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# Kagami-Ogata Syndrome

Synonym: KOS14

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## Summary

### Clinical characteristics

Kagami-Ogata syndrome is characterized by developmental delay, intellectual disability, feeding difficulty with impaired swallowing, full cheeks, prominent and deep philtrum, small bell-shaped thorax with coat-hanger appearance of the ribs, and abdominal wall defects (omphalocele and diastasis recti). Additional common features include joint contractures, kyphoscoliosis, coxa valga, and laryngomalacia. Cardiac disease and hepatoblastoma have also been reported.

### Diagnosis/testing

The diagnosis of Kagami-Ogata syndrome is established in a proband with suggestive findings and findings on molecular genetic testing that suggest deficient expression of the *RTL1* antisense (*RTL1as*) allele of maternal origin due to one of the following: paternal uniparental disomy of chromosome 14; epimutation (hypermethylation) affecting the normally unmethylated *MEG3*/*DLK1* intergenic differentially methylated region (*MEG3*/*DLK1*:IG-DMR) and *MEG3* transcription start site DMR (*MEG3*:TSS-DMR) on the maternal allele; deletion of the maternally inherited 14q32.2 region that includes *MEG3*/*DLK1*:IG-DMR and/or *MEG3*:TSS-DMR, and may include *RTL1as*; deletion of the maternally inherited *RTL1as* but not *MEG3*/*DLK1*:IG-DMR or *MEG3*:TSS-DMR; translocation (or inversion) disrupting the integrity between the maternally inherited *MEG3* promoter at the *MEG3*:TSS-DMR and *RTL1as*.

### Management

*Treatment of manifestations:* Developmental and educational support; mechanical ventilation and oxygen therapy as needed after birth; tracheostomy as required; monitor and treat upper and lower respiratory tract infections; treatment of scoliosis per orthopedist; treatment of joint contractures per rehabilitation medicine specialist; tube feeding typically required for poor weight gain; gastrostomy tube feeding as needed; feeding training; treatment of cardiac disease per cardiologist; standard treatment of hepatoblastoma with surgery and chemotherapy; social work and family support.

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*Surveillance:* Monitor developmental progress, educational needs, for evidence of aspiration or respiratory insufficiency, progression of kyphoscoliosis and joint contractures, nutritional status, safety of oral intake, constipation, and family and care coordination needs at each visit. Echocardiogram annually; abdominal ultrasound and serum alpha-fetoprotein every three months until age three to four years.

*Agents/circumstances to avoid:* Avoid exposure to respiratory infections; individuals with Kagami-Ogata syndrome may develop respiratory failure with respiratory infections, especially during infancy.

## Genetic counseling

The recurrence risk of Kagami-Ogata syndrome is dependent on the genetic mechanism underlying deficient expression of the maternal *RTL1as* allele in the proband. In most affected individuals, the underlying genetic mechanism occurs as a *de novo* event and the recurrence risk to sibs is not increased. Less commonly, a parent of a proband has a predisposing genetic alteration associated with an increased recurrence risk to sibs. Recurrence of Kagami-Ogata syndrome has been reported in sibs with maternally derived deletions. If a deletion or translocation involving the chromosome 14q32.2 imprinted region has been identified in the proband, prenatal testing and preimplantation genetic testing are possible. Methylation testing of fetal DNA to examine abnormal methylation patterns of the DMRs (*MEG3/DLK1*:IG-DMR and *MEG3*:TSS-DMR) is not recommended; while DNA extracted from amniotic fluid is currently believed to provide the most reliable tissue source for evaluating fetal methylation status, false negative findings have been reported.

# Diagnosis

No consensus clinical diagnostic criteria for Kagami-Ogata syndrome have been published.

## Suggestive Findings

Kagami-Ogata syndrome **should be suspected** in individuals with the following clinical findings, especially specific (pathognomonic) findings in addition to characteristic but not specific findings and nonspecific findings [Kagami et al 2015, Ogata & Kagami 2016].

**Specific (pathognomonic) findings**

- Full cheeks and prominent and deep philtrum (See Figure 1.)
- Small bell-shaped thorax with coat-hanger appearance of the ribs (See Figure 2.)

  Note: Coat-hanger angle is increased from mid-gestation through childhood. Mid-to-widest thorax ratio is decreased from birth through early childhood [Miyazaki et al 2011, Kagami et al 2015, Ogata & Kagami 2016, Kuriki et al 2022].

**Characteristic but not specific findings**

- Abdominal wall defects such as omphalocele and diastasis recti
- Placentomegaly
- Polyhydramnios

**Nonspecific findings**

- Craniofaciocervical features such as frontal bossing, hirsute forehead, blepharophimosis, depressed nasal bridge, anteverted nares, puckered lips, micrognathia, and short, webbed neck
- Relatively large birth weight
- Developmental delay (moderate to severe)
- Feeding difficulty with impaired swallowing

- Joint contractures
- Kyphoscoliosis

**Note:** Characteristic face, small bell-shaped thorax with coat-hanger appearance of the ribs, and omphalocele can be observed on fetal ultrasound and MRI from the second trimester [Chen et al 2019, Igreja da Silva et al 2019, Molinet Coll et al 2021, Kuriki et al 2022].

## Establishing the Diagnosis

The diagnosis of Kagami-Ogata syndrome **is established** in a proband with suggestive findings and findings on molecular genetic testing that suggest deficient expression of the *RTL1* antisense (*RTL1as*) allele of maternal origin due to one of the following (see Table 1):

- Paternal uniparental disomy of chromosome 14 (upd(14)pat) (~50% of affected individuals)
- Epimutation (hypermethylation) affecting the normally unmethylated *MEG3*/*DLK1* intergenic differentially methylated region (*MEG3*/*DLK1*:IG-DMR) and *MEG3* transcription start site DMR (*MEG3*:TSS-DMR) of maternal origin (~25% of affected individuals)
- Deletion of the maternally inherited 14q32.2 region that includes *MEG3*/*DLK1*:IG-DMR and/or *MEG3*:TSS-DMR, and may include *RTL1as* (~20% of affected individuals)
- Deletion of the maternally inherited *RTL1as* but not *MEG3*/*DLK1*:IG-DMR or *MEG3*:TSS-DMR (~5% of affected individuals)
- Translocation (or inversion) disrupting the integrity between the maternally inherited *MEG3* promoter at the *MEG3*:TSS-DMR and *RTL1as* (rare)

**Molecular genetic testing** for Kagami-Ogata syndrome includes recommended first-tier testing (methylation-specific multiple ligation-dependent probe amplification [MS-MLPA]) and second-tier testing (parent-of-origin analysis for chromosome 14) as needed to identify the molecular cause and clarify recurrence risk (see Figure 3).

