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Gene Determinants and Perinatal Growth Phenotype

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Abstract

Perinatal growth phenotype is largely determined by genes, nutrient supply, placental transport function, environment, and growth hormones. Recently, gene mutation and expression have been reported to play an important role in perinatal growth and development. Perinatal growth epigenetics, a new concept in growth phenotype, has been accepted in fetal programming. This paper outlines the findings of perinatal phenotype in several studies and summarizes fetal growth restriction, birth defects, angiotensinogen gene mutation and pathological phenotypes of placenta, and the occurrence of other pregnancy complications. We review genetic approaches to IUGR, especially those related to growth factor genes, gene mutations and epigenetics with abnormal perinatal characterizations. We also discuss gene study directions, which should be valuable in elucidating mechanisms employed by the fetus and prevent the development of abnormal perinatal outcomes.

Keywords: Gene; Epigenetics; Fetal growth; Birth defect; Placenta

Introduction

Fetal growth is determined by many factors. These include genes, maternal nutrient supply, placental transport function, nutrient concentration gradient between maternal and fetal blood, placental blood flow, etc. Among these factors, gene determinants play an important role. Their mutation and expression are related to the perinatal growth phenotype [1-5]. In this review, perinatal growth phenotype will focus on growth and development from intrauterine pregnancy to the neonatal period after birth.

Regardless of what exactly affects the growth of fetus or infant, one important pathway most likely involved is growth factors and their interaction with their receptors [6-8]. Furthermore, the genes that affect vascular development will affect the vessels in the placenta, a key organ that transports nutrients from mother to fetus, which influences the growth of the fetus [9-11]. In addition, recent studies demonstrated an increasing tendency for neonatal birth defects, which might be considered a result from environmental changes [12]. Scientists believe that gene expression might influence the phenotype, so the term "fetal growth epigenetics", a new conception of fetal programming influenced by the expression of genes has been established [13-16].

The perinatal growth phenotype affected by gene determinants or epigenetics might be presented as abnormal growth, such as intrauterine growth restriction, small or large for gestational age, or birth defects. The information in this paper concludes findings in our previous study on perinatal growth and birth defects, reviews the genetic approaches and epigenetics studies in recent years. It would be valuable to elucidate the mechanisms employed by perinatal growth and help to develop interventional strategies that might make early diagnoses or prevent the development of fetal abnormal growth or birth defects.

Genetics and Perinatal Phenotype

Gene mutations and perinatal growth phenotype

Many publications presented that some certain gene mutations are associated with perinatal growth abnormalities (Table 1). Insufficiency of CDK19 gene caused by pericentric inversion of chromosome 6 results in microcephaly, nystagmus, congentital bilateral falciform, retinal folds, and mental retardation [2]. Insulfficient expression of NFIA gene, caused by a deletion at chromosome 1p32-p31, can cause ventriculomegaly, abnormality of external genitalia, and IUGR [3]. Smigiel [17] reported two neonates who died of restrictive dermopathy. DNA analysis was performed and compound heterozygous frame shifting mutations were identified in exon 1 and exon 5 at the ZMPSTE24 gene. Autosomal recessive inheritance was confirmed. Insufficient function of Ascl2 affects all three layers of placenta and causes Intrauterine Growth Restriction (IUGR) [18]. The c-fos gene expression is critical in the oxidative stress pathway of

Table 1: Gene mutations and perinatal phenotypic characteristics.

Gene	Gene mutation effects	Phenotypic effects and complications
11b-HSD2	Depress glucocorticoid metabolism	IUGR, small placenta [4].
Ascl2	Affect placenta development	Three layers malformation, IUGR [18].
CDK19	Chromosome breakpoints in 6p12.1 and 6q21	Microcephaly, congenital bilateral falciform retinal folds, nystagmus, and mental retardation [2].
GSTP1	Affect glutathione transferase enzymes pathway	Fetal growth and neonatal growth [20].
IGF1R	Novel c.420del mutation in exon 2 of the IGF1R gene	Reduced IGF1R expression and represents haploinsufficiency of the IGF1R gene. IUGR and neonatal growth retardation [8].
NFIA	Chromosome 1p32-p31 deletion syndrome	Ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and intrauterine growth restriction in the third trimester [3].
TFRC	Affect transferrin receptor function	IUGR [13].
ZMPSTE24	Fetal growth	IUGR, dermopathy, neonatal death [17].

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mice with fetal alcohol syndrome. Administration of alcohol during pregnancy results in altered gene expression through the stress signal pathway. C-fos expression in the decidua increases from 6 to 24 hours after alcohol injection, but does not change in the embryo, which may contribute to alcohol-induced damage in fetal alcohol syndrome (Table 1) [19].

Epigenetics and perinatal growth phenotype

Scientists have been considering the evidence from studies in the field of obesity and other areas that elucidate mechanisms by which the environment can modify gene expression which results in an individual's phenotype. Maternal dietary and behavioral factors determine epigenetic changes in fetus, neonates, and even adults [21]. DNA methylation and histone modifications are used to determine how the same DNA sequence generates different cells, lineages and organs, i.e., the phenotype. Environmental disturbing factors during pregnancy, such as nutrition, metabolism and behavior, affect epigenetic processes and potentially influence offspring with a predisposition to obesity during adulthood. The mechanisms causing birth weight changes and adverse pregnancy outcomes are complex. In addition to the focus on genetic mutations, epigenetics are associated with perinatal growth phenotype [22] (Table 2).

Many studies have reported that imprinted genes play a central role in placental development and function, and they are related to a variety of perinatal growth disorders [14-16,23,34]. Gene inactivation studies in mice and chromosomal rearrangements in humans have demonstrated that many of these imprinted genes play key roles in placental development and function as well as in fetal growth. Those studies have also demonstrated that imprinted genes act in a complex manner at many levels between the mother and fetus. Animal models support that imprinted genes play a significant role in perinatal growth.

Table 2: Epigenetics and perinatal phenotypic characteristics.

