Uniparental Disomy 14 (UPD14)

rarechromo.org

Uniparental disomy 14

Uniparental disomy 14, also known as UPD14, is a chromosome disorder. Chromosomes are the microscopically small structures in the nucleus of the body's cells that carry genetic information. There are 46 chromosomes per cell, arranged as pairs numbered 1 to 22 and the sex chromosome pair, two Xs for a girl and an X and a Y for a boy. In each pair, one chromosome has usually come from the father and the other from the mother. In people with uniparental disomy (UPD) both chromosomes in one of the 23 pairs have come from the same parent.

The result of UPD is a duplicate presence of genes from one parent and no input from the other parent. When all the genes come from the mother, this is termed maternal UPD, sometimes shortened to mUPD or UPDmat. When all the genes come from the father, this is termed paternal UPD, sometimes shortened to pUPD or UPDpat. For most chromosomes having all the genes from one parent does not matter, but for certain chromosomes or parts of them it does make a difference. One of these is chromosome 14 and the effects of maternal UPD14 are different from the effects of paternal UPD14. This is partly due to the fact that chromosome 14 contains imprinted genes, genes that have a different level of activity in maternal and paternal chromosomes.

How rare is UPD14?

UPD14 appears to be rare although investigators now believe that many cases go unrecognised. By 2004, 35 cases of maternal UPD14 had been described in medical journals. Paternal UPD appears to be generally less common than maternal and this is true of UPD14; by 2005, 18 children with paternal UPD had been described in the medical literature (Aretz 2005; Kagami 2005; Kotzot 2005). By 2020, over 200 UPD14 diagnoses had been reported, with roughly 2/3 being on the maternal chromosome.

Main features

The features depend on whether both chromosome 14s are from the father or from the mother. When both chromosomes come from the mother the overall effects are not usually severe and it is quite possible that there are people with undiagnosed mUPD14 who do not appear abnormal in any major way. When both chromosomes come from the father, the effects are generally more far-reaching.

Sources

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain abstracts and articles from *Unique*. The leaflet also draws on information from *Unique*, whose members with UPD14 were surveyed in 2003. This information is referenced U.

Main features

When the chromosome 14s come from the mother – mUPD14 or UPD14mat

These are typical features for the syndrome. Individual children will have some but probably not all the features and to a greater or lesser degree.

- Small for dates during pregnancy and short eventual stature
- Puberty typically starts early, on average in the ninth year
- Typically, normal intellectual ability or a mild degree of learning difficulty

Other features vary, but may include:

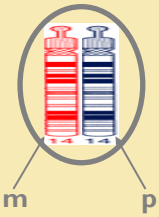
- Physically, children reach their developmental milestones on time or slightly late. Any delay is caused in part by the typical hypotonia (floppiness, low muscle tone) and extremely mobile joints
- Premature birth in around one third of pregnancies
- Speech delay
- Feeding difficulties as a baby
- Marked tendency to overweight and obesity from early or middle childhood
- Small hands and feet
- Scoliosis (spinal curvature)
- High cholesterol levels (in four children in ten)

Typical facial features include a broad or high forehead, a fleshy tip of the nose and slight blepharophimosis (narrowing of the horizontal opening of the eyelids). These features are subtle and may be more obvious to a doctor than to a parent.

(Sutton 2000; Kotzot 2004, 2005)

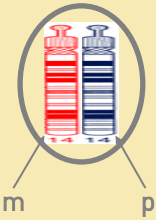
Appearance

Apart from being short, the appearance of children with mUPD14 is usually unremarkable. Overweight without an increase in appetite is a common finding in children over seven. This early-onset overweight means that some children are originally thought to have Prader-Willi syndrome, an unrelated chromosome disorder.

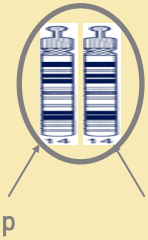


A cell containing one chromosome 14 from the father and one from the mother. This is the normal situation.

A cell showing maternal UPD14.



A cell containing one chromosome 14 from the father and one from the mother. This is the normal situation.



