Genetic Variations and Risk of Placental Abruption: A Genome-Wide Association Study and Meta-analysis of Genome-Wide Association Studies

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Abstract

Introduction—Accumulating epidemiological evidence points to strong genetic susceptibility to placental abruption (PA). However, characterization of genes associated with PA remains incomplete. We conducted a genome-wide association study (GWAS) of PA and a meta-analysis of GWAS.

Methods—Participants of the Placental Abruption Genetic Epidemiology (PAGE) study, a population based case-control study of PA conducted in Lima, Peru, were genotyped using the Illumina HumanCore-24 BeadChip platform. Genotypes were imputed using the 1000 genomes reference panel, and >4.9 million SNPs that passed quality control were analyzed. We performed a GWAS in PAGE participants (507 PA cases and 1,090 controls) and a GWAS meta-analysis in 2,512 participants (959 PA cases and 1,553 controls) that included PAGE and the previously reported Peruvian Abruptio Placentae Epidemiology (PAPE) study. We fitted population stratification-adjusted logistic regression models and fixed-effects meta-analyses using inverse-variance weighting.

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Results—Independent loci (linkage-disequilibrium<0.80) suggestively associated with PA (P-value< 5e-5) included rs4148646 and rs2074311 in *ABCC8*, rs7249210, rs7250184, rs7249100 and rs10401828 in *ZNF28*, rs11133659 in *CTNND2*, and rs2074314 and rs35271178 near *KCNJ11* in the PAGE GWAS. Similarly, independent loci suggestively associated with PA in the GWAS meta-analysis included rs76258369 near *IRX1*, and rs7094759 and rs12264492 in *ADAM12*. Functional analyses of these genes showed trophoblast-like cell interaction, as well as networks involved in endocrine system disorders, cardiovascular diseases, and cellular function.

Conclusions—We identified several genetic loci and related functions that may play a role in PA risk. Understanding genetic factors underlying pathophysiological mechanisms of PA may facilitate prevention and early diagnostic efforts.

Keywords

Placental abruption; genome-wide association study; meta-analysis

INTRODUCTION

Placental abruption (PA) is the premature detachment of an implanted placenta from the uterus due to the rupture of maternal vessels in the decidua basalis prior to delivery of the fetus [1]. It is one of the leading causes of maternal and neonatal morbidity and mortality [2, 3]. Worldwide, the prevalence of PA is estimated to be 1% [1, 4], with considerable geographic variation [5]. Pathophysiologic mechanisms of PA, also shared by other perinatal disorders such as preeclampsia [3] and preterm delivery [6], include chronic hypoxemia [7], uteroplacental ischemia and infarctions [8].

Etiologic factors related to PA have not been fully described. To date, non-genetic risk factors associated with increased risk of PA include hypertensive disorders [8], advanced maternal age [1], grand-multiparity, thrombophilia, cigarette smoking [9], illicit drug use (particularly cocaine) and trauma to the abdomen [8–12]. However, most PA cases do not exhibit these known risk factors [13]. PA tends to aggregate in first degree relatives of women with PA [14, 15], suggesting a role for genetic predisposition [16–18]. Accumulating evidence from GWAS and candidate gene studies also suggest that there are underlying genetic risk factors in the pathogenesis of PA [19–23]. Our group previously reported several loci (including SNPs in *SMAD2 MIR17HG, DGKB, FLI-1, CETP, LIPC, Akt, NFKB, PI3K, THRB, CTNNA2, TNFRSF1A,* and *ZNRF3*) that are associated with PA [19–22]. However, previous candidate gene and GWAS studies were sparse and small in size.

As a multi-factorial disease, characterizing genetic susceptibility for PA requires comprehensive investigations of genetic variations at the genome-wide level. We performed a new GWAS and a GWAS meta-analysis of PA, the largest GWAS of PA to date. We also examined functions and functional relationships of genes represented by association signals using canonical pathway analyses and functional annotation tools.

METHODS

Study Settings and Study Populations

The study was conducted among participants of the Placental Abruption Genetic Epidemiology (PAGE) and the Peruvian Abruptio Placentae Epidemiology (PAPE) studies, case-control studies of PA conducted in Lima, Peru. Both PAGE and PAPE studies were independently recruited, had similar study objectives and study designs. Description of the PAPE study and findings of the PA GWAS among PAPE study participants have been previously reported [19–22]. PAGE study participants were recruited among women who were admitted for obstetrical services to antepartum wards, emergency room, and labor and delivery wards of participating hospitals between March 2013 and December 2015. Participating hospitals were Instituto Nacional Materno Perinatal, Hospital Rebagliati, Hospital San Bartolome, Hospital Hipolito Unanue, Hospital Arzobispo Loayza, Hospital Dos de Mayo, and Hospital Maria Auxiliadora. Participants who were less than 18 years of age, delivered multiple (non-singleton) infants, had medical records that were insufficient to determine the presence or absence of PA (described below), and reported taking blood thinning medications were excluded from the study. Participants with other diagnoses associated with third trimester bleeding (e.g. placenta previa) were excluded. Participants from PAGE study included 522 PA cases and 1147 controls. The meta-analysis included PAGE study participants and participants of the previously reported PAPE GWAs (490 PA cases and 500 controls) for a total of 1012 PA cases 1647 controls. Study protocols of both studies were approved by the Institutional Review Boards (IRBs) of participating institutions and the Swedish Medical Center, Seattle, WA, where the studies were administratively based. All participants of both studies provided written informed consent in accordance with the principles of the declaration of Helsinki. There was no overlap in participants across the two studies.

