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Review and Hypothesis: Syndromes With Severe Intrauterine Growth Restriction and Very Short Stature—Are They Related to the Epigenetic Mechanism(s) of Fetal Survival Involved in the Developmental Origins of Adult Health and Disease?

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Diagnosing the specific type of severe intrauterine growth restriction (IUGR) that also has post-birth growth restriction is often difficult. Eight relatively common syndromes are discussed identifying their unique distinguishing features, overlapping features, and those features common to all eight syndromes. Many of these signs take a few years to develop and the lifetime natural history of the disorders has not yet been completely clarified. The theory behind developmental origins of adult health and disease suggests that there are mammalian epigenetic fetal survival mechanisms that downregulate fetal growth, both in order for the fetus to survive until birth and to prepare it for a restricted extra-uterine environment, and that these mechanisms have long lasting effects on the adult health of the individual. Silver–Russell syndrome phenotype has recently been recognized to be related to imprinting/methylation defects. Perhaps all eight syndromes, including those with single gene mutation origin, involve the mammalian mechanism(s) of fetal survival downsizing. Insights into those mechanisms should provide avenues to understanding the natural history, the heterogeneity and possible therapy not only for these eight syndromes, but for the common adult diseases with which IUGR is associated. © 2010 Wiley-Liss, Inc.

Key words: IUGR; syndromes; imprinting; epigenetic; Bloom syndrome; Dubowitz syndrome; Floating–Harbor syndrome; MOPD II; Mulibrey-Nanism; SHORT syndrome; 3-M syndrome; Silver–Russell syndrome phenotype; fetal survival mechanism; developmental origins of adult health and disease

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INTRODUCTION

The theory behind developmental origins of adult health and disease (DOHaD) suggests that there are mammalian fetal survival mechanisms which can program fetal restricted growth, both in order for the fetus to survive to birth and to prepare that individual for a restricted extra-uterine environment [Gluckman and Hanson, 2005; Gluckman et al., 2008]. Such mechanisms would have to do with both survival of the individual and of the species. In numerous populations around the world it has been established that children who were small for gestational age (SGA) at birth will be prone later in life to developing diabetes, hypertension, heart disease, hypercoagulability, hypercholesterolemia, and osteoporosis [Forrester et al., 1996; Moore et al., 1996, 1999; Stein et al., 1996; Nilsson et al., 1997; Stanner et al., 1997; Barker, 1998; Pettitt and Knowler, 1998; Sorensen et al., 2000; Law et al., 2001; Yajnik et al., 2003]. This suggests that being SGA in utero, for whatever reason, programs or reprograms the human fetus to a set of metabolic pathways that enhance intrauterine survival and the chances for survival in infancy.

How small is small? There appears to be a direct relationship between any weight below the normal 25th centile and increasing the risk for these adult sequelae, no matter what the reason for the

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low birth weight (e.g., prematurity, IUGR syndromes, infection, etc.). Thus, it seemed worthwhile to review some of the known common syndromes of intrauterine growth restriction (IUGR) and look for features suggesting that the same or similar mechanisms are utilized in the development of fetal and childhood restricted growth in those syndromes [Hochberg and Albertsson-Wikland, 2008]. This article will review eight syndromes of severe IUGR which also have postnatal short stature and look for the common and overlapping features. The article is aimed at helping clinicians to make specific diagnoses and at developing a better understanding of the fetal mechanisms of in utero survival.

The causes of pre and postnatal growth restriction are numerous. The diagnostician approaching a child with short stature must consider bone disorders, nutritional disorders, congenital anomalies, metabolic diseases, emotional factors, infection, endocrine disorders, normal variation, and numerous syndromes which involve chromosomal abnormalities, teratogens, and genetic etiologies [Gorlin et al., 2001; Jones, 2006; Winter-Baraitser Dysmorphology Database, 2007; Genetest/GeneClinics, 2009: http://www.genetests.org; OMIM, 2009]. The assumption has always been that diseases, or any disease process in children, can limit normal childhood growth—the body seems to focus on dealing with the disease at the expense of energy that would be used for growth [Hochberg and Albertsson-Wikland, 2008].

The first distinguishing feature in the differential diagnosis of short stature in children is whether there was IUGR (e.g., whether the affected child was small for its gestational age at the time of birth). In general, this is considered to be below the third centile at whatever gestational age. This first diagnostic step also identifies those infants who might have "needed" to adjust their intrauterine growth pattern and intrauterine metabolic pathways. The children who were small for dates (e.g., SGA) at birth used to be called "primordial dwarfism," then intrauterine growth retardation, and now IUGR—implying some force led to a decreased growth rate in utero. Obviously premature infants are small compared to full term infants, but the issue is whether an infant is small for their gestational age. Normal growth curves for various gestational stages are well established [Hall et al., 2007]. A concern that in utero growth restriction has occurred is usually based on weight; however, there are good standards for length and occipital frontal circumference for each stage of in utero development. In developed countries, all three of these are usually recorded on the birth record, as well as placental weight.

A recent WHO study in seven countries involved mothers who had good nutrition prior to pregnancy and their term infants were breastfed for at least 6 months, establishing what are probably optimum healthy birth weights and infant growth patterns. Interestingly, they are almost identical in all ethnic and geographic areas [SACN/RCPCH Expert Group on Growth Standards, 2007].

As a rule of thumb, any weight below the third centile for gestational age is considered IUGR. Thus, anything below 2.8 kg/6.4 pounds or 19 in./48 cm in length at term calls for evaluation. In general, in a situation of intrauterine growth compromise, the fetus seems to preserve brain growth. Thus weight will be the first thing that is lost in situations of fetal nutritional restriction, then length and then OFC [Gluckman and Hanson, 2005; Gluckman et al., 2005; Hochberg and Albertsson-Wikland, 2008]. Thus, the clinician needs to make comparison between the centiles of these three measurements to establish their relationships [Hall et al., 2007]. Part of this evaluation is to determine whether there is proportionate IUGR or disproportionate IUGR (the second step in differential diagnosis). Most disproportionate intrauterine growth restriction is related to some type of osteochondrodysplasia. About one-third of intrauterine growth restrictioned infants catch up in their growth centiles over the first 6 months of extra-uterine life [Jones, 2006]; however, they may still be at risk for the above-mentioned adult disease processes. This review relates to infants with proportionate IUGR who maintain relatively proportionate growth restriction and short stature postnatally.

In some ways, centiles lose their meaning when the affected infant is way, way below the third centile. The eight syndromes to be discussed in this review fall into that category. In such a situation, it is often appropriate to compare the measurements to the 50th centile for a specific age or gestational age (e.g., is the child proportional for a normal 32 week gestation, or for a normal 2 year old, etc.). The differential diagnosis of very short stature which is proportional and began in utero is very broad, including such syndromes as Cornelia de Lange, Rubenstein–Taybi, Johansson–Blizzard, and Hallerman–Strieff, but most of those syndromes are easily recognizable by their strikingly abnormal phenotype. In addition, of course, there are many chromosomal syndromes, products of confined placental chromosomal mosaicism and teratogens which may give a similar picture, and are part of the differential diagnosis of proportionate IUGR. The eight syndromes to be discussed are more severely growth restricted in utero and after birth, and have less unique or striking other features. Each of the eight conditions differs from the others by specific craniofacial features and natural history, but they are similar enough that over the first few years it is often difficult to make a specific diagnosis without gene mutation testing. They also seem to relate to fetal rather than embryonic mechanisms of "downsizing," since malformations secondary to organ formation or structural abnormalities (e.g., primarily embryonic processes) are relatively rare in these syndromes.

