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Original Article

The first case of Al-Raqad syndrome in Japan is associated with a homozygous *DCPS* exonic variant resulting in aberrant splicing

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ABSTRACT

Background: Cases of unexplained neurodevelopmental disorder (NDD) are often accompanied by multiple congenital anomalies. With recent advances in genetic analysis technology, whole-exome sequencing (WES) has become a powerful diagnostic tool for unexplained NDD patients, but variants of unknown significance are sometimes detected in them.
Methods: WES identified a variant in a 2-year-old boy with NDD associated with multiple congenital anomalies who had no abnormal findings in G-banding and array comparative genomic hybridization (array CGH). mRNA analysis was performed on the variant using the patient's peripheral blood leukocytes following *in silico* analysis to confirm its effect on splicing.
Results: WES revealed a novel homozygous single base substituting variant of unknown significance (VUS), which was carried heterozygously by the patient's parents (*DCPS*, NM_014026.6: c.200A>G, p.(Lys67Arg)). *In silico* analysis predicted that this variant may cause aberrant splicing, and mRNA analysis revealed a 48-bp deletion from the 3′ end of exon 1. Biallelic variants of *DCPS* are known to cause Al-Raqad syndrome, a quite rare disorder which presents NDD with multiple malformations. This disease has been reported in only eight individuals from five Middle Eastern or Caucasian families but never in the Japanese but the symptoms of the present case were similar to reported cases of this syndrome.
Discussion: We successfully diagnosed a case of unexplained NDD as Al-Raqad syndrome by WES along with mRNA analysis. Single base substitution with judged VUS can be pathogenic by causing aberrant splicing and, therefore, *in silico* analysis and subsequent RNA sequence are necessary to prove its pathogenicity.

1. Introduction

Neurodevelopmental disorder (NDD) including global developmental delay and intellectual disabilities has a variety of causes, which are generally classified as acquired or genetic. Cases of unexplained NDD are sometimes accompanied by multiple congenital anomalies. G-banding and array comparative genomic hybridization (array CGH) have long been used as tests for these cases. For patients who have not been diagnosed by these tests, targeted panel sequencing or whole-exome sequencing (WES) is now being intensively performed with the recent advances in next-generation sequencing technology. This has led to a number of unexplained NDD cases being genetically diagnosed. A recent meta-analysis showed that the diagnostic yield of exome sequencing for NDD was 36 %, and specifically 53 % for NDD plus associated conditions [1]. Recently, the guidelines of the American College of Medical Genetics and Genomics (ACMG) have strongly recommended that WES or whole-genome sequencing be considered as the first- or second-line test for pediatric patients with congenital anomalies, intellectual disability, and developmental delay [2].

A definitive genetic diagnosis provides many benefits to patients,

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families, and treating physicians because it allows specific care and management, as well as easier access to associations of rare diseases for patients and their families. It also enables accurate genetic counseling to be provided to parents; this can, for example, help them to estimate the risk of their next child suffering from the same condition. As comprehensive analyses such as WES have become more accessible in recent years and there are more opportunities to diagnose rare diseases, variants of unknown significance are often detected. In these cases, accurate assessment of the pathogenicity of the variant is required.

RNA splicing is an essential molecular mechanism for gene expression that removes introns from precursor mRNA and joins together exons to form the mature mRNA. Splicing signals are sequence-specific elements located at exon–intron boundaries (splice sites), the polypyrimidine tract, and branch points [3]. Various congenital genetic diseases are now known to be caused by aberrant splicing, and up to 50 % of all disease-causing variants disrupt splicing [4]. While variants in the canonical ±1,2 splice site are easily recognized because they are very likely to cause splicing defects, other classes of variants such as missense, synonymous, non-canonical splice site, and deep intronic variants are often overlooked because it is unclear whether they actually cause aberrant splicing. Whether or not a variant is pathogenic may depend on whether it causes aberrant splicing.