Gene	Gene expression	Phenotypic effects and complications.
c-fos	Decreased expression	Fetal alcohol syndrome [19].
DIO3	Type 3 deiodinase, highly expressed in placenta and fetus.	IUGR and hypothyroidism [23].
DLK1	Growth promoter, expressed in placental villi.	Methylation defects associated with IUGR [16].
HBII-85/PWScr	C/D Box small RNA	Implicated in Prader Willi, Postnatal growth retardation [24].
HYMAI	Non-coding RNA, expressed in fetus.	Transient neonatal diabetes and IUGR [25].
IGF2	Growth Factor, decreased expression in placenta	Placental and fetal growth restriction [26].
KCNQ1OT1	Non-coding RNA, Control placental Kcnq1 domain	Involved in Beckwith-Wiedemann syndrome [27].
MAGEL2/NDNL1	Similarity to NDN	Neonatal growth retardation, alter metabolism [28].
MEST	Neuronal differentiation	Fetal growth restriction, smaller placentas [29].
PEG3	Inhibits WNT-signaling	Placental and fetal growth restriction and abnormal maternal behavior [30].
PEG10	Retrotransposon-derived gene	Severe growth retardation, absence of spongiotrophoblast layer, embryonic lethality [31].
PLAGL1 Zac1	Tumor suppressor	Skeletal defects, neonatal lethality, IUGR, and disrupted transactivation of Igf2 [32].
SFRP2	WNT signaling	Reduction in vitro of extra villous trophoblast invasion [33].

Cell proliferation is very active during the early embryo phase. The proliferation depends on cell division. The quicker division, the shorter phase of G0 and G1 phase. In another words, less proliferation will have more cells in G0 or G1 phases, active proliferation will have more S+G2+M phases. Using flow cytometry to analyze the cell cycle, we found that the ratio of the cells in G0+G1 phases to the total cells was increased and the ratio of the cells in S+G2+M phases to the total cells was decreased in fetal brain, liver and placenta in rabbits exposed to passive smoking. In brain, this change was more prominent. It means that the proliferations of the fetal cells and placenta were inhibited significantly, and the growth retardation of the fetus was the result. It is demonstrated that the cell transformation from G1 to S phase was restricted by smoking [35,36].

During early embryo development, the first embryo differentiation establishes two cell lineages. They are the inner cell mass that forms all the tissues of the adult, and the trophectoderm that eventually produces placental structures. In general, the inner cells become gene hypermethylated while the trophectoderm is hypomethylated and these patterns are preserved throughout the whole period of gestation [37,38].

In order to gain insights of the importance of epigenetic regulation in fetal growth, Lambertini [34] investigated methylation status of imprinted genes by comparing IUGR with normal placentas. They found that the gene length is highly correlated with methylations. Growth restricted placentas have encompassing genes that are actively expressed. Kumar et al. [39] confirmed that the growth promoting imprinted gene expression increased and the growth suppression imprinted gene expression decreased with the advancing of gestational age. He found that the ZNF127 gene expression was up regulated and the PHLDA2 gene expression was down regulated [39]. Another excellent example of imprinted genes can be found in McMinn's study [40]. He showed that a small group of imprinted genes (PHLDA2, MEST, MEG3, GATM, GNAS, and PLAGL1) and additional genes acting in endocrine signaling (LEP, CRH, HPGD, INHBA), tissue growth (IGF1), immune modulation (INDO, PSG-family genes), oxidative metabolism (GLRX), vascular function (AGTR1, DSCR1) and metabolite transport (SLC-family solute carriers) were affected in IUGR placentas.

Multiple imprinted loci have been reported to have abnormal methylation in association with IUGR, for example, at the IGF2/H19 locus, methylation decreased in IUGR placentas [16,41,42] (Table 2). Besides the imprinted gene expression changes in IUGR, a growing number of animal studies show that specific environment exposure can influence fetal DNA methylation/demethylation [43]. These effects can permanently affect health outcomes later in life and are heritable across generations [44].

Methylation alteration to the environment can occur even before conception [45]. Environment can also influence the remethylation time and pattern after conception [46]. This methylation pattern change can be seen in Wu et al. [47] study that the methyltransferase activity was increased in the mouse embryos exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), leading an up-regulation of methylation of H19/igf2 imprinted gene. During the development of the embryo, the embryo demethylates most of its genes between fertilization and implantation but the maintenance of imprinted genes through the preimplantatin period is essential for normal embryonic development. These effects are important for

the development of the embryo [48,49]. Additionally, demethylation in the embryo might remove epigenetic modification effects from parental gametogenesis. At different times in the uterus, fetal DNA undergoes methylation/demethylation depending on the cell, tissue, or organ based on developmental and environmental factors. Furthermore, some genes predisposing obesity might be affected by maternal diet habits. This effect could be seen in the study to expose mice to a genistein diet leading to an increased methylation of the retrotransposon located in the Agouti gene [43]. Even after birth, the methylation patterns continue to adjust in the somatic cells [50].

Gene expression and large for gestational age birth

Placental studies on the expression of human placental Growth Hormone (GH) and chorionic somatomammotropin (CSH) locus, which is situated on chromosome 17q22-24, demonstrated interesting results [51]. Placental GH2, CSH1, and CSH2 genes expression was reduced significantly in preeclampsia cases. However, in pregnancy with large for gestational age newborns or maternal gestational diabetes, a different expression of GH2 was detected. In conclusion, the results demonstrated a consistent relationship of fetal growth regulation, maternal metabolism and the expression of hGH/CSH genes.

IGF-II and relaxin both cause proliferation of human amniotic epithelial cells. Studies showed a relationship of relaxin gene and IGF-II gene expression levels to neonatal birth weight and amniotic membrane surface area. It suggests that relaxin increases the development of fetal membranes. Its expression level was significantly greater in the membranes from macrosomic infants compared to normal infants [52].

