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# Patient With Prolidase Deficiency due to an Homozygous *PEPD* Variant, Induced by Paternal Uniparental Isodisomy of Chromosome 19

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## ABSTRACT

Uniparental disomy (UPD) is a rare phenomenon in which both copies of a chromosome are inherited from a single parent. This can lead to genomic imprinting disorders and recessive disorders due to the presence of recessive pathogenic variants in both alleles. Additionally, depending on the mechanisms by which UPD occurs, mosaic aneuploidies may arise. Here we report the case of a patient with prenatal manifestations of intrauterine growth restriction and polyhydramnios, and postnatal manifestations of multiple congenital anomalies, developmental delay, and facial dysmorphisms. Prenatal exome sequencing targeting the fetal phenotype allowed the detection of uniparental isodisomy of chromosome 19. After birth, exome reanalysis revealed a homozygous pathogenic variant in the *PEPD* gene. This is the first case of prolidase deficiency due to UPD ever described. Prolidase deficiency is a low-prevalence disease with significant morbidity and mortality. Early diagnosis is essential to provide prognostic information, design an appropriate interdisciplinary follow-up program, and anticipate complications. This case highlights the importance of phenotypic assessment and postnatal clinical follow-up, as well as comprehensive genetic analyses to better understand complex phenotypes.

## 1 | Introduction

Uniparental disomy (UPD) occurs when an individual inherits both homologous chromosomes, or part of them, from a single progenitor, without genetic material being contributed from the other parent (Engel 1980). Several mechanisms are known to cause UPD, including meiotic nondisjunction during gamete formation and normal ploidy recovery during embryo development. UPD can cause human diseases through different mechanisms (Siegel and Slavotinek 2005), including expression deregulation of imprinted genes, secondary homozygosity of pathogenic variants in recessive genes, or the presence of mosaic aneuploidies.

Here we present the case of a fetus with prenatal detection of paternal isodisomy of chromosome 19 (iUPD19). UPDs in chromosomes 6, 7, 11, 14, 15, and 20 are widely known to directly lead to imprinting disorders, such as Silver-Russell (chromosome 7) or Prader-Willi and Angelman syndromes (chromosome 15) (Kearney et al. 2011). UPDs affecting other chromosomes have also been reported in the scientific literature (Chen et al. 2023; Liehr 2010). However, UPD for chromosome 19 is less frequent. This chromosome is the most gene-dense human chromosome, with also high density of repetitive regions: nearly 55% of this chromosome consists of repetitive elements, while the genome average is 44.8% (Grimwood et al. 2004). GpC content of

chromosome 19 is also unusually high, with an average of 48% in chromosome 19 compared to the average of 41% in the whole human genome. This raises the possibility that chromosome 19 might present more nucleotide diversity (within and between species) and may have more variation in DNA methylation that regulates gene expression (Harris et al. 2020). In 2011, Choufani et al. raised the hypothesis that uniparental inheritance of two copies of chromosome 19 might be lethal and that biparental inheritance carries epigenetic marks indispensable for normal development (Choufani et al. 2011). In 2018, Yeung et al. published the first human case of paternal UPD19 (Yeung et al. 2018). It was a case of monochorionic diamniotic twins, one of which (referred to as twin A in the original article) presented intrauterine growth restriction (IUGR) and oligohydramnios in the prenatal period, while the other one presented polyhydramnios. These features could be related to the twin-to-twin transfusion syndrome, present in 10%–15% of monochorionic twin pregnancies in the general population (Miller 2021). It cannot be ruled out that the UPD is also related to these findings, since chromosome 19 contains genes with regulatory roles that may influence angiogenesis, such as *TGFB1*, or related to growth, such as *PEG3*. However, the association between UPD or chromosome 19 and twin-to-twin transfusion syndrome has not yet been established. In accordance with this, Twin A was born smaller than twin B, presenting a body length under the 3rd centile and weight at 3rd–10th centiles, while twin B presented body length at 3rd-10th centiles and weight at 25th–50th. After birth, twin A presented both ventricular and atrial septal defects, global developmental delay, mild dysmorphic features, hypotonia, and stereotypies. However, twin B presented with similar dysmorphic features, hypotonia, and mild developmental delay. According to a personal communication, their last follow-up with a pediatric neurologist was at age 7. At that moment, twin B was studying the first year at a regular primary school, while twin A was studying at a regular kindergarten (to be promoted to the same primary school as twin B). Growth parameters of twin A were height at the 10th percentile, weight at 25th–50th, and head circumference at 3rd–10th percentile, while twin B had average growth parameters all along. Developmental assessment showed twin A had low-average normal intelligence and twin B had normal intelligence. In view of their normal intelligence and having support in regular school, both twins did not need further follow-up at the neurology clinic afterwards. Exome sequencing (ES) was performed on the twins, but no pathogenic variants were detected.