A cell showing paternal UPD14.

Main features

When the chromosome 14s come from the father – pUPD14 or UPD14pat

These are the typical features of the syndrome. Individual children will have some but probably not all the features and to a greater or lesser degree. Only three children have been described beyond babyhood, so most of these features only apply to young babies.

- Excess amniotic fluid of mother while pregnant (polyhydramnios)
- Low birthweight and premature birth
- Small chest and narrow, bell-shaped ribcage, causing underdeveloped lungs and serious respiratory problems in newborn babies. The appearance of the ribs on X-ray has been compared to a coat hanger. Three children have been described in middle childhood (ages 5 to 9); they outgrew their severe respiratory problems
- Short arms and legs
- Hernias, including ventral wall hernia (diastasis recti). This appears as a ridge of muscle running from the breastbone to the navel whenever your baby strains and is caused by a separation of the right and left sides of the muscle covering the front of the abdomen. Some babies are born with an omphalocele, where part of the intestine protrudes at birth through a large hole in the abdomen near the navel
- Some level of learning difficulty. This has generally been described as moderate to severe but with so few cases it is impossible to be certain
- Marked feeding difficulties as a young baby, so that some babies need direct feeding to the stomach via a gastrostomy tube

Unusual, if subtle, facial features, including small ears, protruding upper lip, small palpebral fissures (opening between the upper and lower eyelids), hairy forehead and short neck.

(Wang 1991; Sutton 2000; Kagami 2005)

Learning

Overall, the effects of maternal UPD14 on a child's intellectual ability are mild. There appears to be a slight loss relative to the expected family norm, so parents with above average intelligence may have a child of average intellectual ability. However, there is little published information, and much of what follows is gleaned from the experience of *Unique* members.

A boy assessed at age 9 had an IQ of 90 to 100. He was reported to be very eager to learn, had great skill with jigsaws but had difficulties with arithmetic. In the first years of high school, one child is in the top 10 per cent. Only maths is reported to be 'a struggle'.

One *Unique* member, now at university, achieved A grades throughout her school career in history and English. At age 7 she was 'reading far beyond her age level' and was judged to be a correspondingly competent and talented writer. By late primary school her maths was no longer a top grade but problems only emerged in the later years of high school when her typical A grades slipped to a C. She also experienced specific difficulty with graphic arts, having difficulty in understanding the sense of a complex diagram and in remembering diagrams and pictures.

In addition, this high-achieving student experienced problems with the low strength and tone in her hands when large amounts of writing were required from upper primary years into high school. A mild delay in drawing and spatial orientation has also been observed in a child aged 3.

The first person described in the medical literature with mUPD14 was of above average intelligence.

The effects of paternal UPD14 on intellectual ability are believed to be more severe but very few people have been followed up long term.

(Temple 1991; Hordijk 1999; Sanlaville 2000; U)

Speech and communication

There are few informative reports, but the overall impression is that people with UPD14 have specific speech and language delay. However, catch-up may occur at least in children with maternal UPD14 and in some children verbal IQ outstrips performance.

There is one report in the medical literature of a 9-year-old with a verbal IQ of 95 against an overall IQ of 86 (Antonorakis 1993; Cox 2004; U).

Sitting, moving, walking, handling

Maternal UPD14 may have an effect on a child's mobility development. Hypotonia, loose ligaments and motor delay have been noted in around three-quarters of children, although the low muscle tone may no longer be obvious past babyhood. Feet are typically tiny, affecting walking, and children may need special shoes. When their hands are also tiny, holding objects (like a pen, a cup) between the finger and thumb and manipulating them may be difficult.

Families say ...

"The doctors said there was no problem. She was just not a very robust child.
It is my belief that her physical problems may have been able to be improved upon if she had had early interventions such as physiotherapy and occupational therapy.

Developmental milestones may be achieved slightly late, with sitting recorded around 8 to 12 months and walking from 14 months upwards and children benefit from regular, intensive occupational and physiotherapy.

Swimming, low impact aerobics and ankle-specific exercises were judged helpful.