Against this background, the purpose of this study is to analyze the effect on splicing of a novel *DCPS* exonic variant detected by WES and to evaluate its pathogenicity by assessing it together with the clinical phenotype of a patient showing unexplained NDD with multiple congenital anomalies.

2. Methods

2.1. Patient

The patient was a 2-year-old boy with a variety of anomalies including intellectual disability, delayed motor development, muscle hypotonia, micrognathia, epicanthus, lower auricle, arthrogryposis, peripheral pulmonary artery stenosis, micropenis, and cryptorchidism. His height and weight were within normal ranges at the age of 2 years. He experienced an episode of growth retardation and maternal polyhydramnios during the perinatal period and also suffered an episode of transient thrombocytopenia in the early postnatal period. His parents were not consanguineous, had no history of illness, and he was their first child.

Initially, G-banding and array CGH were performed to determine the cause of the patient's condition, but no abnormalities were detected. For further investigation to find the underlying cause, WES was performed with the consent of the parents.

2.2. Whole-exome sequencing

WES was performed as described previously [5]. Specifically, genomic DNA was extracted from the peripheral blood of the patient and his parents using a QuickGene-Auto S DNA Blood Kit (Kurabo Industrial Ltd., Osaka, Japan). WES was performed using NovaSeq 6000 (Illumina, San Diego, CA, USA) and SureSelect Human All Exon V6 (Agilent Technologies, Santa Clara, CA, USA). Data analysis was performed following the Genome Analysis Toolkit (GATK) from the Broad Institute and their "Best Practices" workflows [6].

We used the following public exome databases to reference allele frequencies: the Human Genetic Variation Database (HGVD) and the Japanese Multi Omics Reference Panel (jMorp) for the Japanese population, as well as the Genome Aggregation Database (gnomAD) for other ethnicities. Additional variant annotations were obtained from ClinVar, Database of Single Nucleotide Polymorphisms (dbSNP), and the Human Gene Mutation Database (HGMD®) Professional.

Candidate variants found in WES were evaluated according to ACMG and the Association for Molecular Pathology (AMP) guidelines [7] and those that did not match the phenotype described in the Online Mendelian Inheritance in Man (OMIM) were excluded. Standard Sanger sequencing was performed to confirm the variants detected by WES and to determine whether the patient's parents shared the same variant, using the following primers: forward (5′-GACGCAGCTCCTCAACTAGG-3′) and reverse (5′-TGGTATTTTCCAGCCGAGAT-3′).

2.3. In silico splicing prediction

We evaluated the potential effect of variants on splicing using multiple algorithms including SpliceSiteFinder-like (http://www.interactive-biosoftware.com), MaxEntScan (http://hollywood.mit.edu/burgelab/maxent/Xmaxentscan_scoreseq.html), and NNSplice *via* Alamut software v.2.11 (Interactive Biosoftware, Rouen, France; http://www.interactive-biosoftware.com) with the default settings. Additionally, SpliceAI-lookup, a deep learning-based tool to identify splice variants on a web-based interface (https://spliceailookup.broadinstitute.org/), was used to assess the potential of splicing defects using Δ score>0.2 as the cut-off [8].

2.4. mRNA analysis

Peripheral blood leukocytes of the patient and the healthy control were used to extract total RNA with the RiboPure™ RNA Purification Kit, Blood (Thermo Fisher Scientific, Waltham, MA, USA), along with an RNA stabilization agent (RNA Later; Thermo Fisher Scientific). The obtained total RNA underwent reverse transcription to generate cDNA using ReverTra Ace -α-® (TOYOBO, Osaka, Japan). The obtained cDNA was then amplified by PCR using a forward primer located in exon 1 (5′-GACGCAGCTCCTCAACTAGG-3′) and a reverse primer located at the boundary of exons 2 and 3 (5′-CGGTCGTCTTTACATCATTCA-3′). Reverse transcriptase PCR products were cut from the gel, extracted using the gel extraction kit (QIAGEN, Hilden, Germany), and subjected to Sanger sequencing. The *DCPS* cDNA sequence was deposited in the NCBI database (NCBI ID: NM_014026.6).