After Yeung's et al. publication, other UPD19 reports have been published. Davis et al. published a patient with UPD19 in 2019 that presented IUGR, respiratory failure at birth, hypotonia, facial diplegia and ophthalmoplegia, turricephaly, restrictive lung disease and intellectual impairment (Davis et al. 2019). In this last case, part of the phenotype was attributable to a homozygous pathogenic variant in the *RYR1* gene, originated by the UPD. The *RYR1* gene encodes the skeletal muscle ryanodine receptor, a key intracellular calcium release channel essential for excitation–contraction coupling. Disruption of *RYR1* function through pathogenic variants impairs calcium homeostasis, thereby leading to the characteristic neuromuscular phenotype; this would explain some clinical manifestations present in the patient such as hypotonia, respiratory failure, and ophthalmoplegia. Slavotinek et al. presented another patient in 2020 with short long bones, short stature, anemia, osteopenia and delayed fine and gross motor development, among other manifestations, carrying both UPD19 and a variant in the *EXOSC5* gene (Slavotinek et al. 2020). Song et al. reported in 2021 an individual carrying a UPD19 that, contrary to the previous case, did not present any phenotypic abnormalities (Song et al. 2021). Finally, Procopio and Schneider presented an additional case of UPD19 in a patient with oculocutaneous albinism, neurodevelopmental disorder, autoimmune hepatitis and pregnancy history of significant IUGR (Procopio and Schneider 2023). Personal communication with the authors revealed that the patient also presented recurrent infections, nystagmus and liver enzyme abnormalities; unfortunately, the family did not follow-up and massively parallel sequencing was not performed.

In our case, the UPD also led to homozygosity of a pathogenic variant in a gene associated with an autosomal recessive disease: prolidase deficiency (OMIM#170100). This condition was first described in 1974 by Powell et al., in a man that presented an increased urinary excretion of proline-containing peptides due to a deficiency in the prolidase enzyme (Powell et al. 1974). A patient with similar clinical findings had been previously published (Goodman et al. 1968), but Powell's work was the first to directly demonstrate the enzymatic deficiency.

Nowadays, prolidase deficiency is a well characterized disease, known to be caused by biallelic pathogenic variants in *PEPD*, located on the long arm of chromosome 19, at position q13.11. This gene encodes prolidase, an enzyme that is essential in protein metabolism, collagen turnover, and matrix remodeling (Eni-Aganga et al. 2021). There are three different mRNA transcripts. The canonical transcript, NM_000285.4, is translated into a 493 amino acid protein and contains 15 exons. Its impairment causes disturbances in many cell functions, which can cause the affection of multiple organs and systems: patients with this condition present skin lesions, recurrent infections (particularly of the skin and respiratory tract), dysmorphic facial features, variable intellectual disability, and organomegaly (typically splenomegaly, but occasionally associated with hepatomegaly) with elevated liver enzymes (Rossignol et al. 2015). High phenotypic variability among patients belonging to the same family has been described (Spodenkiewicz et al. 2020; Eni-Aganga et al. 2021).

Diagnosis of prolidase deficiency can be made by determining the enzyme activity or screening for excreted amino dipeptides in urine. However, the preferred method to establish a definitive diagnosis is the genetic study of the *PEPD* gene, since most of the alterations described in this gene are detectable by sequence analysis (single nucleotide variants (SNVs) or small intragenic deletions/insertions) (Rossignol et al. 2021); gene-targeted deletion/duplication analysis could be performed if there is still missing one or two causative variants (Eni-Aganga et al. 2021).

