Genetic Syndromes Determined by Alterations in Genomic Imprinting Pathways
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Objectives  After completing this article, readers should be able to:

1. Explain the concept of imprinting and differential expression of parental genes.
2. Discuss the concept of epigenetic genome modification.
3. Delineate the pathogenesis of imprinting disorders, especially the effect on prenatal and postnatal growth and metabolism.
4. Recognize the infantile presentation of six imprinting–related disorders.

Abstract
Genomic imprinting appears to be a mammal-specific phenomenon whereby differential gene expression according to parent of origin has evolved as a means to regulate many complex pathways related to growth, metabolism, and neurologic development. Imprinting is accomplished by an epigenetic mechanism involving, for example, methylation of specific sequences, without changing the underlying genetic code. This process occurs with very specific timing in relation to development of an embryo and is reset in the sex-specific gametes of each individual. Epigenetic deregulation of the imprinting process is the cause of specific genetic syndromes, many of which show alterations in growth, metabolism, and neurologic development. In fact, it has been demonstrated that alterations of a single imprinting control region (IGF2/H19) can lead to opposite disorders of congenital growth (Beckwith-Wiedemann syndrome and Silver-Russell syndrome). Recently, it has been suggested that the use of assisted reproductive techniques such as in vitro fertilization may heighten the susceptibility of embryos to epigenetic deregulation, leading to increased risk for certain imprinting disorders. Also, the knowledge that imprinted genes are involved in pathways of fetal and placental growth has prompted researchers to look into the role of imprinting in intrauterine growth restriction. This may have consequences well beyond the newborn period because epidemiologic studies have shown a strong link between poor fetal growth and the susceptibility to glucose intolerance and insulin resistance syndrome in adults.

Introduction
Humans inherit one complete copy of the genome from each parent, and until recently, autosomal genes were assumed to be expressed equally from each parental allele. In the 1980s, however, the phenomenon of genomic imprinting was described, whereby a small subset of mammalian genes is expressed only from the maternal allele, while other genes are expressed only from the paternal allele. It is currently believed that at least 100 human genes are subjected to imprinting, showing differential expression, depending on the parent of origin. Many imprinted genes are clustered in chromosomal domains of up to several megabases (Mb) of DNA. Regulation of the parental-specific expression of imprinted genes is accomplished without changing the underlying DNA sequence of the genes and, therefore, is consid-
tered an “epigenetic” phenomenon. This is made possible by the presence of specialized sequence elements called imprinted control regions (ICRs) that are “marked” by parental-specific epigenetic modifications. This can result in differential DNA methylation patterns for the maternal versus paternal allele. The allele-specific methylation, or “mark,” is maintained throughout development and adult life and, in many cases, is associated with lack of expression of one or more genes. The mark is erased in the primordial germ cells and reset during gametogenesis (for males) or near the time of fertilization or early embryonic development (for females) for the new parent-of-origin. Many genes are imprinted identically in every cell of the body, although some imprinting of genes is tissue-specific.

Genomic imprinting may have developed for pathways that require very specialized control of gene expression. For example, many imprinted genes are regulators of growth and metabolism. The Haig parent-offspring conflict hypothesis, which often has been quoted to explain the evolution of genomic imprinting, recognizes the different interests of the mother and father in providing maternal resources via the placenta to a developing offspring. The hypothesis is that the paternal genome has adopted an opportunistic approach to maximize acquisition of maternal resources for his offspring, despite the long-term cost to the mother and her future offspring. This assumes that for most mammals, the mother’s future offspring will not share the same father. The mother, on the other hand, is equally related to all of her offspring and, therefore, is invested in preserving resources for future pregnancies. The result is that the paternal genome is biased in favor of expressing genes that maximize fetal growth, while the maternal genome expression is vested in controlling the growth of the fetus. Therefore, it is not surprising that many imprinted genes are involved in pathways regulating growth and metabolism in both the placenta and the fetus.

Various mechanisms have been described that alter gene expression of imprinted alleles and lead to recognizable human disorders. In most of these conditions, the presence of phenotypic findings depends on whether the altered gene or chromosome was inherited from the mother or the father. Some of the mechanisms leading to imprinting disorders include chromosomal anomalies such as uniparental disomy (UPD), which results when both members of a chromosome pair are inherited from the same parent; translocations; or large deletions removing one or more genes from the imprinted cluster. Less commonly, ICRs can be altered by microdeletions and point mutations. In some patients, there is no discernable alteration in DNA sequence, which suggests that an epigenetic phenomenon affecting the function of the imprint may have occurred during early development.