Eventually, most children acquire a range of mobility skills, including horse riding, playing impact sports and swimming as well as more complex skills such as driving a car. However, specific activities may not be possible for all. A 15-year-old boy was described as being unable to ride a bicycle.

These are snapshot observations of children with mUPD14 at different ages:

- At 4, her balance was poor and she needed to lean for support while sitting or standing. The preschool teacher showed concern at her lack of strength and obvious problems with playground equipment.
- At age 8, her swaying gait was noted. She jumped, but with an effort and landed clumsily, and could only hop a little.
- At age 13 a deficit in upper limb coordination was diagnosed.
- At age 19, problems remained in these areas: balance; muscle strength, affecting her ability to turn on taps and open screw-top jars; fastening some buttons on clothes.

(Aretz 2005; U)

Medical concerns

Maternal UPD14

> “ Her immunity does seem to be lower than others and she is often sicker with viruses, compared to the rest of the family.

Ear infections

Repeated ear infections occur more often than would be expected by chance – affecting all children in one report in the medical literature. Among *Unique* members, recurrent ear infections occur and respiratory infections affected one member who developed asthma at 3 and had repeated tonsil infections as a late teenager (Falk 2005; U).

Continuing joint problems

There have been no reports in the medical literature of continuing joint problems in mUPD14. These observations come from the *Unique* survey.

“ At age 14 a paediatrician noted sports injuries causing painful, swollen joints especially after landing from a jump or turning suddenly with her feet planted. “

“ At age 19, problems remained in these areas: maintaining the same position while sitting, standing or lying down; susceptibility to sprains, especially of ankles; balance; muscle strength, affecting her ability to turn on taps and open screw-top jars; fastening some buttons on clothes. “

Scoliosis

Reports in the medical literature show that almost half of affected children have some measure of spinal curvature (scoliosis). (Berends 1999).

Head growth

Rapid postnatal head growth is seen in a large minority of babies, but it stops spontaneously. Three children and an adult have been reported to have hydrocephalus. However, this resolved naturally without the need for a shunt (Temple 1991; Sutton 2000; U).

High cholesterol levels

Hypercholesterolaemia has been seen in around one child in three with mUPD 14. One *Unique* members have high cholesterol levels (hypercholesterolaemia) and follows a low cholesterol diet (Sutton 2000; U). Two children developed **maturity-onset diabetes of the young** (Kotzot 2005).

Paternal UPD14

Babies with paternal UPD14 have more obvious initial medical problems, including significant impairment of lung capacity. As newborn babies, they most likely need ventilatory assistance or supplemental oxygen. However, reports show that children can outgrow their respiratory problems and the characteristic bell-shaped appearance of the ribcage may normalise. One 9 year old child developed a seizure disorder (Wang 1991; Kagami 2005).

Early puberty

Early puberty, starting around age 7 to 10 years, is a hallmark of maternal UPD14; in one research report this was mentioned in every child over the age of 8. However, a 15-year-old boy has been described in whom puberty started at 12 years, and a 14-year-old girl who had her first period at 11 years, so even this feature is variable (Cox 2004; Aretz 2005).

Hormone treatment to suppress ovarian function in girls holds puberty at bay and allows children some catch-up growth. It is given by injection or an implant under the skin and once treatment stops, normal hormone function returns.

One *Unique* member was given Androcur (cyproterone, an anti-androgen hormone) by the age of 8 to delay puberty until age 11. An unwanted side effect of treatment was the large weight gain she experienced at first. After treatment, she proceeded through a normal puberty. At 19, she had erratic periods, and was to trial a combined oral contraceptive. *Unique* has no information on fertility.

Short stature

Short stature is a hallmark of mUPD14. The growth delay starts before birth and the postnatal growth rate puts most children in the lowest three per cent of the population for height. Information on final adult height is limited, but one *Unique* member, with a birthweight of 2300g/5lb1oz, achieved at age 14 a height of 145.6 cm (4' 9") with the possibility that she might achieve a final adult height of 4' 11". However, there is a research report of a boy who started a growth spurt at age 8, so his height moved from being short to average (Hordijk 1999; U).

