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# Genetics Corner: "Coat-hanger" ribs and Bell-Shaped Thorax in an Infant with Paternal Uniparental Disomy for Chromosome 14

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**Clinical Summary:**

In 2007, a genetic consultation was requested for a 31-week gestation female infant with omphalocele and a bell-shaped thorax. A fetal ultrasound had detected a fetal cystic hygroma, scalp edema, and an abdominal wall defect. An amniocentesis was performed, and fetal chromosome analysis was normal: 46,XX. There was limited prenatal care. The mother denied teratogenic exposures during the pregnancy. The infant was born by emergency C-section for fetal distress to a 19-year-old primigravida mother in preterm labor. Amniotic fluid was meconium stained. BW was1535 g (50$^{th}$ %ile). APGAR scores were 1$^{1}$ (-2 respiratory, reflex, color and tone and -1 rate), 5$^{5}$ (-2 reflex, -1 respiratory, color, tone) and 8$^{10}$ (-1 tone and reflex). She was intubated and transferred to the NICU.

The family history was non-contributory, although the mother, all 6 of her siblings (including four maternal half-siblings), and maternal grandmother, who were of African American ancestry, had postaxial polydactyly.

An echocardiogram detected a medium-sized patent ductus arteriosus (PDA), patent foramen ovale (PFO) with stretched septum primum, and severe pulmonary hypertension (PPHN). On an abdominal ultrasound exam, there was mild pelviectasis, bilateral ureterectasis, and a dilated bladder.

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A radiographic survey noted bell-shaped thorax and rib deformities. Twelve pairs of ribs were seen without evidence of segmentation anomaly of the spine. Outside expert review of the radiographs described the narrow, bell-shaped thorax, 'coat-hanger' ribs (Figure 1) with anterior beaking of vertebrae on the lateral view and suggested the diagnosis of uniparental disomy (UPD) of chromosome 14. Molecular genetic testing using microsatellite markers and comparing the infant's sample with her parents' confirmed paternal UPD for chromosome 14 (isodisomy).

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The infant had a complicated NICU course. She could not be weaned from ventilatory support for pulmonary hypoplasia and restricted, narrow thorax. During the last two weeks of her life, she required higher pressures and more respiratory support. She had several episodes of respiratory arrest and CPR. She died in the NICU at two months of age.

***"UPD can be isodisomic when the two chromosomes are derived from the same homolog (sister chromatids) or heterodisomic, when the two chromosomes are different, each derived from one of the two homologs that make up the chromosome pair. Chromosome microarrays were not widely available when this patient was diagnosed in 2007. It is noteworthy that routine chromosome analysis was performed in this child, but conventional chromosome analysis (that produces a karyotype) cannot detect UPD."***

**Discussion:**

This infant with an abdominal wall defect and "coat-hanger" ribs has clinical features consistent with Kagami-Ogata syndrome (KOS), which was caused by paternal uniparental disomy for chromosome 14 (pUPD14). Uniparental disomy describes the inheritance of both members of a pair of chromosomes (or a portion of a chromosome pair) from only one parent.

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The phenomenon of *genomic imprinting* (Figure 2) affects gene expression from the chromosome 14q32.2 region. Genes located in this region are differentially expressed based on the parent of origin. Genomic imprinting, an epigenetic phenomenon, affects gene expression by modifying molecules that bind to DNA and thereby regulate it. The best understood of several epigenetic changes is the addition of methyl groups to cytosine residues, which effectively keeps the DNA tightly coiled and stops gene expression. In normal circumstances, only one of the chromosomes 14 (chr 14) is methylated, and the other is unmethylated. Differentially methylated regions (DMRs) occur during the formation of the egg or sperm and are determined by the sex of the parent that contributed that chromosome. The paternally-derived chr 14 is normally methylated, and the maternally-derived chr 14 is normally unmethylated. When both copies of chr 14 are methylated, there is no gene expression from the genes normally expressed from the maternally-derived chr 14. This effectively silences these maternally expressed genes, also called MEGs.