2.5. Ethics

This study was performed in accordance with the ethical standards of the Institutional Review Board of Kobe University Graduate School of Medicine and was approved by the ethics committee of Kobe University (IRB approval nos. 86). All experiments were performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent for the study and the publication was obtained from the patient's parents.

3. Results

A homozygous single-nucleotide substitution in *DCPS* (NM_014026.6: c.200A>G, p.(Lys67Arg)) was detected by WES. This variant is located at the last but one nucleotide in exon 1 of *DCPS*. The patient's parents were heterozygous carriers of this variant (Fig. 1). It was not reported in HGMD® Professional and ClinVar. It was defined as rs887621009 in dbSNP and its allele frequency was reported to be 0.033435 % of East Asian in gnomAD v4.1.0 and 0.0742 % in jMorp 60KJPN, but it was absent from HGVD. Also, there were no homozygous individuals with this variant within these databases.

Aggregating the information listed in HGMD® Professional, eight individuals from five families had previously been diagnosed with Al-Raqad syndrome, caused by homozygous or compound heterozygous variants of *DCPS* [9–12]. The clinical manifestations of these previously reported patients and the present case are shown in Table 1. In addition to developmental delay with hypotonia and intellectual disability, various malformations such as micrognathia, deep-set eye, low-set ear, and cardiac anomaly were similar to those in previously reported cases.

In silico analysis predicted that this variant may cause aberrant

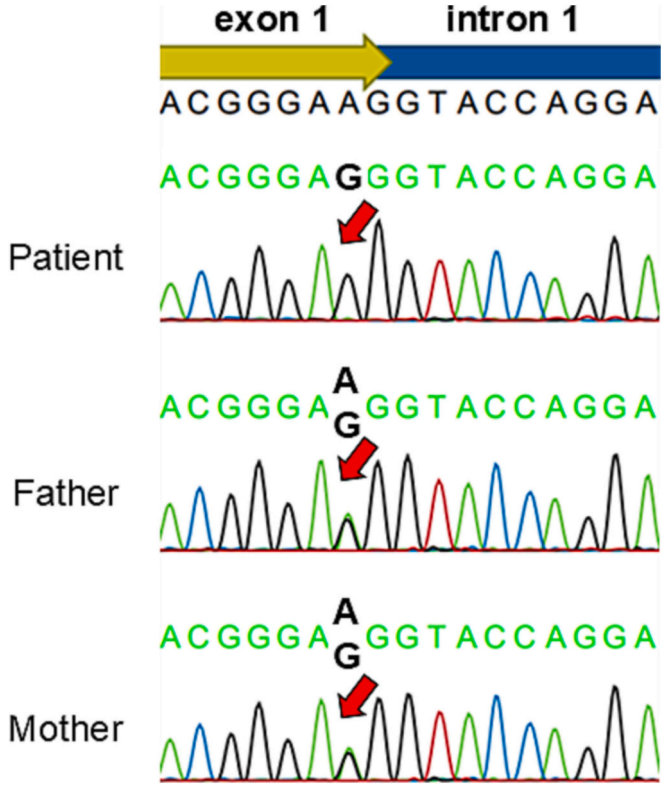

Fig. 1. Results of direct Sanger sequencing using genomic DNA.
A homozygous single-nucleotide substitution in *DCPS* (NM_014026.6: c.200A>G) was detected by WES. This variant is located at the last but one nucleotide in exon 1 of *DCPS*. The patient's parents were heterozygous carriers of this variant.

splicing. The variant was associated with reductions in splicing prediction scores from 70.9 to 61.9 by Splice Site Finder-like, from 7.9 to 2.8 by MaxEntScan, from 0.8 to no score by NNSplice, and from 5.8 to 1.6 by GeneSplicer. SpliceAI-lookup predicted that this variant would lead to donor loss (score = 0.91) resulting in aberrant splicing of exon 1. In addition, the variant was predicted to cause donor gain (score = 0.25) at 97 bp upstream of the 3′ end (*i.e.*, the 98th position from the 3′ end) of exon 1 (Suppl. Fig. S1).

mRNA analysis revealed a different splicing pattern in the patient than in the healthy control. In the patient, aberrant splicing with a 48-bp deletion from the 3′ end of exon 1 was predominantly detected, with a small amount of normal splicing as well (Fig. 2 and Suppl. Fig. S2).

