Uniparental disomy (UPD) is a condition in which both copies of a chromosome pair are inherited from one parent. Heterodisomy results from inheriting two different alleles from one parent, whereas isodisomy results from inheriting two copies of a single allele. Both heterodisomy and isodisomy can cause imprinting disorders, whereas isodisomy can unmask recessive disorders. Occasionally, isodisomy causes both imprinting disorders and recessive disorders in one patient.

Argininosuccinic aciduria (ASA) is the second most common urea cycle disorder. ASA is an autosomal recessive disorder caused by biallelic pathogenic variants in ASL (MIM #608310) on chromosome 7. Patients with ASA can present with a neonatal-onset hyperammonemic crisis or a broad late-onset phenotypic spectrum ranging from hyperammonemic crisis to slowly progressive neurocognitive signs and symptoms without apparent hyperammonemia.

Silver-Russell syndrome (SRS) is characterized by prenatal and postnatal growth retardation, relative macrocephaly, body asymmetry, feeding difficulty, and a prominent forehead. Additional clinical features include triangular face, fifth finger clinodactyly and brachydactyly, scoliosis, excessive sweating, and hypoglycemia. SRS is a genetically heterogeneous syndrome; maternal UPD of chromosome 7 (UPD(7)mat) has been identified in 5–10% of patients with SRS.

Previously, Li et al. described a girl with ASA and SRS. The patient had a pathogenic variant of ASL (NM_000048.4:c.2T>A) unmasked by maternal isodisomy of chromosome 7. Her phenotype was relatively mild compared to that of patients with neonatal-onset ASA. As no further cases have been reported, it remains unknown whether patients with ASA and SRS show phenotypic variations. Here, we report another patient with this combination. The phenotype of the present case was more severe than that of a previous case, demonstrating a phenotypic variation in the combination of argininosuccinic aciduria and SRS.

We describe a patient presenting with argininosuccinic aciduria and Silver-Russell syndrome (SRS). SRS was caused by maternal uniparental disomy of chromosome 7 (UPD(7)mat). UPD(7)mat also unmasked a maternally inherited splicing variant in ASL on chromosome 7, leading to the onset of argininosuccinic aciduria. The phenotype of the present case was more severe than that of a previous case, demonstrating a phenotypic variation in the combination of argininosuccinic aciduria and SRS.

Human Genome Variation; https://doi.org/10.1038/s41439-022-00211-y

© The Author(s) 2022
Table S3) showed that the patient had maternal UPD of chromosome 7, which consisted of both heterodisomy and isodisomy (Fig. 2D and Supplementary Table S3).

This report describes a patient who presented with the comorbidibity of ASA and SRS. ASA was presumably caused by a pathogenic intronic variant of ASL in the patient, which was unmasked by maternal isodisomy. The intronic variant resulted in a splicing alteration that caused a translational frameshift. The abnormal transcript probably escaped nonsense-mediated mRNA decay, given the frameshift with the premature termination codon in the last exon. Nevertheless, this variant was likely pathogenic because the affected C-terminal region was involved in the four enzymatic sites of the ASL homotetramer (Supplementary Fig. S1). The SRS-like phenotypes of the patient (Supplementary Table S1) cannot be explained by ASA. Along with these SRS-like signs, atypical trio genotypes (homozygous variants in the child with the absence of the same variant in the father) strongly indicated that UPD(7)mat contributed to the phenotype. Microsatellite analysis confirmed UPD(7)mat.