Growth hormone treatment (involving daily injections of synthetic hormone) may be tried from mid-childhood and hormone treatment given to delay early puberty will also boost final adult height.

Behaviour

There are almost no published reports of any effect of UPD14 on behaviour, but babies and some children have been noted to be quiet and placid. There is a reference to a 4 year old as 'a pleasant child with good social contact' but also to a seven-year-old who has temper tantrums if she is not treated as she wants and requires a well-structured environment. The *Unique* experience is that UPD14 causes no behavioural problems, and one member is reported to be 'a very easy going person' and extremely popular (Berends 1999; Hordijk 1999; Sanlaville 2000; Aretz 2005; U).

Independence

Young people with mUPD 14 may well be able to function independently in society, marry and hold down a job, depending chiefly on their level of learning ability. One *Unique* member is living away from home and driving

her own car. However, skills that underpin independence may develop late. Two *Unique* members were late to stop bedwetting and everyday skills such as undoing cans and holding mugs and cutlery posed problems due to lax joints.

> "She is a very determined young woman and it has been my husband's and my belief that she should pursue her interests and attain her independence.

Food and eating

Half of all babies with maternal UPD are reported in the medical literature as having neonatal feeding problems and there are a number of reports of babies needing to be tube-fed because of weak sucking. Feeding difficulties have been described as universal in young babies with paternal UPD14.

By mid childhood the concern is the marked tendency to put on weight, which occurs most typically from age 7 despite a normal or even low appetite and is recorded in many research reports as well as in the *Unique* membership. Reports in the medical literature show that two children with UPD developed obesity after age one, with their weight moving from the lowest curve on the growth chart to the highest. One girl put on weight so fast that her thighs developed stretch marks; however, most of the fat was centred on her waist and tummy, the typical pattern for the weight gain associated with mUPD14.

There is a research report describing how food became an increasing obsession for one child from the age of 7 and this has been echoed in *Unique*'s experience. The *Unique* experience is that hormone treatment can act as the trigger for rapid weight gain. One member experienced rapid weight gain as a response to being prescribed a combined oral contraceptive (Berends 1999; Hordijk 1999; Kagami 2005; U).

> "Having now breastfed two more children, I realise she was a very slow feeder.

Pregnancy with UPD14

In pregnancies with mUPD14, the baby's slow growth may be noted, typically in the last three months. Premature labour and birth is frequent, with four out of nine babies with mUPD being born early.

Intrauterine growth retardation is not a typical feature of pUPD14 but premature birth is, with and 12 out of 13 babies born between 29 and 37 weeks. A key feature of paternal UPD14 is excess amniotic fluid during the mother's pregnancy (polyhydramnios)

What causes UPD14?

UPD14 can happen in a variety of different situations. Most commonly, just after conception (when a baby is made) the fertilised egg has a chromosome 14 trisomy – three chromosome 14s instead of two. The fertilised egg attempts to correct the trisomy by disposing of one chromosome 14. This is known as 'trisomy rescue' or 'postzygotic correction'. Instead of disposing of one of the two chromosomes from the one parent, the single chromosome 14 from the other parent is lost, leaving two 14s from the same parent.

The trisomy may have been caused by the failure of chromosomes in either the egg or the sperm to separate. This is especially likely in maternal UPD when the mother was older than average at the time of conception. However, in UPD14 the trisomy occurs especially often when one or other parent has what is known as a Robertsonian translocation. In a Robertsonian translocation, the long arms of certain chromosomes (13, 14, 15, 21 or 22) fuse and the short arms are lost. At egg or sperm creation, the two fused chromosomes act as a single unit, and this can lead to trisomy in the embryo.

For more information on Robertsonian translocations, see the *Unique* leaflet Robertsonian translocations.