METHODS AND RESULTS

The conditions to be discussed in this review will be Bloom syndrome, Dubowitz syndrome, Floating–Harbor syndrome, MOPD II syndrome, Mulibrey-Nanism, SHORT syndrome, 3-M syndrome, and Silver–Russell syndrome phenotype. OMIM, London Medical Database—Dysmorphology, and Gene Clinics were reviewed for references to published articles about the eight conditions. These were reviewed and summarized.

The features of each condition also changes as the affected individual ages. Some of these changes are known; however, most reports of all eight conditions are in young individuals and so the natural history and changing phenotypes with age are not always clearly defined. Confirmation of phenotype as it relates to genotype (e.g., specific mutations) has only really been possible in Bloom syndrome thus far. Last but not least, heterogeneity is known to exist both with regard to different mutations (Bloom, MOPD II, Mulibrey) in the responsible gene, to different genes (3-M), and to different mechanisms (SRS phenotype). The published reports of

the three disorders for which the genetic mechanism is still unknown (Dubowitz, Floating–Harbor, and SHORT) also suggest heterogeneity.

Table I lists the average term delivery dates, birth weights, length and head circumference, and the average adult height for each disorder. The table is arranged with the largest average delivery weight at the top, and the smallest at the bottom. It can be seen that average size at birth does not necessarily correlate with adult height. As adults, the tallest condition is the SHORT syndrome, then Mulibrey-Nanism, then Bloom syndrome, with MOPD II being the very shortest as adults as well as the smallest at birth.

Figure 1 is a composite of the "classic" facial features of affected individuals taken from the literature. The specifics are in the legend.

Bloom Syndrome

Bloom syndrome was first described in 1954 [Bloom, 1954, 1966]. The natural history has been well defined since German began a registry of cases and has been able to follow the natural history. The syndrome has been characterized by IUGR (average birth weight at term is 1,850 g, and birth length 44 cm), sunlight sensitivity leading to telangiectasia erythema with subsequent scarring and a tendency to chromosome breakage (with dicentrics, tetraradial figures and a high frequency of sister chromatid exchange), an immunologic deficiency, infertility in males and an increased risk for neoplasia. Average adult height in males is about 148 cm (130–162 cm) and in females about 139 cm (122–151 cm).

Clinically, Bloom syndrome is described as having mild microcephaly, and malar hypoplasia with the development of telangiectasia erythema in a butterfly distribution on the face and on the hands and feet. These areas of skin develop pigmentary abnormalities and atrophic scars with sun exposure. This is usually noticed by 2 years of age. There are often feeding problems in the newborn period [Keutel et al., 1967]. A high squeaky voice may be noted. Chronic infections are seen, particularly of the lung (20% of affected individuals). These are probably related to the associated immune deficiency which manifests with reduced IgA, IgG, and IgM. Puberty and Bone Age are usually delayed. There may be mild mental retardation or normal IQs with learning disability. Male infertility with azospermia and small testes are usually present. Females are fertile, but have premature menopause [Chisholm et al., 2001]. Type II diabetes may occur after puberty (16% by age 23 years). An increased risk of cancer is present, particularly for leukemia, lymphomas, squamous cell carcinomas, and Wilms' tumor. At least 44% of affected individuals have developed some type of cancer by the age of 25 years (leukemia by 22 years, solid tumors by 35 years) [Mohaghegh and Hickson, 2001]. The oldest reported affected individual was 48 years old [German, 1992].

Bloom syndrome (OMIM 210900) is an autosomal recessive disorder with mutations of the BML gene (15q26.1) which is a protein homologous to RecQ helicase [Ellis et al., 1995]. The BML protein unwinds DNA in the 3′–5′ direction along a bound strand of DNA. It is a nuclear cell cycle regulator [Ellis and German, 1996; Auerbach and Verlander, 1997]. Deficiency leads to hypermutability, thus modification of standard cancer treatment regiments may be necessary. Information on over 150 patients is in the registry maintained by German and Passarge [Passarge, 1991]. Sixty-four different mutations have been identified with two unique Ashkenazi mutations. Among Ashkenazi Jews, the carrier rate is about 1% [Roa et al., 1999]. Laboratory tests helpful in making a diagnosis of Bloom syndrome include chromosome breakage studies, and immunoglobin studies to identify a deficiency of IgA, IgG, and IgN, as well as mutation analysis.

Dubowitz Syndrome

Dubowitz syndrome was first described by Dubowitz [1965]. Average birth size at term is 2,300 g, 45 cm, and OFC of 31 cm. It is characterized by mild microcephaly (90%) at birth, high sloping forehead (80%), flat supraorbital ridges (90%), and an eczema-like skin disorder which develops on face and flexion areas shortly after birth and clears by 2–4 years (more than 50%). Sparse hair is usually seen especially in the frontal hair area (70%) and lateral eyebrows (45%). There are short palpebral fissures, ptosis (35%), and ocular hypertelorism with prominent epicanthal folds

TABLE I. Average Birth Weight and Height, Average Adult Height, and Head Size of the Eight Syndromes Arranged by Decreasing Size at Birth

Syndrome	Term delivery average	Adult height average	OFC
Floating–Harbor	2,460 g, 46.8 cm	Slow growth, 130–140 cm	OFC wnl for age, Mild MR
Mulibrey	2,400 g, 45 cm	2nd best growth, 150 cm	Relative macrocephalic
Dubowitz	2,300 g, 45 cm	5th best growth, 146 cm	MR 75%, microcephaly 100%
SHORT	2,200 g, 44 cm	Best postnatal growth, 154 cm	OFC about 10% for age
3-M	2,200 g, 40 cm	Slow growth, 120–136 cm	Relative macrocephaly
Bloom	1,850 g, 44 cm	4th best growth, 148 cm males, 139 cm females	Mild MR, mild microcephaly
SRS phenotype, (heterogenous)	1,200 g – 2,500 g, 35 cm – 50 cm	3rd best growth, 150 cm males, 140 cm females	Relative macrocephaly
MOPD II	1,000 g, 35 cm	Worst growth, 100 cm	Start off with proportionate OFC, but become microcephalic