4. Discussion

Here, we present the first diagnosis of a Japanese case of Al-Raqad syndrome, which has previously been reported in only eight cases, achieved through WES along with mRNA analysis. In this case, splicing pattern analysis was conducted to assess the pathogenicity of the *DCPS* exonic variant located at the last but one base of exon 1, which was suspected of being causative of Al-Raqad syndrome.

DCPS is located on chromosome 11q24.2 and its product acts as a scavenger mRNA decapping enzyme that functions in the last step of the 3′-end mRNA decay pathway [12,13]. Al-Raqad syndrome (MIM #616459) is a rare autosomal recessive congenital disorder associated mainly with developmental delay, intellectual disability, and prenatal and postnatal growth retardation, accompanied by craniofacial anomalies, skin hypopigmentation, cardiac malformations, congenital hypotonia, microcephaly, and skeletal anomalies. It is caused by homozygous or compound heterozygous variants in *DCPS*.

Aggregating the information on reported cases of Al-Raqad syndrome, NDDs such as intellectual disability and developmental delay always appear to occur, but the complications vary. The similarities between previously reported cases of Al-Raqad syndrome and the present case involve not only intellectual disability and developmental delay, but also prenatal growth retardation, micrognathia, deep-set eye, low-set ear, joint laxity, and hypotonia. Various cardiac malformations have also been reported to complicate such cases and, in the present case, peripheral pulmonary artery stenosis was observed. Meanwhile, micropenis and cryptorchidism were findings seen only in the present case.

Exonic single-nucleotide substitutions are sometimes complicated and require careful evaluation. Compared with canonical ±1,2 splice variants, the possible roles of exonic single-nucleotide substitutions located near exon–intron boundaries in mediating splicing defects tend to be overlooked. They are recognized as missense or nonsense variants, but often cause aberrant splicing. In particular, canonical sequences in exons at the 5′ splice site have a high potential to disrupt normal splicing [14,15]. The 5′ splice site is characterized by a consensus sequence, which includes the last three bases of exons and the first six nucleotides of introns—MAG|GURAGU (M is A or C and R is A or G; position −3 to position +6) at exon–intron boundaries [16]. Upon the substitution of these nucleotides, we must assume that splicing aberrations will occur. In fact, we have reported that exonic single-nucleotide substitutions at the last, last but one, and last but two nucleotides of *COL4A5* cause high rates of aberrant splicing [17,18].

DCPS c.200A>G disrupted the original exon 1 donor site, and the site with relatively high potential for an association with aberrant splicing 48 bp upstream of the original donor site became the new donor site (Fig. 3). SpliceAI-lookup predicted that this variant would cause donor gain at 97 bp upstream of the 3′ end of exon 1, but instead a new donor site was actually created 48 bp upstream of the 3′ end of exon 1. This discrepancy reminded us that *in silico* analysis alone is insufficient to clarify whether a variant causes aberrant splicing.