The image on the right shows a Robertsonian translocation chromosome made by a fusion of the long arms of chromosomes 13 and 14. In the picture it is marked der(13;14). One person in 1,300 in the general population has this type of Robertsonian chromosome. When someone with this chromosome rearrangement forms sperm or eggs, there is a risk that they will contain either the separate chromosome 13 and the fused 13;14 chromosome or the separate chromosome 14 and the fused 13;14 chromosome. If the latter happens, there is a possibility that a pregnancy can start with three chromosome 14s. An attempt to correct the situation by one chromosome 14 being discarded can lead to UPD14.

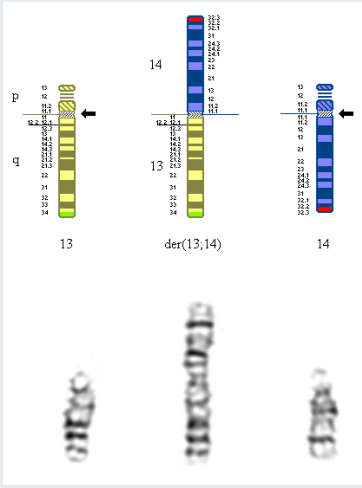


Image courtesy Guy's & St Thomas' Cytogenetics Department

A recent study was carried out, detailing results of prenatal tests where one parent carried a Robertsonian translocation (Moradkhani 2019). The retrospective study covered over 10 years of testing from 28 genetic laboratories in France. Robertsonian translocations involving chromosome 14 were identified as having been passed on to 586 fetuses from either the mother or father (394 Rob(13;14), 52 Rob(14;15), 112 Rob(14;21) and 28 Rob(14;22). In this study, only one fetus was identified as having UPD14, which was a result of her mother's Robertsonian translocation Rob(13;14). No UPD14 was identified in fetuses where the translocation was not passed on.

This study shows that the risk of having a child with UPD14 due to a Robertsonian translocation involving chromosome 14 is significantly less than previously estimated. The study suggests the risk is 0.06%. Moradkhani (2019) do not recommend prenatal testing for UPD for such pregnancies since the risk of losing the pregnancy due to invasive testing is greater than the risk of having a child with UPD14. Exceptions include when both parents carry a Robertsonian translocation involving chromosome 14 and/or the detection during pregnancy of a single abnormal ultrasound finding.

An additional feature in some children is the presence of fully trisomic cells (cells with three chromosome 14s) alongside UPD cells. This mosaicism is likely to account for the mostly highly variable effects of UPD14.

Another explanation for UPD14 is known as monosomy correction, the reverse story to trisomy correction. When the egg is fertilised at conception and the baby is made, one chromosome 14 is missing. In the earliest stages of cell division just after fertilisation, the embryo tries to correct this monosomy, by making a copy of the only chromosome 14 present.

How is UPD14 diagnosed?

Signs suggesting UPD14 may be detected in pregnancy, in the newborn period or in later childhood. In pregnancy intrauterine growth retardation may be the only sign or, in paternal UPD, an ultrasound scan may reveal the characteristic combination of a hernia in the abdominal wall, underdeveloped chest and a ribcage that looks narrow and bell-shaped with short ribs. There will typically be excess amniotic fluid.

In the newborn period the only signs in maternal UPD14 may be hypotonia or feeding difficulties. Paternal UPD14 is usually obvious directly after birth as it typically causes respiratory distress that is severe enough for babies to require ventilation. Maternal UPD14 is more likely to escape attention, possibly until precocious puberty suggests the diagnosis.

A conventional chromosome analysis on cells from amniotic fluid or a blood sample usually reveals either a normal karyotype or a Robertsonian translocation. Molecular marker analysis is required to show UPD.

Can it happen again?

In trisomy correction where the karyotype appears normal, there appears to be no increased risk of another child being born with UPD14. Where the karyotype shows a Robertsonian translocation, the parents should be offered a test of their own chromosomes. This may show that both parents have normal chromosomes or that one parent also has a Robertsonian translocation. There are a number of possible outcomes if one parent has a Robertsonian translocation which you can talk over with your genetic service. For more information, see also the *Unique* guide Robertsonian translocations (Fokstuen 1999).

Inform Network Support

Rare Chromosome Disorder Support Group

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