Data Collection

PAGE study participants were interviewed by trained personnel using standardized structured questionnaires to collect information on sociodemographic characteristics and risk factors including maternal age, marital status, employment status during pregnancy, medical history, smoking, and alcohol consumption (both current and pre-pregnancy). Maternal medical records were abstracted to obtain information on the course and outcomes of the pregnancy, and to ascertain PA case/control status. PA cases were identified through daily review of emergency room admission logbooks, labor and delivery admission logbooks, and the surgery report book (where post-operative diagnoses are registered). Controls were randomly selected from eligible pregnant women who delivered at participating hospitals during the study period and who did not have a diagnosis of PA in the current pregnancy. Maternal saliva was collected, plated and stored using the Oragene™ saliva cell collection kits (OGR500 and OGR250, DNA Genotek Ottawa, Canada).

DNA Extraction and Genotyping

Genomic DNA were extracted using Qiagen DNAeasy™ system and manufacturer protocols (Qiagen, Valencia, CA). Genotyping to characterize genome-wide variation (>300,000

SNPs) was conducted using the Illumina HumanCore-24 BeadChip platform (Illumina Inc., San Diego, CA).

Data Quality Control and Imputation

Genotype data quality control procedures were applied before data analyses. SNPs were excluded if they had excessive missing genotype (SNPs with genotype call rate of <95%), deviated from Hardy-Weinberg equilibrium (HWE) (p<1e-05), and had low minor allele frequency (MAF<0.05). The total number of SNPs, directly genotyped, that remained for further analysis in PAGE and the combined (meta-analysis) PAGE and PAPE studies were 232,960 and 205,100, respectively. Individuals (N=53) were excluded if they were duplicates or related (Identity by Decent [IBD] value>0.9), had more than 5% of genotyping failure rate (N=67), had excess heterozygosity rate (outside the range of mean ± 3 standard deviations of heterozygosity rate; N=6), had genotype data that was inconclusive regarding sex (N=8), and failed test of divergent ancestry (if principal components were outside the range of [−0.02, 0.02]; N=12). The total number of individuals that remained for further analysis for PAGE GWAS and the GWAS meta-analysis (combined PAGE and PAPE studies) were 1,597 (507 cases and 1090 controls) and 2,512 (959 cases, and 1553 controls), respectively.

After quality control, SNP imputation was conducted to infer unobserved genotypes. The genotype data were phased using SHAPEIT [24] to infer haplotypes and improve imputation accuracy using the 1000 Genomes haplotypes. Phased haplotypes were then used to impute our non-typed SNPs using IMPUTE2 [25]. After imputation and further quality control (filtering SNPs with imputation certainty score (Info)<0.3, HWE<0.00001, genotyping call rate<0.05, and MAF<0.05), a total of 5,400,957 and 4,983,952 SNPs were evaluated in the PAGE study and the meta-analysis, respectively.

Statistical Analyses

Mean and standard deviations for continuous variables and proportions (percentages) for categorical variables were used to compare the characteristics of PA cases and controls across PAGE and the combined PAGE and PAPE study populations. Study-specific GWAS analyses were conducted in PAGE using logistic regression models, with PA as the dependent variable, and, each SNP and adjustment factors (population stratification) as independent variables using SNPTEST v2 [26]. Adjustment for population stratification was conducted by including principal components (PCs) in the models and examining the degree of genetic variability due to admixture, assessed using scree plots [27]. PCs were computed using the 1000 genomes population reference [28]. Adjusted odds ratios (OR), corresponding 95% confidence intervals (CIs), and their genomic control corrected p-values (λ_{GC}) corresponding to each copy of the risk allele of the SNPs were estimated. We assumed additive genetic risk models with estimates corresponding to a linear increase of PA risk associated with the presence of 0, 1, and 2 risk alleles.

In the meta-analysis, individually analyzed PAGE and PAPE study results were combined after study specific standard error values were transformed to correspond to the logarithm of the ORs [29]. Fixed effects meta-analysis was conducted using the inverse variance

weighting method implemented in METAL [30]. GWAS meta-analysis results were additionally corrected for λ_{GC} based on all SNPs, as described above [29]. The Q-statistic and I^2 measures were calculated to estimate between-study heterogeneity. SNPs with pronounced heterogeneity ($I^2 >75\%$) were identified and further analyzed using the alternative random-effects meta-analysis approach recommended in previous studies [29, 31]. These sensitivity analyses were conducted using GWAMA [32]. Statistical analyses software used in these analyses included R (version i386 3.1.2) and SAS (Version 13).

Pathway and Functional Analyses

Genes represented by PAGE GWAS and GWAS meta-analysis signals with suggestive significance (p<5e-5) were further interrogated for functional relationships using analytical tools - Ingenuity Pathway Analysis (IPA, Ingenuity, Redwood, CA) [33], online databases assisted by FUMA (Functional Mapping and Annotation of GWAS) [34], and the human protein atlas [35]. In the IPA analysis based on the Ingenuity Pathways Knowledge Base (IPKB), gene-enrichment of networks was assessed using network score, negative log of P-values of a modified Fisher's exact test.

In FUMA, SNPs with suggestive significance were queried against the 1000 genomes Admixed American (AMR) reference panel for any SNPs flanking 250kb of the index SNP and in linkage disequilibrium (LD) with the index SNP (r^2 0.6). Gene-set and functional effect annotations were examined using ANNOVAR [36]. Combined Annotation Dependent Depletion (CADD) score, a deleteriousness score of variants computed by integrating 63 functional annotations was reported for most relevant functional variants [37]. In addition, FUMA summarized chromatin interaction mapping using 15-core chromatin state predicted by ChromHMM15 [38] for 127 tissue/cell types [39]. SNPs (top hits associated with PA) were queried using FUMA evaluate their biological functionality as expression quantitative trait loci (eQTL) and involvement in chromatin interaction. Information on eQTL were obtained from GTEx v6 [34] that includes gene expression database of 53 tissue types in >70 samples.