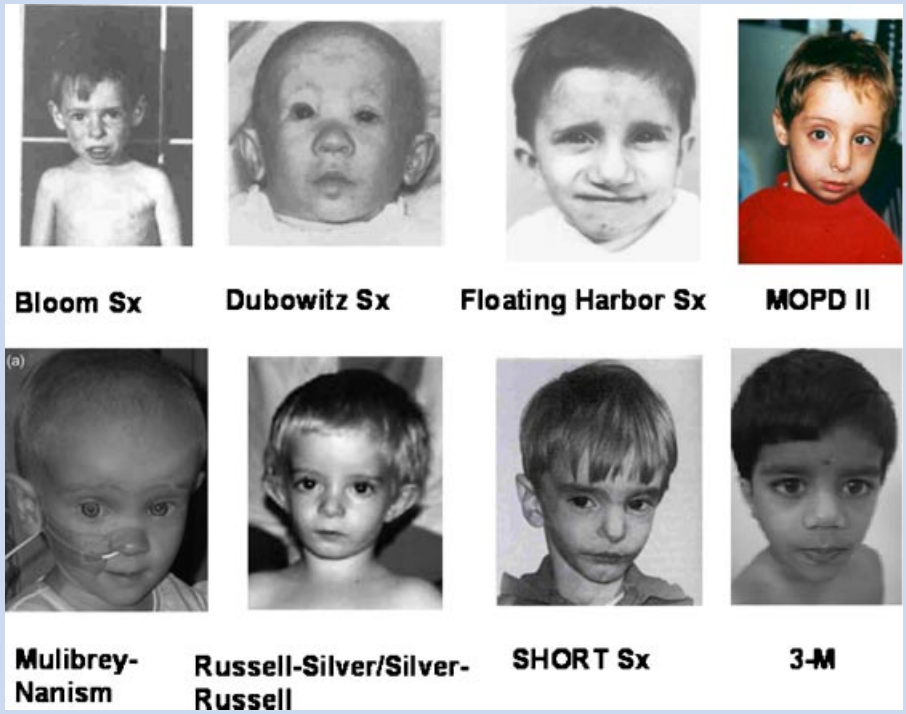

FIG. 1. Photos of individuals with Bloom syndrome, Dubowitz syndrome, Floating–Harbor syndrome, MOPD II syndrome, Mulibrey-Nanism syndrome, Silver–Russell syndrome phenotype, SHORT syndrome, and 3-M syndrome. The composite of individuals with a "classic case" of the eight syndromes reveal that they all have triangular lower face. The lower row all have prominent foreheads and small facial bones. Bloom syndrome—note rash in sun -exposed area [from Keutel et al., 1967]. Dubowitz syndrome—note short palpebral fissures, missing lateral eyebrows and eczema like changes on cheeks [from Gorlin et al., 2001, p. 378]. Floating–Harbor syndrome—note short philtrum, bulbous nose with broad base and low hanging columella [Feingold, 2006]. MOPD II—note prominent nose, relatively small head [from Hall et al., 2004]. Mulibrey-Nanism—note frontal bossing, flat bridge of nose and mid face [from Hämäläinen et al., 2006]. Silver–Russell syndrome phenotype—note asymmetry and triangular shaped face with large forehead and small facial bones [from Price et al., 1999]. SHORT syndrome—note hypoplastic alae and dimple on the chin [from Gorlin et al., 2001, p. 1028]. 3-M syndrome—note long philtrum, full tips, hypoplastic mid face [from Huber et al., 2009].

(60%). Blepharophimosis is present in 50%. The nose has a broad nasal tip (50%) and a broad base. There are usually failure to thrive, feeding difficulties, and muscle tone abnormalities. Bone age is delayed. Initially, affected individuals have a small chin (80%) which becomes longer and square with age, giving a long face with a triangular shape. The ears appear low set, are usually prominent (75%), and unusually folded. Micrognathia is frequent. The palate may have a high arch with velopharyngeal insufficiency and 20% have cleft palate. Fifty-five percent of affected individuals have a high pitched voice and 30% a hoarse cry. Speech is usually delayed (67%). Individuals are often hyperactive (75%) and shy, but with aggressive behavior and with short attention span. Developmental delay may be mild to moderate (72%); however, as many as 30% seem to have normal intelligence. Clinodactyly of the fifth finger is seen in 50%, and 20% have mild syndactyly of 2–3 toes. Fifty percent of males have hypospadias and cryptorchidism. Leukemia, lymphoma, neuroblastoma, aplastic anemia, and rhabdomyosacroma have all been reported, but rarely [Al-Nemri et al., 2000]. Bone age is usually delayed. Subcutaneous fat is decreased. Average adult height is 146 cm (140 cm for females, 155–161 cm for males). As adults, almost 100% have relative microcephaly [Orrison et al., 1980; Parrish and Wilroy, 1980; Moller and Gorlin, 1985; Küster and Majewski, 1986; Winter, 1986; Tsukahara and Opitz, 1996].

Additional anomalies are common and include: trigonencephaly, prominent metopic suture, relatively large eyes, esotropia, incomplete retinal development, crowding irregular teeth, hypoplasia of upper ears, reticulated thin blond sparse hair, sacral dimple, single flexion crease of hand, short broad first toe, preaxial polydactyly, stroke, aberrant sublcavian artery, hypoparathyroidism, diaphysis rectus, hyperpigmentation of skin, seizures, leg length discrepancy, partial vaginal septation, vertebral fusion, and congenital heart disease.

Approximately, 150 cases have been reported [Tsukahara and Opitz, 1996]. Autosomal recessive inheritance is assumed since both males and females are affected in equal numbers and many families have consanguinity (OMIM 223370). There may be subtypes [Ilyina and Lurie, 1990], one including anorectal anomalies and craniosynostosis, a second type with immunodeficiency and frequent infections, and possibly a third type with low cholesterol [Ahmad et al., 1999]. A specific gene has not been identified. Because of the small palpebral fissures and IUGR fetal alcohol spectrum is part of the differential diagnosis. The oldest reported affected individual is 30 years old [Hansen et al., 1995].

Floating–Harbor Syndrome

The name Floating–Harbor comes from the names of the institutions where affected individuals were first described: Boston Floating Hospital by Pelletier and Feingold [1973] and Harbor General Hospital by Leisti et al. [1974]. It is characterized by IUGR, but normal head circumference for age. Average birth weight at term is 2,460 g with length of 46.8 cm, and OFC normal for gestational age. The craniofacies is characterized as round and becoming triangular with aging. There is a prominent nose with broad bulbous tip to the nose together with a prominent nasal bridge. Eyes are prominent early and become deep-set later [Hersh et al., 1998; Ala-Mello and Peippo, 2004; Feingold, 2006]. Mouth is wide with thin lips. There is a broad, low hanging columella and short philtrum, giving the appearance that the columella is "tucked up" under the rest of the nose. The nares are large and the alae are hypoplastic. The ears are apparently low set and posteriorly rotated. Affected individuals have normal motor development, but developmental delay, characterized by speech delay (100%) and expressive language delay, with 50% having mild mental retardation [Davalos et al., 1996]. Some have hyperactivity at an older age. They also often have clinodactyly, with hypoplasia of the 5th nail, and broad thumbs. They may have decreased subcutaneous tissue, and a relatively short neck with a low hairline. Many are described as hirsute and/or having long eyelashes. About 50% have joint laxity. Occasionally, there is a high-pitched voice. Celiac disease with high gliadin antibodies has been reported in four affected individuals [Ala-Mello and Peippo, 1996]. Tethered cord with symptoms has been described [Wiltshire et al., 2005], as well as trigoencephaly [Midro et al., 1997]. The bone age is delayed in most individuals, but puberty usually occurs on time, suggesting that there may be an underlying bone dysplasia. Coned epiphyses are often present. Fifty percent have brachydactyly, and 45% have clubbed fingers. Pseudoarthrosis of the clavicle has been observed. Additionally malocclusion, ruptured aneurysm [Paluzzi et al., 2008], hypoplastic penis, supernumerary upper incisor, glabellar stork mark, metopic suture synostosis, preauricular pit, hypoplastic thumb, subluxed radial head, AV canal [Ucar et al., 2004], and Sprengel deformity [Hersh et al., 1998], have all been described. One boy with spinal cord ganglioglioma has been reported [Nelson et al., 2009]. Adult height is between 130 and 140 cm. As compared to most of the other disorders described in this review, growth rate falls off over later childhood. The oldest affected reported individual was 46 years old [Lacombe et al., 1995].