Gene mutation, gene expression and birth defects

Birth defects are a major cause of perinatal death and disability. Most birth defects are related to gene abnormalities or result from reasons which can cause gene abnormal expression. There are many reports about gene mutations and birth defects. Gripp et al. [53] identified that FOXC1 mutation caused cardiac anomalies in Axenfeld-Rieger syndrome. Until now, only about 20% of congenital cardiac abnormalities can be attributed to chromosomal anomalies, single gene disorders, or teratogens. There were only about 30 genes to have been reported linked to non-syndromal forms of congenital heart disease [1]. Misceo et al. [54] reported on a congenital heart disease with atypical deletion of 1.5 Mb from chromosome 4p16.3. He reviewed seven previously published patients and found them carrying a similar deletion. They consistently presented post-natal growth delay. By investigating and analyzing the birth defects in 13 medical centers in Changsha, China, we found 1050 birth defects among 64101 infants with a birth defect incidence of 16.38‰ (Table 3). The first five birth defects were dysmelia, cheilognathoschisis, auricle malformation, congenital heart disease, and gastrointestinal tract anomalies (Table 4) [12]. There are two significant changes we were concerned with: the increasing rate of birth defects from year to year and the increasing occurrence of congenital heart disease. The reason for these changes is not clear but may result from epigenetics induced by environmental changes.

Yang et al. [55] have similar findings in birth defect investigations of Shanxi Province in West China and concluded that health care service utilization, unhealthy lifestyle factors, and environment risk factors all seem to be associated with birth defects. The environmental risk factors related to birth defects may include unhealthy lifestyles (such as alcohol, smoking), heavy pollution, drug use, chemical

Table 3: Birth defects incidence (Changsha, China).

Year	Birth (n)	Birth Defect (n)	Incidence (‰)
2000	13268	175	13.19
2001	12445	150	12.05
2002	12598	208	16.51*#
2003	11795	193	16.36*#
2004	13995	324	23.15*#
Total	64101	1050	16.36

*Compared to 2000, p<0.05; # Compared to 2001, p<0.05

Table 4: Birth defects constituent (Changsha, China).

Defects	Occurrence (n)	Constituent Rate (%)	Incidence Rate (‰)
Dysmelia	215	18.28	3.35
Cheilognathoschisis	148	12.59	2.3
Auricle malformation	125	10.63	1.95
Congenital heart disease	112	9.52	1.75
Gastrointestinal tract anomalies	76	6.46	1.18
Hydrocephalus	62	5.27	0.97
Neural tube defect	51	4.34	0.80
Urinary malformation	34	2.89	0.53
Down's syndrome	17	1.45	0.27
Others	336	28.57	5.24
Total	1176	100.00	18.34

pesticide exposure, etc [55]. According to the National Birth Defects Prevention Study, maternal occupational exposure to organic solvents during early pregnancy may be associated with neural tube defects [56]. Furthermore, different occupations might have significant differences in smoking, drinking, folic acid use, and access to prenatal care. All these could affect the intrauterine fetal growth and neonatal development [57]. Many studies demonstrated a relationship between the specific material exposure, which is associated with birth defects, and the gene expression changes [58-60].

Gene Approaches and Perinatal Growth

In an individual embryo, all cells have the same basic set of genetic information stored in DNA, but in different organs the cell proliferation and differentiation depends on the expression of different genes. This small subset of genes allows the cells to produce proteins unique to their functions. Although gene expression is controlled by epigenetic modifications, the gene sequence obviously plays the most important role in the cells proliferation and differentiation.

Growth factor gene and perinatal growth

Many studies have demonstrated a relationship of the level of human placental growth hormones (hPGH), IGF-I, and IGF banding proteins in maternal blood and IUGR [61-63]. Koutsaki et al. [7] aimed to evaluate the expression status of hPGH, (IGF-I), IGFBP-1 and IGFBP-3 genes in placentas from human IUGR pregnancies of no apparent etiology and found that hPGH, IGF1, IGFBP-1, and IGFBP-3 expression is significantly lower than that in the placentas with normal fetal growth, though the causative factors are not known in the alterations of IUGR or that they accompany other pathogenetic mechanisms.

The IGF-I receptor (IGF-IR) is widely expressed in fetal and

postnatal cells. The activation of this receptor after the binding of secreted IGF-I and IGF-II promotes cell proliferation and differentiation. Observations found the IGF-IR gene mutation is associated with low birth weight [64]. Low birth weight and height are found to be related to heterozygous IGH-IR mutations or insufficiency [8,65]. This phenotype presents with family history of low birth weight and a normal increased IGF-I level and/or a normal or increased GH response to GH stimulation test [66,67]. However, it has less response to GH treatment than common small for gestational age short-stature patients [68].

Choi et al. [69] reported a family both with a novel heterozygous mutation of the IGF1R and a segmental deletion encompassing the entire IGF1R result in IGF-I resistance, leading to IUGR and postnatal growth failure. During *in vitro* studies, fibroblasts carrying the IGF-IR gene mutation clearly demonstrated reduced the expression of this gene and subsequently resist IGF-I. It is considered that IGF-IR gene mutations should be used in the diagnosis of familial IUGR with persistent short status [69]. Umbers reported that inflammation of the placenta can cause the disturbance of IGF expression, which leads to IUGR [70].

Experiments in mice clearly demonstrated that IGF-I is a major regulator of both prenatal and postnatal growth. Baker et al. [71] reported that isolated invalidation of IGF1 resulted in restrictions of fetal development (40% delay comparing with wild type mice) and Liu et al. [72] found that postnatal growth was further impaired to reach only 30% of normal mice. Double knockout the IGF gene resulted in more severe growth retardation (Figure 1) [73]. These experiments clearly demonstrated that IGF-I is a major regulator of both pre- and postnatal growth. Several authors have reported on the IGF-IR gene mutations with the observation of birth weight, height, serum IGF-I and complications (Table 5).

