test statistic, P-value, FDR-adjusted P-value, and genetic covariance and standard errors are provided for all pairs of traits.

Supplementary Data 4: Demographic and clinical covariates summary statistics of ELGAN and RICHS samples.

Supplementary Data 5: Summary of in- and out-sample predictive performance of MOSTWAS placental expression models. Mean, standard deviation, 25% quantile, median, and 75% quantile of gene expression heritability, in-sample cross-validation R^2 in ELGAN, and out-sample R^2 in RICHS.

Supplementary Data 6: Summary of 248 significant TWAS gene-trait associations. For each gene and trait, the trait category, chromosomal position of the gene, expression heritability and associated likelihood ratio test P-value, cross-validation predictive performance for gene model, TWAS two-sided weighted burden Z-score and P-value, two-sided permutation test P-value, top SNP and P-value in GWAS among SNPs used in the gene model, distal Z-score and P-value, and identified mediators are provided, in order.

Supplementary Data 7: Over-representation analysis of TWAS genes. Biological process, molecular function, and PANTHER pathway ontologies enriched for TWAS-identified genes associated with each trait at FDR-adjusted P < 0.05.

Supplementary Data 8: Genetic correlations between traits at placental expression-mediated level. For each pair of traits, the genetic correlation, standard error, t-statistic and associated degrees of freedom and P-value is provided.

Supplementary Data 9: Results of fine-mapping of overlapped TWAS genes using FOCUS. Overlapping genes are provided, with the associated trait, chromosomal positions, TWAS two-sided weighted burden Z-scores and P-values, top GWAS SNP information, posterior inclusion probability, and whether they are included in the credible set for the region. The distal Z-score is also provided.

Supplementary Data 10: TWAS-significant genes that do not overlap significant GWAS loci (within 500 kB)

Supplementary Data 11: Susceptibility genes associated with multiple traits. TWAS gene, chromosomal location, and associated trait are provided with genetic correlations between traits at SNP level are provided if significant FDR-adjusted $P < 0.05$.

Supplementary Data 12: Results of ELGAN phenome-wide scan of neonatal outcomes. For each gene and ELGAN phenotype, the effect size, standard error, Wald-type adjusted 95% confidence interval, two-sided Z-score, P-value, and FDR-adjusted P-value are provided.

Supplementary Data 13: Cis-GReX correlations of TWAS-identified genes with metabolic traits in the Hybrid Mouse Diversity Panel. For each correlation at Spearman correlated test FDR-adjusted P < 0.10, the dataset, gene (mouse analog), trait, correlation, and P-value are provided.

Supplementary Data 14: Over-representation analysis of transcription factors identified as mediators. For the transcription-factor encoding genes identified as mediators, functional categories, ontologies, FDR-adjusted P-value of enrichment for one-sided Fisher's exact test, number of overlapping genes in the ontology, and the total number of genes in the ontology is given.

Supplementary Data 15: Trans-eQTL scan using GBAT in RICHS between genetic loci local to MOSTWAS-identified regulatory protein-encoding genes and the expression of the target TWAS gene. The effect size, P-value of two-sided Z-test, and FDR-adjusted P-value are provided.

Supplementary Data 16: Results from MR-Egger to assess causal effects of transcription factors on targeted TWAS genes. For each RP-TWAS pair, the causal estimate, confidence interval, P-value for two-sided Wald-type test, residual standard error, heterogeneity statistic, and heterogeneity P-value for heterogeneity Chi-squared test are provided.

Supplementary Data 17: MOSTWAS-identified CpG site mediators found within ENCODE-identified placenta cis-regulatory sites. For each CpG site mediator that overlaps with a placental cis-regulatory stie, the chromosomal location of the regulatory site, the classification of the regulatory site, tissue, gestational time, sex, and accession number are provided.

Supplementary Data 18: Summary statistics of down-regulated differentially expressed genes in EPS15 knockdown cells. For each gene with FDR-adjusted $P < 0.01$, we provide the gene name, $\log_2$ fold change, standard error, and P-value of two-sided Wald-type test.

Supplementary Data 19: Summary statistics of up-regulated differentially expressed genes in *EPS15* knockdown cells. For each gene with FDR-adjusted $P < 0.01$, we provide the gene name, $\log_2$ fold change, standard error, and P-value of two-sided Wald-type test.

Supplementary Data 20: Over-representation analysis of down-regulated genes. Biological process, molecular function, and PANTHER and KEGG pathway ontologies enriched for down-regulated genes in *EPS15* knockdown cells associated with each trait at FDR-adjusted $P < 0.05$ for one-sided Fisher's exact test.

Supplementary Data 21: Over-representation analysis of up-regulated genes. Biological process, molecular function, and PANTHER and KEGG pathway ontologies enriched for up-regulated genes in *EPS15* knockdown cells associated with each trait at FDR-adjusted $P < 0.05$ for one-sided Fisher's exact test.