About 36 cases have been described [Patton et al., 1991], mostly sporadic. The male/female ratio is 1:2. Consanguinity has been reported, as has one set of affected female siblings. However, advanced paternal age has also been reported. A report of mother to child transmission has occurred three times [Lacombe et al., 1995; Rosen et al., 1998], but may not represent Floating–Harbor syndrome (OMIM 136140). The responsible gene is unknown.

Majewski (Microcephalic) Osteodysplastic Primordial Dwarfism Type II (MOPD II)

Majewski first described MOPD II distinguishing it from two other syndromes of severe IUGR in 1982 [Majewski et al., 1982]. There are probably two cases in Seckel's original article on Seckel bird headed dwarfs that actually have this condition. Relatively normal head size at birth in relationship to body size distinguishes MOPD II from classic Seckel syndrome [Faivre et al., 2002] where there is severe microcephaly and posteriorly slanted forehead at birth. In MOPD II, severe intrauterine growth retardation occurs with birth weight less than 1500 g at term. Average length at term is 35 cm. At birth, the OFC is proportionate (albeit small for a normal sized newborn) since the birth weight, length, and OFC are all approximately normal for 28 weeks when there is a term delivery of MOPD II. However, progressively after birth the head size does not keep up with body growth and true microcephaly (relative to body size) is recognized by 1 year of age [Hall et al., 2004]. The forehead differs from that seen in Seckel syndrome in that individuals with MOPD II do not have a posterior slant to the forehead, but in fact, have a rather tall forehead. The cheeks are full at a young age and then with aging, the face becomes triangular. The eyes and nose are prominent in the first year. Esotropia may be present. The eyeball is short and therefore affected individuals are farsighted and usually benefit from corrective glasses at an early age. The nose becomes quite prominent over time although only the bridge may be raised at birth. With age, the bridge of the nose becomes broad, the tip hypoplastic and the alae underdeveloped. The jaw may appear small. The teeth are dysplastic and small (when compared to the rest of the mouth size, which is small) or even absent [Kantaputra et al., 2004]. There is a high squeaky voice. Café au lait spots may develop with time. A dark pigment and acanthosis are usually seen in the neck and axilla over time. Depigmentation and poikoloderma-like change may occur in sun-exposed skin.

Most affected individuals have feeding problems in the first few years. Affected individuals usually have a very pleasant outgoing personality and may be hyperactive. Intelligence is low for the family, but may be within the normal range.

There are progressive bony changes and increasing loose jointedness leading to subluxation of the knees laterally and sometimes of the hips. Disproportionate shortening of the mesomelic segment occurs with time. Skeletal changes are progressive and include gracile, over-tabulated long bones, delayed ossification (bone age-), short femoral neck, severe coxa vara, mild metaphyseal flaring, high narrow ilia, dislocating radial heads, flattening of vertebrae, and small facial bones. Scoliosis may develop. There is severe postnatal short stature with adult height around 100 cm. No increased growth occurs with growth hormone therapy.

Over time, affected individuals develop truncal obesity. Cutis mamorata is seen early. Affected individuals may develop diabetes with aging. Males have cryptorchidism and micropenis and occasionally hypospadias. Perhaps as many as 25% of affected individuals develop intracranial aneurysms which look like the tortuous overgrowth vessels seen in Moya Moya disease [Nishimura et al., 2003; Kannu et al., 2004; Young et al., 2004]. These aneurysms are treatable, however, may lead to death if untreated [Brancati et al., 2005]. There does not seem to be any particular clinical findings that predisposition to the development of the aneurysms. It is unclear whether the intracranial aneurysms are congenital or develop with time. Hypoplastic kidneys, pachygyria, anemia, scoliosis, and recurrent otitis may be seen [Ozawa et al., 2005].

Growth charts for newborns and childhood are available [Hall et al., 2004] and show severely restricted growth. MOPD II probably represents the extreme of short stature in humans. Affected individuals may live into the fifth decade. The oldest reported affected individual is 39 years old [Hall et al., 2004].

MOPD II is an autosomal recessive disorder with increased incidence of consanguinity (OMIM 210720). It appears to be increased among individuals from the Mediterranean countries, although it is seen in all ethnic groups. It can be quite variable within a family. About 100 cases have been reported. The responsible gene is pericentrin (PCNT) whose protein is part of the centrosome complex [Rauch et al., 2008]. It also appears to play a role in cell division, helping to organize the mitotic spindle for segregation and in aggregating of the spindle. The gene is on 21q22.3. Some reports of pericentric mutations in Seckel syndrome are actually MOPD II individuals [Faivre et al., 2002; O'Driscoll et al., 2003; Griffith et al., 2008].

Mulibrey-Nanism

The name stems from involvement of *mu*scle, *li*ver, *br*ain, and *ey*e, and was first reported as a Finnish disorder by Perheentupa et al. [1970]. IUGR is seen (average weight 2,400 g, length 45 cm), but there is a normal size head for age. Feeding and respiratory difficulties are frequent in infancy. The head shape is dolicocephalic with a high prominent forehead (90%). Ventricles maybe enlarged (44%). The face is triangular (90%) with depressed bridge of the nose (90%). Individuals have muscle wasting and thus the hands and feet appear large. The retina may contain yellow spots and often has a yellowish (79%) tinge. There may be constrictive pericarditis (12%) with congestive failure (35%) presenting during infancy and impairing cardiac function later in life [Eerola et al., 2007]. The heart failure then may lead to an enlarged liver (45%) and prominent abdominal veins in 45%. Hypotonia is present in 70% of infants, but intellectual development is normal. There is a high-pitched voice in 95%. A nevus flammeus is seen over the forehead and bridge of the nose (65%) and even on the limbs. Hypoglycemia is seen in 15%. The sella tursica is often low, shallow, elongated, and J-shaped (90%). The long bones are gracile (100%). In 65% the long bones have thick cortices and narrow medullary canals. Fibrosis dysplasia of the tibia is seen in 25%. There is incomplete breast development in females and ovarian stromal tumors often occur [Karlberg et al., 2004b]. Premature ovarian failure and subsequent infertility have also been observed in females, as well as ovarian fibrothecoma in 55% of women. Wilms' tumor has been reported in 4% [Hämäläinen et al., 2006]. Malocclusion (40%), hypodontia, small tongue, ocular hypertelorism (64%), strabismus, hypoplasia of the choroid, coloboma, corneal dystrophy, partial GH deficiency, thyroid adenomas, hypothyroidism, hypoadrenalism, large ventricles, eosinophilia, cardiac, and renal structural anomalies, and single flexion crease have all been reported.