## 2 | Clinical Report

The patient is a male infant presenting multiple congenital anomalies, including developmental delay and facial dysmorphism. His mother was initially referred to Medical Genetics at 27 weeks and 6 days of gestation due to the observation of IUGR

and polyhydramnios. Subsequently, the patient has been seen by clinical geneticists, the neonatal unit after birth, and followed by a neuropediatrician thereafter. The patient was born to an unrelated couple, with an apparently healthy 2-year-old brother and a 6-year-old half-sister on the mother's side from a previous relationship.

Maternal obstetric history was remarkable with three spontaneous abortions. However, she achieved ongoing pregnancies after endometrial polyp surgery. She was 30 years old at the time of the patient's conception and reported having consumed toxic substances until 2 months before the pregnancy. She appears to have a slight cognitive impairment and reports a history of delayed expressive language development and learning difficulties (primary school as highest academic achievement). Moreover, she has astigmatism, mild upslanting palpebral fissures, full lips, and she seems to have developed hearing loss during the last year. She underwent different genetic testing because of the recurrent miscarriages and her mild intellectual disability: cytogenetic karyotype, ES, arrayCGH, Fragile X analysis, and plasma amino acid analysis (to rule out phenylketonuria) were normal.

After the presentation of IUGR and polyhydramnios in early pregnancy, amniocentesis was performed to run prenatal genetic tests in the fetus. Firstly, a quantitative fluorescent PCR and array CGH were performed without evidence of significant chromosomal imbalances. Thereafter, prenatal clinical ES was performed, and the finding of an abnormally high amount of homozygous variants in chromosome 19 led to the suspicion of UPD for this chromosome. The distribution of regions of homozygosity (ROH) was assessed by AutoMap (https://automap.iob.ch/, Figure 1) and a clear enrichment of ROH on chromosome 19 was detected. To confirm the UPD detected through NGS, a methylation-specific MLPA test was done. The results showed *PEG3* gene hypomethylation, which supported the paternal origin of uniparental isodisomy of chromosome 19 (iUPD19). The karyotype was performed in the patient and in his father, and both turned out to be normal.

The patient was born prematurely at 31 weeks and 1 day of gestation. The birth weight was 1.140 kg (2nd centile) and dysmorphic features were appreciated (dolichocephaly, frontal bossing, low-set ears). He also presented with hyperbilirubinemia and perinatal infections. Five months after the birth, his weight was 6.08 kg (5th centile), his height was 62 cm (4th centile) and his head circumference was 41.2 cm (3rd centile). Additionally, the physical examination revealed a high anterior hairline, conjugated nystagmus, upslanted palpebral fissures, blepharophimosis, long eyelashes, bulbous nose, depressed nasal bridge, exaggerated Cupid's bow, retrognathia, posteriorly rotated ears, short neck, axial hypotonia, upper limb hypertonia, unstable head support and congenital torticollis (Figure 2). Abdominal and testicular echographies showed mild splenomegaly and bilateral hydrocele. Magnetic resonance of the brain showed a bilateral and interhemispheric frontotemporal extra axial space increase and an asymmetry pattern of the cerebral grooves, being deeper in the left hemisphere, specifically in the parietotemporal grooves and the insula. Developmental assessment at 8 months confirmed global development delay. Anemia was also diagnosed at that time. Patient's visit to the neuropediatric unit at 11 months revealed hepatomegaly. At his last assessment in Medical Genetics, at 22 months of age, the patient's weight was 9.15 kg, the height was 79 cm, and his head circumference was 46 cm, all the measurements being below the 1st centile. The patient suffered from recurrent respiratory infections and bronchospasm. On the skin, he had mild eczema on the face (with telangiectasias on the cheeks), trunk, hands, and feet, which was well controlled with topical pimecrolimus. Additionally, he had presented impetigo treated with topical antibiotics, a skin abscess on the left wrist with adequate response to oral antibiotics, and a first ulcer on the back of the thigh. At the neurodevelopmental level, he had achieved unstable sitting, with marked hypotonia in the lower limbs. He began to imitate and respond to his name, had a social smile, and emitted vowel sounds. He followed an early intervention program, with stimulation and physiotherapy. He was being treated with melatonin to help him fall asleep and reduce the number of awakenings.

