

Imprinted Gene Regulation in the Placenta and Fetal Development

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ABSTRACT

During fetal growth and development, placental integrity is of the utmost significance, which determines the success of pregnancy. The placenta is an exceedingly specialized transitory organ that is precisely regulated by endocrine, metabolic and immunological processes. It develops from the blastocyst in a manner that resembles a growing tumor through cellular invasion and angiogenesis but unlike tumor, these processes are strictly controlled. The rapid and undifferentiated growth of the trophoblast gives rise to the villous and the extravillous phenotypes, which differentiates together in order to establish fetal-maternal circulation. While the villous lineage enters the syncytial pathway, the extravillous trophoblast invades the maternal decidua. The aim of this review is to unravel imprinted gene regulation in the placental and fetal development, and their apparent effects on the future health of the fetus using transcriptomic and proteomic approaches. Understanding the genetic influence of placental development and function is of great clinical interest since any variation may lead to pregnancy related complications such as preeclampsia.

Introduction

The development of placenta into the various trophoblast subtypes helps to determine the success of a pregnancy outcome. The human placenta fulfills different functions such as enabling the blastocyst adaptation in utero and nourishment of the developing fetus. Impairment in placentation in early gestational stages is implicated with a number of conditions such as preeclampsia, miscarriages and restriction of intrauterine growth, which may negatively affect the health of the developing fetus or even the future of the child through fetal programming. Previous studies indicate that during the first semester, system genes that are associated with biological mechanism including nucleic acids and protein metabolism, mRNA transcription and other cellular processes are highly expressed and regulated. This indicates the intensity of cellular proliferation and differentiation during this

gestational stage. These findings have been reported by Mikheev, et al. [1] as well as other genomic studies on placental development and function [2]. Synthesis in the placenta secretes large amount of molecules that are essential for its development, metabolism and fetus growth. The factors involved include hormones of the placenta and growth factors which lead to the regulation of gene expression critical for plasticity of the placenta plasticity and functions. Placental investigation requires an approach which is high throughput and thorough methods for example microarray, ribonucleic acid sequencing (RNA-Seq) and/or quantitative reverse transcription-polymerase chain reaction (qRT-PCR) technologies, in tissue analysis for physiology and pathophysiology.

Expression of this transcript correlates with the maternal blood pressure as well as neonatal birth weight, which suggest the role it

plays in pre-eclampsia. These collective reviews for imprinted gene regulation signatures might be used in future as new biomarkers for maternal and fetal complications of pregnancy. In this review, literature search was performed in the last fifteen years in PubMed and Google scholar, using the key terms: placental gene expression / regulation and fetal development. Only published articles with a set gene involved in normal placental function and pathogenesis were considered. We chose recently published to get the true picture of Imprinted Gene Regulation on Placental and Fetal Development, but also cited relevant and important older publications where necessary. Currently there is inadequate information on the effect of gene expression and regulatory mechanisms on placental and fetal development, this review, therefore, will shed more light on gene expression involved in placental and fetal development as well as identifying the areas that needs further studies.

Unique Patterns of Gene Expression in the Placenta

Various mRNA transcripts such as human chorionic gonadotropin β subunit (hCG β), corticotropin-releasing hormone (CRH) and human placental lactogen (PL) have been characterized in maternal plasma [3]. The expression pattern of each gene is dependent on the gestational age. Transcripts such as fetal-derived γ -globin increase in maternal circulation after elective pregnancy termination [4]. Placental transcripts of clinical significance have

been characterized through microarray analysis to generate non-invasive fetal gene profiles [5] including the increased CRH levels in preeclampsia [6] and the decreased HS3ST3A1 mRNA expression in pre-eclamptic placental tissue. The imprinted gene regulation of placenta and fetal development during different gestational stages is summarized in Table 1. Additionally, identified common gene pathways involved in imprinted gene regulation of placental and fetal development are also shown. In mammals, genetic imprinting is a significant process where many genes undergoes epigenetic modification and imprinted specifically in the placenta [7-18]. Placental imprinting appears to be a continuous process that occurs throughout the pregnancy [19]. Data from the entire genome methylation from placental tissue during the first and third trimester indicates a methylation-induced down regulation for a number of tumor related genes as a normal placentation process [20]. In this review, it is reported imprinted genes are expressed in a temporal process in the course of normal human placenta development. The study has also demonstrated differential gene expression of PHLDA2 and IGF2 between first and third trimester of placental tissue. Additionally, gene expression in the placenta is also affected by metabolic conditions such as maternal obesity and gestational diabetes mellitus (GDM) by affecting the energy sensing, which modulates the maternal body mass index (BMI) and GDM on birth weight.

