

CASE REPORT

Complete uniparental disomy of chromosome 1 in a child with isolated developmental delay

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Abstract

Complete uniparental disomy of chromosome 1 (UPD1) is an uncommon genetic finding about which a specific phenotype has not yet been established. We present a boy who has complete paternal UPD1 and isolated developmental delay and suggest that there is no clear phenotype of UPD1.

KEYWORDS

chromosome 1, developmental delay, genetic testing, isodisomy, uniparental disomy

1 | INTRODUCTION

Uniparental disomy (UPD) occurs when an individual receives two copies of a homologous chromosome, from the same parent. UPD can be further characterized as isodisomy when 2 copies of the same homolog are involved or heterodisomy when 2 copies of different homologs are involved. Parent of origin effects have been well described for chromosomes 6,7,11,14, and 20 and suggested for selected other chromosomes.¹ There have been other anecdotal reports of autosomal recessive disorders unmasked by uniparental disomy due to the inheritance of two mutations from one parent.²

We present a boy with isolated developmental delay in the absence of known recessive disorders, who has complete paternal UPD1.

2 | CASE REPORT

A 23-month-old boy was referred for genetics evaluation due to developmental delays. Pregnancy and birth history showed that he was born after an uncomplicated

pregnancy at 38 weeks 6 days gestation via normal spontaneous vaginal delivery without complication. Birthweight was 3.67 kg.

He rolled over at 8 months, crawled at 16 months, and at 23 months he could pull to stand. He had 5 single words and no phrases. He was enrolled in early intervention services and was receiving speech and physical therapies. Bayley Scale of Infant and Toddler Development 4th edition for cognitive and language skills was performed around 18 months of age with a developmental quotient of 75, confirming developmental delays as normal range is considered greater than 85.

Parents were 23 years and 25 years of age with mixed Pacific Islander and European Caucasian ancestry. There was no family history of developmental disabilities, birth defects, or consanguinity.

Physical examination showed appropriate growth of height, weight, and head circumference all between the 50th and 75th centiles. There were no dysmorphic features noted. Neurological examination was generally unremarkable but notable for expressive speech delay limited to 5 words without phrases or two word sentences. Cranial nerves were grossly intact. Reflexes were normal

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bilaterally and motor strength testing was symmetrical in upper and lower extremities. Hypotonia was noted.

MRI of the brain was reported as normal.

2.1 | Laboratory studies

Routine karyotype analysis showed 46,XY normal male result. Chromosome microarray was performed by single nucleotide polymorphisms (SNP) using the Cytoscan® HD platform, which uses more than 743,000 SNP probes and 1,953,000 copy number probes with a median spacing of 0.88 kb. Results noted complete loss of heterozygosity for chromosome 1 and no other aberrations. Follow-up uniparental disomy studies was performed by analysis of chromosomal variable number tandem repeats (VNTRs) and amplified fragment length polymorphisms (AMPFLPs) by polymerase chain reaction and DNA fragment sizing with samples from both parents and confirmed complete paternal isodisomy of chromosome 1. Whole exome sequencing was performed to evaluate for the presence of an autosomal recessive disorder. Exome sequencing was negative for pathogenic or suspected pathogenic variants.

Genetic Counseling included discussion of the sporadic nature of UPD1. The possibility of a later onset genetic disorder due to UPD1 despite unrevealing whole exome sequencing. Recommendations were made for annual Neurology and Genetics evaluation in addition to continued developmental services.

3 | DISCUSSION

Uniparental disomy of chromosome 1 was identified via chromosome microarray using SNP technology showing paternal isodisomy for chromosome 1 with loss of heterozygosity in all regions. Shimojima et al (2013) proposed monosomy rescue was proposed as the most likely mechanism as follows: a nullisomic oocyte arising from meiotic non-disjunction in maternal meiosis II is fertilized with a monosomic sperm, the zygote is monosomic and due to lethality, the paternally derived chromosome is duplicated for compensation.³

There have been normal individuals identified with UPD1^{4,5}. Four individuals with paternal UPD1 and normal karyotype⁴ and one with maternal UPD1 and normal karyotype are reported to have no known clinical issues.⁵

One individual with isolated autism is reported.⁵ However, there does not appear to be a specific phenotype or consistent parent of origin effect.