In view of the patient's clinical course, reanalysis of prenatal exome was proposed. In chromosome 19, a pathogenic homozygous frameshift variant was found in the *PEPD* gene c.838_841del, p.(Glu280IlefsTer40). In light of this new finding, a reanalysis of the mother's ES data was also performed to confirm that the mother was not a carrier of the *PEPD* variant. This change affects exon 12 out of the 15 that constitute the MANE select transcript (NM_000285.4). The variant is predicted to disrupt the reading frame, leading to the appearance of a premature stop codon at the amino acid located at position 319, while the wild type transcript would contain 493 amino acids. Although variants having different protein effects have been described as pathogenic in the *PEPD* gene in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar), most of them are truncating variants: 14 frameshift, 12 nonsense, and 22 affecting the canonical position of splicing, while

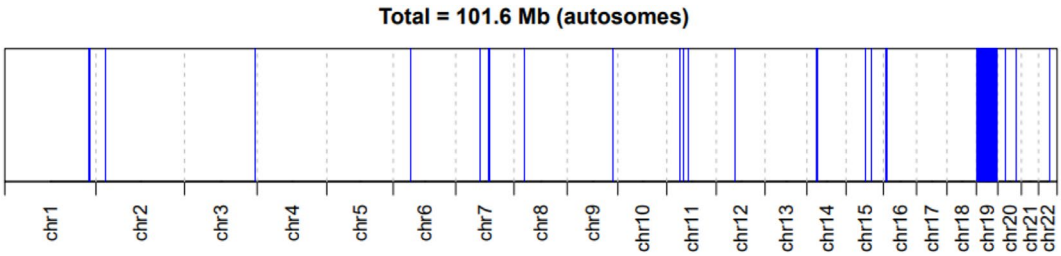


**FIGURE 1** | Representation of ROH (regions of the chromosome that are enriched with ROH are represented in blue) of the patient's autosomes. A clear overrepresentation of ROH in chromosome 19 is shown.

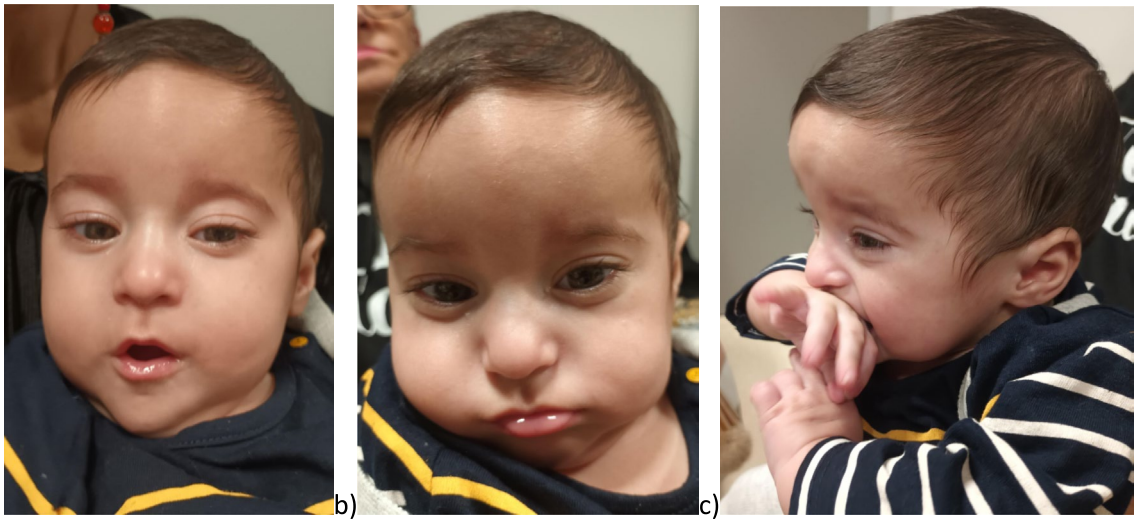

**FIGURE 2** | Images of the patient: (a, b) frontal pictures of the patient's face, in which frontal bossing with prominent metopic ridge, upslanted palpebral fissures with mild proptosis, deep philtrum, prominent cupid-bow of upper lip and retrognathia can be observed; (c) lateral picture of the patient, in which laterally extended eyebrows, long eyelashes, depressed nasal bridge, bulbous nose and posteriorly rotated ears can be observed.