Thus far, only one case report describes ASA caused by an ASL variant unmasked by UPD(7)mat. Overall, the phenotype of the previously reported patient was much milder than that of our patient (Supplementary Table S1). There are two possible explanations for these phenotypic differences. First, the ASL variant in the present case is predicted to be more devastating than that in the previous case. Zielonka et al. suggested that variant-dependent ASL enzymatic activity determines clinical severity; ≤9% of enzymatic activity has been linked to a severe phenotype. The c.1144-9 G > A variant in the present case was predicted to delete 20 amino acids at the N-terminus (p.Ala2_Met21del). The only known pathogenic

Sequencing analysis with a panel including causative genes for urea cycle disorders (ARG1, ASL, ASS1, CPS1, NAGS, OTC, and SLC25A15) revealed a homozygous variant in intron 15 of ASL (NC_000007:c.1144-9 G > A) in the patient. To clarify whether the variant caused splicing alterations, we sequenced ASL transcripts in immortalized lymphoblastoid cell lines established from the peripheral lymphocytes of the patient and his parents. We amplified a region encompassing the boundary of exons 15 and 16 of ASL (primer sequences: forward primer, 5′-CACCAAGAGAACATGGGACA-3′; reverse primer, 5′-CCTGCAGTGACAGCTGGTT-3′) to perform direct sequencing. As a result, we observed a splicing alteration that resulted in a seven-nucleotide insertion (c.1143_1144insCACCCAG) in the transcripts of the patient and his mother, whereas the splicing in the father was normal (Fig. 2A, B). The insertion observed in the patient and his mother was predicted to result in the p.(Met382Hisfs*94) variant with the stop codon in the last exon. The variant was predicted to disrupt a C-terminal region involved in four enzymatically active sites of the homotetramers of the ASL protein (Supplementary Fig. S1), leading to a loss of function of the enzyme. The same variant was previously identified in a patient with ASA.

Trio genotyping showed that the patient’s mother had the same variant in a heterozygous state, whereas the father did not have the variant. These results indicated that the patient had UPD(7)mat or hemizygosity associated with paternal deletion. To distinguish these two conditions, we performed microarray-based comparative genomic hybridization and SNP genotyping (Fig. 2C). As a result, we found that the patient had loss of heterozygosity (LOH) on two segmental regions (~93 Mb in total) of chromosome 7, one of which encompassed ASL (Fig. 2C). No other chromosome had an LOH of >5 Mb. No copy number alteration was identified in chromosome 7. These results strongly suggested that this patient had a maternal isodisomy encompassing ASL. Moreover, microsatellite analysis for nine loci on chromosome 7 (Supplementary Table S3) showed that the patient had maternal UPD of chromosome 7, which consisted of both heterodisomy and isodisomy (Fig. 2D and Supplementary Table S3).

This report describes a patient who presented with the comorbidibity of ASA and SRS. ASA was presumably caused by a pathogenic intronic variant of ASL in the patient, which was unmasked by maternal isodisomy. The intronic variant resulted in a splicing alteration that caused a translational frameshift. The abnormal transcript probably escaped nonsense-mediated mRNA decay, given the frameshift with the premature termination codon in the last exon. Nevertheless, this variant was likely pathogenic because the affected C-terminal region was involved in the four enzymatic sites of the ASL homotetramer (Supplementary Fig. S1). The SRS-like phenotypes of the patient (Supplementary Table S1) cannot be explained by ASA. Along with these SRS-like signs, atypical trio genotypes (homozygous variants in the child with the absence of the same variant in the father) strongly indicated that UPD(7)mat contributed to the phenotype. Microsatellite analysis confirmed UPD(7)mat.

Thus far, only one case report describes ASA caused by an ASL variant unmasked by UPD(7)mat. Overall, the phenotype of the previously reported patient was much milder than that of our patient (Supplementary Table S1). There are two possible explanations for these phenotypic differences. First, the ASL variant in the present case is predicted to be more devastating than that in the previous case. Zielonka et al. suggested that variant-dependent ASL enzymatic activity determines clinical severity; ≤9% of enzymatic activity has been linked to a severe phenotype. The c.1144-9 G > A variant in the present case was predicted to delete 20 amino acids at the N-terminus (p.Ala2_Met21del). The only known pathogenic
variant in the affected region (c.35 G > A, p.(Arg12Gln)) retained 15% enzymatic activity. Second, the severe feeding difficulty in the present report, probably due to SRS, might have accelerated the neurotoxic effect of ASA. Generally, insufficient energy intake promotes catabolism and predisposes patients with urea cycle disorders to hyperammonemic crisis. The patient in the present report had recurrent vomiting even after the placement of a gastrostomy tube, whereas the previously reported patient only had intermittent vomiting without requiring tube feeding.