Average adult height is 150 cm on average (women 126–151 cm, men 136–161 cm) [Balg et al., 1995; Lapunzina et al., 1995; Karlberg et al., 2004a; Sorge et al., 2005]. Little response is seen to growth hormone therapy, but insulin resistance does not develop [Karlberg et al., 2007]. Some features are similar to Meire–Gorlin which should be part of the differential diagnosis. The oldest reported affected individual is 70 years old [Karlberg et al., 2004b].

Mulibrey-Nanism is an autsomal recessive disorder with frequent consanguinity (OMIM 253250). Over 120 cases have been reported, 85% of which are Finnish, but it has also been reported from Argentina, Australia, Egypt, France, Italy, Spain, and Turkey. The condition is due to mutations in the TRIM 37 gene which is on 17q21-q24 [Avela et al., 2000; Kallijärvi et al., 2002; Jagiello et al., 2003; Sorge et al., 2005]. TRIM 37 encodes a proxisomal protein whose function is unknown. A granular cytoplasmic pattern of protein expression is seen in cells. The TRIM 37 protein is a RING B—box coiled protein coil [Avela et al., 2000].

SHORT Syndrome

The SHORT syndrome was reported by Sensenbrenner et al. [1975]. The initials stand for *s*hort stature, *h*yperextensible joints and inguinial *h*ernia, *o*cular depression with deep set and large appearing eyes, *R*ieger anomaly (75%) with megalocornea (75%), anterior segment dystrophy, iris stomal hypoplasia, glaucoma, and lens opacity, and *t*eeth which may be small with enamel delayed in eruption hypoplasia, and with malocclusion. Average birth weight at term is 2,200 g and average birth length is 44 cm. The head appears large, but is about 10% for age. The face is triangular shaped with a broad forehead and small chin and small facial bones. Ocular hypertelorism is present with large appearing, but deep-set eyes and Rieger anomaly. There is hypoplasia of the alae (94%) with a broad nasal bridge and prominent nose with age. Micrognathia is present (65%), often with a dimple on the chin. Dental eruption is delayed and bone age is delayed [Lipson et al., 1989; Verge et al., 1994; Bankier et al., 1995; Brodsky et al., 1996; Joo et al., 1999; Koenig et al., 2003], but epiphyses are large when they do appear, suggesting a disturbance in bone metabolism. Hair is thin. The skin is transparent. The ears are relatively large and posteriorly angulated with parallel antihelix and cruse. Occasionally, there is neurosensory deafness (24%) or functional heart murmur.

There is often speech delay, but intelligence seems to be normal. Feeding problems and failure to thrive occur in infancy. Decreased subcutaneous fat, thought to be a lipodystrophy occurs on the face and upper limbs. Subcutaneous dimples have been seen on the elbows and buttocks. Type II diabetes related to insulin resistance often occurs after puberty or after growth hormone therapy [Aarskog et al., 1983; Schwingshandl et al., 1993; Verge et al., 1994]. Nephrocalcinosis with renal stones has been seen in about 10% of cases [Reardon and Temple, 2008].

The joints of the hands are hyper extensible (35%) and there is clinodactyly of the 5th finger (64%). There are large, cone shaped epiphyses. The long bones are thin and gracile [Haan and Morris, 1998]. Additional features reported are congenital glaucoma, non-ketotic hyperglycemia, delayed menarche, and inguinal hernia. Adult height is around 154 cm, the best of all these syndromes. The oldest affected reported individual was 55 years old [Aarskog et al., 1983].

Approximately 25 cases have been reported and it is not clear whether SHORT syndrome has autosomal recessive [Gorlin et al., 1975] or autosomal dominant inheritance [Bankier et al., 1995; Sorge et al., 1996; Koenig et al., 2003]—both have been reported

(OMIM 269880). There are equal numbers of males and females. The cases reported may be a heterogeneous as the gene is unknown.

3-M Syndrome

The 3-M syndrome is named for the first initial of the first three authors of the article published in 1975 by Miller et al. [1975]. Affected individuals have IUGR with average birth weight of 2,200 g and birth length of 41 cm. They have relatively large heads for body size. The head is dolicocephaly, frontal bossing, and an OFC which are normal for age. They often have feeding and respiratory problems in the newborn period. The face is triangular with hypoplastic mid-face, long philtrum, prominent full lips, and pointed chin. It was described as having a "gloomy appearance" [Le Merrer et al., 1991]. There are quite full eyebrows, wide eyed appearance to the eyes, prominent ears, fleshy nose tip, and there may be crowding of the teeth with a V-shaped dental arch [Winter et al., 1984].

Affected individuals have short broad necks with prominent trapezius and square shoulders. They may have a depressed sternum and short wide thorax. There may be winging of the scapula. Affected individuals are often hypotonic and may have loose joints, and eventually they usually stand in hyperlordosis with a protruding abdomen. There are slender long bones, with diaphyseal constriction, metaphyseal flexing, and thickening of the cortex. The heels are often prominent. The limbs appear short. The vertebrae are tall with reduced AP diameter [van der Wal et al., 2001]. Kyphoscoloiosis may develop.

Intelligence is normal. CNS aneurysms have been reported [Mueller et al., 1992]. Adult height is between 120 and 136 cm. The oldest reported affected individual was 29 years old [Hennekam et al., 1987].

Over 100 cases have been reported, about 1/3 are from the Yabut population in Serbia [Maksimova et al., 2007]. 3-M is an autosomal recessive disorder with increased consanguinity (OMIM 273750). Heterozygotes may have minor clinical features. A responsible gene is CUL7 on 6p21.2 which produces a protein that helps to assemble E3 ubiquitin–ligase complex [Huber et al., 2005] involving the cytoskeletal adaptor OBSLI [Hanson et al., 2009]. Twenty-five different mutations have been identified in 29 families in the CUL7 gene. Heterogeneity appears to exist since one-third of typical affected individuals do not have mutations in CUL7 and do not map to 6p21.1 [Huber et al., 2009].