### First-Tier Testing

**MS-MLPA** that includes simultaneous methylation analysis of *MEG3*:TSS-DMR and deletion analysis of the multiple loci at the 14q32.2 imprinted region including *MEG3*/*DLK1*:IG-DMR, *MEG3*:TSS-DMR, and *RTL1as* is recommended. Note: (1) This testing can distinguish abnormal methylation caused by a deletion from abnormal methylation caused by upd(14)pat or epimutation, information that is important for recurrence risk counseling; (2) This testing can identify deletions of *MEG3*/*DLK1*:IG-DMR but not methylation abnormalities of *MEG3*/*DLK1*:IG-DMR, because the MS-MLPA does not address this methylation pattern.

- **If methylation is abnormal** (identification of hypermethylation of *MEG3*:TSS-DMR) but no deletion is identified, second-tier testing (parent-of-origin testing for chromosome 14) can distinguish upd(14)pat from an epimutation.
- **If methylation is normal** and a deletion of *RTL1as* is identified, second-tier testing can identify the parent of origin of the *RTL1as* deletion.

### Second-Tier Testing

**Parent-of-origin analysis for chromosome 14** using polymorphic DNA markers, which requires a DNA sample from the affected individual and both parents, can distinguish upd(14)pat and biparental chromosome 14 suggesting an epimutation. Note: Karyotype is recommended in individuals with upd(14)pat to identify those with robertsonian translocation or isochromosome 14q and clarify recurrence risk [Ogata & Kagami 2016].

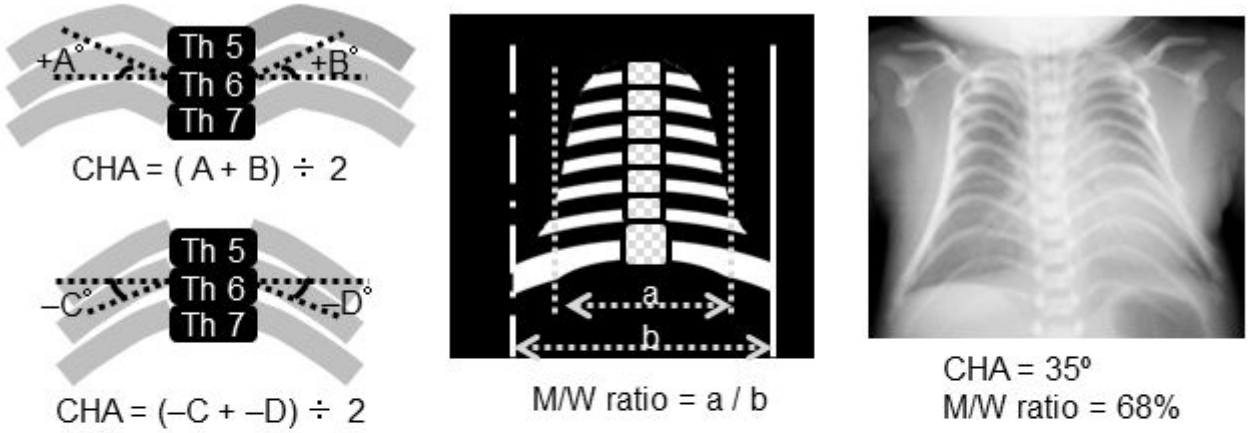
**Parent-of-origin testing for *RTL1as* deletion.** Only a deletion of the maternal *RTL1as* allele results in Kagami-Ogata syndrome. Kagami-Ogata syndrome can be due to an *RTL1as* deletion inherited from the mother or a *de novo* deletion on chromosome 14 of maternal origin.


**Figure 1.** Female at infancy, age two years, and age eight years with Kagami-Ogata syndrome due to a maternally inherited microdeletion of *DLK1*, *MEG3*/*DLK1*:IG-DMR, *MEG3*:TSS-DMR, *MEG3*, *RTL1*/*RTL1as*, *MEG8*, and a centromeric part of the snoRNA genes. Characteristic full cheeks and prominent and deep philtrum are observed from infancy through childhood.

Adapted from Ogata & Kagami [2016]

**Other testing options** (not recommended)

- Methylation analysis (methylation-specific PCR, bisulfite sequencing, and pyrosequencing) can detect abnormal methylation pattern at 14q32.2 but cannot distinguish deletion from upd(14)pat and epimutation.
- High-density SNP array analysis can detect smaller deletions and uniparental isodisomy of 14q32.2 but cannot detect uniparental heterodisomy of 14q32.2.




| | CHA | | M/W ratio | |
|---|---|---|---|---|
| | Control | KOS14 | Control | KOS14 |
| 30 weeks of GA | +9 ~ +26° (n=25) | +39° (n=1) | … | … |
| At birth | –11 ~ +1.9° (n=10) | +28 ~ +45° (n=8) | 82 ~89% (n=10) | 58 ~ 80% (n=8) |
| ~ 5 years | –21 ~ +15° (n=10) | +25 ~ +45° (n=3) | 83 ~ 98% (n=10) | >78% (n=3) |
| ~ 10 years | –9.3 ~ +20° (n=10) | … | 83 ~ 98% (n=10) | … |

**Figure 2.** Chest radiograph of a Japanese neonate with Kagami-Ogata syndrome. The coat-hanger angle (CHA) is increased from 30 weeks' gestation through age five years in individuals with Kagami-Ogata syndrome. CHA is the average of the right and left angles between the horizontal axis at the sixth costovertebral junction and the peak point of the sixth posterior rib. Note: If the ribs slope downward, the midpoint of the sixth rib is used for CHA measurement. The mid-to-widest thorax ratio is decreased in infants and young children with Kagami-Ogata syndrome.

CHA = coat-hanger angle; GA = gestational age; KOS14 = Kagami-Ogata syndrome; M/W ratio = mid-to-widest thorax ratio

Adapted from Kagami et al [2015] and Ogata & Kagami [2016]

