**Maternal Uniparental Disomy of Chromosome 20: A Novel Imprinting Syndrome of Growth Failure**

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**Short Title**: Maternal Uniparental Disomy of Chromosome 20

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**Funding Sources:** Funding for the evaluation of one patient was through the Newlife Foundation for Disabled Children, Wessex Comprehensive Research network, National Institute for Health Research, and Medical Research Council. No funding for the remaining parts of the study was secured. ME, TE, KT and DJGM are members of the European network of congenital imprinting disorders (EUCID.net), supported by COST (BM1208).

**Financial Disclosure Statements:** None of the authors have a financial relationships relevant to this article to disclose.

**Conflict of Interest Statements:** None of the authors have a conflict of interest to disclose.

Abstract:

Purpose: Maternal uniparental disomy of chromosome 20 (UPD(20)mat) has been reported in only four patients, three of whom also had mosaicism for complete or partial trisomy of chromosome 20. In this study, we evaluated the largest cohort of individuals with UPD(20)mat to determine the clinical significance of this condition.

Methods: We studies phenotypic and genomic findings of a series of seven new patients with UPD(20)mat.

Results: All seven individuals with UPD(20)mat had intrauterine growth retardation, short stature, and prominent feeding difficulties with failure to thrive often requiring gastric-tube feeds as the common feature.

Genomic data in most patients are indicative of UPD as a result of trisomy rescue after meiosis II non-disjunction.

Conclusion: We describe the first natural history of the disorder, and the results of therapeutic interventions, including the frequent requirement of direct gastric feedings only in the first few years of life, and the suggestion that growth hormone supplementation is likely safe and effective for this condition. We suggest that UPD(20)mat can be regarded as a new imprinting disorder and its identification requires specialized molecular testing, which should be performed in patients with early-onset idiopathic isolated growth failure.

**Keywords**: Failure to Thrive, Feeding Difficulties, Short Stature, Maternal Uniparental Disomy, Imprinting Disorders

**INTRODUCTION**

Uniparental disomy (UPD) is defined as the presence of a whole or parts of a chromosome pair originating from only one parent. Heterodisomy is the inheritance of both of the non-identical homologous chromosomes, and isodisomy is the inheritance of two identical copies of one chromosome. Due to recombination, both hetero- and isodisomy can be observed in UPD. Although patients with UPD can be euploid, there can still be phenotypic consequences from altered gene expression due to imprinted genes, from residual aneuploidy, or in isodisomy from uncovering mutations associated with a recessive disorder.

Currently, eight human imprinting syndromes have been reported with a diverse range of phenotypes, although most involve aberrant growth. (for review: http://upd-tl.com/upd.html ). Chromosomes 6, 7, 11, 14, 15, and 20 harbor imprinted genes associated with well-described syndromes, and the phenotypes from maternal and paternal UPD of the same chromosome can be strikingly different1. For example, paternal UPD of chromosome 11 is one cause of the overgrowth disorder Beckwith-Wiedemann syndrome; maternal UPD of chromosome 11 is associated with Silver-Russell syndrome, where patients generally show prenatal growth restriction, postnatal growth failure with relative head sparing, triangular facies, asymmetry, and feeding difficulties. In a similar way, paternal UPD 14 leads to developmental delay, dysmorphic facial features, skeletal abnormalities and joint contractures, but maternal UPD 14 patients (Temple Syndrome) demonstrate intrauterine growth failure (IUGR), growth delay, central hypotonia, developmental delay, and early onset of puberty.2,3