RESULTS

Socio-demographic, medical and obstetric characteristics of PA cases and controls of the PAGE study and the combined PAGE/PAPE studies are shown in Table 1. PA cases were more likely to deliver earlier (i.e., shorter gestational age), deliver infants with lower birth weight, and have a diagnosis of preeclampsia in the current pregnancy as compared with controls. Compared with controls, PA cases tended to report smoking and illicit drug use during pregnancy.

We did not observe significant genomic inflation or deviation from expectation when examining the QQ plots of the PAGE GWAS and the GWAS meta-analysis (λ_{GC} PAGE=1.00; λ_{GC} meta-analysis=0.99; Figure 1). The top independent signals of the PAGE GWAS with suggestive statistical significance (p<5e-5), included rs4148646 (odds ratio [OR]=0.67; p=1e-6; effect allele frequency [EAF]=0.63) and rs2074311 (OR=0.68; p=2e-6; EAF=0.64) in *ABCC8*, rs2074314 (OR=0.68; p=1e-6; EAF=0.64) and rs35271178 (OR=0.69; p=4e-6; EAF=0.62) near *KCNJ11*, rs7249210 (OR=2.11; p=3e-6; EAF=0.09),

rs7250184 (OR=2.09; p=4e-6; EAF=0.09), rs7249100 (OR=2.08; p=4e-6; EAF=0.09) and rs10401828 (OR=2.05, p=4e-6; EAF=0.09) in *ZNF28*, and rs11133659 (OR=2.12; p=4e-6; EAF=0.09) in *CTNND2* genes (Figure 2, Table 2, **and** Supplementary Table 1).

In the GWAS meta-analysis, the top independent SNPs that were suggestively associated with PA, included rs76258369 (OR=1.56; p=3e-6; EAF=0.16) near *IRX1*, rs7094759 (OR=0.74; p=4e-6; EAF=0.48) and rs12264492 (OR=0.73; p=4e-6; EAF=0.40) in *ADAM12* gene, rs30080 (OR=0.73; p=5e-6; EAF=0.42) and rs7704841 (OR=0.73; p=6e-6; EAF=0.42) in *DOCK2*, rs11995662 (OR=0.61; p=5e-6; EAF=0.10) in *PDGFRL*, rs4867606 (OR=1.82; p=6e-6; EAF=0.10) in KCNIP1, rs2291228 (OR=1.37; p=8e-6; EAF=0.42) near *FAM196B*, rs799758 (OR=1.47; p=9e-6; EAF=0.18) in *GALNT13*, and rs17837210 (OR=1.80; p=9e-6; EAF=0.07) near *FAM124A* (Figure 2, Table 2, **and** Supplementary Table 2).

In IPA analysis, networks (scores>15) enriched by 27 genes represented by 174 PAGE GWAS hits (with p<5e-5) included networks for developmental disorder, endocrine system disorders, organismal injury and abnormalities, molecular transport, cardiac arrhythmia, and cardiovascular disease (Table 3). The functional annotation and mapping of PAGE GWAS hits in *ABCC8, KCNJ11, ZNF28,* and *CTNND2* genes identified trophoblast-like cell chromatin interactions (Table 4). Rs5215 in *KCNJ11* (CADD score=12.4) had the highest deleteriousness score. Significant networks represented by the top 27 genes are displayed in Supplementary Figure 1a, highlighting molecules implicated in cardiovascular disease and cardiac arrhythmia pathway. Networks (scores>24) enriched by 36 genes represented by the top 149 GWAS meta-analysis hits (with p<5e-5) included networks for cellular function and maintenance, cell-to-cell signaling and interaction, and lipid metabolism (Table 3). Trophoblast-like cell chromatin interactions were also identified for genes *ADAM12, DOCK2, PDGFRL, LOC105374318,* and *FAM124A* represented by GWAS meta-analysis hits. Among the top hits, rs72841199 in *DOC2* had the highest deleteriousness score (CADD score=17.3) (Table 4). Significant networks represented by the top 36 genes are displayed in Supplementary Figure 1b, highlighting molecules implicated in cell signaling/cell-cell interaction and lipid metabolism pathway. Significant networks represented by the genes from top hits include cellular movement and cell morphology (Supplementary Table 4).

DISCUSSION

While we did not find genome-wide significant hits (p<5e-8), we identified several SNPs and networks that are potentially associated with increased PA risk. These include SNPs in/ near *ABCC8, KCNJ11, ZNF28, CTNND2, IRX1, ADAM12, DOCK2, PDGFRL, KCNIP1, FAM196B, GALNT13* and *FAM124A* genes as well as networks involved in endocrine system disorders, cardiovascular disease, and cellular function and maintenance. Several SNPs in these genes were mapped to trophoblast-like cell chromatin interaction, suggesting potential pregnancy related cell-type-specific regulatory activity.

Previous candidate gene and GWA studies of PA have reported several genetic loci associated with PA. A systematic review (483 cases and 1476 controls) of candidate gene studies identified that SNPs in Factor V Leiden 1691 G→A (*F5*) gene, also linked with