We further carefully evaluated this variant regarding its pathogenicity. Al-Raqad syndrome is considered a loss-of-function disease [9,12]. The present case involved a 48-bp deletion (*i.e.*, an in-frame variant of p.Leu53_68del), so loss of function was not inevitable as the reading frame was preserved. Moreover, all reported *DCPS* variants related to Al-Raqad syndrome, including two splice site variants, are also in-frame variants. c.201+2T>C and c.636+1G>A are reported to cause the insertion of 7 and 15 amino acids, respectively [9,12]. Furthermore, the DCPS protein is essential for cell embryogenesis and cell viability, and a mouse model with its knockout was shown to be embryonically lethal [19]. Thus, null homozygous variants of *DCPS* are considered to be incompatible with life [10,11]. Additionally, the DCPS protein is composed of two domains, the N-terminal domain (amino acids 1–147) and the C-terminal domain (amino acids 148–336), both of which play important roles in mRNA decapping [13,20]. The N-terminal domain, which is disrupted in the present patient, primarily functions in facilitating cap binding [20]. In the present case, a 48-bp deletion and a small amount of normal splicing coexisted. However, given that amino acid substitutions occur even when splicing is normal, and that two cases of homozygous missense variants have been reported [10,11], we considered that normal splicing did not preclude the pathogenicity of this variant. Although this study has the limitation that we did not perform functional analysis of the DCPS protein, the above findings strongly suggest that the variant we detected is disease-causing.

In summary, genetic testing technology is continuing to evolve, making the detection of rare diseases such as Al-Raqad syndrome increasingly likely. However, careful assessment is required to properly evaluate the pathogenicity of variants, such as detailed observation of the clinical findings and evaluation of mRNA levels. Patients and their families will benefit if they can obtain a definitive genetic diagnosis through a precise diagnostic approach.

Table 1
Clinical features and genomic data of the patients with Al-Raqad syndrome.

Patients	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Present case
Variants detected	c.636+1G>A	c.636+1G>A	c.636+1G>Ac.947C>T	c.201+2T>C	c.201+2T>C	c.201+2T>C	c.206C>T	c.918G>C	c.200A>G
Amino acid changes	p. Gln212_Leu213ins15	p. Gln212_Leu213ins15	p.Gln212_Leu213ins15 p. Thr316Met	p. Les67_Val68ins7	p.Les67_Val68ins7	p.Les67_Val68ins7	p.Thr87Met	p.Glu306Asp	p.Leu53_Val68del
Zygosity	Homozygous	Homozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Country	Pakistan	Pakistan	Pakistan	Jordan	Jordan	Jordan	Italy	Iran	Japan
Age of onset	Since birth	Since birth	Since birth	Since birth	Since birth	Since birth	Since birth	Since birth	Since birth
Age of diagnosis (year)	21	17	10	5	2	0	2	5	2
Sex	Male	Female	Female	Male	Male	Male	Female	Male	Male
Birth weight (g)	NA	NA	NA	2,400 (-2.4SD)	2,300 (-2.5SD)	2,900 (-1.7SD)	1,200 (-4.2SD)	3,200 (-1.3SD)	2,870 (-1.4SD)
Birth length (cm)	NA	NA	NA	51 (-0.7SD)	48 (-2SD)	NA	38 (-7.5SD)	48 (-2SD)	50.5 (0.12SD)
Head circumference at birth (cm)	NA	NA	NA	31 (-2.7SD)	33 (-2SD)	NA	27 (-8SD)	36 (normal)	32.7 (-1.0SD)
Height at last follow-up (cm)	157.5 (-2.6SD) at 21 y/o	147 (-2.36 SD) at 17 y/o	119.5 (-3SD) at 10 y/o	107 (-3.5SD) at 8 y/o	80 (-7.5SD) at 6.5 y/o	64.5 (-8.8SD) at 3.5 y/o	71.5 (-3.3SD)	96.5 (-3.4SD)	83.0 (-0.9SD)
Intellectual disability	Yes	Yes	Yes	Yes	Yes	Yes	Yes (Speech delay)	Yes	Yes
Devolopmental delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neuromuscular findings	NA	NA	Hypotonia	Hypotonia, Epilepsy	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia
Microcephaly	Absent	Absent	Yes	Yes	Yes	Yes	Yes	Yes	Absent
Deep-set eye	NA	NA	NA	Yes	Yes	Yes	Absent	Yes	Yes
Low-set ear	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes
Simple helices	NA	NA	NA	Yes	Yes	Yes	Yes	Absent	Absent
Micrognathia	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes
Micropenis	NA	NA	NA	NA	NA	NA	NA	NA	Yes
Cryptorchidism	NA	NA	NA	NA	NA	NA	NA	NA	Yes
Joint laxity	Absent	Absent	Absent	Yes	Yes	Yes	Absent	Yes	Yes
Brachydactyly	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Absent
Hypopigmentation	Absent	Absent	Absent	Yes	Yes	Yes	Yes	Yes	Absent
Cardiac anomaly	NA	NA	NA	Cardiac atrial septal defect	Cardiac atrial septal defect	Cardiac atrial septal defect	Cardiac atrial septal defect	Minimal dilated left ventricle, intraventricular septum shift to right	Peripheral pulmonary stenosis
Reference	Ahmad (2015) [9]	Ahmad (2015) [9]	Ahmad (2015) [9]	Ng (2015) [12]	Ng (2015) [12]	Ng (2015) [12]	Alesi (2018) [10]	Masoudi (2019) [11]	-