Silver–Russell Syndrome Phenotype (SRS)

In 1953, Silver et al. described a syndrome of IUGR with normal head size and asymmetry of the body [Silver et al., 1953]. Russell [1954] reported cases with no asymmetry. SRS phenotype is characterized by a small body compared to the head, but the head is usually normal size for age and is therefore big relative to the body size. The disproportion is sometimes described as pseudohydrocephaly or macrocephaly, but in fact the head size is just normal for age; whereas, relatively, there is decreased height and weight particularly at birth and subsequently compared to normal for age. Most affected individuals are relatively underweight for length. Reported birth weights range from 1200 to 2,500 g and birth lengths from 35 to 60 cm. Most affected infants are born at term. Placentas are usually quite small [Sibley et al., 2005; Yamazawa et al., 2008a]. Undoubtedly, heterogeneity exists in what has been reported as SRS phenotype.

Most affected individuals remain at or below the 3rd centile during childhood. About 50% of reported cases have asymmetry with hemihypotrophy of the small side. They often have feeding problems in the newborn period and fail to thrive. Many have long-term gastrointestinal symptoms [Anderson et al., 2002]. Delayed bone age is almost always seen. There is a triangular shaped face with a relatively high forehead and small facial bones. Clinodactyly is frequently seen (68%), as are a single palmar flexion crease (25%), mildly short fingers (48%), occasionally mild syndactyly (20%), and camptodactyly (22%). Café au lait spots (19%) may develop. A high pitch or squeaky voice is present in 20%. Twelve percent have congenital dislocated hips. Hypoglycemia, excessive sweating, and tachycardia are seen in infancy in about half of affected individuals. Intellectual development is usually normal although motor development may be delayed. Speech delay and learning problems are seen in UPD 7. Hypospadias, cryptorchidism, urethal valves, and inguinal hernias are present in up to 50% of males [Ortiz et al., 1991]. Scoliosis develops in about 36% of cases. If asymmetry is present it is likely to lead to leg length inequality which then needs to be treated to avoid compensatory scoliosis and inevitable uneven wear and tear of the large joints [Escobar et al., 1978; Price et al., 1999; Hitchens et al., 2001b]. Cardiac conduction defects, atrial septal defect, pulmonary stenosis, and renal asymmetry have been reported. Cancer seems to be rare in SRS phenotype although hepatocellular carcinoma and astrocytoma have been described [Chitayat et al., 1988; Fenton et al., 2008]. Growth hormone therapy has little effect, but may alter insulin resistance. The oldest reported affected individual was 56, but life expectancy appears to be normal.

Recently, Silver–Russell syndrome has been recognized to be an epigenetic-genomic imprinting problem [Abu Amero et al., 2007; Rossignol et al., 2008] (see Table II). Bartholdi et al. [2009] developed a clinical scoring scheme that helps identify individuals with an epigenetic basis for their SRS. Approximately, 10% of cases are related to maternal uniparental disomy (UPD) of chromosome 7 [Kotzot et al., 1995; Preece et al., 1997; Price et al., 1999; Russo et al., 2000; Hannula et al., 2001; Dupont et al., 2002; Binder et al., 2008]. These individuals have milder phenotype, but also have speech delay probably related to lack of a paternal FOXZ gene and may require special education [Kotzot et al., 2000; Feuk et al., 2006]. In addition, maternal UPD 7 individuals (probably related to trisomy 7 rescue) have more asymmetry, feeding difficulties, and excessive sweating, as well as less facial features than non-maternal UPD 7 SRS phenotype individuals [Kotzot et al., 2000; Hannula et al., 2001; Font-Montgomery et al., 2005]. Two areas on chromosome 7—7p11.2 to 13 [Joyce et al., 1999; Yoshihashi et al., 2000; Hitchins et al., 2001a; Monk et al., 2002b] and 7q32 [Nakabayashi et al., 2002] have been implicated in cases of SRS phenotype; however, the specific imprinting defects have not been fully illucidated [Hitchins et al., 2001a,b; Kobayashi et al., 2001; McCann et al., 2001; Monk et al., 2002a; Binder et al., 2008] in most cases, but point mutations have been found in GRB10 (7p11-p13) in 2 out of 58 SRS patients [Yoshihashi et al., 2000].

Probably 50–65% of Silver–Russell syndrome phenotype individuals are related to demethylation of areas of 11p15 [Eggermann

TABLE II. Chromosome Regions Involved in Epigenetic/Imprinting Changes Associated With Silver–Russell Syndrome

Chromosome region	Imprinted genes in region	% SRS phenotype
7		
UPD mat		10
p11.1-p14	FOX2 (pat)	
Partial Mat UPD (e.g., inherited duplication 7p11.2-p13)	GRB 10, IGFBP1, IGFBP3 (mat)	
Pericentric inversion		
Point mutation		
q21-qter		2
Mat dup and partial UPD	PEG1/MEST mat	
Ring 7	CoPg2, Copg2AS, CPA4	
11p15	IGF2 pat	50–65
Mat dup 11p	H19 mat	
Mat UPD (mosaic)	ICRI hypomethylation	
Methylation in the DMR (imprinting center—ICRI)		
Mat centrometric duplication 11p15		
15q26.1-qter ring or deletion	IGFIR	<1
17q23.3-q25		
Point mutation and gene deletions	KPNA2, CHS1, GRB2, and GRB7	<1

et al., 2005, 2006, 2008b; Gicquel et al., 2005; Bliek et al., 2006; Abu Amero et al., 2008; Priolo et al., 2008; Scott et al., 2008; Yamazawa et al., 2008a; Zeschnigk et al., 2008; Bartholdi et al., 2009]. Most affected individuals have hypomethylation at both H19 and IGF2, however, some have hypomethylation at one or the other gene, but not both. These findings suggest IGF2 plays an important role in growth determination and H19 hypomethylation is related to severity of features; however, the exact mechanism of growth failure is unclear [Binder et al., 2008].

Most SRS cases are sporadic, but both siblings and father to daughter transmission have been observed with imprinting defects [Bartholdi et al., 2009]. The phenotype with 11p15 methylation abnormalities is more severe than that seen in maternal UPD 7. Netchine et al. [2007] and Bruce et al. [2009] have also correlated the degree of hypomethylation with the severity of growth restriction. Tissue specific mosaicism of hypomethylation may give rise to asymmetry. Interestingly, discordance in monozygotic twins for SRS phenotype correlates with epigenetic changes showing hypomethylation in the affected twin [Gicquel et al., 2005; Yamazawa et al., 2008b]. Duplications of 11p15 in the centromeric region [Schönherr et al., 2007] also gives SRS phenotype as does mosaic maternal UPD 11p15 [Bullman et al., 2008]. The methylation changes in 11p15 appear to be the functionally opposite of Beckwith–Weidemann overgrowth syndrome [Schönherr et al., 2007; Eggermann et al., 2008a] and the degree of hypomethylation may correlate with severity of findings [Bruce et al., 2009]. However, Beckwith–Weidemann affected individuals slow down their excessive growth and are more normal in size as adults, while SRS individuals stay relatively small without much catch up growth as adults.

Chromosome 14q32.2 involves an imprinted region where the methylation states of MEG3, DLK3 and the intergenic differentially methylated region (DMR) can produce a recognizably phenotype of intrauterine and postnatal growth restriction [da Rocha et al., 2008; Hosoki et al., 2008]. It is characterized by hypotonia, frontal bossing, micrognathia, and small hands which would not all be typical for SRS. Mat UPD of this region also involves precocious puberty and truncal obesity. Early on, it was confused with SRS phenotype [Mitter et al., 2006].