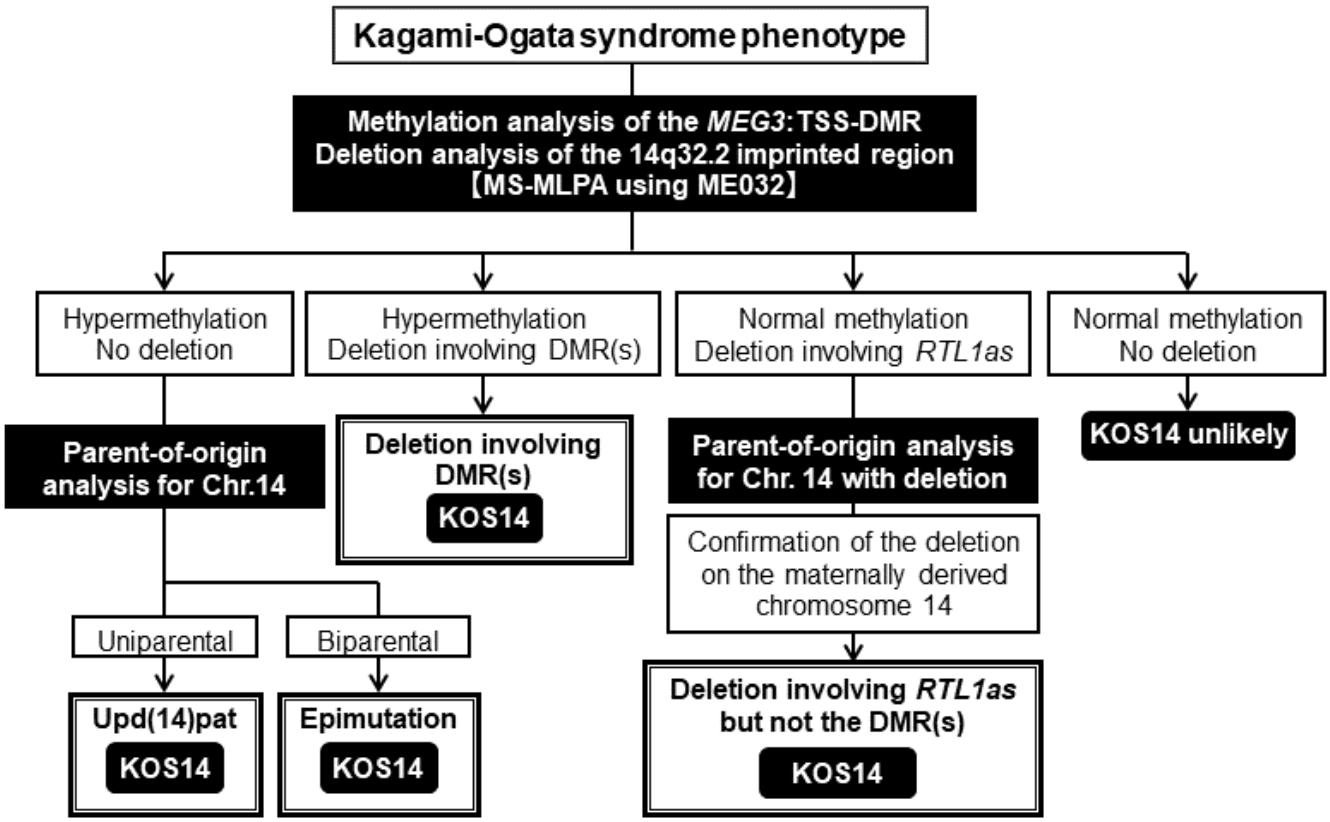



**Figure 3.** Testing algorithm to establish the diagnosis and molecular cause of Kagami-Ogata syndrome

Chr. = chromosome; DMR = differentially methylated region; KOS14 = Kagami-Ogata syndrome; MS-MLPA = methylation-specific multiple ligation-dependent probe amplification; *RTL1as* = *RTL1* antisense; TSS = transcription start site; upd(14)pat = paternal uniparental disomy of chromosome 14

**Table 1.** Molecular Genetic Testing Used in Kagami-Ogata Syndrome

| Method | Genetic Mechanism [1] | Proportion of Probands Identified by Method [2] |
|---|---|---|
| MS-MLPA [3] | upd(14)pat | ~50% |
| | Epimutation (hypermethylation) of *MEG3*:TSS-DMR (maternal) | ~25% |
| | Deletion of *MEG3*/*DLK1*:IG-DMR &/or *MEG3*:TSS-DMR (maternal) | ~20% |
| | Deletion of *RTL1as* (maternal) [4] | ~5% [5] |

*Table 1. continued from previous page.*

| Method | Genetic Mechanism [1] | Proportion of Probands Identified by Method [2] |
|---|---|---|
| Karyotype | Translocations &/or inversions disrupting the integrity between the *MEG3* promoter & *RTL1as* | Extremely rare [6] |
| | Robertsonian translocations incl 14q | Rare |

DMR = differentially methylated region; IG = intergenic; MS-MLPA = methylation-specific multiple ligation-dependent probe amplification; TSS = transcription start site; upd(14)pat = paternal uniparental disomy of chromosome 14

*1.* See Molecular Genetics for more details and see Figure 4.

*2.* Ogata & Kagami [2016], Omark et al [2021], Mackay et al [2022], Eggermann et al [2023]

*3.* Identification of hypermethylation of *MEG3:*TSS-DMR establishes the diagnosis of Kagami-Ogata syndrome. However, deletion analysis (included in MS-MLPA) and parent-of-origin analysis are required to distinguish upd(14)pat, epimutation, and deletions involving the DMRs.

*4.* Parent-of-origin analysis is necessary to confirm that the *RTL1as* deletion is present on the maternally inherited chromosome 14.

*5.* Deletion of *RTL1as* (maternal) without deletion of *MEG3*/*DLK1*:IG-DMR or *MEG3:*TSS-DMR has been identified in five individuals with Kagami-Ogata syndrome. The frequency of such deletions may be overestimated, because of the publication bias that such a rare condition would be reported preferentially.

*6.* A translocation disrupting the integrity between the maternally inherited *MEG3* promoter at the *MEG3:*TSS-DMR and *RTL1as* has been identified in one individual with Kagami-Ogata syndrome.

# Clinical Characteristics

## Clinical Description

Kagami-Ogata syndrome is characterized by developmental delay, intellectual disability, feeding difficulty, full cheeks and prominent and deep philtrum, small bell-shaped thorax with coat-hanger appearance of the ribs, and abdominal wall defects (omphalocele and diastasis recti). Additional common features include joint contractures, kyphoscoliosis, coxa valga, and laryngomalacia. Cardiac disease and hepatoblastoma have also been reported [Kagami et al 2015, Ogata & Kagami 2016]. To date, approximately 100 individuals have been diagnosed with Kagami-Ogata syndrome [Sakaria et al 2021; Mackay et al 2022; Smith et al 2024; T Ogata & M Kagami, unpublished observations].