Imprinting-related disorders can be categorized generally into those affecting growth, hormones and metabolism, or neurologic development, but many syndromes manifest symptoms in multiple organs and pathways simultaneously. In this article, we describe six imprinting disorders (Table), including clinical manifestations in the newborn period and beyond, and briefly discuss the various mechanisms of altered imprinting-related gene expression for each.

**Beckwith–Wiedemann Syndrome (BWS)**

Although there is significant phenotypic variability in infants who have BWS, the hallmark features at birth include macrosomia, large placenta, polyhydramnios, and abdominal wall defect. Almost 90% of affected infants have birthweights/lengths at greater than the 97th percentile for gestational age, and 9% to 35% have cardiac anomalies, many of which involve cardiomegaly. The intellectual development of affected individuals usually is normal.

Approximately 25% of affected individuals have hemihypertrophy at birth or during the first few postnatal years. Some 30% to 50% of babies who have BWS have hypoglycemia, and this should be screened for in the first few days after birth. Hypothyroidism, polycythemia, hypocalcemia, and hyperlipidemia are also common.

Characteristic facial features of BWS include anterior ear lobe creases and posterior auricular pits, facial nevus flammeus, prominent eyes, infraorbital creases, hemihyperplasia of the face, and macroGLOSSIA (Fig. 1). The syndromic facial appearance is much more obvious in the first few postnatal years, becoming less pronounced with time. Abdominal wall defects are common and include (but are not limited to) umbilical hernia, omphalocele, and diastasis recti. Infants who have BWS often have renal anomalies, and the liver, spleen, pancreas, kidneys, and adrenals also may be enlarged. Wilms tumor and hepatoblastoma are rapidly growing tumors of early childhood that have been well-described in BWS. Because the overall risk for abdominal tumor development in affected individuals is approximately 7.5%, it is recommended that children in whom BWS is suspected or diagnosed be followed every 3 months with abdominal ultrasonography until the age of 6 to 8 years.

BWS results from either genetic or epigenetic changes in chromosome 11p15.5. This imprinted domain spans 1 Mb and includes two separately regulated regions, each...
controlled by its own ICR. The KIP2/LIT1 domain contains a maternally methylated ICR, which regulates multiple genes bidirectionally over long distances. The other domain, IGF2/H19, contains a paternally methylated ICR that achieves short-range interactions between the two genes, IGF2 and H19, and their regulatory regions.

Almost 50% of patients who have BWS have an imprinting defect of KIP2/LIT1, resulting in loss of maternal methylation of the ICR. This is believed to reduce maternal expression of CDKN1C, a maternal negative regulator of cell proliferation and fetal growth. Interestingly, these patients are at low risk for Wilms tumor, but remain at increased risk for other intra-abdominal tumors. Approximately 10% to 20% of those who have BWS have paternal UPD of chromosome 11p15.5, often exhibiting somatic mosaicism for the defect. This results in two copies of the paternally imprinted domain and no copies of the maternal region. The somatic mosaicism is believed to be responsible for the asymmetry often seen in BWS. A gain of methylation on the maternal IGF2/H19 region results in biallelic IGF2 expression and is responsible for 2% to 7% of BWS cases. Another 5% to 10% of patients have mutations in the maternal CDKN1C gene, which often are transmitted as