Isodisomy is an important etiology underlying autosomal or X-linked recessive disorders. A previous report demonstrated that one out of 2000 individuals from a general population had UPD of one or two chromosomes. More than half of the identified UPD was complete or partial isodisomy. We expect that there are other cases of ASA combined with SRS due to UPD(7)mat. Considering that feeding difficulty due to SRS theoretically may promote catabolism, the possible coexistence of SRS should be considered during the management of ASA.

In conclusion, we presented a patient in whom UPD(7)mat caused ASA and SRS. The present case report demonstrates the phenotypic variation in cases of ASA combined with SRS and suggests that the possible complications of SRS should be considered in the management of ASA.

HGV DATABASE
The relevant data from this Data Report are hosted at the Human Genome Variation Database at https://doi.org/10.6084/m9.figsshare.hgv.3222.

REFERENCES
1. Robinson, W. P. Mechanisms leading to uniparental disomy and their clinical consequences. BioEssays N. Rev. Mol. Cell. Dev. Biol. 22, 452–459 (2000).
2. Yamazawa, K., Ogata, T. & Ferguson-Smith, A. C. Uniparental disomy and human disease: an overview. Am. J. Med. Genet. C. Semin. Med. Genet. 154C, 329–334 (2010).
3. Benn, P. Uniparental disomy: origin, frequency, and clinical significance. Prenat. Diagn. 41, 564–572 (2021).
4. Bulli, C. et al. Recessive congenital myotonia resulting from maternal isodisomy of chromosome 7: a case report. Cases J. 2, 7111 (2009).
AUTHOR CONTRIBUTIONS
A.H. and M.F. drafted the manuscript and contributed to the conception and design of the case report. T.O., T.S., M.K., K.I., K.M., M.K., and Y.F. contributed to the acquisition and interpretation of the data. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

COMPETING INTERESTS
The authors declare no competing interests.

CONSENT FOR PUBLICATION
Written informed consent was obtained from the patient’s parents for publication of this case report.

ADDITIONAL INFORMATION

ACKNOWLEDGEMENTS
We would like to thank Ms. Ikuko Kageyama for her technical assistance. We also wish to express our gratitude to the senior medical editor at the National Center for Child Health and Development for editing this manuscript. The present study was funded by the National Center for Child Health and Development 2022A-1 (to M.F.), the Takeda Science Foundation (to M.F.), and the Japan Society for the Promotion of Science 22K15932 (to A.H.)

AUTHOR CONTRIBUTIONS
A.H. and M.F. drafted the manuscript and contributed to the conception and design of the case report. T.O., T.S., M.K., K.I., K.M., M.K., and Y.F. contributed to the acquisition and interpretation of the data. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

COMPETING INTERESTS
The authors declare no competing interests.

CONSENT FOR PUBLICATION
Written informed consent was obtained from the patient’s parents for publication of this case report.

ADDITIONAL INFORMATION

ACKNOWLEDGEMENTS
We would like to thank Ms. Ikuko Kageyama for her technical assistance. We also wish to express our gratitude to the senior medical editor at the National Center for Child Health and Development for editing this manuscript. The present study was funded by the National Center for Child Health and Development 2022A-1 (to M.F.), the Takeda Science Foundation (to M.F.), and the Japan Society for the Promotion of Science 22K15932 (to A.H.)

AUTHOR CONTRIBUTIONS
A.H. and M.F. drafted the manuscript and contributed to the conception and design of the case report. T.O., T.S., M.K., K.I., K.M., M.K., and Y.F. contributed to the acquisition and interpretation of the data. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

COMPETING INTERESTS
The authors declare no competing interests.

CONSENT FOR PUBLICATION
Written informed consent was obtained from the patient’s parents for publication of this case report.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41439-022-00211-y.

Correspondence and requests for materials should be addressed to Atsushi Hattori.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022