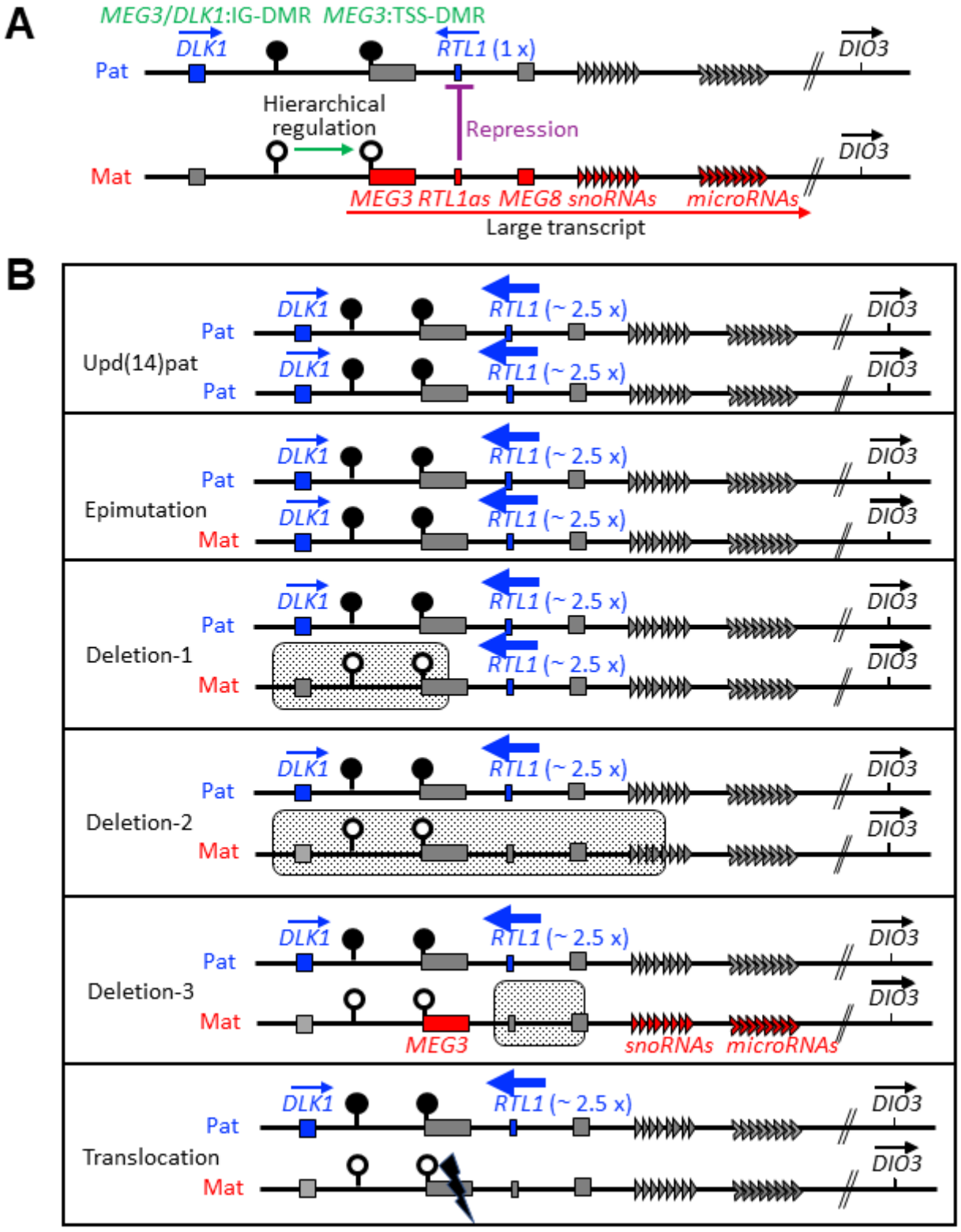



**Figure 4.** Chromosome 14q32.2 imprinted region and representative genetic causes leading to Kagami-Ogata syndrome. The black and white circles represent methylated and unmethylated differentially methylated regions (DMRs), respectively.

A. Structure and character of the imprinted region

B. Expression dosage of imprinted genes in several conditions. Stippled areas denote deleted region, and the cutting mark indicates the translocation breakpoint.

**Table 2.** Kagami-Ogata Syndrome: Frequency of Select Features

| Feature | | % of Persons w/ Feature [1] | Comment |
|---|---|---|---|
| **Pregnancy & delivery** | Polyhydramnios | >95% | |
| | Placentomegaly | ~85% | Placenta size >120% of normal |
| **Development & cognition** | Developmental delay | >95% | Moderate to severe |
| | Intellectual disability | 100% | |
| **Nutrition & growth** | Feeding difficulty | >95% | |
| | Prenatal overgrowth | >50% | Birth length &/or weight >2 SD above mean |
| | Postnatal growth deficiency | ~35% | Height &/or weight >2 SD below mean |
| **Craniofacial features** | Full cheeks & prominent & deep philtrum (most common & specific features) | >90%-95% | Additional features incl frontal bossing, hirsute forehead, blepharophimosis, depressed nasal bridge, anteverted nares, puckered (somewhat narrow & tented) lips, micrognathia, & short, webbed neck |
| **Skeletal abnormalities** | Small bell-shaped thorax | 100% | |
| | Coat-hanger appearance of ribs | 100% | |
| | Joint contractures | 60%-65% | |
| | Kyphoscoliosis | ~40% | |
| | Coxa valga | ~33% | |
| **Respiratory** | Laryngomalacia | ~40% | |
| **Abdominal wall defects** | Diastasis recti | 65%-70% | |
| | Omphalocele | ~30% | |
| **Other features** | Cardiac disease | 25% | |
| | Hepatoblastoma | 5%-10% | |

SD = standard deviations

*1.* Kagami et al [2015]; similar data have been summarized by Sakaria et al [2021].

**Pregnancy and delivery.** Polyhydramnios is typically identified in the second trimester at a median gestational age of 25.5 weeks (range: 14-30 weeks' gestation); amnioreduction is required in most pregnancies after 25 weeks' gestation (~80%) and in almost all pregnancies after 30 weeks' gestation. Polyhydramnios is due to placentomegaly and impaired swallowing. Thoracic and abdominal abnormalities are found on prenatal ultrasound in ~40% of fetuses from approximately 25 weeks' gestation. Premature delivery is frequent (~80%), with a median gestational age at delivery of 32.5 weeks (range: 30-35 weeks' gestation).

**Developmental delay.** Head control occurs at a median age of seven months (range: 3-36 months). Sitting without support occurs at a median age of 12 months (range: 8-25 months). Walking without support occurs at a median age of 25.5 months (range: 20-49 months). Only mild delay has been reported in two individuals with

Kagami-Ogata syndrome: one individual with an epimutation [Higashiyama et al 2022] and one with mosaic paternal uniparental disomy of chromosome 14 (upd(14)pat) [Haug et al 2017].

**Intellectual disability.** Intellectual disability is reported in all individuals, with a median IQ of 55 (range: 29-70).

No abnormal brain MRI findings were delineated in five individuals examined.

**Growth.** Prenatal growth is well preserved and birth weight and length are usually above the mean. Range in birth weight is 0.1 standard deviations (SD) below the mean to 8.8 SD above the mean, and range in birth length is 1.7 SD below the mean to 3.0 SD above the mean. However, postnatal growth is frequently compromised primarily due to poor nutrition related to respiratory failure and feeding difficulty. In individuals age one to 15 years, range in weight is 6.0 SD below the mean to 4.0 SD above the mean, and range in length/height is 8.7 SD below the mean to 1.1 SD above the mean.

**Craniofacial features** (see Figure 1) in individuals with Kagami-Ogata syndrome include frontal bossing (~75%), hirsute forehead (~70%), blepharophimosis (70%-75%), full cheeks (>90%), depressed nasal bridge (>90%), anteverted nares (80%), prominent and deep philtrum (>95%), puckered (somewhat narrow and tented) lips (>50%), micrognathia (~100%), and short, webbed neck (>90%). Craniofacial features are typically present in infancy and consistently recognizable during childhood. While many of the craniofacial features are nonspecific, full cheeks and prominent and deep philtrum are very common and appear specific to Kagami-Ogata syndrome.