Abbreviations: NA, not available; SD, standard deviation.

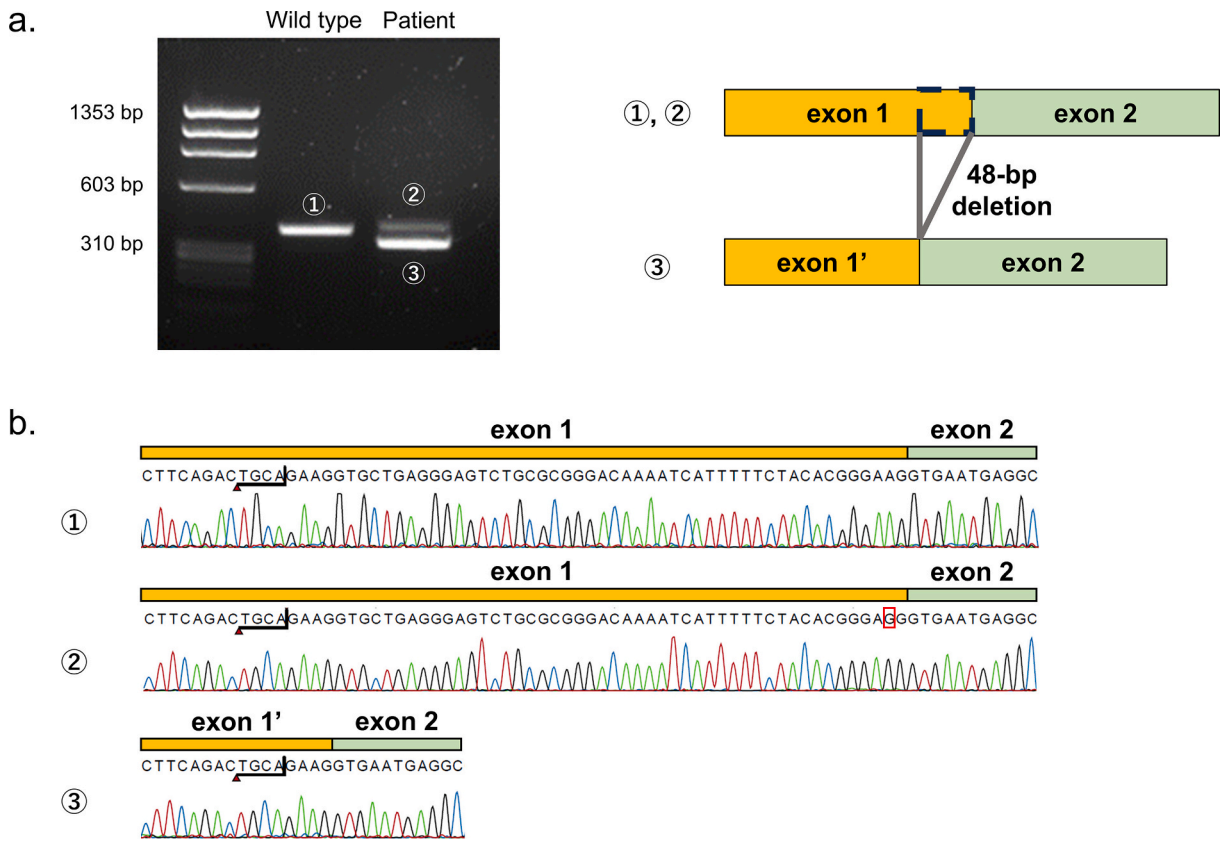

Fig. 2. mRNA analysis and schematic representation of the variant-related changes.
Results of electrophoresis and direct sequencing of the reverse-transcription polymerase chain reaction product with wild-type (healthy control) and patient blood samples.
a. Left panel shows the electrophoresis results. The wild type exhibited a single band, while the patient exhibited two bands. Right panel shows a schematic image of the detected aberrant splicing.
b. Direct sequencing revealed a 48-bp deletion and a small amount of normal splicing in the patient's sample, while only normal splicing was detected in the wild type. The red box indicates the single nucleotide change within normal splicing.

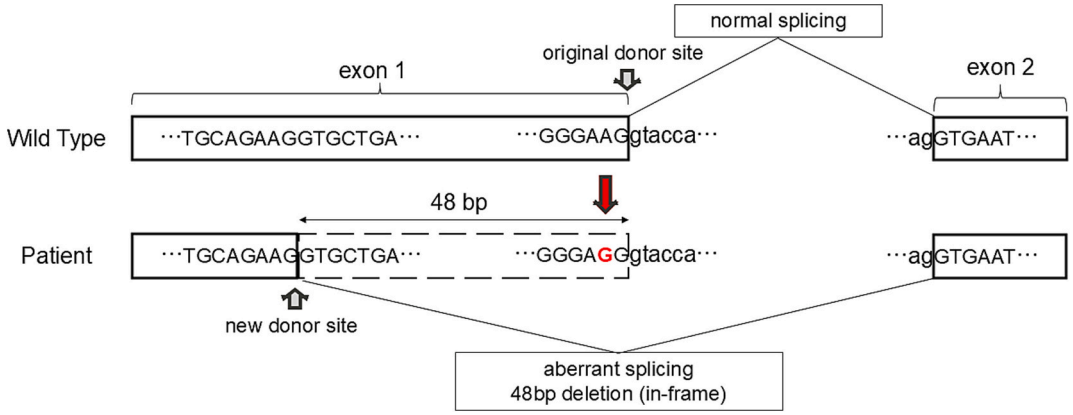

Fig. 3. Schematic representation of the splice donor site change in *DCPS* c.200A>G.
DCPS c.200A>G disrupted the original exon 1 donor site, and the site with relatively high potential for an association with aberrant splicing 48 bp upstream of the original donor site became the new donor site.

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Author contribution

N.H., S.N., and M.N.: conception and design; N.H., S.N., H.H., and M. N.: data collection and analysis; S.N., H.H., I.Y., T.Y., K.H., U.C., N.C., H. T., Y.T., and M.N.: data interpretation; S.N., N.H., and M.N.: collection of patient samples and clinical information; N.H. and S.N.: drafting the article; I.S., Y.H., M.N., and N.K.: critical revision of the article. All

authors approved the final version of the manuscript for publication.

Data statement

The data used for this study, although not available in a public repository, will be made available to other researchers upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2025.104366.