KOS occurs when genes on the maternally-derived 14q32.2 are not expressed: *MEG3* and *IG* DMRs. Paternal UDP14 is the most common cause of KOS, but it can also be caused by a microdeletion or epimutation involving these differentially methylated regions (DMRs) (Figure 3)

Paternal UPD14 is the cause of KOS in 2/3 of patients. UPD can follow a phenomenon known as *trisomy rescue*. When two homologs from a chromosome pair fail to segregate into two daughter cells during parental meiosis, the germ cell is disomic instead of haploid. After fertilization, the resulting zygote is trisomic for that chromosome pair. As many trisomies are not viable, the embryo can survive only if one of the extra chromosomes is lost, so-called trisomy rescue. When this happens, about a third of the time, the chromosome originating from the haploid (normal) gamete is eliminated, resulting in a cell with two chromosomes from a pair that originated from the same parent UPD (3).

***"Of the other mechanisms that can generate UPD, monosomy rescue is the most likely in our patient. This rescue occurs when a gamete without a copy of chr 14 is fertilized by a normal haploid gamete that then duplicates its single copy of chr 14, which populates both members of the chr 14 pair in the surviving zygote."***

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gamete without a copy of chr 14 is fertilized by a normal haploid gamete that then duplicates its single copy of chr 14, which populates both members of the chr 14 pair in the surviving zygote. This coupling results in 2 identical chromosomes 14, also called *isodisomy*, which can be detected on SNP (single nucleotide polymorphism) chromosome microarray analysis. Microarray analysis can also detect deletions in the imprinted region from the maternally-derived chromosome 14. Both inherited and *de novo* Robertsonian translocations involving chromosome 14 increase the risk for KOS due to trisomy and monosomy rescue. This was ruled out in our patient by her normal chromosome analysis.

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Methylation analysis is recommended as a first-tier test in evaluating suspected KOS because it detects hypermethylation of *IG*-DMR and *MEG3*-DMR regardless of the mechanism. Chromosome analysis *and* chromosome microarray testing should be ordered to detect a Robertsonian translocation involving chr 14 or a copy number variant or isodisomy of chromosome 14, respectively.

The most striking feature of KOS (1,2) is the characteristic 'coat-hanger' appearance of the ribs on plain radiographs. The ribs bow in the cranial direction posteriorly and in the caudal direction anteriorly. This rib arrangement is considered a pathognomonic feature. The dysmorphic facial features of KOS are recognizable as a facial 'gestalt': full cheeks, short palpebral fissures, broad, flat nasal bridge, protruding philtrum, and small ears. Abdominal wall defects, including omphalocele, placentomegaly, and polyhydramnios, are common (Figure 4). Respiratory failure from pulmonary hypoplasia and pulmonary insufficiency causes infantile death, and survivors can have short stature and intellectual disability.

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**Practical applications:**

1. Recognize the significance of a bell-shaped thorax with "coat-hanger" ribs in diagnosing Kagami-Ogata syndrome (KOS), a disorder caused by abnormalities affecting the differentially methylated region on distal chromosome 14.
2. Understand that the most common cause of KOS is paternal uniparental disomy for chromosome 14.
3. Recall that UPD, caused by *trisomy rescue* or *monosomy rescue*, is not detectable with a routine chromosome analysis, but other causes of KOS, including a Robertsonian translocation of chr 14, can be detected by conventional chromosome analysis.
4. Order methylation analysis, chromosome analysis, and chromosome microarray. Isodisomy for chromosome 14 to diagnose Kagami-Ogata syndrome.