heritable thrombophilia, are potentially associated with PA [23]. Inferences from these earlier studies, however, are limited in part because of statistical imprecision of relative risk estimates attributable to small sample sizes. More recent studies identified SNPs in genes *AGT, KDR, F2* and *THBD* that are involved in coagulation, rennin-angiotensin, angiogenesis, inflammation, and B-vitamin metabolism [20]. SNPs in *CAMK2B, NR1H3, PPARG, PRKCA, THRB, COX5A, NDUF* family and *COX10* genes, involved in mitochondrial biogenesis and oxidative phosphorylation [22], that are associated with PA have also been reported. In addition, genes known to control circadian rhythms (e.g., *CRY2, ARNTL*, and *RORA*) were also associated with increased risk of PA [21]. The first three GWAS studies of PA, conducted by our group, [19, 20, 22] suggest SNPs in *SMAD2, MIR17HG, DGKB, FLI-1, CTNNA2, TNFRSF1A*, and *ZNRF3* genes, as well as networks of lipid metabolism and cell signaling represented by *CETP, LIPC, COX10, THRB, Akt, NFKB, PI3K* genes are associated with PA risk. Most of the previously described genes were not represented by the SNPs in our list of top GWAS hits with statistically suggestive association. In the current GWAS meta-analysis, we identified the following SNPs in genes with known functional significance in PA that were associated with PA before multiple testing correction: rs10919196 (OR=1.20 [95%CI:1.03–1.40]) and rs9332544 (OR=1.19 [95%CI:1.00–1.43]) in *F5* gene [23], rs2009705 (OR=1.18 [95% CI: 1.02–1.36]) in *CAMK2B* [22], rs4328478 (OR=1.19 [95%CI:1.04–1.36]) in *PRKCA* [22], and rs11107847 (OR=0.84 [95%CI:0.74–0.94]) in *NDUFA12* [22]. In Supplementary Table 3, we provide a list of nine SNPs in four genes (*PCSK6, GALNT13, LINC01019*, and *NEDD4L*) that were suggestively associated with PA in both the PAGE study and the meta-analysis.

Notable findings from this study include common protein coding variants that are associated with PA. For instance, in our study, the C allele of rs757110, a coding SNP near *ABCC8*, was potentially associated with increased risk of PA (OR=1.47 [95%CI:1.27–1.72]). *ABCC8*, ATP binding cassette subfamily C member 8 gene, has been associated with GDM, type-2 diabetes, and hyperglycemia-cardiovascular risk [40]. ATP-sensitive potassium (KATP) channel is one of the most abundant potassium channels in myometrium [41]. Functional KATP channels, which are expressed in human pregnant myometrium, may contribute to enhanced uterine contractility associated with the onset of labor [42], common clinical findings in PA. The network analyses showed that network of genes including the two potassium channel genes *ABCC8* and *KCNJ11* were among genes involved in organismal injury and abnormalities, and endocrine system disorder diseases.

The associations we found between PA and two common exonic variants (rs5219 and rs5215) in *KCNJ11* (ATP sensitive inward rectifier potassium channel, subfamily J, member 11) are noteworthy because the SNPs have already been recognized to be clinically relevant in the development of gestational and type-2 diabetes [43]. A systematic review of GWAS studies that evaluated SNPs in relation to gestational diabetes mellitus (GDM) identified that the T allele of rs5219 is associated with an increased risk of GDM (pooled OR=1.15 [95%CI:1.06–1.26]) [44]. Several other studies highlight the roles of *KCNJ11* in the etiology of GDM, neonatal diabetes and maternal metabolism [45, 46]. Although the link between GDM and PA is unknown, maternal hypertensive disorders of pregnancy, particularly maternal history of chronic hypertension, risk factors of GDM, have been among the most consistently noted risk factors for PA [8]. Our findings may signal a genetic

link between PA and GDM through the regulatory action of biological pathways involving potassium channels.

This GWAS meta-analysis identified 10 SNPs in *ADAM12* (ADAM metallopeptidase domain 12), a highly expressed gene in the placenta and implicated in cellular function and maintenance. *ADAM12* regulates the migration and invasion of trophoblasts into the lining of the uterus, a critical step in normal placental development [47] [48]. The two *ADAM12* SNPs, rs7094759 and rs12264492 among our top GWAS meta-analysis hits mapped to trophoblast-like cell chromatin interaction in functional analyses. *ADAM12* SNPs and their potential roles in PA risk through trophoblast regulation is particularly intriguing because trophoblastic invasion is thought to lead to vascular malformations and PA [49]. *ADAM12* is also associated with other risk factors of PA such as preeclampsia that have shared etiology and pathophysiology with PA including trophoblast invasion [3, 47]. In addition, *ADAM12* is primarily expressed in the placenta [35], highlighting the potential clinical significance of our findings. Five strongly correlated SNPs (LD>0.8) in *GALNT13* suggestively associated in PAGE GWAS were also suggestively associated in meta-analysis GWAS (P-value<5e-5) (Supplementary Table 3). *GALNT13*, polypeptide N-acetylgalactosaminyltransferase 13 gene, is among a list of differentially expressed genes in preeclamptic tissue samples compared with normotensive tissue samples [50].

Our study identified several significantly enriched pathways (e.g. including organismal injury and abnormalities, lipid metabolism and cardiovascular disease) involving genes represented by top hit SNPs. Previous studies with similar observations highlighted placental ischemia and infarctions as risk factors of PA [8, 51]. Our observation of a lack of a strong signal for a specific disease or function is in line with the current understanding of PA as a complex disorder with potentially multiple underlying pathways. The 27 genes representing our top PAGE GWAS hits and highlighted in our pathway analysis were significantly involved in a function cluster in gene ontology (GO) terms of G-protein coupled glutamate receptor signaling pathway that are important for downstream cellular processes, such as transcription. The 36 genes representing our top meta-analysis GWAS hits also highlighted in our pathway analysis were significantly involved in a function cluster in GO terms of regulation of metabolic and cellular processes.

We queried the top SNP findings in our PAGE GWAS and meta-analysis GWAS using dbPTB [52], PESNPdb [53], and SNPedia [54] databases. None of the SNPs we identified have previously been associated with preeclampsia or preterm birth. However, *ADAM12*, a gene represented by SNPs suggestively associated with PA (rs7094759, rs12264492) and *FTO*, a gene represented by SNPs suggestively associated with PA (rs28637326, rs16953154, rs12598570, rs12934459, rs28613919, and rs12445575), were associated with preeclampsia [47, 54].