Table. Common Features of Imprinting Syndromes Before and After Birth

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features Often Seen Prenatally</th>
<th>Features Often Seen in Infancy</th>
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<tbody>
<tr>
<td>Beckwith-Weidemann syndrome</td>
<td>● Large placenta</td>
<td>● Large birthweight</td>
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<tr>
<td></td>
<td>● Long umbilical cord</td>
<td>● Long birthlength</td>
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<tr>
<td></td>
<td>● Polyhydramnios</td>
<td>● Macroglossia</td>
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<tr>
<td></td>
<td>● Prematurity</td>
<td>● Abdominal wall defects</td>
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<tr>
<td>Silver-Russell syndrome</td>
<td>● Intrauterine growth restriction</td>
<td>● Low birthweight</td>
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<tr>
<td></td>
<td></td>
<td>● Arm/leg length asymmetry</td>
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<td></td>
<td></td>
<td>● Hypotonia</td>
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<td></td>
<td></td>
<td>● Triangular face</td>
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<tr>
<td></td>
<td></td>
<td>● Decreased subcutaneous fat</td>
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<tr>
<td></td>
<td></td>
<td>● Hypotonia with poor suck</td>
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<td></td>
<td></td>
<td>● Failure to thrive</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>● Decreased fetal movement</td>
<td>● Decreased cooing, babbling, and crying</td>
</tr>
<tr>
<td></td>
<td>● Polyhydramnios</td>
<td>● Frequent smiling and grimacing</td>
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<td></td>
<td></td>
<td>● Increased hand/foot sucking</td>
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<td></td>
<td></td>
<td>● Decreased sleep</td>
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<tr>
<td>Angelman syndrome</td>
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<tr>
<td>Albright Hereditary Osteodystrophy</td>
<td>● Round face</td>
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<td></td>
<td></td>
<td>● Short neck</td>
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<tr>
<td></td>
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<td>● Widening of long bones in hands and feet</td>
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<tr>
<td></td>
<td></td>
<td>● +/− Hypocalcemia</td>
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<tr>
<td></td>
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<td>● Failure to thrive</td>
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<td>● Hyperglycemia</td>
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<td></td>
<td></td>
<td>● Dehydration</td>
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<td></td>
<td></td>
<td>● Macroglossia</td>
</tr>
<tr>
<td>Transient Neonatal Diabetes Mellitus</td>
<td>● Intrauterine growth restriction</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. A 3-month-old male who has BWS (left). Note the macroglossia, nevus flammeus, prominent eyes, and infraorbital creases. The features of BWS are no longer evident in the same individual approximately 18 years later (right).
maternal autosomal dominant. Paternal duplications of chromosome 11p15.5 are seen in about 1% of patients. Chromosomal translocations or inversions in this region are found in fewer than 1% of patients. Approximately 13% to 15% of patients have unknown defects.

**Silver–Russell Syndrome (SRS)**

Diagnostic criteria of SRS include intrauterine growth restriction (IUGR) (often not manifesting until the third trimester), with a birthweight less than 3 SD below the mean, fifth-finger clinodactyly, a triangular-appearing face with a pointed chin and broad forehead due to a normal head circumference but small face, and postnatal growth retardation. Other characteristics of SRS include leg or arm length asymmetry (60%), arm span less than height, postnatal growth delay, hypoglycemia sometimes is displayed in infancy and early childhood by increased sweating. Although most affected babies are born at term, the diagnosis is more evident by 6 to 12 months of age, and symptoms are apparent by 1 and 6 years of age. In 2001, criteria to prompt diagnostic genetic testing for PWS were revised to include testing any infant younger than 2 years of age who had hypotonia and a poor suck in the neonatal period. Central obesity is the major cause of morbidity and mortality in PWS, and measures to avoid it must be enforced strictly. A hypothalamic defect is believed to cause individuals who have PWS to lack satiety, causing them to seek constantly edible food as well as frozen or rotting food.

Musculoskeletal problems found in SRS include gait abnormalities and scoliosis caused by leg-length discrepancies. Infrequently, individuals have renal anomalies, including renal tubular acidosis, hydronephrosis, posterior urethral valves, and horseshoe kidney, and renal function studies that include screening renal ultrasonography should be performed. Among the common gastrointestinal problems are esophagitis, gastroesophageal reflux disease, food aversion, and failure to thrive. Many infants who have SRS have less subcutaneous fat, and hypoglycemia sometimes is displayed in infancy and early childhood by increased sweating. Although most affected babies are born at term, the diagnosis is more difficult to make if they are preterm because many of the features are more subtle during early infancy.

Although the molecular etiology of most patients who have SRS remains unknown, about 10% have been shown to have maternal UPD for chromosome 7. This implies an imprinting-related pathogenesis, although the disease-related gene (or genes) has(ve) yet to be identified. Recently, it has been shown that imprinting abnormalities of the IGF2/H19 domain on the Beckwith-Wiedemann region of chromosome 11p15.5 can result in SRS. **Hypermethylation** of the IGF2/H19 ICR is seen in BWS, and **hypomethylation** of the same region is seen in SRS. It is interesting that both disorders have abnormalities of growth and asymmetry as common features. Fortunately, patients who have SRS do not appear to be at increased risk for tumor development. More work is required to discern what percent of patients who have SRS actually have the IGF2/H19 imprinting mutation. Of further interest, five patients who had growth failure/SRS also were reported to carry maternal duplications of chromosome 11p15, which is the opposite finding of patients who have BWS and are known to carry paternal duplications of the same region.