Table 1: Gene expression and regulation during placental and fetal development.

Species Name	Placenta and Gestational Age	Methods/Techniques	Results/Findings	References
Human	At the term placentas	RNA sequencing	Amount of genes modulated in amnion (938) chorion (865) and decidua tissues (944) These genes associated with placenta abnormalities such as prolactin receptor, and insulin-like growth factor 2 and genes enriched with interleukin-1 pathway	[7]
Human	1 st trimester	qRT-PCR	Cysteine dioxygenase (CDO) mRNA is up-modulated at term placentas compared to 1st trimester placentas	[8]
Human	1 st and 3 rd trimester	Microarray	7519 genes are expressed differently between 1st and 3rd trimesters Genes up-regulated in the 1st trimester are involved biological process include cell proliferation, differentiation and angiogenesis Genes up-modulated in the 3rd trimester are involved in the following biological process; cell surface receptor-mediated signal transduction, G-protein mediated signaling, ion transport, neuronal activities an chemosensory perception	[9]
Human	2 nd and 3 rd trimesters	Microarray	gene expression are observed slightly during 14 to 24 wks Differential modulated genes of 418 at 3rd trimester as compared to mid gestation functional role of these gene includes differentiation, motility, transcription, extracellular matrix dissolution among others	[10]
Mice	Embryonic days	Microarray	599 genes are Differentially modulated The genes up-regulated are linked with fatty acid metabolism, angiogenesis and transport	[11]
Human	At term preeclampsia/ healthy	Microarray	HLA-DRB1, but not HLA-A RQ and CSTM2 RQ genes, is up-regulated in placenta tissue with preeclampsia HLA-A and HLA-DRB1 expression are associated with reduction in birth weight but not placenta weight	[12]
Human	Placenta with preeclampsia (35 to 39 wks)	Microarray	modulated gene (58 genes) are involved in immune system, oxidative stress, signaling, growth and development pathways Particular genes recognized have been associated with preeclampsia (CYP11A and CDKN1C)	[13]

Human	Placenta with preeclampsia (34 to 37 wks)	Microarray	2019 gene are found to be expressed differently; CD4 are down modulated LEP, FLT1, PAPP2, INHA, SIAE and ENG are up regulated	[14]
Human	Varies	Meta gene analysis	Differential gene expression of autophagy-associated genes	[15]
Human	Term	Meta gene analysis	Genes Identified for specific preeclampsia such as: LEP, HTRA4, SPAG4, LHB, TREM1, FSTL3, CGB, INHA, PROCR and LTF genes The highly affected pathways in preeclampsia placenta include Wnt, ErbB, PPAR, Hedgehog signaling, mRNA surveillance and pathway	[16]

Note: CDO, Cysteine dioxygenase; HLA-DRB1, Human Leucocytes Antigen, DRB1 beta chain; CYP11A, Cytochrome P11A; CDKN1C, Cyclin Dependent Kinase Inhibitor 1C; LEP, Leptin; FLT1, Fms Related Receptor Tyrosine Kinase 1; PAPP2, Pappalysin 2; INHA, Inhibin, alpha; SIAE, Sialic Acid Acetyltransferase; ENG, Endoglin; HTRA4, high-temperature requirement A 4; SPAG4, Sperm Associated Antigen 4; LHB, Luteinizing hormones beta-subunit; TRM1, Triggering Receptor Expressed On Myeloid Cells 1; FSTL3, Follistatin Like 3; CGB, Chorionic gonadotropin beta; PROCR, Protein C Receptor; LTF, Lactotransferrin.