Glucocorticoid gene and perinatal growth phenotype

Prenatal stress or exposure to excess of glucocorticoids might have a link between fetal development maturation and adult pathophysiology [74]. In a variety of animal models (Table 6), prenatal stress, glucocorticoid exposure and inhibition 11β hydroxysteroid dehydrogenase (11β-HSD1) reduced birth weight and caused increases in adult blood pressure, glucose levels, hypothalamic-pituitary-adrenal (HPA) axis activity and anxiety-related behaviors. In humans, mutations in the gene that encodes 11β-HSD2 are associated with low birth weight. Low birth weight is associated with higher cortisol levels throughout life. In addition, over exposure to glucocorticoids induced an increase expression of p73, which is associated with fetal brain growth restriction [75]. Caffeine overconsumption increases maternal glucocorticoids level. It induces the histone methylation of IGF-1 and decrease the IGF-1 signaling pathway activity, which resulted in skeletal growth retardation [76]. Guo et al. [77] uses maternal baboon nutrient reduction to induce specific increases of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). It demonstrated that this overexpression of 11β-HSD1 may contribute to sexual dimorphism in the programming of exaggerated cortisol regeneration in liver and adipose tissues and offsprings' susceptibility to metabolic syndrome. A transgenic mouse study on Stat5 trascription factor found that it is dependent for the normal function of glucocorticoid receptor, which plays an essential role in the stimulation of growth hormone. Stat5 deficiency shows a dramatic reduction in body size [78]. An interesting study on glucocorticoids regulation study on transgenic mice with inducible β-cell glucocorticoid coregulator over expression demonstrate that glucocorticoids receptor and its coregulator-peroxisome proliferator coactivator (PGC-1α) over expression exhibited impaired glucose tolerance at adult age associated with reduced insulin secretion, decreased β-cell mass, and β-cell hypotrophy whereas β-cell PGC-1α overexpression from adult age had no consequence on β-cell function [79].

Obviously, the epigenetic effects on perinatal growth phenotype exist. Intriguingly, some of these effects seem to be inherited by subsequent generations that are unexposed to exogenous glucocorticoids at any point in their lifespan from fertilization. Adverse prenatal environmental factors can permanently influence the physiological metabolism of the embryo, which demonstrated

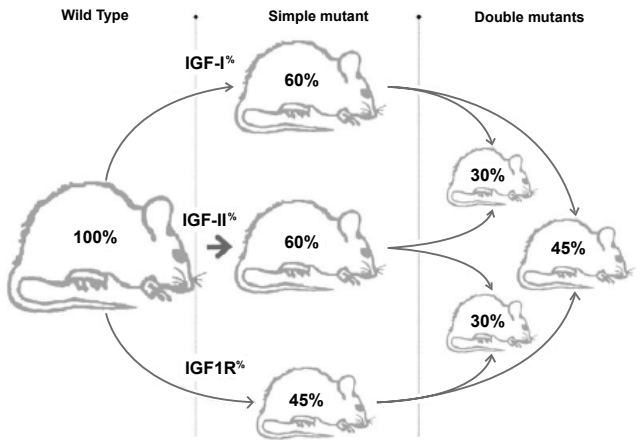

Figure 1: Effects of disruption insulin growth factor (IGF) system on fetal growth in mice. Defect of IGF-I or IGF-II resulted in 60% body weight of the normal mice, Defect of IGF-I receptor resulted in 45% body weight of the normal ones. Breeding between IGF-I and IGF-II defects or between IGF-II and IGF-I receptor defects both resulted in 30% body weight of normal mice. Breeding IGF-1 and IGF-1 receptor defects resulted in 45% body weight of the normal mice [71-73].

Table 5: IGF-I receptor mutations and perinatal phenotype.

Gene Mutation	Birth Weight (SD)	Birth Height (SD)	Other Characteristics
Arg108Gln/Lys115Asn	-3.5	-4.8	Microcephaly, abnormal speech [64].
Arg59Ter	-3.5	-3.0	Microcephaly, Delay in speech [64].
Arg709Gln	-1.5	-2.6	Mental retardation [64].
Arg281Gln	-3.1	-5.0	Decreased cell proliferation [66].
Gly1050Lys	-2.1	-4.0	Insulin resistance [67].
Gly1125Ala	-1.8	-3.6	Microcephaly, clinodactyly, delayed menarche, diabetes mellitus [65].
Val599Glu	-2.3	-2.1	Developmental delay [68].

Table 6: Glucocorticoids metabolism related gene and perinatal growth phenotype.

Gene	Gene mutation effects	Phenotypic effects and complications
Stat5	Affects the glucocorticoids receptor function	Dramatic reduction in body size [78].
AKT1/2	I increased corticosterone and decreased IGF-1mRNA expression	Skeletal growth retardation [76].
p73	Enhanced corticosterone levels	Fetal brain growth restriction [75].
11β-HSD1	Exaggerated cortisol regeneration	Offspring metabolic syndrome [77].
PGC-1α	Influence glucocorticoid receptor function	Reduced insulin secretion, decreased β-cell mass, and β-cell hypotrophy [79].

as an increase of cardiovascular, metabolic, neuroendocrine, and psychiatric disorders in adulthood.

Angiotensinogen gene and placental vascular development

Small for gestational age has been reported to be associated with insufficient placental circulation, which may be the result from failed maternal physiological changes such as abnormal spiral artery remodeling and reduced maternal blood volume. Morgan reported that spiral artery remodeling might be related to the AGT gene [9]. We examined maternal blood DNA in 174 patients with intrauterine growth restriction, 62 patients with placental abruption, and 60 patients with both preeclampsia compared with the control group comprised 400 consecutive cases of women with term pregnancies and infants with birth weight between the fifth and 95th percentiles. DNA analysis on fetal blood demonstrated high frequencies of Thr235 alleles in IUGR (59.1%) compared with the normal control fetus (37.9%) (IUGR vs control: p<0.01) (Table 7).