**Prader-Willi and Angelman Syndromes**

*Prader-Willi Syndrome (PWS)*

The most prominent features of PWS are infantile central hypotonia that causes great difficulty with sucking and failure to thrive, followed by rapid weight gain between 1 and 6 years of age. In 2001, criteria to prompt diagnostic genetic testing for PWS were revised to include testing any infant younger than 2 years of age who had hypotonia and a poor suck in the neonatal period. Central obesity is the major cause of morbidity and mortality in PWS, and measures to avoid it must be enforced strictly. A hypothalamic defect is believed to cause individuals who have PWS to lack satiety, causing them to seek constantly edible food as well as frozen or rotting food.

Other cardinal features of PWS include developmental delay; cognitive impairment (mean intelligence quotient ranges from the 60s to low 70s); a characteristic facial appearance (Fig. 2); and congenital hypogonadism in the form of cryptorchidism (almost 100%), scrotal hypoplasia (~75%), small penis (~35%), or hypoplasia of the labia minora and clitoris (~75%). Approximately 90% of affected individuals untreated with growth hormone have short stature relative to family members. Variable features of PWS include sleep disturbance/sleep apnea, hypopigmentation, small hands and feet for height age, narrow hands with a straight ulnar border, esotropia, myopia, thick saliva, speech articulation defects, skin picking, and a high pain threshold. Unusual skill with jigsaw and word-finding puzzles has been reported.

*Angelman Syndrome (AS)*

Unlike PWS, AS is difficult to diagnose at birth or during infancy because the developmental delay only becomes evident by 6 to 12 months of age, and symptoms are nonspecific at this time. In retrospect, infants who have AS often have decreased cooing, babbling, and crying. The first sign of AS may be early or frequent smiling, and there often is increased hand and foot sucking during infancy. Affected infants and toddlers frequently have hyperactivity, manifested by putting objects in their mouths and moving from object to object. Infants usually display happy grimacing (Fig. 3) and have a cheerful
disposition, although there have been cases where irritability, hyperactivity, crying, and shrieking are the prevailing behaviors. Other symptoms during infancy include abnormal sleep patterns and an overall decreased need for sleep, seizures before 12 months of age (25%), and strabismus (30% to 60%).

The diagnosis usually is made between the ages of 3 and 7 years, when the hallmark features of AS become evident. Children who have AS consistently have severe developmental delay, ataxic gait or tremors of the hands and limbs, absence of speech, seizures, and any combination of increased paroxysmal laughing, smiling, characteristic hand-flapping movements, and hyperactive behavior. Affected individuals usually have a structurally normal brain, although magnetic resonance imaging or computed tomography scan may reveal mild cortical atrophy or dysmyelination. More than 80% of affected children have absolute or relative microcephaly by age 2 years. Also common is an abnormal electroencephalographic tracing characterized by a large amplitude and slow spike wave pattern. Some 20% to 80% of individuals have hypopigmented skin and eyes, tongue thrusting and tongue swallowing disorders, prominent mandibles, widely spaced teeth, wide mouths, brachycephaly, and increased sensitivity to heat. Most affected individuals are nonverbal.

Both PWS and AS most commonly are caused by deletions spanning a 4-Mb region of chromosome 15q11-q13, but the resulting syndrome is determined by the parent of origin of the deleted chromosome. Approximately 70% of patients who have PWS have paternal chromosome 15 deletions, and 68% of AS is caused by maternal deletions of the same chromosomal region. Likewise, maternal UPD for chromosome 15 results in 25% of PWS cases, and paternal UPD for the same region is responsible for 7% of AS cases. The PWS/AS region consists of five or more imprinted genes, four of which (SNRPN, NDN, MAGEL2, and MKRN3) are exclusively paternally expressed; the UBE3A gene has been shown to demonstrate tissue-limited maternal ex-
pression. Absence of a functional maternal UBE3A allele is believed to be the cause of AS. Both PWS and AS can result from alterations to the ICR. Most commonly these are changes that have occurred sporadically, but DNA mutations of the ICR also can occur and may carry up to a 50% recurrence risk in future siblings.

**Albright Hereditary Osteodystrophy (AHO)**

AHO, also known as pseudohypoparathyroidism or pseudopseudohypoparathyroidism, has a wide range of symptoms, including short stature, obesity, rounded face, low nasal bridge, short neck, dental defects, osteoporosis, cataracts, subcutaneous ossifications and characteristic shortening and widening of long bones in the hands and feet, as well as syndactyly between the second and third toes. Mental retardation is present in some, but not all, patients.