Several strengths of our study deserve mention. This study is, to date, the largest GWAS study of PA that has the potential to enhance our understanding of genetic variations in maternal genome that contribute to a multi-factorial heritable disorder such as PA. We studied Peruvians, a relatively understudied population. In addition, we performed imputation to comprehensively characterize genome-wide variation and additional

functional pathway analyses, utilizing state-of-the-art bioinformatics tools, to highlight the biological functions of our genetic findings.

Some limitations of the study merit attention. Although our current study is the largest GWAS on PA to date, it is still underpowered to evaluate small effects. We did not find associations for SNPs that reached genome-wide significance. Another limitation is the potential misclassification of sub-clinical PA (i.e. those not presenting with abnormal vaginal bleeding). These may either introduce bias in the interpretation of our study results or reduce power of our study. Comparing severe placental abruption with mild abruption and/or non-abruption cases may minimize this limitation and facilitate epidemiologic and genetic research [55]. To assess the role of term/preterm delivery and preeclampsia status on observed associations, we conducted independent sensitivity analyses excluding term PA cases and controls as well as excluding preeclampsia cases and controls. Findings from these sensitivity analyses were in general similar to what we report in the current manuscript, with similar estimates (odds ratios), although 95% confidence intervals were wider as expected (attributable to smaller sample size for these sensitivity analyses). Finally, findings from our study population may not be generalizable to other populations.

Findings from this study lend evidence for several genetic loci that may influence PA. These genetic loci included clinically-relevant protein-coding variants (e.g. *ABCC8* and *KCNJ11*), as well as genes that are known to be highly expressed in the placenta (e.g. *ADAM12*) and myometrium (e.g. *ABCC8*) [35]. Understanding these pathophysiological mechanisms may help accelerate preventative and early diagnostic efforts to reduce the burden of PA, an important public health problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Genetic variations are potentially associated with placental abruption (PA) risk.

- Variations in genes participating in diverse cellular functions are related to PA.

- PA-related gene variations mapped to trophoblast-like cell chromatin interaction.

- Findings enhance understanding of underlying mechanisms of PA.

- Findings may also facilitate PA-related preventative and early diagnostic efforts.

