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Uniparental Disomy as a Mechanism for X-linked Chondrodysplasia Punctata 1 (CDPX1)

Woods E[1], Yates T M[2], Kanani F[2], Balasubramanian M[2,3]

1. Sheffield Children's Hospital NHS Foundation Trust, UK
2. Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, UK
3. Department of Oncology & Metabolism, University of Sheffield, Sheffield, UK

Corresponding author:

Dr. Meena Balasubramanian, Sheffield Clinical Genetics Service, Sheffield Children's Hospital NHS Foundation Trust, Western Bank, Sheffield S10 2TH; Phone: +44 1142717025; Fax: +44 114 2737467; E-mail: meena.balasubramanian@nhs.net

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There are no conflicting interests.

Abstract

Objective: We describe a female infant with X-linked Chondrodysplasia Punctata (CDPX1) as a result of maternal isodisomy of the X chromosome.

Method: Targeted Sanger Sequencing and targeted Next Generation Sequencing of *ARSL* was used to test for the familial variant.

Results: This patient was homozygous for *ARSL* NM_000047.2: c.1227_1228delinsAT p.(Ser410Cys) familial variant, consistent with a diagnosis of CDPX1.

Discussion: Uniparental disomy is a type of chromosomal variation. Although not necessarily pathogenic, it can cause imprinting disorders, X-linked recessive disorders in females, and be a cause of autosomal recessive conditions when only one parent is a carrier.

Conclusion: The patient described highlights that uniparental disomy can be a rare cause of X-linked recessive conditions. This mode of inheritance has not been previously described in this condition.

Introduction

Chondrodysplasia Punctata (CDPX1) is a rare, X-linked, bone and cartilage disorder causing shortened distal digits (brachytelephalangy), epiphyseal stippling and nasomaxillary hypoplasia, with variable phenotype from mild to severe symptoms including spinal cord stenosis, mixed sensori-neural and conductive hearing loss, respiratory involvement and learning disability (Braverman et al., 2008). There is variable expressivity in clinical features, with most affected having mild bony symptoms that improve with time, but some with more severe features such as cervical cord compression or stenosis, dysplasia or subluxation of cervical vertebra, central apnoea, tracheal stenosis or nasal obstruction requiring surgical fixation (Nino et al., 2008). There is no genotype-phenotype correlation of which features will be apparent (Casarin A et al., 2009).

CDPX1 is caused by loss of arylsulfatase E; an enzyme involved with hydrolysis of sulphate esters, important in bone and cartilage composition. This deficiency is due to pathogenic variants in *ARSL* gene at Xp22.3, which is detected by gene sequence analysis in up to 3/4 of patients and by chromosomal studies in ¼ of patients, with detection of Xp deletions or rearrangements (Vrecar I et al., 2015).

We report a female infant with CDPX1 resulting from maternal UPD of the X chromosome, with homozygous mutation of *ARSL*. The mother had known heterozygous carrier status of *ARSL* missense variant, which was detected following the diagnosis of CDPX1 in her first male child. There have been no reports of CDPX1 in a female resulting from X-chromosome UPD in the literature to date.

Results

Clinical report

This patient is a female baby, born in good condition by normal vaginal delivery at 39+5 weeks gestation, as the second child to consanguineous parents. Antenatal scans revealed polyhydramnios. Detailed antenatal anomaly scan showed a flattened nasal bridge with the possibility of cleft palate. The mother was known to be a carrier of beta-thalassaemia and had carrier status of *ARSL* missense variant, and had a previous son who had died at the age of 1 month from respiratory complications associated with inheriting X-linked CDP. Cell free foetal sex determination was carried out prenatally, predicting the foetus to be female. Parents were counselled that female offspring would be at 1 in 2 (50%) risk of inheriting the *ARSL* variant and being a carrier of X-linked recessive chondrodysplasia punctata.