**Thoracic abnormalities with respiratory failure.** A small bell-shaped thorax is evident in infancy. Objective assessment of increased coat-hanger angle and decreased mid-to-widest thorax ratio is possible from fetal life through childhood (see Figure 2). The shape of the thorax appears normal after infancy, whereas coat-hanger appearance of the ribs remains discernible throughout childhood. Because of the thoracic anomalies, mechanical ventilation with oxygen has been required in more than 90% of individuals, with a median duration of one month (range: 0.1-17 months). Tracheostomy is sometimes necessary due to severe laryngomalacia.

**Other skeletal abnormalities.** Contractures at various joints, kyphoscoliosis, and coxa valga are also reported. The severity of these findings is variable among affected individuals.

**Feeding/gastrointestinal manifestations.** Tube feeding was required in all individuals who survived more than one week, with a median duration of 7.5 months (range: 0.1-89 months). Diastasis recti is common, and omphalocele can also occur. Abdominal wall weakness may cause constipation.

**Cardiac disease.** Cardiovascular malformations are recognized in ~25% of affected individuals. Of eight individuals who have been confirmed to have cardiac malformations, two have atrial septal defect, one has ventricular septal defect, four have patent ductus arteriosus, and one has pulmonary stenosis. These cardiac lesions are mild and do not require intensive medication or surgery. No individuals have been reported to have cardiomyopathy or conduction defects.

**Hepatoblastoma** has been identified in three individuals during infancy out of the 100 reported individuals to date.

**Other.** Simple seizure was reported in one individual [Kagami et al 2015].

**Prognosis.** Mortality is relatively high before age five years (20%-25% of individuals), but increased mortality is not observed in those with Kagami-Ogata syndrome older than age five years. The cause of death is variable; respiratory failure constitutes the primary cause of death. To date, nine adults age 18 years and older with Kagami-Ogata syndrome have been identified, including four unpublished individuals; the oldest affected individual is age 35 years [Smith et al 2024; T Ogata & M Kagami, personal observations].

## Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been identified [Kagami et al 2015].

Note: Paternal uniparental disomy of chromosome 14, epimutations, and deletions that do not include *RTL1as* are associated with approximately five times the *RTL1* expression compared to controls, whereas deletions including *RTL1as* are associated with approximately 2.5 times the *RTL1* expression (see Molecular Genetics). However, because of the small number of deletions including *RTL1as*, it is unknown if the phenotype is milder in individuals with approximately 2.5 times the *RTL1* expression than in individuals with five times the *RTL1* expression compared to controls.

## Penetrance

Penetrance is complete, and affected individuals invariably show full cheeks, prominent and deep philtrum, and small bell-shaped thorax with coat-hanger appearance of the ribs. However, there could be bias in that molecular studies are performed only when individuals have certain clinical features. In this regard, two individuals with upd(14)pat mosaicism have been reported to date; one individual has a mild phenotype, while the other has a typical Kagami-Ogata syndrome phenotype [Haug et al 2017, Li et al 2021]. Thus, some mosaic individuals with nearly normal phenotype may have been overlooked.

## Nomenclature

Kagami-Ogata syndrome has also been referred to as upd(14)pat syndrome. However, the term upd(14)pat syndrome may be misleading, as Kagami-Ogata syndrome can be caused by genetic mechanisms other than paternal uniparental disomy of chromosome 14. Thus, "Kagami-Ogata syndrome" has been proposed to describe the unique clinical entity caused by various (epi)genetic aberrations affecting the chromosome 14q32.2 imprinted region.

## Prevalence

To date, approximately 100 individuals with Kagami-Ogata syndrome have been reported [Mackay et al 2022, Eggermann et al 2023]. In Japan, 76 individuals with Kagami-Ogata syndrome (some of whom are reported in the literature) have been identified [T Ogata & M Kagami, personal observations]. It is likely that many individuals remain undiagnosed.

# Genetically Related (Allelic) Disorders

**Temple syndrome** (OMIM 616222) is primarily caused by absent expression of *DLK1* (absence of *RTL1* expression may also be involved) [Kagami et al 2017b]. Temple syndrome results from maternal uniparental disomy of chromosome 14 (upd(14)mat), epimutation (hypomethylation of the normally methylated paternal *MEG3*/*DLK1*:IG-DMR and paternal *MEG3*:TSS-DMR), and deletions and sequence variants affecting *DLK1* (and *RTL1*) of paternal origin. (Loss of the normally methylated DMRs of paternal origin does not cause epigenetic alteration.) Clinical features of Temple syndrome include hypotonia, pre- and postnatal growth deficiency, relative macrocephaly, feeding difficulty during infancy, and central precocious puberty in later ages [Ioannides et al 2014, Kagami et al 2017b]. Unlike Kagami-Ogata syndrome, thoracic and abdominal abnormalities are uncommon in Temple syndrome [Prasasya et al 2020].

# Differential Diagnosis

**Table 3.** Disorders of Interest in the Differential Diagnosis of Kagami-Ogata Syndrome

| Gene(s) / Genetic Mechanism | Disorder | MOI | Features of Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/Kagami-Ogata syndrome | Distinguishing from Kagami-Ogata syndrome |
| Abnormal methylation pattern at 11p15.5; CNV involving 11p15.5; or *CDKN1C* pathogenic variant | Beckwith-Wiedemann syndrome | See Footnote 1. | • Polyhydramnios<br>• Placentomegaly<br>• Omphalocele<br>• Overgrowth<br>• Hepatoblastoma (↑ risk) | Absence of:<br>• Characteristic face w/full cheeks & prominent & deep philtrum<br>• Small bell-shaped thorax w/coat-hanger appearance of ribs |
| >20 genes incl:<br>*DYNC2H1*<br>*IFT140*<br>*KIF7*<br>*NEK1*<br>*WDR19*<br>*WDR34* | Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia—Jeune syndrome) (OMIM PS208500) | AR | Small thorax | |
| *GPC3* | Simpson-Golabi-Behmel syndrome type 1 | XL | • Polyhydramnios<br>• Abdominal wall defects<br>• Overgrowth<br>• Hepatoblastoma (↑ risk) | Absence of small bell-shaped thorax w/coat-hanger appearance of ribs |

AR = autosomal recessive; CNV = copy number variant; MOI = mode of inheritance; XL = X-linked

*1.* Reliable recurrence risk assessment requires identification of the genetic mechanism in the proband that underlies the abnormal expression of imprinted genes in the BWS critical region. While the majority of families have a recurrence risk of less than 1%, certain underlying genetic mechanisms may be associated with a recurrence risk as high as 50% (see Beckwith-Wiedemann Syndrome).