There have been only a few patients reported with UPD of chromosome 20. UPD(20)pat results in Pseudohypoparathyroidism type 1b (OMIM # 603233), characterized by resistance to parathyroid hormone (PTH) in kidneys, presenting as hypocalcemia, hyperphosphatemia and abnormally high PTH levels. There are only a few patients with UPD(20)mat that have been described in the literature. (REF) Complicating their characterization, most of these patients with UPD(20)mat had other related structural alterations resulting in partial or complete trisomy for chromosome 20. The first reported patient with UPD(20)mat had a mosaic karyotype with 46, XY and 47, XY, +mar, with the marker chromosome comprising the centromere and pericentromeric segments of chromosome 20.4 A second patient was diagnosed prenatally with mosaic trisomy 20, and was non-mosaic for UPD(20)mat in blood postnatally.5 A third patient with mosaic trisomy 20 had trisomy in 98% of amniotic fluid, 100% of placenta and urine sediment, and 10% of peripheral blood.6 The presence of trisomy in these individuals complicates the clinical implication of UPD(20)mat. A fourth patient was identified by screening 51 patients with IUGR and post-natal growth delay, and no trisomic cells were identified, making him the only reported case of isolated UPD(20)mat.7 Additionally, one case of UPD(20)mat with non-mosaic trisomy 20p is included in the UPD database ([http://upd-tl.com/upd.html](https://webmail.ukaachen.de/owa/redir.aspx?C=rhdBrB4yc06OS0eU_W87lSBYAFyuxdEIOmnJmRTx25Z1pF4hvXSh6uZyR9AMphBrTQAfYOQmuEw.&URL=http%3a%2f%2fupd-tl.com%2fupd.html)). This was a 16-month-old male with short stature, dysmorphic features, right inguinal hernia, hypospadias, mild cardiac defect and feeding difficulties that required gastric feeding. The method of UPD detection is unclear for this patient, therefore this case is not used for further comparison.

Seven new individuals with UPD(20)mat without evidence of trisomy are described in this report. All individuals share the phenotype of IUGR and “idiopathic” failure to thrive, severe enough that five out of seven patients required chronic gastric tube feedings. Beyond the growth phenotype, there are no additional shared features. The probands are not overtly dysmorphic and have no major congenital abnormalities. Three of eight patients were reportedly affected with 5th finger clinodactyly, which is higher than the general population. They do not demonstrate major developmental delay, and are all currently in mainstream education working at grade level. Therefore we suggest that UPD(20)mat can be regarded as a novel imprinting disorder of IUGR, extreme feeding difficulties from birth, and short stature.

**METHODS**

This study was deemed exempt by the official institutional review board at the Children’s Hospital of Philadelphia and the other contributing institutions. Clinical testing using the single nucleotide polymorphisms (SNP) chromosomal microarray platforms Illumina 610k, OMNI 1M, and 850k arrays and Affymetrix Cytoscan identified UPD(20)mat in patients 1-5. In general, UPD was suspected in samples with homozygosity limited to only one chromosome, particularly when greater than 10 Mb in size,or terminally located.1,8 Confirmation of UPD was carried out by analyzing several thousand informative parental genotypes across the entire chromosome 20. Patient 6 was identified by methylation-specific multiplex ligation-dependent probe amplification (MS MLPA) using a *GNAS*-specific assay (ME-031-B; MRC Holland, Amsterdam/NL). UPD(20)mat was then confirmed by typing of chromosome 20 specific microsatellite markers and SNP array analysis (Affymetrix 6.0 SNP array, Santa Clara, CA/USA). Patient 7 was identified through recruitment to the Imprinting Disorders Finding Out Why Study (IDFOW: Southampton and South West Hampshire Ethics approval 07/H0502/85) and investigated by methylation-specific polymerase chain reaction (PCR) of multiple imprinted loci, including those on chromosome 20. Results were confirmed by analysis of chromosome 20-specific microsatellites.9

**RESULTS**

Patient 1:

Patient 1 was a nine-year-old female with short stature and feeding difficulties from birth. She was born to a 39-year-old mother after a spontaneous pregnancy at 38 weeks with a birth weight of 2200 grams (g) (<3rd%, 50th% for 35 weeks gestation); there were no complications during the pregnancy or delivery. At age three months she was diagnosed with failure to thrive (FTT) attributed to reflux. Despite aggressive medical management of the reflux she required nasogastric tube feeding from age three months to three years. In addition, she attended an intensive outpatient feeding program that enabled her to advance to full oral feeds independently. She was first evaluated by medical genetics at eight months for isolated FTT. Chromosome analysis, subtelomere analysis, fluorescent in-situ hybridization testing for 22q11.2 deletion, and a comprehensive metabolic panel were all normal. During this time she was followed by a pediatric endocrinologist for poor growth. The patient was started on growth hormone (GH) at age eight years for idiopathic short stature after GH stimulation testing and *SHOX* gene sequencing were normal. She also had a bone age that was consistent with chronologic age and showed no signs of puberty. She grew four inches in the first year on growth hormone. However, during this time she was diagnosed with scoliosis and wore a back brace for 16 hours per day; she did not have any central hypotonia or other predisposing factors for scoliosis. Academically, she worked at grade level in school and did not require extra help in the classroom. At age nine years she had an unremarkable physical exam with no dysmorphic features; height was 121 centimeters (cm) (5th%) and weight was 23 kilograms (kg) (5th%). Her family history was unremarkable: her mother was 159.2 cm (75th%) tall and had menarche in middle school; her father was 164.4 cm (25th%) tall and had normal puberty. The patient had a 10-year-old brother who was healthy and of normal stature. A genome-wide SNP array identified homozygosity for the entire chromosome 20. Parental testing confirmed maternal origin of UPD.

Patient 2:

Patient 2 was born to a 38-year-old mother after an uncomplicated spontaneous pregnancy via cesarean section at full term weighing 2600 g (3rd%). She first came to medical attention in the newborn period because of poor feeding, which was thought to be due to “sensory issues”. She required nasogastric tube feedings from nine months to two years, but still had poor growth through that time despite adequate caloric intake. There are no reported developmental issues, and she was performing without extra help at grade level. On her last exam at age eight her height was 110.9 cm (<3rd%; 50th% for 5.5 years); weight was 15.9 kg (<3rd%; 50th% for 4 years); head circumference was 49.5 cm (3rd%). She had mildly low-set ears with thickened helices bilaterally and a narrow palate. She also had multiple lightly-pigmented spots on her back, chest, abdomen, extremities and head with a few darker macules, not consistent with classic café-au-lait spots due to their color and borders. She did not have a bone age performed and showed no signs of puberty. Her family history was unremarkable; her father was 171 cm tall (50th%), and experienced normal puberty. Her mother was 155 cm tall (25th%), and also was reported to have normal puberty. A healthy brother was of average stature. The proband had negative testing for LEOPARD syndrome and Neurofibromatosis. A genome-wide SNP array identified homozygosity for the entire chromosome 20; parental samples have been requested to confirm parent-of-origin.

Patient 3:

Patient 3 was the male product of a spontaneous pregnancy born by vaginal delivery to a 43-year-old mother at 38 weeks gestation with a birth weight of 2400g (3rd%). There were no pregnancy complications and an amniocentesis performed for advanced maternal age was reported as normal 46, XY. The patient had problems gaining weight in the first months of life; at 19 months he weighed 8.6 kg (<5th%, 50th% for 8 months), and at most recent examination aged four, he had a height of 78 cm (<5th%, 50th% for 14 months.) Due to FTT from poor oral intake he required nasogastric tube feeds from age 22 months to four years. He also had a tonsillectomy to improve potential dysphagia affecting his ability to consume enough calories, but it did not improve his intake significantly. His developmental milestones were all normal. Family history was significant for his mother having a miscarriage with a trisomy 18 karyotype. His mother was 165 cm (75th%) tall and his father was 178 cm (75th%) tall; they were in good health. The patient had one sister who was reportedly tall for her age. On his last exam at age four years his height was 80.5 cm (5th%), his weight was 9.32 kg (<5th%; 50th% for a 12 months), and he had a head circumference of 47.75 cm (25th%). He had epicanthic folds and one lightly pigmented spot, but no other abnormalities. A genome-wide SNP array identified an interstitial 28.5Mb region of homozygosity from chromosome 20p12.1to q13.13 spanning the centromere. Parental testing confirmed maternal origin of the UPD.