**FIGURE 3** | Representation of the distribution of variants reported in both ClinVar and gnomAD in the *PEPD* gene, extracted from GnomAD 4.1.0 (https://gnomad.broadinstitute.org/gene/ENSG00000124299?dataset=gnomad_r4). Around the position of our variant (circled in red), there are several loss of function variants described in ClinVar as pathogenic or likely pathogenic variants.

only nine are missense. The variant identified in our patient has only been reported in a heterozygous individual from the general population in the GnomAD database (https://gnomad.broadinstitute.org/variant/19-33401846-TACTC-T?dataset=gnomad_r4). There is one entry in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/variation/2761247/) from a commercial laboratory that identified the variant as heterozygous on a carrier screening panel, in a patient with unknown affected status (personal communication). However, the variant has not been published in the literature before. It is located in a gene region in which several other pathogenic loss-of-function variants (Figure 3) have been reported.

All this evidence suggested a pathogenic effect of the variant on the protein, which has been definitively confirmed: urine studies showed massive imidodipeptiduria, consistent with the prolidase deficiency diagnosis.

Other rare homozygous variants have been detected on chromosome 19, but according to current knowledge, none of them are related to the patient's phenotype (Table 1):

## 3 | Discussion

UPD is an infrequent but widely described phenomenon. In this report, we have described a case of UPD19, which is quite infrequent compared to other more typical UPDs such as those affecting chromosomes 6, 7, 11, 14, 15, and 20, associated with known imprinting disorders. Before any UPD19 had ever been published, Choufani et al. had raised the hypothesis that UPD19 might be lethal. The presence of UPD19 in mosaic in the patients described would support Choufani's hypothesis. In our case, the patient's phenotype is clearly related to the presence of a homozygous pathogenic variant in the *PEPD* gene, which allows the diagnosis of prolidase deficiency to be reached. The patient shows some of the most frequent clinical signs of this disorder: recurrent infections, skin lesions, anemia, splenomegaly, developmental delay, and facial dysmorphism. He is the first case ever described of prolidase deficiency due to this pathogenic mechanism.

However, it is not possible to determine whether some clinical manifestations are due to the UPD itself. For example, IUGR was

**TABLE 1** | List of additional rare homozygous variants identified in chromosome 19 in the index case that meet the following criteria: Quality filter is PASS; frequency is ≤1 in gnomAD v2.1.1 and in the internal frequency database of the company; variant type is missense, nonsense, frameshift, or affecting the canonical splice site.

| Genomic location (hg19) | Variant |
|---|---|
| 19:4817911 | *TICAM1*(NM_182919.4):c.479C>T, p.(Ser160Phe) |
| 19:7965392 | *LRRC8E*(NM_025061.6):c.1989_1991del, p.(Asn663del) |
| 19:8976336 | *MUC16*(NM_001414686.1):c.43140G>A, p.(Trp14380Ter) |
| 19:15566949 | *RASAL3*(NM_022904.3):c.1687G>A, p.(Glu563Lys) |
| 19:17838775 | *MAP1S*(NM_018174.6):c.2582G>A, p.(Arg861His) |
| 19:19655137 | *CILP2*(NM_153221.2):c.1783G>A, p.(Asp595Asn) |
| 19:51015693 | *ASPDH*(NM_001114598.2):c.577A>C, p.(Thr193Pro) |
| 19:51507066 | *KLK9*(NM_012315.2):c.497A>G, p.(Asn166Ser) |
| 19:52394770 | *ZNF649*(NM_023074.4):c.619G>A, p.(Val207Met) |
| 19:53344534 | *ZNF468*(NM_001008801.2):c.1013A>G, p.(Tyr338Cys) |
| 19:57931806 | *ZNF17*(NM_001330617.2):c.952C>T, p.(His318Tyr) |