# Management

No clinical practice guidelines for Kagami-Ogata syndrome have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Kagami-Ogata syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 4.** Kagami-Ogata Syndrome: Recommended Evaluations Following Initial Diagnosis

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Development** | Developmental assessment | • To incl gross motor & fine motor skills, adaptive, cognitive, & speech-language eval<br>• Eval for early intervention / special education |
| **Neurologic** | Neurologic eval | |
| **Respiratory** | Respiratory eval immediately after birth | Most infants present w/respiratory failure due to upper or lower respiratory infection, esp during infancy & early childhood. |

*Table 4. continued from previous page.*

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Musculoskeletal** | Orthopedics / physical medicine & rehab / PT & OT eval | To incl assessment of:<br>• Contractures & kyphoscoliosis<br>• Mobility, ADL, & need for adaptive devices<br>• Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) |
| **Gastrointestinal/ Feeding** | • Gastroenterology / nutrition / feeding team eval<br>• Assessment of height & weight | • To incl eval of aspiration risk & nutritional status<br>• Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk. |
| **Cardiac disease** | Echocardiogram | |
| **Tumorigenesis** | Abdominal ultrasound for hepatoblastoma | |
| | Serum AFP | Serum AFP level should be reviewed by a physician w/experience interpreting AFP levels if possible (e.g., oncologist, clinical geneticist) |
| **Genetic counseling** | By genetics professionals [1] | To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of Kagami-Ogata syndrome to facilitate medical & personal decision making |
| **Family support & resources** | By clinicians, wider care team, & family support organizations | Assessment of family & social structure to determine need for:<br>• Community or online resources such as Parent to Parent<br>• Social work involvement for parental support<br>• Home nursing referral |

ADL = activities of daily living; AFP = alpha-fetoprotein; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

**Table 5.** Kagami-Ogata Syndrome: Treatment of Manifestations

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Developmental delay / Intellectual disability / Neurobehavioral issues** | See Developmental Delay / Intellectual Disability Management Issues. | |
| **Respiratory failure** | • Mechanical ventilation & oxygen therapy are almost invariably required immediately after birth.<br>• Tracheostomy may be required.<br>• Monitor for & treat upper & lower respiratory tract infections. | |
| **Skeletal abnormalities** | • Treatment of kyphoscoliosis per orthopedist; brace or surgery may be indicated.<br>• Treatment per rehab medicine specialist for joint contractures | |

*Table 5. continued from previous page.*

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Poor weight gain / Growth deficiency** | • Tube feeding is almost invariably required.<br>• Gastrostomy tube feeding as needed<br>• Feeding training/rehab is recommended. | Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia |
| **Cardiac disease** | Treatment per cardiologist | Medication may be indicated; there are no reports of persons w/Kagami-Ogata syndrome having cardiac surgery. |
| **Hepatoblastoma** | Standard treatment w/surgical resection & chemotherapy | |
| **Family/Community** | Ensure appropriate social work involvement to connect families w/local resources, respite, & support. | Ongoing assessment of need for palliative care involvement &/or home nursing |

## Developmental Delay / Intellectual Disability Management Issues

In the absence of knowledge about the detailed clinical course of Kagami-Ogata syndrome, careful follow up appropriate for each affected individual is recommended.

## Motor Dysfunction

**Gross motor dysfunction.** Physical therapy is recommended to maximize mobility and reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

**Fine motor dysfunction.** Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

**Oral motor dysfunction** should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, a nasogastric or gastrostomy tube may be necessary.

**Communication issues.** Consider evaluation for alternative means of communication for individuals who have expressive language difficulties.

## Neurobehavioral/Psychiatric Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies.

# Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

**Table 6.** Kagami-Ogata Syndrome: Recommended Surveillance

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Development** | Monitor developmental progress & educational needs. | At each visit |
| **Respiratory** | Monitor for evidence of aspiration, respiratory insufficiency. | |
| **Skeletal abnormalities** | Monitor for progression of kyphoscoliosis & joint contractures. | |
| **Feeding** | Eval of nutritional status & safety of oral intake | |
| **Gastrointestinal** | Monitor for constipation. | |
| **Cardiac** | Echocardiogram | Annually |
| **Hepatoblastoma** | • Abdominal ultrasound<br>• Serum AFP | Every 3 mos until age 3-4 yrs [1, 2] |
| **Family/Community** | Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning). | At each visit |

AFP = alpha-fetoprotein
*1.* Sakaria et al [2021]
*2.* This screening has been recommended for hepatoblastoma in Beckwith-Wiedemann syndrome [Kalish et al 2017, Kalish et al 2024].

## Agents/Circumstances to Avoid

Avoid exposure to respiratory infections; individuals with Kagami-Ogata syndrome may develop respiratory failure with respiratory infections, especially during infancy.

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

The recurrence risk of Kagami-Ogata syndrome is dependent on the genetic mechanism underlying deficient expression of the maternal *RTL1as* allele in the proband. Genetic mechanisms known to be causative of Kagami-Ogata syndrome include the following:

- Paternal uniparental disomy of chromosome 14 (upd(14)pat) *
- Epimutation (hypermethylation) of the normally unmethylated *MEG3*/*DLK1* intergenic differentially methylated region (*MEG3*/*DLK1*:IG-DMR) and *MEG3* transcription start site DMR (*MEG3*:TSS-DMR) of maternal origin *

- Deletion of the 14q32.2 region that includes *MEG3*/*DLK1*:IG-DMR and/or *MEG3*:TSS-DMR, and may include *RTL1as* *
- Translocation (or inversion) disrupting the integrity between the maternally inherited *MEG3* promoter at the *MEG3*:TSS-DMR and *RTL1as*

In most affected individuals, the underlying genetic mechanism occurs as a *de novo* event and the recurrence risk to sibs is not increased. Less commonly, a parent of the proband has a predisposing genetic alteration (e.g., a maternally transmitted deletion) associated with an increased recurrence risk to sibs.

* If the diagnosis of Kagami-Ogata syndrome in the proband has been established by identification of hypermethylation of *MEG3*/*DLK1*:IG-DMR and *MEG3*:TSS-DMR, deletion analysis (if not already performed in conjunction with methylation analysis via MS-MLPA) and parent-of-origin analysis are required to distinguish upd(14)pat, epimutation, and deletions involving the DMRs. Parent-of-origin analysis for chromosome 14 using polymorphic DNA markers (which requires a DNA sample from the proband and both parents) can distinguish upd(14)pat and biparental chromosome 14 suggesting an epimutation (see Establishing the Diagnosis and Figure 3).

## Risk to Family Members

**Parents of a proband**

- The parents of a proband with Kagami-Ogata syndrome are not affected with Kagami-Ogata syndrome but may have a predisposing genetic alteration associated with the disorder such the following:
    - Maternal deletion involving the DMRs (*MEG3*/*DLK1*:IG-DMR and/or *MEG3*:TSS-DMR) and, in some individuals, *RTL1as*. Recurrence of Kagami-Ogata syndrome has been reported in sibs with maternally derived deletions [Kagami et al 2008, Beygo et al 2015, Kagami et al 2015, Luk 2017].