References

[1] Srivastava S, Love-Nichols JA, Dies KA, Ledbetter DH, Martin CL, Chung WK, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med 2019;21:2413–21.
[2] Manickam K, McClain MR, Demmer LA, Biswas S, Kearney HM, Malinowski J, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the american college of medical genetics and genomics (ACMG). Genet Med 2021;23:2029–37.
[3] Cartegni L, Chew SL, Krainer AR. Listening to silence and understanding nonsense: exonic mutations that affect splicing. Nat Rev Genet 2002;3:285–98.
[4] Lord J, Baralle D. Splicing in the diagnosis of rare disease: advances and challenges. Front Genet 2021;12:689892.
[5] Hanafusa H, Yamaguchi H, Kondo H, Nagasaka M, Juan Ye M, Oikawa S, et al. Dravet syndrome and hemorrhagic shock and encephalopathy syndrome associated with an intronic deletion of SCN1A. Brain Dev 2023;45:317–23.
[6] Van der Auwera GA, Carneiro MO, Hartl C, Poplin R, Del Angel G, Levy-Moonshine A, et al. From FastQ data to high confidence variant calls: the genome analysis toolkit best practices pipeline. Curr Protoc Bioinformatics 2013;43:11.0.1–.0.33.
[7] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the american college of medical genetics and genomics and the association for molecular pathology. Genet Med 2015;17:405–24.
[8] Jaganathan K, Kyriazopoulou Panagiotopoulou S, McRae JF, Darbandi SF, Knowles D, Li YI, et al. Predicting splicing from primary sequence with deep learning. Cell 2019;176:535–48.e24.
[9] Ahmed I, Buchert R, Zhou M, Jiao X, Mittal K, Sheikh TI, et al. Mutations in DCPS and EDC3 in autosomal recessive intellectual disability indicate a crucial role for mRNA decapping in neurodevelopment. Hum Mol Genet 2015;24:3172–80.
[10] Alesi V, Capolino R, Genovesea S, Capriati T, Loddo S, Calvieri G, et al. An additional patient with a homozygous mutation in DCPS contributes to the delination of Al-Raqad syndrome. Am J Med Genet A 2018;176:2781–6.
[11] Masoudi M, Bereshneh AH, Rasoulinezhad M, Ashrafi MR, Garshasbi M, Tavasoli AR. Leukoencephalopathy in Al-Raqad syndrome: expanding the clinical and neuroimaging features caused by a biallelic novel missense variant in DCPS. Am J Med Genet A 2020;182:2391–8.
[12] Ng CK, Shboul M, Taverniti V, Bonnard C, Lee H, Eskin A, et al. Loss of the scavenger mRNA decapping enzyme DCPS causes syndromic intellectual disability with neuromuscular defects. Hum Mol Genet 2015;24:3163–71.
[13] Liu H, Rodgers ND, Jiao X, Kiledjian M. The scavenger mRNA decapping enzyme DcpS is a member of the HIT family of pyrophosphatases. EMBO J 2002;21:4699–708.
[14] Krawczak M, Reiss J, Cooper DN. The mutational spectrum of single base-pair substitutions in mRNA splice junctions of human genes: causes and consequences. Hum Genet 1992;90:41–54.
[15] Sahashi K, Masuda A, Matsuura T, Shinmi J, Zhang Z, Takeshima Y, et al. In vitro and in silico analysis reveals an efficient algorithm to predict the splicing consequences of mutations at the 5′ splice sites. Nucleic Acids Res 2007;35:5995–6003.
[16] Zhang MQ. Statistical features of human exons and their flanking regions. Hum Mol Genet 1998;7:919–32.
[17] Aoto Y, Horinouchi T, Yamamura T, Kondo A, Nagai S, Ishiko S, et al. Last nucleotide substitutions of COL4A5 exons cause aberrant splicing. Kidney Int Rep 2022;7:108–16.
[18] Okada E, Aoto Y, Horinouchi T, Yamamura T, Ichikawa Y, Tanaka Y, et al. Aberrant splicing caused by exonic single nucleotide variants positioned 2nd or 3rd to the last nucleotide in the COL4A5 gene. Clin Exp Nephrol 2023;27:218–26.
[19] Bail S, Kiledjian M. DcpS, a general modulator of cap-binding protein-dependent processes? RNA Biol 2008;5:216–9.
[20] Liu SW, Jiao X, Liu H, Gu M, Lima CD, Kiledjian M. Functional analysis of mRNA scavenger decapping enzymes. Rna 2004;10:1412–22.