During early human gestation, there is a high expression of ATP Binding Cassette Subfamily B Member 1 (ABCB1) mRNA and P-glycoprotein (P-gp protein), which could remarkably reduce near term [21,22]. However, there are inconsistent findings on the gestational expression of breast cancer resistance protein (ABCG2)/ATP-binding cassette subfamily G member 2 (BCRP) in human placenta [23,24]. While some studies have findings showing no change in expression, others have reported a significant increase or decrease in expression [25-27]. The inconsistent findings are attributed to the limited number of placental tissues used in the studies or even the sample quality. Only a few studies have explored the relative expression of drug transporters in human placental tissue. Some of the studies report a high expression of BCRP compared to that of P-gp in primary term trophoblast cells [28]. There is a remarkable reduction in P-gp levels at term labor but the relative expression of P-gp and BCRP during early stages of pregnancy is yet to be understood. There is also limited understanding on the regulation of placental ABCB1/P-gp and ABCG2/BCRP but a number of regulatory elements and transcription factors of ABCB1 and ABCG2 gene promoters have been reported to be significance in gene activation.

Placental RNA Quality and Quantity

Evaluation of the quality and quantity RNA is essential for analysis of gene expression; this is reflected in degraded samples which might influence the interpretation of RNA expression levels. Study by Monk et al., [19] on imprinted genes specific to human placenta taken from first and third trimester placental tissue along with maternal and third trimester paternal blood samples was largely by biallelic gene expression (cyclooxygenase 2 and 5B (COX2, COX5B) and cytochrome P450 (CYP) 2D1 and -2D7 isoforms (CYP2D1, CYP2D7)) throughout the gestational period. Validation of these genes by PCR reported a specific regulation of COX2 and COX5B in cases with smoking history regardless of gestational age. Studies report that there are epigenetic modifications that may directly influence the size; morphology as well as transport capacity of the placenta [20]. Samples of Placental tissue from preterm and term deliveries alleged to be from preterm labor

presented a significant increase in expression of TNF α and IL6, with decreased expression of IFN γ [29]. The placental epigenetic status can be influenced by environmental factors that may in turn affect the fetal growth and development [21].

Gene Annotations

For gene annotations, Protein Analysis Through Evolutionary Relationships (PANTHER) [30] software system has been used to analyze gene sequence and relate them to their particular biological processes and molecular roles (<http://www.pantherdb.org>). The signaling pathways involved during normal placental development have been identified using Bonferroni correction for multiple testing and expression data analysis tool [9]. Analysis of Pathways of differential gene expression between first and third trimester of the placenta reported angiogenesis to be extremely active in first trimester.

Placental Gene Imprinting

Fetal growth and development of the placenta are regulated by imprinted genes in mammalian species and are thought to have co evolved with placentation (Table 2). In majority of mammals, autosomal genes are expressed co-dominantly from the two parental chromosomes. The process of monoallelic expression is attained through epigenetic asymmetry between parental alleles such as maternal gene expression specific to the placenta and are imprinted regardless of their elevated level of expression in decidua as in the case of Tissue Factor Pathway Inhibitor 2 (Tfpi2) [31]. As a result, false-positive maternal expression due to decidua contamination can be distinguished from actual imprinting by making use of in situ staining or from backcrosses whereby homozygous embryos are formed in a heterozygous mother. In such cases, the allele detected can be absent in the embryo's genome which signify maternal contamination [32]. Placenta contains several specific imprinted transcripts, which are mainly found in the large imprinted domains as shown in Table 2. For instance, two clusters of maternally expressed genes specific to the placenta are located on the distal chromosome seven and proximal chromosome seventeen, both of which are regulated by maternally methylated regions, the KvDMR1 and Airn DMRs, respectively [33,34]. In these

DMRs, there are promoters for long ncRNAs. The Airn non coding RNA (ncRNA) transcript silences two adjacent genes, solute carrier family 22 member 2 (SLC22A2) and SLC22A3 in the Igf2r domain [35] through recruitment of histone methyltransferase enzymes such as G9a to the paternal allele [36], and deposit of repressive histone mark on lysine 9 of histone H3 (H3K9me2) [37]. Additionally, Airn cause direct imprinting of Igf2r gene since transcription via the Igf2r promoter on the paternal allele is adequate for silencing, probably by dislocating transcription factors important for Igf2r expression [9]. The long paternal expression of ncRNA KCNQ10T1 on chromosome seven recruit G9a and together with H3K27me3

histone methyltransferase enhancer of zeste homolog 2 (Ezh2), results to the paternal silencing of eight flanking genes within the placenta [38]. Interestingly, within the KCNQ10T1 loci, imprinting is not conserved in human placenta due to lack of allelic repressive histone modifications. The imprinting of SLC22A2 and Insulin-like growth factor 2 receptor (IGF2R) is polymorphic in humans [39]. The role of these genes in placenta-related complications and intrauterine growth restriction should further be investigated along with aberrant genes as biomarkers in complicated pregnancies, in order to help in the diagnosis of at-risk pregnancies during early gestation [40].