Patient 4:

Patient 4 was the male product of intrauterine insemination secondary to lack of spontaneous conception after two years. The pregnancy was complicated by IUGR, first noticed at 32 weeks gestational age, and decreased fetal movement towards the end of the pregnancy. He was born to his 43-year-old mother via caesarian section at 39 weeks gestation with a birth weight of 1960 grams (<3rd%, 50th% for 32 weeks gestation) and a length of 43 cm (<3rd%, 50th% for 32 weeks gestation). He was admitted to the Neonatal Intensive Care Unit (NICU) for poor weight gain and temperature instability. Due to “fatigue when eating” and “texture issues” he was placed on nasogastric tube feeds from the age one year until four years. Additional medical history was notable for a horseshoe kidney, a ventricular septal defect that closed spontaneously, mild asthma, egg allergies, and late eruption of his molar teeth. He also had generalized hypotonia with gross motor delays that placed him about six months behind on his milestones globally; he had normal brain magnetic resonance imaging at age six weeks. Neuropsychological testing was normal except for the gross motor delays. He did well in a regular classroom setting without additional help. At his last examination at age five years he weighed 21kg (75th%) and his height was 108cm (10th%). There were no dysmorphic facial features, but he had a bifid left second toe. A genome-wide SNP array identified an interstitial 40.80 Mb region of homozygosity affecting most of chromosome 20 (20p12.3q13.13), spanning the centromere (Figure 2D). Parental testing confirmed maternal origin of the UPD.

Patient 5:

Patient 5 was a male born to a 37-year-old mother via caesarian section at 37 weeks of gestation for maternal hypertension. The pregnancy was complicated by oligohydramnios late in the pregnancy and breech presentation. The patient had IUGR with a birth weight of 2050g (<5th%, 50th%for 34 weeks), length of 46.5 cm (5th%), and a head circumference of 31.5 cm (<5th%, 50th% for 33.5 weeks.) He remained in the NICU for seven days for feeding difficulty and hypoglycemia. His feeding issues persisted despite medical management, and he was found to be hypotonic at four months. A neuromuscular workup including muscle ultrasound was unable to provide a diagnosis for his hypotonia. At eight months he began feeds via nasogastric tube, which was converted to a percutaneous gastric tube at 18 months. He continued to have slow growth with a slightly delayed bone age; despite normal levels of growth hormone he was started on supplemental growth hormone therapy at five years, which resulted in a moderate growth acceleration. By age six years he was able to support his growth without gastric feeds and his gastrostomy tube was removed. He was in a normal classroom at grade level and doing well. His family history was remarkable for Stickler syndrome in a paternal uncle, paternal aunt, and paternal cousin. His mother was healthy and 152 cm (25th%) tall. His father was also in good health, was 172 cm (75th%) tall, and did not have signs of Stickler syndrome. A healthy sister was reported to be of average stature. On most recent examination at age six the patient had bilateral 5th finger brachyclinodactyly and one irregular patch of increased pigmentation on his left thigh, but was otherwise non-dysmorphic. He was 104 cm (<3rd%, 50th% for 4.5 years) tall, weighted 14.4 kg (<3rd%, 50th% for 3.5 years), and head circumference was 49.25 cm (10th-25th%). He was originally given a clinical diagnosis of Silver-Russell Syndrome before he was found to have UPD(20)mat. A SNP chromosomal array detected two regions of homozygosity, a 6Mb region on the p terminus and a 20Mb interstitial region from 20p11.21 to q13.12 spanning the centromere. Parental testing confirmed maternal origin of the UPD.

Patient 6:

Patient 6 was a twelve-year-old boy. After an uneventful pregnancy he was born spontaneously to a 38-year-old mother in the 38th week of gestation. He was small for gestational age (SGA) at a length of 47 cm (3rd%) and a weight of 2240 g (< 1st%; 50th% for 35 weeks). He demonstrated feeding difficulties with poor sucking, but breast feeding was ultimately successful and he was also supplemented with a high-calorie diet. His growth was slow, between thefirstand third centile, which was in contrast to his expected genetic growth potential as his healthy parents were tall (mother 183 cm, father 196 cm, both >95th%). He had one older and one younger sister; both had growth parameters in the upper normal range. At age two years the proband had mild muscular hypotonia with hyperlordosis, but no further dysmorphic signs, and psychomotor development was normal. Insulin Growth Factor 1 (IGF-1) and Insulin Growth Factor Binding Protein 3 (IGFBP-3) levels were initially within the normal range, but decreased in childhood and partial GH deficiency was diagnosed by stimulation tests at the age of nearly five years. Since that time he has continuously taken GH therapy, which led to catch-up growth to a height between the 75th to 90th centile. He has not developed further medical problems and is in a regular classroom setting. MS MLPA using a *GNAS*-specific assay indicated UPD(20)mat, heterodisomy UPD(20)mat was then confirmed by microsatellite typing and SNP array analysis.

Patient 7:

Patient 7 was a nine-year-old female. She was born to a 42-year-old mother via a caesarean section at 39 weeks, indicated for breech presentation and low amniotic fluid index. Birth weight was 2400 g (<1st%, 50th% for 35 weeks). There were early feeding problems, but nasogastric feeding was not initiated. During early childhood, weight fell to three SDs below the mean, proportionate with height and head circumference measurements. At presentation at 3.75 years her initial investigations included: a bone age delayed by more than one year, a normal female karyotype, normal thyroid function, a negative sweat test, no anti-tissue transglutaminase antibodies, and low normal IGF-1 levels. GH response to an insulin tolerance test at six years was suboptimal and brain MRI showed a normal pituitary. She has shown a good response to GH treatment, which commenced at age seven years. On examination at age 6.5 years her height and weight were around the 0.4th centile and her head circumference was >-3SD. She had a high-pitched voice and a triangular face with posteriorly angulated ears. There was bilateral fifth finger clinodactyly, and mild syndactyly of the second and third toes. There was no skeletal asymmetry, or café-au-lait patches. Her palate was intact and there were no other unusual findings on clinical examination. At age 9.3 years, her height was 119.4 cm (<2nd%), weight was 25 kg (25th%) and head circumference was 49.7 cm (>-3SD). Early development was entirely normal, and there were no difficulties in meeting educational targets. An older brother weighed 3.700 kg at birth, and was healthy and well-grown at 17 years of age. Her mother and father were of average height, but the latter reported a delayed puberty and consequently relative short stature during childhood. The maternal grandmother was reported to be short (approximately 154 cm, 5-10th %), but there was no additional family history of short stature. Given the phenotypic overlap with Silver-Russell syndrome, tests for UPD7(mat) and methylation abnormalities were performed, which were normal. Methylation-sensitive PCR investigations at a number of additional differentially methylated regions, including three loci on chromosome 20 (*NNAT*, *L3MBTL1* and *GNAS/NESP/NESPAS*), suggested UPD(20)mat. Subsequent microsatellite analyses with parental samples supported this diagnosis. In-situ hybridization studies performed on uncultured buccal cells showed no evidence of trisomy 20 mosaicism.

**DISCUSSION**

We present clinical and molecular evidence for a novel imprinting disorder caused by maternal uniparental disomy of chromosome 20 (UPD(20)mat syndrome), based on studies of seven new patients. This disorder is characterized by mild prenatal growth restriction, severe postnatal short stature with proportional head circumference, and profound feeding difficulty. Four previously-reported patients and an additional patient from the UPD database with UPD(20)mat demonstrated this pattern of growth delay and failure-to-thrive; however, their diagnoses were complicated by mosaic trisomy 20 (Table 1). It is possible that residual undetected trisomy mosaicism contributes to the phenotype of the patients presented here; however, the striking similarities in the phenotype implicate UPD as the causative factor. Additionally, growth delay and failure-to-thrive are not reported in six patients with mosaic trisomy 20 where the disomic cell line had biparental inheritance, providing additional evidence that UPD(20)mat is necessary for this phenotype (Table 1). 10-12 Furthermore, there are no reports about UPD(20)mat carriers with a normal clinical outcome. Taken together, this suggests that UPD(20)mat leads to growth restriction, early feeding difficulties and severe postnatal growth delay. In our series there is no evidence for significant developmental delay, as all individuals are doing well in an age-appropriate classroom setting, although three of the seven patients have a history of hypotonia. Four of the patients in this series responded to growth hormone treatment. This included two patients with demonstrable growth hormone deficiency, which was also reported previously in a single case.7 Additional variable features found in previously-published individual cases may be the result of the chromosomal abnormalities that lead to the formation of the UPD(20)mat, such as mosaic trisomy 20, or homozygosity for pathogenic variants in disease-associated genes.