λ_{GC} PAGE = 1.00
λ_{GC} Meta-analysis = 0.99

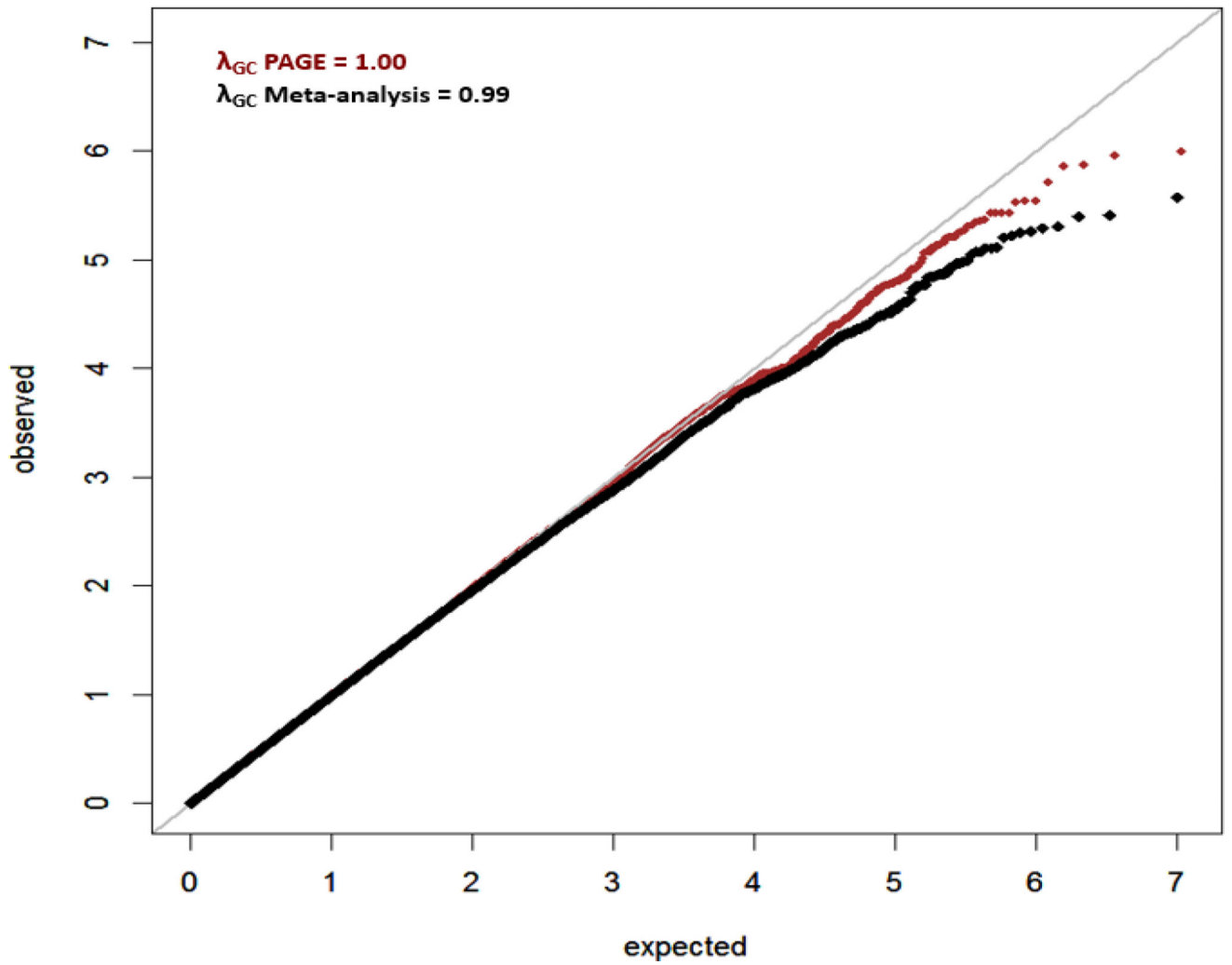**Figure 1.**
Quantile-Quantile plots of associated p-values and their genomic control inflation factor for PAGE and meta-analysis studies.
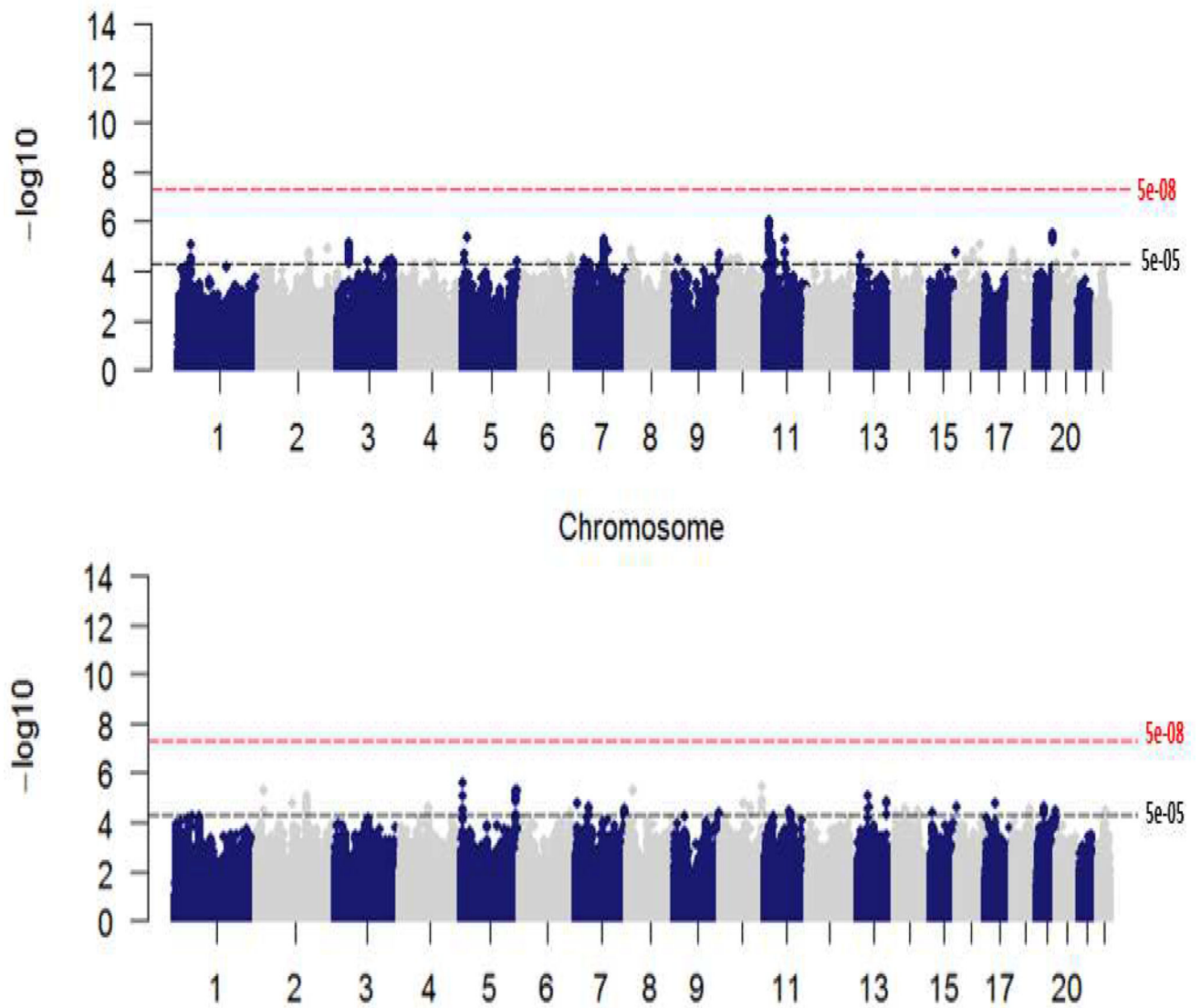
Figure 2.
Manhattan plot associated p-values by chromosomal location. Top: PAGE; Bottom: Meta-analysis. Genome-wide significance p-values are indicated by red dots, and suggestive significance p-values are indicated by black dots.

Table 1

Selected characteristics of the study populations

Characteristics	Placental Abruption Genetic Epidemiology (PAGE) Participants			Meta-analysis		
	Cases (N=507)	Controls (N=1090)	P-value	Cases (N=959)	Controls (N=1553)	P-value
	%	%		%	%	
Maternal age at delivery (years)[1]	28.4±6.7	27.5±6.6	0.93	28.1±6.6	27.6±6.6	0.79
Maternal age at delivery (years)			0.22			0.83
18–19	6.8	11.7		8. 2	10.7	
20–29	51.0	50.7		51.4	51.1	
30–34	20.8	19.9		20.8	20.3	
35	21.4	17.7		19.5	18	
Education high school	67.3	73.5	**0.03**	69.6	72.6	0.62
Married/living with partner	86.1	87.1	0.56	84.7	87	0.12
Employed during pregnancy	55.0	53.9	0.69	49.8	51.3	0.74
Pre-pregnancy body mass index (BMI) (kg/m^2)	25.0±4.6	25.4±4.6	0.61	24.4±4.3	24.9±4.5	0.65
Pre-pregnancy BMI (kg/m^2)			0.53			0.16
Lean (< 18.5)	2.8	2.0		4. 0	2. 3	
Normal (18.5–24.9)	56.1	55.6		59.6	59.3	
Overweight (24.9–30.0)	10.9	12.8		27.8	27.2	
Obese (30.0)	30.2	29.6		8.7	11.2	
Planned pregnancy	38.5	32.8	**0.03**	38.7	35.4	0.42
Smoked during pregnancy	1.0	1.0	0.96	2.3	1.2	**0.03**
Alcohol use during pregnancy	3.9	2.8	0.20	4.8	3.2	0.33
Drug abuse during pregnancy	0.6	0.3	0.34	0.6	0.2	0.08
Preeclampsia	21.4	6.3	**<0.001**	24.6	6.6	**<0.001**
Vitamins use during pregnancy	84.6	86.1	0.47	77.9	81.4	0.62
Gestational age at delivery[1]	34.3±4.4	39.0±1.2	**<0.001**	34.8±4.3	38.8±1.8	**<0.001**
Infant birthweight (grams)[1]	2390±939	3418±484	**<0.001**	2398± 902	3343±561	**<0.001**