Rings and deletions of 15q26.1 have been reported [Tamura et al., 1993; Rogan et al., 1996; Harada et al., 2002] with SRS phenotype as have chromosomal rearrangements in 17q22 to 25 [Midro et al., 1993; Dörr et al., 2001] and 17q25 point mutations [Eggermann et al., 1998; Hitchins et al., 2002]. These may also be related to genomic imprinting/epigenetic changes (either methylation of DNA or changes in configuration of histones).

Over 700 cases of SRS phenotype have been reported, most recently with molecular studies. Rarely SRS syndrome phenotype has been reported in families as an autosomal recessive [Fuleihan et al., 1971; Teebi, 1992; Õunap et al., 2004] or an autosomal dominant trait [Duncan et al., 1990; Al-Fifi et al., 1996; Joyce et al., 1999; Yoshihashi et al., 2000]. Even X-linked inheritance has been suggested [Hitchins et al., 2001b]. Most recently, Bartholdi et al. [2009] reported father and daughter with SRS phenotype and an epimutation at 11p15. Two families with siblings affected by hypomethylation of H19 and IGF2 were postulated to represent germline mosaicism in the normal father.

A similar phenotype has also been reported with chromosome 1q trisomy [van Haelst et al., 2002]; deletions of 6q [Nowaczyk et al., 2008], 8q11-14 [Schinzel et al., 1994], 14q [Hosoki et al., 2008], 18p [Christensen and Nielsen, 1978], 18q11-14 [Schinzel et al., 1994], and trisomy 18 mosaicism [Hook and Yunis, 1965; Claveau et al., 1967; Pavone et al., 1970; Chauvel et al., 1975], suggesting that if methylation studies are negative, chromosome studies and CGH array should be considered in individuals with features of SRS. SRS phenotype is also relatively common in one of monozygotic twins and triplets [Nyhan and Sakati, 1977; Samn et al., 1990; Bailey et al., 1995; Gicquel et al., 2005; Yamazawa et al., 2008a]. Most recently SRS has been reported to be associated with the use of assisted reproductive technologies [Kallen et al., 2005; Svenson et al., 2005;

Bliek et al., 2006; Kagami et al., 2007; Douzgou et al., 2008] raising the issue of deficiency of methyl donors in the IVF culture media. Interestingly, there are few distinguishing clinical features among all the SRS phenotype individuals in which different epigenetic abnormalities, mechanisms and inheritance patterns have been reported, suggesting that the epigenetic changes may influence a common metabolic pathway of intrauterine restricted growth during fetal life [Binder et al., 2008].

In summary, each of these eight syndrome have unique features (Table III), but also have many overlapping features (Table IV) which may give clues to the biochemical and developmental pathways that they involve. The syndromes also have many features in common (Table V) in addition to severe in utero and postnatal growth restriction. These common features include: large

TABLE III. Unique Characteristic Features of the Eight Syndromes

- Bloom syndrome
  - Mild microcephaly
  - Malar hypoplasia
  - Telangiectasia erythema on sun-exposed surfaces
  - SCE, chromosome breaks
- Dubowitz syndrome
  - Blepharophimosis ± ptosis
  - Microcephaly
  - Eczema like disorder on face and flexion surfaces
  - Sparse hair and lateral eyebrows
- Floating–Harbor syndrome
  - Unusual face with
    - Prominent, and later deep set eyes
    - Broad nose with bulbous tip and broad, low hanging, "tucked up" columella
    - Short philtrum
    - Large mouth
  - Joint laxity and hirsutism
- MOPD II
  - Prominent nose with hypoplastic tip and alae
  - Small teeth
  - Increasing joint laxity and pigment
  - Progressive microcephaly
- Mulibrey-Nanism
  - Dolicocephaly with high forehead, depressed bridge of nose
  - Yellow pigment and pigmentary deposits in eyes
  - Constrictive pericarditis and heart failure
  - Fibrocystic changes in long bones, J shaped sella
- SHORT syndrome
  - Rieger anomaly with large, then deep set appearing eyes
  - Prominent nose with hypoplastic alae as adults
  - Chin dimple
- 3-M syndrome
  - Long philtrum
  - Prominent full lips
  - High forehead, broad neck
  - Short thorax, often with bony abnormalities
- Silver–Russell syndrome phenotype
  - 50% asymmetric
  - Mat UPD 7—learning disability
  - Relatively large head for body size

TABLE IV. Overlapping Features of the Eight Syndromes

- Broad high forehead
  - Mulibrey
  - SHORT
  - 3-M
  - SRS
- Small teeth
  - MOPD II
  - SHORT
- Malar rash
  - Bloom
  - Dubowitz
- Nose
  - Broad, fleshy
    - Dubowitz
    - Floating–Harbor
    - 3-M
  - Prominent
    - MOPD II
    - SHORT as adult
- Hypoplastic nasal alae
  - Floating–Harbor
  - MOPD II
  - SHORT
- DD/MR
  - Bloom—normal IQ, learning disability
  - Dubowitz—mod
  - Floating–Harbor—normal IQ speech delay—mild DD
  - MOPD II—mild—mod
  - UPD 7—speech delay
  - SHORT—speech delay
- High voice
  - Bloom
  - Dubowitz
- Hypogonadism
  - Bloom
  - Dubowitz—males
  - Mulibrey—females
  - SHORT—males
  - 3-M—males
  - R-S—males
- Aneurysm
  - Floating–Harbor
  - MOPD II
  - 3-M
- Type 2 diabetes
  - MOPD II
  - SHORT
- Lipodystrophy
  - Floating–Harbor—occasional
  - SHORT
- Localized bone defects
  - Mulibrey
  - MOPD
- Progressive bone changes
  - Floating–Harbor
  - MOPD II
- Cancer
  - Bloom
  - Dubowitz
  - Floating–Harbor
  - Mulibrey
  - Silver-Russell

TABLE V. Features That Are Seen in Common in the Eight Syndromes in Addition to Severe in Utero and Postnatal Growth Restriction

Large appearing head (often normal size for age)
Triangular shaped face
Decreased subcutaneous fat
Delayed bone age
Feeding difficulties in infancy
Infertility with hypospadius and cryptorchidism in males and early menopause in females
Clinodactyly of the fifth finger
Changes in the bones characteristic of lack of weight bearing, including gracile long bones, short femoral necks, tall vertebrae, and thin ribs
Lack of a growth response to growth hormone therapy
Small placenta

appearing head, triangular-shaped face, decrease subcutaneous fat, delayed bone age, feeding difficulties in infancy, infertility with hypospadias and cryptorchidism in males and early menopause in females, clinodactyly of the 5th finger, bony changes characteristic of the lack of weight bearing (including tall vertebrae, short femoral necks, thin ribs, and gracile long bones), lack of growth response to growth hormone therapy and a small placenta. It seems likely that these common features reflect a common pathway(s) related to in utero growth restriction.