DNA analysis demonstrated that maternal and fetal AGT Thr235 allele frequencies are significantly related to IUGR, preeclampsia, and placental abruption [10]. The AGT Thr235 allele may predispose women to deliver growth-restricted fetuses and has a higher frequency of pregnancy complications such as preeclampsia or placental abruption [11] (Table 7). In addition, quantitative pathological studies on placenta found that placental capillary area decreased significantly in homozygous Thr235 placentas compared to the homozygous Met234 placentas. IUGR placentas had similar capillary area changes as in TT placentas. The placentas of pregnant rabbits exposed to tobacco smoke showed reduced microvilli accompanied by fatty degeneration and mitochondrial swelling [56] (Figure 2 and Table 8).

Table 7: Maternal AGT Thr235 genotypes and pregnancy complications.

Groups	No.	Genotype			*p value*
		MM (%)	MT (%)	TT (%)	
Control	400	170 (42.5)	158 (39.5)	72 (18.0)	
IUGR	174	33 (19.0)	66 (37.9)	75 (43.1)	<0.001
Preeclampsia+IUGR	60	11 (18.3)	24 (40.0)	25 (41.7)	<0.001
Placental Abruption	62	9 (14.5)	27 (43.5)	26 (41.9)	<0.001

MM: homozygous for AGT Met235 allele; MT: heterozygous
TT: homozygous for AGT Thr 235 allele; IUGR: intrauterine growth restriction

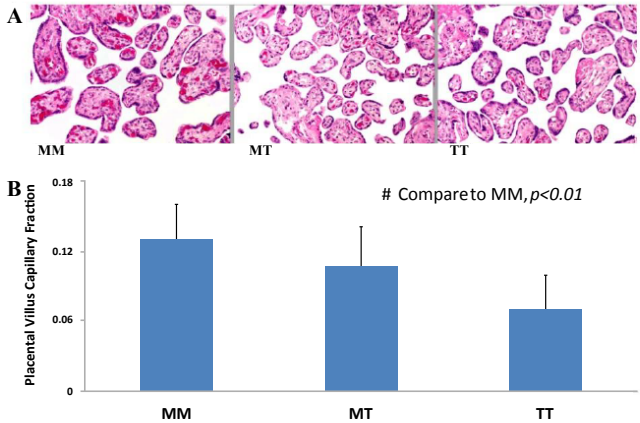

Figure 2: Placental villus capillary development. **(A)** Placental cross section demonstrated less capillary area (red) in placentas of AGT TT homozygous genotype than that of AGT MM genotype placentas (capillary area, TT vs MM p<0.05). (HE staining). **(B)** Statistics of placental villus capillary volume fraction. MM: AGT Met235 homozygous, MT: AGT Met235Thr heterozygous, TT: AGT Thr235 homozygous.

Table 8: AGT genotype and placental pathological phenotype.

AGT genotype	MM	MT	TT
No. of placentas	8	13	14
Clinical findings:			
Maternal age (yrs)	26.0 ± 4.7	26.6 ± 6.6	29.8 ± 6.5
Gestational age (wks)	36.2 ± 4.5	36.6 ± 1.9	36.7 ± 3.1
Fetal birth wt. (g)	2730 ± 967	2642 ± 541	2620 ± 535
Placental quantitative findings:			
Villous volume/1cm^3 placenta (cm^3)	0.668 ± 0.034	0.626 ± 0.022**	0.587 ± 0.059**#
Capillary volume/1cm^3 placenta (cm^3)	0.131 ± 0.029	0.107 ± 0.034	0.070 ± 0.030**
Intervillous volume/1cm^3 placenta (cm^3)	0.332 ± 0.034	0.374 ± 0.022**	0.413 ± 0.059**#
Volume of trimmed Placenta (cm^3)	324.8 ± 128.0	355.2 ± 80.3	374.1 ± 70.2
Villous total volume per placenta (cm^3)	215.8 ± 81.8	222.1 ± 50.7	219.9 ± 52.6
Intervillous space per placenta (cm^3)	108.9 ± 47.8	133.1 ± 31.1	154.2 ± 38.6*
Villous capillary volume per placenta (cm^3)	45.1 ± 27.4	41.4 ± 23.2	26.6 ± 14.4*
Percentage of villous capillary volume (%)	19.81 ± 5.12	17.41 ± 7.3	12.06 ± 5.45*
Villous surface area per placenta (m^2)	9.029 ± 3.285	9.560 ± 2.031	10.370 ± 2.725

Data are demonstrated as mean ± SE; *Compare to MM, p<0.05; **compare to MM, p<0.01; # compare to MT, p<0.05.

Genetics and Perinatal Growth-Problems and Future Directions

Most birth defects and perinatal growth anomalies are multifactorial and arise through various combinations of genetic and environmental contributors. Only a small part of birth defects and growth anomalies can be attributed to chromosomal abnormalities or single gene disorders. For gene studies, there were only limited numbers of genes studied among the thousands of genes that are expressed. In fact, a lot of genes are associated with the perinatal growth phenotype. To evaluate their roles in affecting perinatal growth we still need the accumulation of multiple collections of the mutation, phenotype, epigenetics, metabolotics of the perinatal growth characteristics. Furthermore, most of the pathways in altering gene expression altering are undiscovered. Basic study on the pathways involved in the genes may help us to understand why and how the phenomenon occurred at the molecular level.

Although the definition and diagnosis of perinatal growth abnormal can be simply defined with the normal growth chart, perinatal growth is still an extremely complex phenotype to dissect because of many factors, such as maternal, fetal, placental, and environmental factors. Almost all gene expression studies were based on small numbers of samples. Though studies on gene expression found gene dysregulated in abnormal perinatal growth, most of these genes, such as IGF-1, IGFBP1, corticotropin-releasing hormone, etc. are supported by reports identifying genes related to regulating cell division and proliferation. We still are unable to know if it is a compensated response to the fetal restricted growth or a reason induced by fetal growth restriction. Using the transgenic engineering technique in animals to study some specific gene may provide an ideal model to study the phenotype related to these genes found in clinical human beings.