One case with complete maternal UPD1 was reported in a child with autism; uniparental isodisomy 1 (isoUPD1) was suggested as the potential candidate region of the

disorder but not confirmed.⁶ Other individuals with complete paternal UPD1 with multiple differing clinical phenotypes have been reported: a patient with neonatal seizures, extreme hypotonia, profound intellectual disability, and cortical blindness⁷; a patient with short attention span, short stature, joint hypermobility, impaired T-cell function, immunoglobulin G deficiency, abnormalities of hair, skeletal issues, and dysmorphic features⁸; and a patient with minor facial anomalies, myopathy, sterility, short stature, hearing loss, ptosis, and scoliosis and a karyotype of 46,XX,i(1)(p10),i(1)(q10).⁹ Multiple tissues were not reported to have been studied in these individuals. Mosaicism cannot totally be resolved as a trisomic or monosomic cell line could potentially exist and be related to the phenotype.

Multiple individuals with maternal or paternal UPD1 have been reported to manifest recessive disorders, due to the inheritance of two mutations from a phenotypically normal carrier parent.¹⁰ These disorders include: Zellweger syndrome, T-cell immunodeficiency, Leber congenital amaurosis, maple syrup urine disease, hereditary pyropoikilocytosis, restrictive dermopathy-like phenotype, Hutchinson-Gilford progeria, Herlitz junctional epidermolysis bullosa, CD45-deficient severe combined immunodeficiency, Chediak Higashi syndrome, infantile hypophosphatasia, morbid obesity due to leptin receptor abnormality, Stargardt disease, pycnodysostosis, glycogen storage disease type III, congenital insensitivity to pain with anhidrosis, Charcot-Marie-Tooth disease type 1B, camptodactyly-arthropathy-coxa vara pericarditis syndrome, complement factor H deficiency and endocapillary glomerulonephritis, susceptibility to atypical hemolytic uremic syndrome, Usher syndrome type II, hypomyelinating leukodystrophy, rhizomelic chondrodysplasia punctate type 2, and fumarase deficiency.⁵ Complete maternal isodisomy of chromosome 1 was identified in a patient affected with Pelizaeus Merzbacher-like disorder due to novel mutation in the *GJC2* gene.³ A child with glycogen storage disease type 3 and growth restriction was also reported.¹¹ Because genomic studies such as whole exome sequencing were not reported with these individuals, other recessive disorders are not fully excluded.

There are few cases reported with complete UPD1. This case supports the notion that there is no consistent phenotype for UPD1. Developmental delays have been reported, but are rarely noted. Phenotypic issues in these patients are due more commonly due to rare recessive disorders with genetic variants located on chromosome 1.

AUTHOR CONTRIBUTIONS

All three authors—(VW, LG, RW)—have met the following criteria: (1) Have made substantial contributions to conception and design, or acquisition of data, or analysis

and interpretation of data; (2) Been involved in drafting the manuscript or revising it critically for important intellectual content; (3) Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and (4) Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. VW provided case report with manuscript draft. LG provided case identification and analysis and draft review. RW provided draft review and editing. Prior to submitting the article, all authors agreed on the order in which their names will be listed in the manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICAL APPROVAL

Written permission from the subject's parents was obtained prior to submission of the case report. Anonymity was maintained. The report was reviewed by an internal Institutional Review Board at Laboratory Corporation of America prior to submission to Clinical Case Reports. All parties agreed that the rights of the patient were respected in this process.

CONSENT

Written informed consent was obtained from the patient's family to publish this report in accordance with the journal's patient consent policy.

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