[1] mean ± standard deviation;

[2] p-values are from Chi-square test/Fisher's exact test for the categorical variables and student t-test for continuous variables.

Table 2

Top 10 independent SNPs that have the lowest association p-values for analyses examining genome-wide genetic variations and placental abruption risk among PAGE and Meta-analysis studies.

Gene	Chromosome	SNP[*]	Effect Allele	Effect Allele Frequency	Odds Ratio (95% Confidence Interval)	Empirical p-value
PAGE Study						
ABCC8	11	rs4148646	G	0.633	0.67 (0.58,0.79)	1.00E-06
KCNJ11	11	rs2074314	T	0.635	0.67 (0.58,0.79)	1.40E-06
ABCC8	11	rs2074311	G	0.623	0.68 (0.58,0.80)	1.90E-06
ZNF28	19	rs7249210	A	0.09	2.11 (1.54,2.87)	3.00E-06
KCNJ11	11	rs35271178	T	0.623	0.69 (0.59,0.81)	3.80E-06
ZNF28	19	rs7250184	C	0.091	2.09 (1.53,2.84)	3.80E-06
ZNF28	19	rs7249100	G	0.091	2.08 (1.53,2.84)	3.80E-06
ZNF28	19	rs10401828	C	0.093	2.05 (1.51,2.78)	4.30E-06
CTNND2	5	rs11133659	A	0.088	2.12 (1.54,2.92)	4.40E-06
ZNF28	19	rs146312	T	0.072	2.00 (1.49,2.70)	5.30E-06
Meta-analysis						
IRX1	5	rs76258369	C	0.164	1.56 (1.30,1.88)	2.80E-06
ADAM12	10	rs7094759	T	0.482	0.74 (0.65,0.84)	4.00E-06
ADAM12	10	rs12264492	G	0.404	0.73 (0.64,0.83)	4.10E-06
DOCK2	5	rs30080	C	0.424	0.73 (0.63,0.83)	5.00E-06
PDGFRL	8	rs11995662	C	0.1	0.61 (0.49,0.75)	5.20E-06
KCNIP1	5	rs4867606	A	0.099	1.82 (1.41,2.36)	5.50E-06
LOC105374318	2	rs219551	T	0.142	1.64 (1.33,2.04)	5.80E-06
DOCK2	5	rs7704841	G	0.422	0.73 (0.64,0.84)	6.40E-06
FAM196B	5	rs2291228	G	0.424	1.37 (1.19,1.56)	7.90E-06
GALNT13	2	rs799758	C	0.176	1.47 (1.24,1.74)	8.60E-06
FAM124A	13	rs17837210	C	0.072	1.80 (1.39,2.33)	8.60E-06

[*] hg19 build 37 dbSNP

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Table 3

Significant networks represented by top 27 genes from top PAGE GWAS hits and 36 genes from top GWAS meta-analysis hits (p<1e-5).