Some specific imprinted genes are related to abnormal perinatal growth. Their function could be classified in two categories. The first

decreases fetal growth as a disturbing factor and the second increases fetal growth as a compensatory response when sensing the fetus is at risk. We expect to reduce negative gene expression effects and increase the expression of positive genes to improve perinatal outcomes. It will be a long distance from the basic animal model studies to clinical applications to reach this point using gene-regulating techniques.

References

1. Blue GM, Kirk EP, Sholler GF, Harvey RP, Winlaw DS (2012) Congenital heart disease: current knowledge about causes and inheritance. Med J Aust 197: 155-159.
2. Mukhopadhyay A, Kramer JM, Merkx G, Lugtenberg D, Smeets DF, et al. (2010) CDK19 is disrupted in a female patient with bilateral congenital retinal folds, microcephaly and mild mental retardation. Hum Genet 128: 281-291.
3. Chen CP, Su YN, Chen YY, Chern SR, Liu YP, et al. (2011) Chromosome 1p32-p31 deletion syndrome: Prenatal diagnosis by array comparative genomic hybridization using uncultured amniocytes and association with NFIA haploinsufficiency, ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and intrauterine growth restriction. Taiwan J Obstet Gynecol 50: 345-352.
4. Börzsönyi B, Demendi C, Pajor A, Rigó J Jr, Marosi K, et al. (2012) Gene expression patterns of the 11ß-hydroxysteroid dehydrogenase 2 enzyme in human placenta from intrauterine growth restriction: the role of impaired feto-maternal glucocorticoid metabolism. Eur J Obstet Gynecol Reprod Biol 161: 12-17.
5. Mandò C, Tabano S, Colapietro P, Pileri P, Colleoni F, et al. (2011) Transferrin receptor gene and protein expression and localization in human IUGR and normal term placentas. Placenta 32: 44-50.
6. Randhawa R, Cohen P (2005) The role of the insulin-like growth factor system in prenatal growth. Mol Genet Metab 86: 84-90.
7. Koutsaki M, Sifakis S, Zaravinos A, Koutroulakis D, Koukoura O, et al. (2011) Decreased placental expression of hPGH, IGF-I and IGFBP-1 in pregnancies complicated by fetal growth restriction. Growth Horm IGF Res 21: 31-36.
8. Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, et al. (2003) IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. N Engl J Med 349: 2211-2222.
9. Morgan T, Craven C, Lalouel JM, Ward K (1999) Angiotensinogen Thr235 variant is associated with abnormal physiologic change of the uterine spiral arteries in first-trimester decidua. Am J Obstet Gynecol 180: 95-102.
10. Zhang XQ, Varner M, Dizon-Townson D, Song F, Ward K (2003) A molecular variant of angiotensinogen is associated with idiopathic intrauterine growth restriction. Obstet Gynecol 101: 237-242.
11. Zhang XQ, Craven C, Nelson L, Varner MW, Ward KJ (2007) Placental abruption is more frequent in women with the angiotensinogen Thr235 mutation. Placenta 28: 616-619.
12. Chen PY, Xie ZD, Wu Y, Ji MJ, Zhao SQ (2007) Perinatal birth defects in 5 years in Changsha. Zhong Nan Da Xue Xue Bao Yi Xue Ban 32: 520-523.
13. Jones JE, Jurgens JA, Evans SA, Ennis RC, Villar VA, et al. (2012) Mechanisms of fetal programming in hypertension. Int J Pediatr 2012: 584831.
14. He H, Liyanarachchi S, Akagi K, Nagy R, Li J, et al. (2011) Mutations in U4atac snRNA, a component of the minor spliceosome, in the developmental disorder MOPD I. Science 332: 238-240.
15. Edery P, Marcaillou C, Sahbatou M, Labalme A, Chastang J, et al. (2011) Association of TALS developmental disorder with defect in minor splicing component U4atac snRNA. Science 332: 240-243.
16. Turner CL, Mackay DM, Callaway JL, Docherty LE, Poole RL, et al. (2010) Methylation analysis of 79 patients with growth restriction reveals novel patterns of methylation change at imprinted loci. Eur J Hum Genet 18: 648-655.
17. Smigiel R, Jakubiak A, Esteves-Vieira V, Szela K, Halon A, et al. (2010) Novel frameshifting mutations of the ZMPSTE24 gene in two siblings affected with restrictive dermopathy and review of the mutations described in the literature. Am J Med Genet A 152A: 447-452.
18. Oh-McGinnis R, Bogutz AB, Lefebvre L (2011) Partial loss of Ascl2 function affects all three layers of the mature placenta and causes intrauterine growth restriction. Dev Biol 351: 277-286.
19. Poggi SH, Goodwin KM, Hill JM, Brenneman DE, Tendi E, et al. (2003) Differential expression of c-fos in a mouse model of fetal alcohol syndrome. Am J Obstet Gynecol 189: 786-789.
20. Slama R, Gräbsch C, Lepeule J, Siroux V, Cyrys J, et al. (2010) Maternal fine particulate matter exposure, polymorphism in xenobiotic-metabolizing genes and offspring birth weight. Reprod Toxicol 30: 600-612.
21. Junien C, Nathanielsz P (2007) Report on the IASO Stock Conference 2006: early and lifelong environmental epigenomic programming of metabolic syndrome, obesity and type II diabetes. Obes Rev 8: 487-502.
22. Suter M, Abramovici A, Aagaard-Tillery K (2010) Genetic and epigenetic influences associated with intrauterine growth restriction due to in utero tobacco exposure. Pediatr Endocrinol Rev 8: 94-102.
23. Hernandez A, Martinez ME, Fiering S, Galton VA, St Germain D (2006) Type 3 deiodinase is critical for the maturation and function of the thyroid axis. J Clin Invest 116: 476-484.
24. Skryabin BV, Gubar LV, Seeger B, Pfeiffer J, Handel S, et al. (2007) Deletion of the MBII-85 snoRNA gene cluster in mice results in postnatal growth retardation. PLoS Genet 3: e235.
25. Ma D, Shield JP, Dean W, Leclerc I, Knauf C, et al. (2004) Impaired glucose homeostasis in transgenic mice expressing the human transient neonatal diabetes mellitus locus, TNDM. J Clin Invest 114: 339-348.
26. Dilworth MR, Kusinski LC, Cowley E, Ward BS, Husain SM, et al. (2010) Placental-specific Igf2 knockout mice exhibit hypocalcemia and adaptive changes in placental calcium transport. Proc Natl Acad Sci U S A 107: 3894-3899.
27. Mohammad F, Mondal T, Guseva N, Pandey GK, Kanduri C (2010) Kcnq1ot1 noncoding RNA mediates transcriptional gene silencing by interacting with Dnmt1. Development 137: 2493-2499.
28. Bischof JM, Stewart CL, Wevrick R (2007) Inactivation of the mouse Magel2 gene results in growth abnormalities similar to Prader-Willi syndrome. Hum Mol Genet 16: 2713-2719.
29. McMinn J, Wei M, Sadovsky Y, Thaker HM, Tycko B (2006) Imprinting of PEG1/MEST isoform 2 in human placenta. Placenta 27: 119-126.
30. Murphy SK, Wylie AA, Jirtle RL (2001) Imprinting of PEG3, the human homologue of a mouse gene involved in nurturing behavior. Genomics 71: 110-117.
31. Ono R, Nakamura K, Inoue K, Naruse M, Usami T, et al. (2006) Deletion of Peg10, an imprinted gene acquired from a retrotransposon, causes early embryonic lethality. Nat Genet 38: 101-106.
32. Varrault A, Gueydan C, Delalbre A, Bellmann A, Houssami S, et al. (2006) Zac1 regulates an imprinted gene network critically involved in the control of embryonic growth. Dev Cell 11: 711-722.
33. Guilleret I, Osterheld MC, Braunschweig R, Gastineau V, Taillens S, et al. (2009) Imprinting of tumor-suppressor genes in human placenta. Epigenetics 4: 62-68.
34. Lambertini L, Lee TL, Chan WY, Lee MJ, Diplas A, et al. (2011) Differential methylation of imprinted genes in growth-restricted placentas. Reprod Sci 18: 1111-1117.
35. Zhang XQ (1993) The change in dynamics of cell proliferation cycle by passive smoking in fetal rabbit]. Zhonghua Fu Chan Ke Za Zhi 28: 720-722, 759.
36. Greenwood PL, Slepetis RM, Hermanson JW, Bell AW (1999) Intrauterine growth retardation is associated with reduced cell cycle activity, but not myofibre number, in ovine fetal muscle. Reprod Fertil Dev 11: 281-291.
37. Santos F, Hendrich B, Reik W, Dean W (2002) Dynamic reprogramming of DNA methylation in the early mouse embryo. Dev Biol 241: 172-182.
38. Dean W, Ferguson-Smith A (2001) Genomic imprinting: mother maintains methylation marks. Curr Biol 11: R527-530.
39. Kumar N, Leverence J, Bick D, Sampath V (2012) Ontogeny of growth-regulating genes in the placenta. Placenta 33: 94-99.
40. McMinn J, Wei M, Schupf N, Cusmai J, Johnson EB, et al. (2006) Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. Placenta 27: 540-549.