AHO is caused by heterozygous inactivating mutations of the G protein alpha-subunit (Gs alpha) of the GNAS gene. Gs alpha is imprinted in a tissue-specific manner; in renal proximal tubules, thyroid, pituitary, and ovaries, it is expressed only from the maternal allele. Therefore, patients who have Gs alpha mutations that are maternally inherited likely show resistance to parathyroid hormone, thyroid-stimulating hormone, and gonadotropins, in addition to the clinical findings of AHO. When this occurs, the resulting syndrome also is known as pseudohypoparathyroidism. Paternally inherited mutations of the same gene result only in AHO, also known as pseudopseudohypoparathyroidism.

One phenotype of pseudohypoparathyroidism type 1B patients have parathyroid hormone resistance but no AHO because they do not carry a mutation of the Gs alpha subunit. Rather, they have an imprinting defect that leads to a paternal-specific methylation pattern on both alleles. When familial, this can be caused by deletion of a nearby gene believed to be responsible for establishing the maternal imprint, thus leading to autosomal dominant maternal inheritance of pseudohypoparathyroidism type 1B.

**Transient Neonatal Diabetes Mellitus (TNDM)**

TNDM occurs in approximately 1 in 200,000 neonates within the first postnatal month and resolves, on average, at 3 to 6 months of age. The classic presentation is IUGR, failure to thrive, hyperglycemia, and dehydration by 4 to 6 weeks of age. This is associated with a failure of insulin production in response to glucose feeding. Macroglossia also may be seen in TNDM. Many affected patients present with type II diabetes mellitus later in life.

Many patients who have TNDM have a defect related to an imprinted region on chromosome 6q24. Patients who have UPD for 6q24 have been described, as have patients who have 6q24 duplications. Two imprinted genes, ZAC and HYMAI, are located in this region, along with a putative ICR that is believed to regulate the unmethylated paternal expression of these genes. Over-expression can result from imprinting defects that lead to loss of methylation of the maternal allele. Because the phenotype of TNDM also includes growth retardation, the question was raised whether there was a link to the BWS/SRS region on 11p15. In vitro, ZAC drove the expression of the noncoding RNA transcribed from the KIP2/LIT1 domain of the BWS region. More work is required in this area to see if ZAC and KIP2/LIT1-controlled genes function in a common pathway involved in fetal growth.

**Suggested Reading**


Goldstone AP. Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. Trend Endocrinol Metab. 2004;15:12–20


5. Beckwith–Wiedemann syndrome is a genetic syndrome determined by alterations in genomic imprinting pathways involving chromosome 11p15.5. Of the following, the most frequent mechanism of altered imprinting in Beckwith–Wiedemann syndrome is:

A. Chromosomal microdeletion.
B. Hypermethylation of the maternal IGF2/H19 imprinting control region.
C. Loss of maternal methylation at the KIP2/LIT1 domain.
D. Paternal duplication of chromosome 11p5.5.
E. Paternal uniparental disomy of chromosome 11p5.5.

6. A term male newborn has severe intrauterine growth restriction, triangular face with broad forehead and pointed chin, leg length asymmetry, fifth finger clinodactyly, and cryptorchidism. Of the following, the most likely genomic imprinting disorder in this infant is:

A. Albright hereditary osteodystrophy.
B. Angelman syndrome.
C. Beckwith–Wiedemann syndrome.
D. Prader–Willi syndrome.
E. Silver–Russell syndrome.

7. Although most genomic imprinting disorders can manifest in the newborn period, the diagnosis may be delayed until after infancy in some cases. A 3-year-old girl is being seen in the follow-up clinic for severe developmental delay. Her history during infancy is notable for frequent hand- and foot-sucking, a cheerful disposition, and decreased sleep. Of the following, the most likely genomic imprinting disorder in this infant is:

A. Albright hereditary osteodystrophy.
B. Angelman syndrome.
C. Beckwith–Wiedemann syndrome.
D. Prader–Willi syndrome.
E. Silver–Russell syndrome.

8. Transient neonatal diabetes mellitus is a rare disorder of genomic imprinting. Its clinical presentation includes intrauterine growth restriction, failure to thrive, hyperglycemia, and dehydration. Of the following, the imprinting defect in transient neonatal diabetes mellitus is most likely to involve:

A. Chromosome 6.
B. Chromosome 7.
C. Chromosome 11.
D. Chromosome 15.
E. Chromosome 21.
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