DISCUSSION

The presence of epigenetic/imprinting defects in Silver–Russell syndrome phenotype leads one to ask questions about what has been learned over the last two decades regarding genomic imprinting as a reflection of epigenetic control processes in humans, and how it may relate to these eight conditions. Imprinting defects such as Prader–Willi and Angelman syndromes have made it clear that genomic imprinting effects can be caused by chromosomal deletions, UPD, point mutations, chromosomal duplications, mutations in imprinting controls centers, and methylation changes (such as those leading to loss of imprinting). Further, imprinted genes are known to cluster together in coordinately regulated domains [Bartholdi et al., 2009]. It has also become clear that genomic imprinting effects gene expression differently in different tissues at different times during development. There are also differences in mammalian species as to which genes are genomically imprinted. Mosaicism of imprinting effects can be seen within an individual and genomic imprinting control may change with aging [Martin, 2005]. Recently, many other mechanisms related to the control of gene expression (such as the families of small RNAs) are being recognized and could be involved in genomic imprinting processes.

In addition to the recognition that the Silver–Russell syndrome phenotype involves abnormalities of epigenetic control, mutations of specific genes have been found in four of these syndromes of severe IUGR with postnatal growth restriction: 3-M syndrome (a ubiquitization defect), Mulibrey-Nanism, (a peroxisomal function defect), MOPD II (a centrosomal function/mitotic spindle defect), and Bloom syndrome (a DNA repair defect). These mutated genes obviously represent quite different cellular functions and yet the individuals affected with these conditions share many similar phenotypic features. For the most part, the effects of these gene mutations on growth is still unclear. It seems quite possible that some of these common phenotypic features (Table V) result from a process of fetal "downsizing" which is part of a universal mammalian mechanism adjusting fetal size in response to the placenta/mother recognizing and communicating to the fetus that "there is a problem."

Little is known about the adult natural history of these eight syndrome. The few reported adult cases suggest that there is a predisposition to cancer (which is known to involve loss of imprinting) [Baylin and Jones, 2007], type 2 diabetes, infertility, and other chronic disorders such as osteoporosis. Studies of the DOHaD correlate small size at birth with an increased risk for chronic adult disorders including diabetes, metabolic syndrome, adiposity, hypertension, coronary heart disease, stroke, hypercoagulatability, hypercholesterolemia, and osteoporosis [Gluckman et al., 2008]. These observations suggest in an indirect way, that there must be in utero metabolic/biochemical mechanism(s) for downsizing of the mammalian embryo/fetus in the presence of stress, maternal nutritional insufficiency, placental insufficiency, etc., which help the fetus survive, but then programs adult metabolism to be predisposed to certain common adult diseases [Gluckman et al., 2008].

The concept of fetal programming suggests that there are critical periods in fetal development during which insults or stimulants can lead to lasting effects on structure and function [Gilbert, 2006; Hochberg and Albertsson-Wikland, 2008]. Fetal, and even infant programming in terms of the development of neuropathways is well established to use epigenetic processes [Francis et al., 1999]. Pediatricians and neuroscientists know that if the visual and auditory pathways are not "used" during the first two years, they will not ever function in what is considered to be a normal way. Less work has been done on the establishment and maintenance of metabolic pathways. There is clearly an interaction via the placenta between mother and fetus reflecting mother's nutrition with regard to protein, cholesterol, glucose, sodium, and other essential compounds. Maternal nutrition has a major effect on fetal growth [Hochberg and Albertsson-Wikland, 2008]. Maternal stress, drugs, and other environmental factors are also known to be associated with growth affects on the developing fetus [Kapoor et al., 2006].

Evolutionary theory suggests that in order to survive, mammals developed a capacity for flexibility in relation to their responses to environmental change [Dawkins, 1986; Trevathan, 1988; Gluckman et al., 2005; Hochberg and Albertsson-Wikland, 2008]. It has been hypothesized that mammals evolved a spectrum of responses to environmental change that led to survival advantage [Price et al., 2003]. The human fetus appears to be particularly responsive and sensitive to maternal metabolic messages, as do infants to nutritional cues up until at least their second year [Gluckman et al., 2008; Hochberg and Albertsson-Wikland, 2008]. It is not entirely clear what all of these signals between the fetus and mother are, but it does appear there may be transgenerational effects [Brook et al., 1999; Cooney, 2006; Hochberg and Albertsson-Wikland, 2008]. For instance in rats, when maternal nutrition is restricted [Pham

et al., 2003], there is programming or reprogramming that leads to fetal growth restriction [McMillen and Robinson, 2005]. The change in metabolic pathways in both pre and post-birth environments appear to be different for the two genders [Pembrey, 2002; Brawley et al., 2003; Schober et al., 2009]. These epigenetic effects on restricting growth may be passed on in subsequent generations [Pembrey, 2002; Emanuel et al., 2004; Fu et al., 2006]. Some changes have been demonstrated by Lane's groups [Pham et al., 2003] to involve the apoptotic pathways thereby decreasing the number of cells in the fetus. These processes involve methylation changes of key genes and appear to have as much as a three generational effect.

Many human populations have been studied for the later effects of IUGR. All ethnic groups studied appear to have increases in specific adult disease processes suggesting again that this is a common mammalian type of response [Gluckman et al., 2008]. The World War II food blockade in Holland showed differences of effect during the different trimesters on the in utero development that then lead to differences in predisposition to disease postnatally [Lumey, 1992; Ravelli et al., 1999]. It is well known that immigrants from developing countries take 2–3 generations to reach their full genetic growth potential when they have migrated to a more favorable environment [Campbell and Perkins, 1988; Brook et al., 1999; Kaati et al., 2002].

Whatever the mechanisms involved are, they may also be at work in the eight syndromes summarized here which are associated with both severe IUGR and severe postnatal growth restriction. Fetal growth restriction may be a response to disease in mother, to a metabolic or genetic disorder in the fetus, or to environmental cues. It appears that individuals with these eight syndromes of severe IUGR do have an increased risk for some chronic disorders diabetes, vascular disorders, and osteoporosis (Tables IV and V). The natural histories of these eight disorders have not been described well enough to know for sure for which other adult conditions they may be at risk. Nevertheless, it makes sense to look for changes in methylation patterns in the genes that show methylation changes related to IUGR in the other seven syndromes since they have been seen in Silver–Russell syndrome phenotype. Such changes seem likely to reflect a universal mammalian survival mechanism involving epigenetic modifications. Thus, these syndromes may provide insight into predisposition to common adult disorders.

It also seems likely that different types of therapy for the adult diseases which have been "programmed" in utero may be required, since the metabolic pathways may be different and/or need reprogramming. For instance, growth hormone given to some of these syndromes does not appear to provide much extra adult height, but it may prevent insulin resistance [Karlberg et al., 2007; Binder et al., 2008]. If there are methylation changes common to all eight of these syndromes of severe IUGR they surely reflect important mammalian fetal biological mechanisms and potential avenues for prevention and therapy for both the syndromes of severe IUGR and the common adult diseases associated with IUGR

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