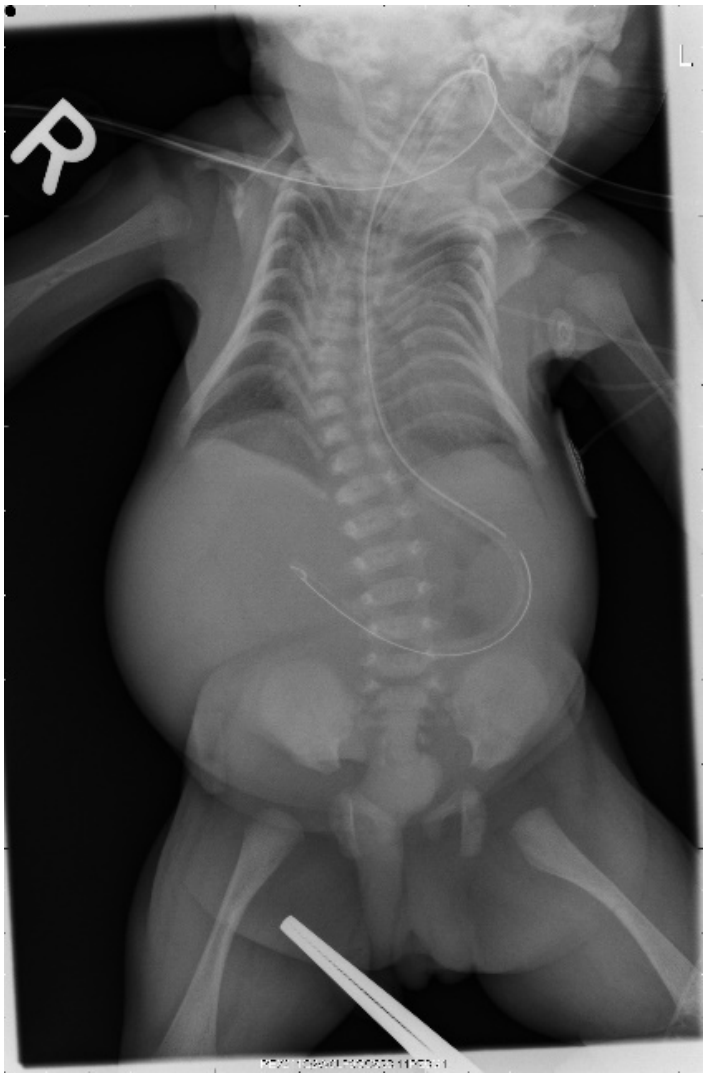


*Figure 1: Our patient had a bell-shaped thorax and "coat-hanger" shaped ribs, features that are key to the diagnosis of Kagami-Ogata syndrome.*

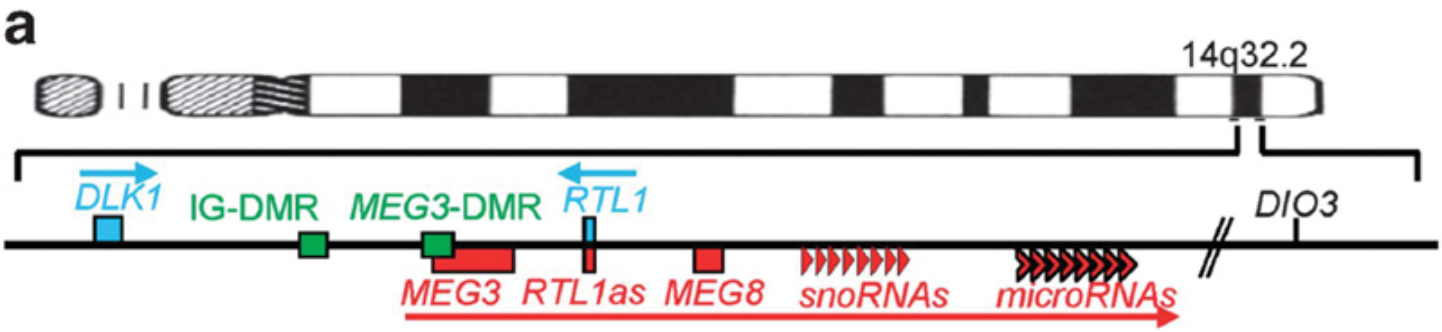


*Figure 2: Paternally expressed genes (PEGs-in blue) and maternally expressed genes (MEGs- in red) on chromosome 14q32.2 (1)*

Hypomethylated DMRs (where genes are expressed) are shown in green, and hypermethylated DMRs (where genes are silenced) are shown in red. Normally, paternal DMRs are hypermethylated, and maternal DMRs are hypomethylated.

All are hypermethylated in uniparental disomy of chromosome 14 with two copies of paternal DMRs.

In maternally derived epimutations, both DMRs of maternal origin are hypermethylated.

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| | Paternal DMRs | | Maternal DMRs | |
|---|---|---|---|---|
| | MEG3 | IG | MEG3 | IG |
| Normal | | | | |
| UPD(14)pat | | | | |
| | | | | |
| Epimutation | | | | |
| Microdeletion | | | | |

*Figure 3: Paternally and maternally differentiated methylated regions (DMRs) (2):*