also observed in all the cases described so far but that of Song et al. Actually, the association of IUGR with other UPDs had previously been described as well (Li et al. 2024). Additionally, the possibility that other recessive variants or misregulation of imprinted genes in chromosome 19 is contributing to the patient's phenotype cannot be ruled out. Other genetic or external factors may also be playing a role, especially given that the mother exhibits neurodevelopmental characteristics of unidentified origin.

This case also highlights the importance of reaching an etiological diagnosis, especially since the disease diagnosed presents significant morbidity and mortality. The confirmation of the diagnosis has allowed the provision of prognostic information, the design of an appropriate interdisciplinary follow-up program, and the anticipation of complications. For example, it is known that patients with biallelic loss-of-function variants, such as our patient, are more likely to develop ulcers and have an earlier age of onset than those with biallelic missense-type pathogenic variants (Rossignol et al. 2021). By the age of 20, 100% of individuals with loss-of-function variants have ulcers, whereas less than 50% of individuals with missense-type variants have ulcers at that age.

Also, it is worth noting that the topical application of 5% proline and 5% glycine has been effective in the treatment of skin lesions in some affected children (Hajjar et al. 2021). Moreover, reaching a specific diagnosis allows attention to therapeutic advances for the specific diagnosis. The diagnosis also led to the activation of a specific alert for the patient in the hospital's computer system, so that clinicians of any specialty can take into account the increased risk of hemophagocytic lymphohistiocytosis/macrophage activation syndrome, which requires emergency treatment. In addition, early treatment of infections must be provided, since these may have a fatal course on the child (Chidambaram et al. 2021).

This case brings to the fore an important consideration regarding the reporting of pathogenic variants identified prenatally, particularly when these variants are unrelated to the observed prenatal phenotype but are known to have severe early-onset implications for the newborn. Given the inherent limitations of fetal phenotyping, there is a strong argument for expanding reporting criteria to include significant findings beyond immediate fetal presentations. In this case, the variant in the *PEPD* gene could have been detected prenatally. However, it was not reported because the analysis was focused exclusively on the features present in the fetus.

## 4 | Conclusions

Not many UPD19 cases have been published so far, suggesting that it is a very rare occurrence. A strong hypothesis to explain this would be the fact that chromosome 19 is the one with the greatest gene density. More research is needed regarding these events to achieve a more precise correlation between the UPD19 and the clinical phenotype of patients in whom it has been detected. One of the clear weaknesses of our case is that we are unable to determine if some clinical features are due to the UPD19 itself, the prolidase deficiency, or other factors.

Carrying out further analyses such as genome or RNA sequencing on the patients described could reveal more variants with an effect on the patient's phenotype, allowing cause-effect relationships to be better determined. It would also be interesting to determine if they are mosaic for the UPD19. This could be related to the fact that this UPD is less frequent than others and also the severity of the clinical manifestations.

Furthermore, reanalysis of the data should be carried out periodically or upon the appearance of new clinical signs, especially taking into account the young age of the patient. Prenatal exome reanalysis based on postnatal assessment was crucial in this case.

Although further discoveries cannot be ruled out, obtaining an etiological diagnosis has already proven to be crucial for patient prognosis, follow-up, and the possible application of early treatments. To do so, a thorough evaluation of the patient's clinical manifestations at all stages and the combination of various genetic diagnostic techniques, emphasizing ES, was essential. Prenatal reporting of incidental findings (like the *PEPD* variant, if it had been detected during the first prenatal assessment of the NGS data) should also be offered to the parents.

### Author Contributions

M.C.-H. and R.M.-S. contributed equally to this work and should be considered joint first author. M.C.-H., R.M.-S. and L.C.-G. were involved in the genetic studies. V.L.-G. performed clinical follow-up. M.C.-H., R.M.-S. and V.L.-G. drafted the manuscript. All authors have approved the final manuscript.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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