Table 2: List of Gene expression in the mouse.

Gene	Chromosome Region	Regional DMR/ICR	Name
Ascl2/Mash2	Dist7	KvDMR	Achaete-scute complex homolog 2
Cd81	Dist7	KvDMR	CD81 antigen
Dcn	Dist10	-	Decorin
Gatm	Prox2	-	Glycine amidinotransferase
Nap114	Dist7	KvDMR	Nucleosome assembly protein 1-like 4
Osbpl5	Dist7	KvDMR	Oxysterol binding protein-like 5
Pon2	Prox6	Peg10 ICR	Paraoxonase 2
Pon3	Prox6	Peg10 ICR	Paraoxonase 3
Ppp1r9a	Prox6	Peg10 ICR	Protein phosphatase 1, regulatory (inhibitor) subunit 9A
Slc38a4/Ata3	Dist15	Slc38a4	Solute carrier family 38, member 4
Slc22a2	Prox17	Igf2r ICE	Solute carrier family 22 (organic cation transporter), member 2
Slc22a3	Prox17	Igf2r ICE	Solute carrier family 22 (organic cation transporter), member 3
Tfpi2	Prox6	Peg10 ICR	Tissue factor pathway inhibitor 2
Th	Dist7	KvDMR and H19 DMD	Tyrosine hydroxylase
Tssc4	Dist7	KvDMR	Tumor-suppressing subchromosomal transferable fragment 4
Tnfrsf23	Dist7	KvDMR	Tumor necrosis factor receptor superfamily, member 23
Osbpl5	Dist7	KvDMR	Oxysterol binding protein-like 5

Placental Gene Regulation

Certain genes in the placenta are under strict epigenetic regulation and therefore prone to genomic imprinting. The variation in epigenetic profiles and allelic expression of imprinted genes in different species reflects the evolutionary dynamic and adaptive phenomenon under epigenetic control [41]. In fetal growth restriction (FGR) the complications with absent end-diastolic blood flow (AEDF) in umbilical artery, the expression of neuropilin 1 (NRP-1) placental is down regulated. NRP-1 plays an important role in angiogenesis and its down regulation may result into lack of sufficient vascular branching as in the case of FGR placental complications that portray an antiangiogenic state [42]. There is a need for further research in order to elucidate the mechanisms involved or to develop new diagnostic and therapeutic tools. Based on various studies, the computation of standardized mean

difference (μ) of the six genes exhibit a differential expression in the initial meta-signature two of the twelve genes (VIM and HSD17B1) were amongst the 688 genes that were differentially expressed, but they were left out during the leave-one-out-analysis [43]. Four genes (Insulin like growth factor Binding protein 1 [IGFBP1], chromogranin A [CGA], TNFSF10/TRAIL and PGF) had no significant differential expression based on the meta-analysis of the original microarray data [44]. The differential expression of genes included in gene list-driven signature in the current analysis, their profiles were similar except for subtilis phage pavia 1 (SPP1), superoxide dismutase (SOD1), and Verona integron-encoded metallo-lactamase (VIM). Studies indicate up regulation and down regulation of SOD1 and VIM in the pre-eclamptic placenta and in the current analysis, they are down regulated. In the pre-eclamptic placenta, SOD1 is one of significantly down regulated genes [45].