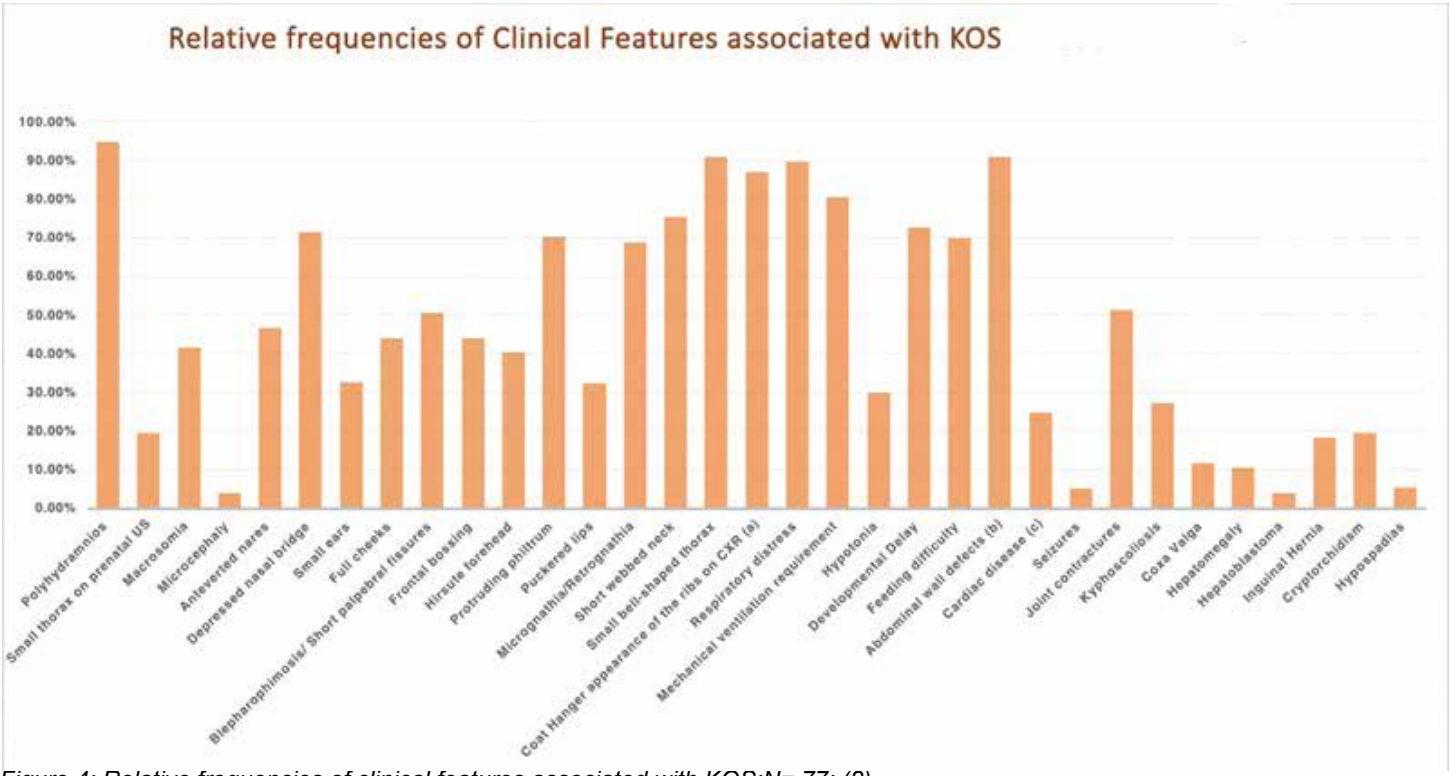


*Figure 4: Relative frequencies of clinical features associated with KOS:N= 77; (2)*

In maternally derived microdeletions, the maternal hypomethylated alleles are absent

***References:***


1. *Ogata T, Kagami M. Kagami-Ogata syndrome: a clinically recognizable upd(14)pat and related disorder affecting the chromosome 14q32.2 imprinted region. J Hum Genet. 2016 Feb;61(2):87-94. doi: 10.1038/jhg.2015.113. Epub 2015 Sep 17. PMID: 26377239; PMCID: PMC4771937.*
2. *Sakaria RP, Mostafavi R, Miller S, Ward JC, Pivnick EK, Talati AJ. Kagami-Ogata Syndrome: Case Series and Review of Literature. AJP Rep. 2021 Mar;11(2):e65-e75. doi: 10.1055/s-0041-1727287. Epub 2021 May 27. PMID: 34055463; PMCID: PMC8159623.*
3. *Eggermann T, Soellner L, Buiting K, Kotzot D. Mosaicism and uniparental disomy in prenatal diagnosis. Trends Mol Med. 2015 Feb;21(2):77-87. doi: 10.1016/j.molmed.2014.11.010. Epub 2014 Dec 2. PMID: 25547535.*


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