At delivery there were no concerns, with APGAR scores of 9 and 9 at 1 and 5 minutes, therefore baby went for routine post-natal care with her mother. Birth weight was 3050g (between 25^{th} – 50^{th} centile). Three days later whilst on the post-natal ward, the baby presented with respiratory distress and feeding difficulty. She was admitted to the Neonatal Unit for oxygen and feeding support where she was noticed to have dysmorphic features.

Although there was no cleft, examination did reveal low set ears and a flattened nasal bridge with crescent-shaped nostrils and noisy breathing. Chest x-ray showed stippling of epiphyses at humeral heads and ribs, but normal lung fields.

Investigations

There were concerns of nasal passage obstruction given the facial features and noisy breathing, but naso-gastric tube was passed with ease. Further inpatient investigations included nasal endoscopy which revealed a small cartilaginous anterior nasal cavity but otherwise normal findings. CT of facial bones showed a patent nasal cavity with no stenosis or obstruction. Initial feeding difficulty secondary

to flattened nasal bridge was overcome with feeding support, by slowly building feeds whilst in a lying position when awake and alert. The baby was discharged home 16 days after admission, once feeding was established and there was no longer a need for supplementary oxygen.

Audiology tests concluded a mild conductive hearing loss but adequate access to sound for speech acquisition. Echocardiography was normal.

Subsequent neuroimaging showed good alignment of the c-spine with some ossification, more marked in the upper thoracic spine. MRI spine was normal with good alignment of bones and no cord problems. There is a plan for further flexion/ extension imaging in the future when able.

At 6 months of age, this baby had normal tone, symmetrical limbs and was feeding and putting on weight well. She was reaching all expected developmental milestones. Head circumference and weight were on the 50th centile for age.

Molecular analysis

Mother was previously identified as being heterozygous for *ARSL* NM_000047.2: c.1227_1228delinsAT p.(Ser410Cys). This variant was classified as likely pathogenic using the ACMG/AMP guidelines (Richards et al., 2015). Targeted Sanger Sequencing with two different primer sets (to rule out allelic dropout) and targeted Next Generation Sequencing of *ARSL* was used to test for the familial variant. This identified a homozygous *ARSL* c.1227_1228delinsATp.(Ser410Cys) variant consistent with X-linked recessive CDP.

Ser410 lies within the N-terminal sulfatase domain where the majority of previously reported pathogenic missense variants occur. Ser410 is buried in the ARSL protein but lies at the internal interface between the conserved N- and C-terminal sulfatase domains. Substitution of serine for cysteine is predicted to have a likely significant effect, interfering with the folding of the C-terminal domain. The variant has not previously been reported in the gnomAD database.

Discussion

We report the first case of CDPX1 as a result of uniparental inheritance in a female patient; both X chromosomes carrying the mutation inherited from maternal origin. The milder phenotype of this patient, in comparison to the sibling, is likely due to residual activity of the mutated protein and *ARSL* escaping X-inactivation.

UPD describes when a chromosome pair is inherited from only one parent, rather than one half of each chromosome pair being inherited from each parent. UPD can result from several mechanisms: trisomic rescue, monosomy rescue, and gamete complementation (Engel, 2006).

Failure of non-disjunction in meiosis, whereby 2 abnormal gametes are created – one containing both copies of the chromosome (disomy), and one containing no copies of the chromosome (nullisomy) - therefore leads to conception with trisomy or monosomy (Shaffer et al., 2001). A second rescue event may then occur whereby one chromosome is lost in a trisomic cell during mitosis, or, there is generation and gain of a second copy of a monosomic chromosome (as in monosomy rescue), both resulting in normal karyotype numbers (Shaffer et al., 2001). UPD of the entire chromosome can also be caused by gamete complementation, whereby union of a gamete containing two copies of a chromosome joins with a gamete containing no chromosome, resulting in two copies of a chromosome from a single gamete (Zneimer, 2014). Somatic replacement of derivative chromosome will also result in entire chromosome UPD, whereas post-zygotic events will cause partial chromosome disomy via somatic recombination or gene conversion (Shaffer et al., 2001).