      If a proband with Kagami-Ogata syndrome has a maternally inherited deletion, the mother with the same deletion is theoretically predicted to have Kagami-Ogata syndrome when the deletion is derived from her mother, or Temple syndrome when the deletion is derived from her father and involves *DLK1* (deletion of *DLK1* is a disease-causing factor for Temple syndrome but not for Kagami-Ogata syndrome) (see Genetically Related Disorders).

      Transmission of a deletion from a mother with Temple syndrome to a child with Kagami-Ogata syndrome has been reported in several families [Kagami et al 2008]. Transmission of a deletion from a mother with Kagami-Ogata syndrome to a child with Kagami-Ogata syndrome has not been reported to date.
    - Maternal translocation (or inversion) disrupting the integrity between the *MEG3* promoter and *RTL1as*
    - Paternal or maternal robertsonian translocation involving chromosome 14 or isochromosome 14q (1(14q)).
- Evaluation of the parents to clarify recurrence risk is recommended; specific testing recommendations depend on the genetic mechanism underlying Kagami-Ogata syndrome in the proband (see **Sibs of a proband**).

**Sibs of a proband.** The risk to sibs depends on the underlying genetic mechanism in the proband and the genetic status of the parents. If the genetic mechanism underlying Kagami-Ogata syndrome in the proband is:

- **Paternal uniparental disomy of chromosome 14.** If the genetic mechanism underlying Kagami-Ogata syndrome in the proband is upd(14)pat, karyotype of the proband is recommended to identify those with a robertsonian translocation or i(14q) [Ogata & Kagami 2016]. If a robertsonian translocation or i(14q) is

identified in the proband (or if the chromosomal status of the proband is unknown), parental karyotyping is recommended.
    - If both parents have normal karyotypes, it is presumed that upd(14)pat occurred in the proband as a *de novo* event and the recurrence risk to sibs is <1%.
    - If either of the parents has a robertsonian translocation or i(14q), the recurrence risk to sibs is increased. Note: While upd(14)pat mediated by parental robertsonian translocation has been identified in multiple individuals with Kagami-Ogata syndrome [Wang et al 2020], sib recurrence of upd(14)pat mediated by this mechanism has not been reported.
- **Epimutation (hypermethylation) of the maternally inherited DMRs.** If the genetic mechanism underlying Kagami-Ogata syndrome in the proband is epimutation (hypermethylation) of the maternally inherited DMRs, it is presumed that hypermethylation occurred in the proband as a *de novo* event and the recurrence risk to sibs is <1%. Additional testing of the proband and the parents is not required to clarify recurrence risk. Note: (1) The underlying genetic mechanism of hypermethylation is unknown. (2) Kagami-Ogata syndrome associated with multilocus imprinting disturbance (MLID) has not been reported [Kagami et al 2017a].
- **Deletion involving the maternally inherited 14q32.2 imprinted region.** If the genetic mechanism underlying Kagami-Ogata syndrome in the proband is deletion involving the maternally inherited 14q32.2 imprinted region, targeted deletion analysis is recommended for the mother of the proband.
    - If the deletion identified in the proband is not identified in maternal leukocyte DNA, it is presumed that the deletion occurred in the proband as a *de novo* event and the recurrence risk to sibs is <1%. Note: Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a deletion that is present in the germ (gonadal) cells only. (Gonadal mosaicism for a deletion involving the 14q32.2 imprinted region has not been reported to date.)
    - If the mother of the proband has the deletion, the risk to sibs is 50%. Recurrence of Kagami-Ogata syndrome has been reported in sibs with maternally derived deletions [Kagami et al 2008, Beygo et al 2015, Kagami et al 2015, Luk 2017]. (Note: If the deletion includes *DLK1* and the mother inherited the deletion from her father, the mother likely has Temple syndrome.)
- **Translocation or inversion disrupting the integrity between the maternally inherited *MEG3* promoter and *RTL1as***. If the genetic mechanism underlying Kagami-Ogata syndrome in the proband is translocation or inversion disrupting the integrity between the maternally inherited *MEG3* promoter and *RTL1as*, karyotype analysis is recommended for the mother of the proband.
    - If the mother of the proband has a normal karyotype, it is presumed that the translocation (or inversion) occurred in the proband as a *de novo* event and the recurrence risk to sibs is <1%.
    - If the mother of the proband has the same translocation or inversion, the recurrence risk to sibs is increased.

**Offspring of a proband.** Many individuals with Kagami-Ogata syndrome are not yet of reproductive age and, to date, individuals with Kagami-Ogata syndrome are not known to reproduce. However, reproductive function is predicted to be preserved in Kagami-Ogata syndrome and the following recurrence risk issues should be considered:

- If the proband has a deletion involving the 14q32.2 imprinted region, offspring of the proband are at risk for Kagami-Ogata syndrome or Temple syndrome depending on the sex of the proband and the deletion size. If the proband is a female, offspring are predicted to have a 50% risk of Kagami-Ogata syndrome. If the proband is male and the deletion encompasses *DLK1*, offspring are predicted to have a 50% risk of Temple syndrome.
- If the proband has a chromosome alteration predicted to result in uniparental disomy in offspring (e.g., a robertsonian translocation or isochromosome 14q), offspring of the proband are at risk for upd(14)pat-mediated Kagami-Ogata syndrome or upd(14)mat-mediated Temple syndrome, depending on the sex of

the proband and the underlying mechanism for the development of uniparental disomy (i.e., trisomy rescue or monosomy rescue).

**Other family members**

- If the mother of the proband is heterozygous for a deletion involving the 14q32.2 imprinted region, the mother's sibs are at risk of having the deletion.
- If a chromosome alteration involving 14q32.2 (e.g., a translocation) is identified in the mother of the proband, the mother's sibs are at risk of having the chromosome alteration.

## Related Genetic Counseling Issues

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to the parents of affected individuals.

## Prenatal Testing and Preimplantation Genetic Testing

### Positive Family History

**Genomic variants**

- If a deletion or translocation involving the chromosome 14q32.2 imprinted region has been identified in the proband, prenatal testing using fetal DNA from samples obtained by chorionic villus sampling or amniocytes and preimplantation genetic testing are possible [Sasaki et al 2014, Sabria-Back et al 2022].
- If the proband has Kagami-Ogata syndrome as the result of upd(14)pat (and chromosome analysis of both parents is normal) or an epimutation (hypermethylation), the recurrence risk is presumed to be <1% and prenatal/preimplantation genetic testing is likely unwarranted.