Hypoxia/ischemia compromise pre-eclamptic placentas and hypoxia-inducible factor-1 alpha (HIF-1 α) mainly mediate gene expression. Over 10% of the meta-signature genes that are up regulated are directly targeted by HIF-1 α CREB binding protein (CREBBP)/EP300, which is a key transcriptional co activator of HIF-1 α , therefore, low CREBBP/EP300 level may reduce the placenta's ability to respond to shortage of oxygen, which worsen the pre-eclamptic state [43]. A study from previous work indicated the concentration of tumor necrosis factor (TNF- α), interleukin 1 alpha (IL-1 β) and IL-6 in serum was higher in GDM group compared to the control group. Forkhead box O1 (FoxO1) expression was detected in adipose tissue of both the placenta and fetus. When compared to the control group, the gene and protein expression of FoxO1 & TNF- α was higher in the GDM group in both tissues [46]. Another study also reported a positive co-relation between FoxO1 expression in the placenta with homeostatic model assessment of Insulin Resistance (HOMA-IR) and TNF- α . TNF- α gene stimulation increases FoxO1 expression in trophoblast cell cultures. Deletion of FoxO1 in the cells reduces TNF- α -induced expression of IL-6 and IL-1 β pro-inflammatory cytokines [47]. These findings indicate that FoxO1 plays as a pro-inflammatory factor in GDM as well as in IR by interacting with TNF- α , a pro-inflammatory cytokine that helps to modulate the acute phase reaction and first discovered in placenta and amnion [37]. The insulin-like growth factor-binding protein (IGFBP) also known as pregnancy-associated plasma protein A2 (PAPPA2), protease that is highly expressed in the placenta is up regulated in pre-eclampsia; HELLP (Haemolytic anaemia, Elevated Liver enzymes, and Low Platelet count) syndrome [48].

High expression of PAPPA2 results to abnormal placental development and its up regulation may be meant to compensate for placental pathology. Oxidative stress and hypoxia are among other conditions that affect the expression of PAPPA2 in pre-eclamptic placenta; TNF- α and prostaglandin E2 (PGE2) results to the up regulation of Pappalysin 2 (PAPPA2) [49]. Hypoxia, which is common in pre-eclamptic placenta results to PAPPA2 expression. These findings confirm the hypothesis of up regulation of PAPPA2 as a result of placental pathology as opposed to the assumption that high PAPPA2 levels cause preeclampsia [50]. The aryl hydrocarbon receptor (AhR) and peroxisome proliferators-activated receptor gamma (PPAR γ) are also reported to regulate ABCG2/BCRP and ABCB1/P-gp [51]. However, the role of transcription factors such as p53 and AP-1 on the expression of placental drug transporter genes requires further elucidation.

Placental DNA Methylation

Extensive research has been done on the effect of imprinted methylation on a number of placental abnormalities stated in the DNA methyltransferase 1o (DNMT1o) model, initially, DNA methylation determined on fifteen imprinted gametic differentially methylated domains (gDMDs) is thrice during the last half of gestation period [52]. The mean methylation fraction across twelve

non-redundant gDMD EpiTYPER amplicons for the wild-type as well as mutant specimens at the respective time points, methylation was less in DNMT1o-deficient placental tissues at embryonic 12.5 day (E12.5), E15.5 and E17.5. At E12.5 it showed a significant reduction in the average methylation for all gDMDs (wild-type and mutant placentas) [53]. The average gDMD methylation was 0.283 for a total of 23 E15.5 DNMT1o-deficient placentas, which was significantly lower as compared to the wild-type 0.382 [54,55]. In one study, Meta-analysis was carried out in placenta by RNA microarray in 116 pre-eclamptic and 139 normotensive pregnancies using statistical and standard bioinformatics procedures [43], where pathway analysis of the expression signature in genes interactions were deduced as well as differentially expressed genes resulting to 388-gene meta-signatures of pre-eclamptic placenta. The analysis indicated the role of hypoxia/HIF1A pathway in the expression of pre-eclamptic gene profile which was consistent with previous reports [56]. Analysis of protein interaction networks showed that CREBBP/EP300 is a new element key to pre-eclamptic placental transcriptome and there is a high incidence of preeclampsia in pregnant women carrying fetus with a mutation in CREBBP/EP300 which normally lead to Rubinstein-Taybi Syndrome [57]. From the 388-gene-preeclampsia meta-signature reported, important information can be generated on the role of these genes in the placental tissue such as CREBBP/EP300 and the related pathways, which can be utilized as functional molecules or biomarkers in preeclampsia. Understanding the molecular basis of preeclampsia may help in development of therapeutic measures to alleviate placental pathologies [58].