The uniparental chromosomes may be entirely heterozygous (heterodisomy) or homozygous (isodisomy) or a mixture of both (Conlin et al., 2010). If a trisomy rescue UPD is due to errors in meiosis I or meiosis II, errors are only reflected in the status of the sentromeric region (isodisomic or not). If non-disjunction occurs during meiosis I, it will result in heterodisomy with possible homozygosity of chromosome ends due to cross-overs, whereas if it occurs in meiosis II, it will result in isodisomy of at least the centromeric region with possible heterozygosity of chromosome ends due to cross-overs (Zneimer, 2014). In this patient, SNP array suggested likely segmental UPD which

suggests either a post-zygotic mechanism due to cross-over between X-chromatids, or more likely, mechanism by trisomic rescue (with paternal X loss) after a maternal meiosis-I error, with later cross-over to give homozygosity of the distal Xp segment.

The identification of UPD in this patient was through molecular genetic investigation of X-linked disease. UPD of the X chromosome has been documented in cases shown in Table 1 (below). Other cases of UPD have been said to be identified through evaluation of mosaicism, investigation for a suspected imprinting syndrome or structurally abnormal chromosome (Shaffer et al, 2001). We are also aware of a family with another type of Chondrodysplasia as a result of UDP; Rhizomelic Chondrodysplasia Punctata (RCDP). This is a rare, autosomal recessive developmental disorder characterised by shortening of the proximal long bones (rhizomelia), calcific stippling of the epiphyses, facial dysmorphism, vertebral coronal clefts, cerebellar atrophy, seizures, congenital cataracts, and severe limitation of growth and learning disability (Braverman & Moser, 2012).

The recurrence risk for maternal X chromosome UPD extremely low. Therefore, the risk of CDPX1 in any further female offspring for the parents of this patient is negligible. The risk of CDPX1 in any further male offspring will, as with the nature of X-linked conditions, be 50%. In this case, the maternal carrier status was already known due to a previous son with the condition. This shows that although it is extremely rare for a female child to also develop this X-linked condition, it is still possible.

Conclusion

This case of CDPX1 highlights this mechanism as a cause of disease. Uniparental disomy should be considered as a rare cause for autosomal recessive and X-linked conditions with or without known parental carrier status.

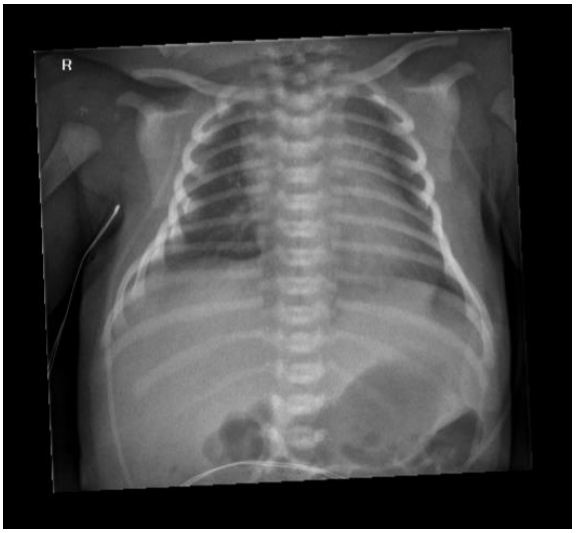
Uniparental disomy of X chromosome – all reported cases			
Clinical features/diagnosis	*Heterodisomy/Isodisomy*	*Parental origin*	*Reference*
Duchenne Muscular Dystrophy	Isodisomy	Maternal	Quan et al., 1997
Fragile X Phenotype	Isodisomy	Maternal	Kim et al., 2020
Features of Turner's syndrome, severe learning disability, profound respiratory problems	Isodisomy	Maternal	Migeon B R et al, 1996
Usual Turner's phenotype, moderate learning disability	Isodisomy	Maternal	Yorifuji et al., 1998
Usual Turner's phenotype, moderate learning disability	Isodisomy	Paternal	Yorifuji et al., 1998
3 asymptomatic cases detected in large population study who were referred for non-invasive prenatal testing	Unknown	Unknown	Samango-Sprouse C et al., 2016
2 asymptomatic cases detected in a study for UPD of sex chromosomes in men	Isodisomy	Maternal	Avivi et al., 1992
Polysomy X phenotype	Heterodisomy	Maternal	Robinson et al., 1995
Polysomy X phenotype	Heterodisomy	Maternal	Fritz et al., 1998
Severe learning disability, lymphoedema, high arched palate, short metacarpals, kidney abnormalities	Isodisomy	Maternal	Turner et al., 2000
2 *possible* cases with normal intellectual development	Isodisomy	Maternal	Matsuo et al., 2000
Haemophilia A in proband and father	Isodisomy	Paternal	Vidaud et al., 1998