41. Tabano S, Colapietro P, Cetin I, Grati FR, Zanutto S, et al. (2010) Epigenetic modulation of the IGF2/H19 imprinted domain in human embryonic and extra-embryonic compartments and its possible role in fetal growth restriction. Epigenetics 5: 313-324.

42. Diplas AI, Lambertini L, Lee MJ, Sperling R, Lee YL, et al. (2009) Differential expression of imprinted genes in normal and IUGR human placentas. Epigenetics 4: 235-240.

43. Dolinoy DC, Weidman JR, Waterland RA, Jirtle RL (2006) Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environ Health Perspect 114: 567-572.

44. Anway MD, Cupp AS, Uzumcu M, Skinner MK (2005) Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308: 1466-1469.

45. Reik W, Dean W, Walter J (2001) Epigenetic reprogramming in mammalian development. Science 293: 1089-1093.

46. Surani MA (2001) Reprogramming of genome function through epigenetic inheritance. Nature 414: 122-128.

47. Wu Q, Ohsako S, Ishimura R, Suzuki JS, Tohyama C (2004) Exposure of mouse preimplantation embryos to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters the methylation status of imprinted genes H19 and Igf2. Biol Reprod 70: 1790-1797.

48. Shiao YH, Crawford EB, Anderson LM, Patel P, Ko K (2005) Allele-specific germ cell epimutation in the spacer promoter of the 45S ribosomal RNA gene after Cr(III) exposure. Toxicol Appl Pharmacol 205: 290-296.

49. Smith FM, Garfield AS, Ward A (2006) Regulation of growth and metabolism by imprinted genes. Cytogenet Genome Res 113: 279-291.

50. Weaver IC, Champagne FA, Brown SE, Dymov S, Sharma S, et al. (2005) Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. J Neurosci 25: 11045-11054.

51. Männik J, Vaas P, Rull K, Teesalu P, Laan M (2012) Differential placental expression profile of human Growth Hormone/Chorionic Somatomammotropin genes in pregnancies with pre-eclampsia and gestational diabetes mellitus. Mol Cell Endocrinol 355: 180-187.

52. Millar LK, Reiny R, Yamamoto SY, Okazaki K, Webster L, et al. (2003) Relaxin causes proliferation of human amniotic epithelium by stimulation of insulin-like growth factor-II. Am J Obstet Gynecol 188: 234-241.

53. Gripp KW, Hopkins E, Jenny K, Thacker D, Salvin J (2013) Cardiac anomalies in Axenfeld-Rieger syndrome due to a novel FOXC1 mutation. Am J Med Genet A 161A: 114-119.

54. Misceo D, Barøy T, Helle JR, Braaten O, Fannemel M, et al. (2012) 1.5Mb deletion of chromosome 4p16.3 associated with postnatal growth delay, psychomotor impairment, epilepsy, impulsive behavior and asynchronous skeletal development. Gene 507: 85-91.