Molecules in Network	Score	Number of Genes from GWAS	Top Disease and Functions	P-value
PAGE Study				
2'-fucosyllactose,**ABCC8**,Akt,ANGPTL1,basic calcium phosphate crystal,beta-hydroxyisovaleric acid,Cyp2p9,DNMT1,ERBB4,ERK,ERK1/2,INSRR,Insulin,**ITGA9**,**KCNJ11**,L-leucine,**NEDD4L**,NFkB (complex),NRG3,NRG4,NUCB2,Pronsulin,Prprc,SLC22A8,SLC3A1,**SLIT3**,**S NCA**,**SOX5**,squalene,STYX,Tardbp,**TFAP2E**,**VAV2**,Ybx1-ps3	26	11	Developmental Disorder, Endocrine System Disorders, Gastrointestinal Disease	1.00E-25
7SNGF,ADH7,BMP2,BMP8B,C16orf87,Cul,CltC,Gm8587/Snrpa,GNA14,GPR161,GPX2,**GRM3**,Groucho,GSTT2,GSTT2B,HDAC3,Hdac1l,IKBKG,IL1,IL4,**MACROD1**,MEPE,MOV10,**NCR3LG1**,NFE2L2,**PCSK6**,PRDM4,PRDM6,**PSMB2**,QPRT,SAP30l,SLC7A8,**SSI8l**,**LXPO7**,**ZMYM4**	20	9	Dermatological Diseases and Conditions, Organismal Injury and Abnormalities, Cancer	1.00E-38
5,6,7,8-tetrahydrobiopterin,AGTrCa/insulin,Camkk,CNGA3,CTNNA1,1,**CTNND2**,CYTH3,**DLGAP1**,DMD,GALNT9,**GALNT 13**,IQSEC3,ITIH4,KCNA4,KCNAB1,KCNN3,KCNN3,LRRC7,miR-7a-5p (and other miRNAs w/seed GGAAGAC),NOS1,NPR3,**PAMR1**,RGN,**RIMBP2**,SCN5A,SCN7A,SGCD,**SNTB1**,SNTG1,**SYNE1**,WBSCR17	15	7	Molecular Transport, Cardiac Arrythmia, Cardiovascular Disease	1.00E-14
Meta-analysis				
ADAM12,APP,beta-estradiol,**BRD3**,Brd4,CALML4,**CMSS1**,**CRTC1**,**DOCK2**,**ERICH3**,**FAM124A**,**FLIP1L**,**GALNT13**,GPR88,HTT,IGSF6,KRAS,MDM2,mir-548,MPV17L,**MTUS1**,**PALD1**,**PDGFR L**,PP2D1,PTPN20,PTTG2,PXN,ROCK1,SLC13A3,SRF,TGFB1,THSD4,TMEM44,**VPS41**,ZNF706	32	14	Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance	1.00E-31
AJAP1,ATP5A1,**ATP5S**,**CAMK1D**,CSRNP3,**FAM196B**,Gagsus/Q/β3/Gγ13,ITPKA,JPH3,L-dopa,,MPPE1,Na+,**NEDD4L**,Ne+,**PDE1C**,PDE6C,PDE7B,PLD6,PLPP6,PPP1CA,PRPF18,PRR16,**RAP1GAP2**,REM1,REM2,**RHBDL3**,SLC10A4,SLC24A2,**SLC24A4**,SLC8B1,**SNCA**,**SYNE1**,**TMEM132D**,VAT1L,YWHAZ	24	11	Psychological Disorders, Cell-To-Cell Signaling and Interaction, Drug Metabolism	1.00E-23
ALB,AMT,**ATP10A**,Ca2+,**CACNA1I**,Ces2e,**COX16**,CTNNB1,**DPP6**,FAIM2,FAS,**FBXO31**,FCAMR,GPR160,HNF4A,HPR,HRC,IGDCC4,JNHBC,**KCNIP1**,**L2IIGDIA**,MSRA,MSRB2,**MYO7A**,NEURL2,NFYB,PAQR5,**PCSK6**,PITPNM3,PRND,PRRG2,QTRT2,**TMEM87B**,ZCCHC9,ZNF345	24	11	Dermatological Diseases and Conditions, Immunological Disease, Lipid Metabolism	1.00E-23

Genes highlighted in **Bold** are the 27 genes and 36 genes representing top PAGE GWAS hits and meta-analysis GWAS hits

Table 4

Functional annotation of top 10 independent SNPs that have the lowest association p-values for analyses examining genome-wide genetic variations and placental abruption risk among PAGE and Meta-analysis studies.

Gene	Gene Description	SNP*	Chromosome:Position*	Functional Annotation Analysis (FUMA)			Ingenuity Pathway Analysis (IPA)
				SNP Function	CADD Score	Chromatin Interaction Mapped	Disease Function of Gene
PAGE Study							
ABCC8	ATP binding cassette subfamily C member 8	rs4148646	11:17415190	intronic	2.15	Trophoblast-like cell; Mesendoderm	Developmental Disorder, Endocrine System Disorders, Gastrointestinal Disease
		rs2074311	11:17421860	intronic	2.04	-	
KCNJ11	Potassium inwardly rectifying channel, subfamily J, member 11	rs2074314	11:17411821	5upstream	1.42	-	Developmental Disorder, Endocrine System Disorders, Gastrointestinal Disease
		rs35271178	11:17411020	5upstream	8.38	-	
ZNF28	Zinc finger protein 28	rs7249210	19:53337340	intronic	4.52	Trophoblast-like cell; Mesendoderm	-
		rs7250184	19:53337426	intronic	0.18	-	
		rs7249100	19:53337326	intronic	0.01	-	
		rs10401828	19:53336367	intronic	-	-	
CTNND2	Catenin delta 2	rs11133659	5:11628509	intronic	1.66	-	Molecular Transport, Cardiac Arrythmia, Cardiovascular Disease
Meta-analysis							
ADAM12	ADAM metallopepti dase domain 12	rs7094759	10:127852106	intronic	4.92	Trophoblast-like cell; Mesendoderm	Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance
		rs12264492	10:127854246	intronic	4.28	Trophoblast-like cell; Mesendoderm	
DOCK2	Dedicator of cyto-kinesis 2	rs30080	5:169273557	intronic	1.21	Mesendoderm	Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance
		rs7704841	5:169281214	intronic	3.87	-	
PDGFRL	Platelet derived growth factor receptor like	rs11995662	8:17498730	intronic	1.9	Trophoblast-like cell; Mesendoderm	Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance
KCNIP1	Potassium voltage-gated channel interacting protein 1	rs4867606	5:169924695	intronic	11.68	-	Dermatological Diseases and Conditions, Immunological Disease, Lipid Metabolism

Gene	Gene Description	SNP*	Chromosome :Position*	Functional Annotation Analysis (FUMA)			Ingenuity Pathway Analysis (IPA)
				SNP Function	CADD Score	Chromatin Interaction Mapped	Disease Function of Gene
LOC105374318	-	rs219551	2:21540711	ncRNA_intronic	1.83	Trophoblast-like cell; Mesendoderm	-
FAM196B	Family with sequence similarity 196 member B	rs2291228	5:169288732	3downstream	0.49	-	Psychological Disorders, Cell-To-Cell Signaling and Interaction, Drug Metabolism
GALNT13	Polypeptide N-acetylgalact osaminyltra nsferase 13	rs799758	2:155262144	intronic	1.36	-	Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance
FAM124A	Family with sequence similarity 124 member A	rs17837210	13:51856010	3utr	3.03	Trophoblast-like cell; Mesendoderm	Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance
IRX1	Iroquois homeobox 1	rs76258369	5:3545547	intergenic	2.25	Mesendoderm	-

*
hg19 build 37 dbSNP