Placental Gene Deletion

Achaete-Scute Family BHLH Transcription Factor 2 (Ascl2) gene deletion in the mouse Kcnq1 cluster results to fetal lethality because of the limited development of placenta labyrinth and the resulting in build-up of trophoblast giant cells (TGCs) at E10.5 [59]. Deletion of Cdkn1c or Phlda2 genes found within the Kcnq1 cluster, lead to placental overgrowth [60,61] as well as transgenic over-expression of Cdkn1c or Phlda2 that leads to impaired placental growth [62-64]. The growth and development of the placenta also relies on Igf2, which is a significant part of H19 gene imprinting cluster; as a result, deletion of Igf2 leads to growth restriction of both the placenta and the fetus while Igf2 overexpression lead to overgrowth of the placenta as well as the fetus [65]. In addition, when other imprinted genes are deleted that are not located within the Kcnq1 or H19 clusters, there is also abnormalities in placental phenotypes as in the case of deletion of Igf2r, Growth-factor receptor bound protein 10 (Grb10), or Mesoderm-specific transcript (Mest) which may alter placental growth while deletion of Retrotransposon Gag Like 1 (Rtl1) or Paternally expressed 10 (Peg10) impairs labyrinth development [66]. Mitogen-activated protein kinase kinase 1 (Map2k1) also plays an important role in myeloid translocation gene (MTG) formation and syncytiotrophoblast layer II cells (SynT-II) differentiation.

Deletion of the two Map2k1 alleles in SynT-II in Gcm1Cre mouse line implies that they are not relevant for placenta formation since Map2k1^{flox/-} Rosa^{+/lacZ} Tg^{+/Gcm1Cre} mice were found to be viable [67]. Placenta taken from Map2k1^{flox/-} Rosa^{+/lacZ} Tg^{+/Gcm1Cre} mutants resembled the control group. X-Gal staining indicated that the activation of RosalacZ Cre reporter allele in SynT-II. Moreover, absence of Map2k1 functions in SynT-II result to formation of MTG but do not have an impact on the survival of the embryo [68]. Multilayers of trophoblast giant cells (TGCs) are seen at the maternal-fetal interface in Rac1d/d mice as opposed to a single or double layer seen in Rac1f/f mice. Spongiotrophoblast cells which are a subtype of TGCs are spatially distributed are seen from the expression of TPBPA biomarkers [69] is similar to placenta in Rac1d/d and Rac1f/f mice. in Rac1d/d mice progression of the pregnancy to day 12 showed a high disorganization of the placentae with malformed layers and labyrinth [70]. Decidual expression of Rac1 helps to regulate TGCs proliferation and differentiation at the maternal-fetal interface and allows for correct placenta formation and development [71].

Placenta Gene Mutations

Mutations such as E1A binding protein p300 (EP300) and CREBBP have been associated with disorders during placenta and fetal development such as Rubinstein-Taybi syndrome (RSTS, OMIM 180849 and 613684). RSTS is an autosomal dominant congenital disorder that affects one in every 100,000 newborns. The condition is characterized by facial dysmorphism, mental retardation, skeletal disorders and postnatal growth deficiency [72]. Many of these mutations are due de novo and could be as a result of extensive deletions or point mutations. Though there lacks a clear correlation between the genotype and the phenotype, lack of CREBBP/EP300 histone acetyltransferase action may result to RSTS [73]. A number of preeclampsia cases result to a birth of a child with RSTS [74]. As a result, the fetal genotype is implicated with RSTS and affects the placenta function which leads to high incidences of preeclampsia cases [75]. These findings can be incorporated in the meta-analysis data in non-RSTS mothers to indicate that low CREBBP/EP300 levels impair placenta functioning which increases the chances of the mother developing preeclampsia [76].

Conclusion

There are limited longitudinal studies on placental gene expression in human partly because of ethical constraints. However, studies in mice indicate that transition occur during mid-gestation and same cellular subsets may express different genes without necessarily causing changes in the placental morphology in humans, microarray data from basal plate biopsy from the maternal fetal interface indicate remarkable changes from mid-gestation to term. Plethora of studies on differential gene expression profile are available both for healthy and impaired placentas, particularly in preeclampsia. However, there are limited numbers of studies on differential gene expression profile during normal gestational development of placenta in human. Only a single microarray study

has addressed this gap. This review aimed to explore the molecular pathways as well as physiological changes that occur in the course of gestation that may affect the placental structure and function. We therefore hypothesized that the molecular reorganization and phenotypic variations are needed for normal placental development and can be deduced from the level of genes expressed. More studies are therefore needed to ascertain this.

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Conflict of Interest

The authors declare that they have no competing interests.

Author's Contribution

All authors contributed equally to the work.

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