55. Yang W, Zeng L, Cheng Y, Chen Z, Wang X, et al. (2012) The effects of periconceptional risk factor exposure and micronutrient supplementation on birth defects in Shaanxi Province in Western China. PLoS One 7: e53429.

56. Desrosiers TA, Lawson CC, Meyer RE, Richardson DB, Daniels JL, et al. (2012) Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts. Occup Environ Med 69: 493-499.

57. Agopian AJ, Lupo PJ, Herdt-Losavio ML, Langlois PH, Rocheleau CM, et al. (2012) Differences in folic acid use, prenatal care, smoking, and drinking in early pregnancy by occupation. Prev Med 55: 341-345.

58. Li L, Zhu GQ, Meng T, Shi JY, Wu J, et al. (2011) Biological and epidemiological evidence of interaction of infant genotypes at Rs7205289 and maternal passive smoking in cleft palate. Am J Med Genet A 155A: 2940-2948.

59. Sartiani L, Stillitano F, Luceri C, Suffredini S, Toti S, et al. (2010) Prenatal exposure to carbon monoxide delays postnatal cardiac maturation. Lab Invest 90: 1582-1593.

60. Bruchova H, Vasikova A, Merkerova M, Milcova A, Topinka J, et al. (2010) Effect of maternal tobacco smoke exposure on the placental transcriptome. Placenta 31: 186-191.

61. Sifakis S, Akolekar R, Syngelaki A, De Cruz J, Nicolaides KH (2010) Maternal serum human placental growth hormone at 11 to 13 weeks in trisomy 21 and trisomy 18 pregnancies. Prenat Diagn 30: 212-215.

62. Street ME, Seghini P, Fieni S, Ziveri MA, Volta C, et al. (2006) Changes in interleukin-6 and IGF system and their relationships in placenta and cord blood in newborns with fetal growth restriction compared with controls. Eur J Endocrinol 155: 567-574.

63. Verkauskiene R, Beltrand J, Claris O, Chevenne D, Deghmoun S, et al. (2007) Impact of fetal growth restriction on body composition and hormonal status at birth in infants of small and appropriate weight for gestational age. Eur J Endocrinol 157: 605-612.

64. Kawashima Y, Takahashi S, Kanzaki S (2012) Familial short stature with IGF-I receptor gene anomaly. Endocr J 59: 179-185.

65. Kruis T, Klammt J, Galli-Tsinopoulou A, Wallborn T, Schlicke M, et al. (2010) Heterozygous mutation within a kinase-conserved motif of the insulin-like growth factor I receptor causes intrauterine and postnatal growth retardation. J Clin endocrinol Metab 95: 1137-1142.

66. Inagaki K, Tiulpakov A, Rubtsov P, Sverdlova P, Peterkova V, et al. (2007) A familial insulin-like growth factor-I receptor mutant leads to short stature: clinical and biochemical characterization. J Clin Endocrinol Metab 92: 1542-1548.

67. Walenkamp MJ, van der Kamp HJ, Pereira AM, Kant SG, van Duyvenvoorde HA, et al. (2006) A variable degree of intrauterine and postnatal growth retardation in a family with a missense mutation in the insulin-like growth factor I receptor. J Clin Endocrinol Metab 91: 3062-3070.

68. Wallborn T, Wüller S, Klammt J, Kruis T, Kratzsch J, et al. (2010) A heterozygous mutation of the insulin-like growth factor-I receptor causes retention of the nascent protein in the endoplasmic reticulum and results in intrauterine and postnatal growth retardation. J Clin Endocrinol Metab 95: 2316-2324.

69. Choi JH, Kang M, Kim GH, Hong M, Jin HY, et al. (2011) Clinical and functional characteristics of a novel heterozygous mutation of the IGF1R gene and IGF1R haploinsufficiency due to terminal 15q26.2->qter deletion in patients with intrauterine growth retardation and postnatal catch-up growth failure. J Clin Endocrinol Metab 96: E130-134.

70. Umbers AJ, Boeuf P, Clapham C, Stanisic DI, Baiwog F, et al. (2011) Placental malaria-associated inflammation disturbs the insulin-like growth factor axis of fetal growth regulation. J Infect Dis 203: 561-569.

71. Baker J, Liu JP, Robertson EJ, Efstratiadis A (1993) Role of insulin-like growth factors in embryonic and postnatal growth. Cell 75: 73-82.

72. Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A (1993) Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). Cell 75: 59-72.

73. Netchine I, Azzi S, Le Bouc Y, Savage MO (2011) IGF1 molecular anomalies demonstrate its critical role in fetal, postnatal growth and brain development. Best Pract Res Clin Endocrinol Metab 25: 181-190.

74. Seckl JR, Holmes MC (2007) Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. Nat Clin Pract Endocrinol Metab 3: 479-488.

75. Mouihate A, Al-Bader MD (2013) Glucocorticoid-induced fetal brain growth restriction is associated with p73 gene activation. J Neurosci Res 91: 95-104.

76. Tan Y, Liu J, Deng Y, Cao H, Xu D, et al. (2012) Caffeine-induced fetal rat over-exposure to maternal glucocorticoid and histone methylation of liver IGF-1 might cause skeletal growth retardation. Toxicol Lett 214: 279-287.

77. Guo C, Li C, Myatt L, Nathanielsz PW, Sun K (2012) Sexually Dimorphic Effects of Maternal Nutrient Reduction on Expression of Genes Regulating Cortisol Metabolism in Fetal Baboon Adipose and Liver Tissues. Diabetes.

78. Lin WY, Hu YJ, Lee YH (2008) Hepatocyte nuclear factor-1alpha regulates glucocorticoid receptor expression to control postnatal body growth. Am J Physiol Gastrointest Liver Physiol 295: G542-551.

79. Tronche F, Opherk C, Moriggl R, Kellendonk C, Reimann A, et al. (2004) Glucocorticoid receptor function in hepatocytes is essential to promote postnatal body growth. Genes Dev 18: 492-497.