Although some individuals presented with additional findings, the striking phenotypic similarity is the unexplained feeding difficulty manifesting in early infancy. Generally, the infants did not show a normal hunger drive, would not wake to eat, and would not spontaneously cry to be fed. Despite extensive testing in most patients, no anatomic or physiologic etiology could be found in any of the cases. Five out of seven of the patients depended on direct gastric feeds in infancy until late preschool/early elementary school. They gained weight on feeds, but may have had an increased energy requirement as their improvement was not as great as would be expected for the amount of calories consumed. At the time of last evaluation, they still displayed decreased hunger, generally eating small meals with parental encouragement.

Interestingly, a reported patient with isolated paternal UPD of 20q (UPD(20q)pat) was found to have PTH resistance, but was also more than three standard deviations above normal height and weight at six years.13 The most promising causative locus in the 20q region is *GNAS*, which is known to be imprinted and a cause of human disease. The *GNAS* locus is complex with multiple promoters, differentially methylated regions, and parent-of-origin specific expression limited to certain tissues. Mutations in *GNAS* are associated with a number of diseases including Albright’s hereditary osteodystrophy (AHO) and pseudohypoparathyroidism (PHP) when they occur on the paternal allele, and pseudopseudohypoparathyroidism (PPHP) on the maternal allele. Abnormalities of the paternal imprint at the *GNAS* region has been implicated in obesity.14 There are multiple mouse models showing that loss of paternal alleles leads to decreased adipose tissue, a higher metabolic rate, and poor suckling.15-17 These findings suggest that *GNAS* plays a significant role in feeding, growth, and energy metabolism. Further studies on the *GNAS* expression in our patients are underway to explore its role in the UPD(20)mat phenotype. In addition, there are other potentially important imprinted loci on chromosome 20, such as *L3MBTL1* and *NNAT*, which may also be implicated. This work may lead to insights into the basic science of hunger and metabolism control, and even pharmacologic manipulation of these areas.

Both patients 5 and 7 were investigated as possible Silver Russell syndrome (SRS) and there are many similarities with this phenotype including low birth weight, failure to thrive, post natal growth restriction, severe feeding difficulties, hyperpigmented skin regions, and clindodactyly. These patients differ from SRS as there is no asymmetry, no described prominence of the forehead, and no relative macrocephaly. However more cases need to be reported to make a clear distinction between this phenotype and that of SRS. There is also overlap with UPD(14)mat or Temple Syndrome, which demonstrates growth restriction and hypotonia.

Advanced maternal age is associated with an increased risk of nondisjunction resulting in aneuploidies. Of note is the observation in this study that the mean maternal age is 40 years which provides some evidence that UPD20 may be secondary to aneuploidy rescue. All five patients with high-resolution SNP array testing had genotyping patterns suggesting a meiosis II error or postzygotic mitotic error resulting in maternal UPD. Patients 1 and 2 had homozygosity over the entire chromosome (Figure 2A), and patients 3, 4, and 5 had homozygosity limited to the centromeric region (Figure 2B). This pattern is consistent with trisomy rescue after meiosis II error with evidence of crossing over. The presence of complete heterodisomy would not be readily detected using SNP array technology, unless parental samples are tested up front. Therefore it is important to perform trio testing by SNP chromosomal microarray or by performing short tandem repeat typing over multiple loci on the chromosome.