**Methylation changes.** Methylation testing of fetal DNA to examine abnormal methylation patterns of the DMRs (*MEG3*/*DLK1*:IG-DMR and *MEG3*:TSS-DMR) is not recommended. While DNA extracted from amniotic fluid is currently believed to provide the most reliable tissue source for evaluating fetal methylation status, false negative findings have been reported [Eggermann et al 2016]. Genetic counseling regarding the potential limitations of prenatal testing for epigenetic alterations should be undertaken [Eggermann et al 2016].

**Prenatal findings**

- Even in the absence of obvious clinical findings of Kagami-Ogata syndrome on prenatal ultrasound investigation, a residual risk for recurrence of Kagami-Ogata syndrome remains given the variability in clinical presentation and the limitation of fetal ultrasound studies. A newborn at risk for Kagami-Ogata syndrome should be monitored for respiratory and feeding conditions.
- Maternal serum alpha-fetoprotein concentration may be elevated from the second trimester in the presence of omphalocele [Campbell & Copel 2018].

### Negative Family History

Prenatal testing may be considered when clinical features suggestive of Kagami-Ogata syndrome such as polyhydramnios, characteristic facies, small thorax with coat-hanger appearance of the ribs, and omphalocele are delineated in a fetus not known to be at risk for Kagami-Ogata syndrome. Prenatal testing performed in such conditions has revealed genetic abnormalities consistent with Kagami-Ogata syndrome, including mosaic

upd(14)pat [Suzumori et al 2010, Chen et al 2019, Igreja da Silva et al 2019, Li et al 2021, Molinet Coll et al 2021, Kuriki et al 2022].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

No specific resources for Kagami-Ogata Syndrome have been identified by *GeneReviews* staff.

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table B.** OMIM Entries for Kagami-Ogata Syndrome (View All in OMIM)

| | |
|---|---|
| 608149 | KAGAMI-OGATA SYNDROME |

## Molecular Pathogenesis

The primary underlying factor for the development of Kagami-Ogata syndrome is increased (~2.5 times or ~5 times that of controls) *RTL1* expression due to absence of the functional *RTL1* antisense (*RTL1as*) allele of maternal origin that acts as a *trans*-acting repressor for *RTL1* expression [Kagami et al 2015, Ogata & Kagami 2016]. The maternal 14q32.2 region normally includes unmethylated *MEG3*/*DLK1* intergenic differentially methylated region (*MEG3*/*DLK1*:IG-DMR) and unmethylated *MEG3* transcription start site DMR (*MEG3*:TSS-DMR), resulting in normal expression of *RTL1as*. *RTL1as* expressed from the maternal allele represses *RTL1* expression on the paternal allele (see Figure 4A).

**Structure and character of the 14q32.2 imprinted region**

- This imprinted region contains the germline-derived *MEG3*/*DLK1*:IG-DMR and the postfertilization-derived *MEG3*:TSS-DMR; the protein-coding paternally expressed genes *DLK1* and *RTL1*; and the non-coding maternally expressed genes *MEG3*, *RTL1as*, *MEG8*, and snoRNA and microRNA genes (see Figure 4A).
- Both DMRs are methylated after paternal transmission and unmethylated after maternal transmission in the body; in the placenta, the *MEG3*/*DLK1*:IG-DMR remains as a DMR, but the *MEG3*:TSS-DMR is grossly hypomethylated regardless of parental origin.
- The unmethylated *MEG3*:TSS-DMR and the *MEG3*/*DLK1*:IG-DMR of maternal origin function as imprinting control centers in the body and the placenta, respectively, and the *MEG3*:TSS-DMR can remain unmethylated only in the presence of unmethylated *MEG3*/*DLK1*:IG-DMR, because of the hierarchical regulation of the methylation patterns between the two DMRs [Kagami et al 2010].
- All the non-coding maternally expressed genes are part of a large transcript expressed by the *MEG3* promoter.

Mechanisms of disease causation include paternal uniparental disomy of chromosome 14 (upd(14)pat), epimutation (hypermethylation) of *MEG3*/*DLK1*:IG-DMR and *MEG3*:TSS-DMR of maternal origin, deletion of

*MEG3*/*DLK1*:IG-DMR and/or *MEG3*:TSS-DMR of maternal origin, deletion of the maternally inherited *RTL1as*, or translocation (or inversion) disrupting the integrity between the maternally inherited *MEG3* promoter at the *MEG3*:TSS-DMR and *RTL1as*.

**Paternal uniparental disomy of chromosome 14.** Advanced maternal age at childbirth is a risk factor for the development of monosomy rescue-mediated upd(14)pat [Kagami et al 2012].

**Epimutation** (hypermethylation) of the normally unmethylated *MEG3*/*DLK1*:IG-DMR and *MEG3*:TSS-DMR of maternal origin causes absence of functional *RTL1as* and results in a paternal methylation pattern.

- Abnormal methylation of *MEG3*/*DLK1*:IG-DMR leads to abnormal methylation of *MEG3*:TSS-DMR on the maternally derived allele. There is no report describing hypermethylation of *MEG3*/*DLK1*:IG-DMR alone or *MEG3*:TSS-DMR alone.
- The underlying cause of hypermethylation is unknown, and no multilocus imprinting disturbance (MLID) has been identified in individuals with Kagami-Ogata syndrome [Kagami et al 2017a].

**Deletions including either DMRs**

- Deletions of *MEG3*/*DLK1*:IG-DMR and/or *MEG3*:TSS-DMR of maternal origin cause absence of functional *RTL1as* and a paternal methylation pattern [Kagami et al 2010].
- Three different deletions involving maternally inherited *MEG3*:TSS-DMR alone have caused a paternal methylation pattern [Kagami et al 2010, Beygo et al 2015, Kilich et al 2024].
- DMR deletions that include *RTL1as* result in ~2.5 times *RTL1* expression compared to that of controls; DMR deletions that do not include *RTL1as* result in about five times *RTL1* expression in the absence of functional *RTL1as*.
- When deletions include *DLK1*, this leads to normal *DLK1* expression, whereas when they do not include *DLK1*, this results in around two times the *DLK1* expression seen in controls.
- *MEG* genes are deleted or silenced.

**Deletion of *RTL1as*** (not including *MEG3*/*DLK1*:IG-DMR or *MEG3*:TSS-DMR)

- This deletion results in loss of *RTL1as* expression from the maternally inherited chromosome 14q32.2 and resultant overexpression of *RTL1* without altered methylation.
- *MEG8* is also deleted or disrupted in all deletions of this type reported to date.
- *DLK1* and non-deleted maternally expressed genes are predicted to be expressed normally.

**Translocation** disrupting the integrity between the *MEG3* promoter and *RTL1as* silences transcription of *RTL1as*.

# Chapter Notes

## Author Notes

Tsutomu Ogata (tomogata@hama-med.ac.jp) and Masayo Kagami (kagami-ms@ncchd.go.jp) are actively involved in clinical research regarding individuals with Kagami-Ogata syndrome. They would be happy to communicate with persons who have any questions regarding diagnosis of Kagami-Ogata syndrome or other considerations.

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