Short stature, Turner stigmata	Isodisomy	Paternal	Schinzel et al., 1993
Short stature, mild hypotonia, mild learning disability	Isodisomy	Paternal	Rio et al., 2002
Chondrodysplasia punctata and Turner stigmata in male	Isodisomy	Paternal	Weil et al., 1993
Leri–Weill dyschondrosterosis	Isodisomy	Paternal	Stuppia et al., 1999
Male infertility, normal phenotype	Isodisomy	Maternal	Lee et al., 2014

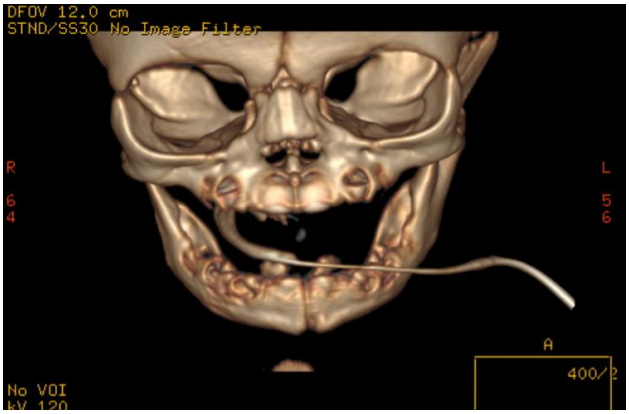
Table 1. Reported cases of UPD X chromosome.

Figures

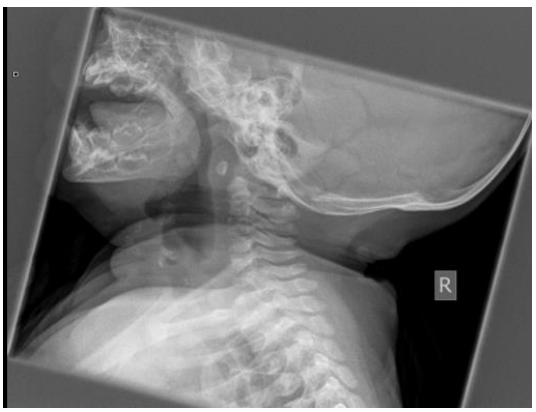
Photographs and X-rays

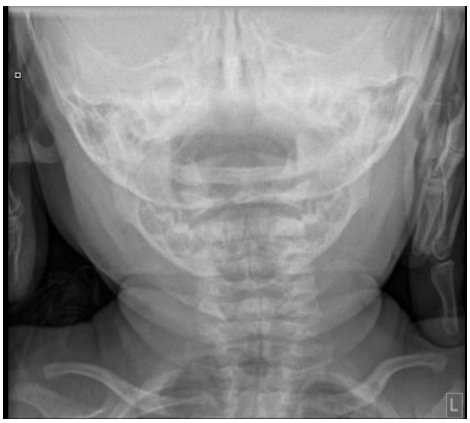


CXR day 2



CT facial bones day 7- patent but cartilaginous anterior nasal cavity





Spinal XR 4 months- stippling and ossification within cervical spine and upper thoracic vertebral bodies

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