Conclusion:

Here we describe UPD(20)mat as an important and novel cause of growth failure and failure-to-thrive, and suggest that it may be defined as a new imprinting disorder. This diagnosis should be considered in patients with these clinical features, and UPD(20)mat testing should be included in the diagnostic workup. These patients each endured a lengthy diagnostic odyssey, including surgery, causing significant stress for the family and increased medical costs. Therefore, in any child with early-onset idiopathic severe feeding difficulty, UPD(20)mat should be considered. Patients who present with Silver-Russell or Temple syndrome, but exclusion of their known molecular disturbances, are strong candidates for UPD(20)mat as there appears to be significant phenotypic overlap. Supporting signs would include IUGR, hypotonia, fifth-finger clinodactyly, and mild abnormalities of skin pigmentation. It is difficult to estimate the prevalence of UPD(20)mat in patients with severe feeding difficulties, as the majority of these patients do not undergo testing that would identify this condition. In addition, it appears that growth hormone therapy should be considered in patients with UPD(20)mat, as all four patients in our series who have received it have experienced linear growth acceleration while taking it. We believe that we will see increased diagnosis and treatment of UPD(20)mat as the condition becomes more recognized across multiple pediatric specialties.

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Figure 1: Patients with maternal uniparental disomy of chromosome 20, there are no overt facial dysmorphisms. Upper panel left to right: Patient One at 11 months, Patient Two at 14 months, Lower panel left to right: Patient Four at 12 months and again at four years.

Figure 2: Chromosomal SNP array results and plausible mechanism for formation. A: Homozygosity over entire chromosome 20; B: Homozygosity spanning the centromere

Table 1: Previously-reported patients with mosaic trisomy 20 with biparental disomic inheritance, mosaic trisomy 20 with maternal disomic inheritance, and isolated maternal uniparental disomy with the seven new patients described here. There is a shared phenotype of failure to thrive and growth delay among the patients with UPD(20)mat.

**Abbreviations:**

UPD(20)mat - Maternal uniparental disomy of chromosome 20; UPD - Uniparental disomy; IUGR - Intrauterine growth failure; PTH - Parathyroid hormone; SNP - Single nucleotide polymorphisms; MS MLPA - Methylation-specific multiplex ligation-dependent probe amplification; PCR - Polymerase chain reaction; FTT - Failure to thrive; GH - Growth hormone; g – Grams; cm – Centimeters; Kg – Kilograms; NICU - Neonatal Intensive Care Unit; IGF-1 - Insulin Growth Factor 1; IGFBP-3 - Insulin Growth Factor Binding Protein 3; AHO - Albright’s hereditary osteodystrophy; PHP – Pseudohypoparathyroidism; PPHP - Pseudopseudohypoparathyroidism

**Contributor’s Statement:**

Surabhi Mulchandani: Ms. Mulchandani conceived the study, participated in patient evaluation, data interpretation, and developed the manuscript.

Elizabeth J. Bhoj: Dr. Bhoj coordinated and supervised data collection, drafted the initial manuscript, and approved the final manuscript as submitted.

Minjie Luo: Dr. Luo participated in data analysis and interpretation, manuscript development and editing, and approved the final manuscript as submitted.

Nina Powell-Hamilton: Dr. Powell-Hamilton participated in patient evaluation, clinical diagnosis, and approved the final manuscript as submitted.

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Karen W. Gripp: Dr. Gripp participated in patient identification, clinical evaluation, manuscript development, and approved the final manuscript as submitted.

Miriam Elbracht: Dr. Elbracht designed and supervised the clinical data in the German center, critically reviewed the manuscript, and approved the final manuscript as submitted.

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I. Karen Temple: Dr. Temple recruited a patient into the study, assisted with design, drafting and review of research manuscript, and approved the final manuscript as submitted.

Holly Dubbs: Ms. Dubbs participated in initial clinical evaluation, critical review of the manuscript, and approved the final manuscript as submitted.

Elaine H. Zackai: Dr. Zackai evaluated and recruited patients into the study and approved the final manuscript as submitted.

Nancy B. Spinner: Dr. Spinner participated in review of data and discussion and editing of the manuscript, and approved the final manuscript as submitted.

Ian D.Krantz: Dr. Krantz saw and recruited patients into the study, assisted with design, drafting and review of research manuscript, and approved the final manuscript as submitted.

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