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Short Communication

Maternal uniparental isodisomy in a patient with autosomal recessive spastic paraplegia type 20

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ABSTRACT

Spastic paraplegia type 20 (SPG20), also known as Troyer syndrome, is a complex form of hereditary spastic paraplegia (HSP), caused by biallelic deleterious variants in the *SPART* gene. We performed whole-exome sequencing (WES) in a 10-year-old boy with spastic paraparesis, dyskinesia, intellectual disability, speech delay, congenital anomalies, white matter changes, and sensorimotor neuropathy. WES revealed a homozygous nonsense variant in exon 4 of *SPART* (Gln374Ter), which was found in a heterozygous state in the mother and absent in the father. Analysis of polymorphisms from WES data indicated maternal uniparental disomy (UPD) of chromosome 13, explaining the observed homozygosity. This case underscores the importance of parental segregation studies when homozygous variants are identified, as UPD significantly impacts genetic counseling and recurrence risk. It also highlights the value of bioinformatics tools in WES trio analysis to detect UPD, improving diagnostic precision in clinical settings.

1. Introduction

Hereditary spastic paraplegia (HSP) comprises a group of rare neurodegenerative disorders marked by progressive lower-limb spasticity. Complicated forms are defined by additional neurological or systemic features, including seizures, ataxia, intellectual disability, peripheral neuropathy, or skeletal anomalies. Spastic paraplegia type 20 (SPG20), or Troyer syndrome, is an autosomal recessive complicated HSP presenting in infancy with progressive spastic paraparesis, distal amyotrophy, pseudobulbar signs, motor and cognitive delay, mild cerebellar signs (dysarthria, dysdiadochokinesia, intention tremor), short stature, choreoathetoid movements, and minor skeletal changes. It is caused by variants in the *SPART* gene (MIM:607111) located at 13q13.3, which encodes spartin, a multifunctional protein involved in the dendritic aggresome-like induced structures (DALIS) formation (Karlsson et al., 2014), lipid droplet biogenesis (Eastman et al., 2009), and cytokinesis (Yang et al., 2008; Renvoisé et al., 2010). Pathogenic *SPART* variants affect lipid droplet surface composition, disrupting lipid-mediated signaling relevant to HSP pathogenesis (Renvoisé et al., 2012).

We report the case of a 10 years old boy with spastic paraparesis, dyskinesia, mild intellectual disability, speech impairment, multiple congenital anomalies, white matter abnormal signs and sensorimotor neuropathy, a clinical picture compatible with the diagnosis of Troyer syndrome due to a novel homozygous mutation in *SPART* gene. Parental segregation analysis and SNP array showed the rare genetic condition of maternal uniparental isodisomy (UPiD). This is the first case of UPiD described in Troyer syndrome.

Abbreviations: HSP, Hereditary spastic paraplegia; SPG20, Spastic paraplegia type 20; UPD, Uniparental Disomy; UPiD, Uniparental Isodisomy; WES, Whole Exome Sequencing; GATK, Genome Analysis Toolkit; ACMG, American College of Medical Genetics and Genomics; IG, Integrative Genomics Viewer; SNP, Single Nucleotide Polymorphism.

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2. Case report

2.1. Clinical data

The proband was a ten-year-old boy, born at the 34th week of gestation by eutocic delivery after a physiological pregnancy. He was the second child of non-consanguineous parents with a negative family history of neurodevelopmental disorders. Due to low neonatal weight and prematurity, he was kept in neonatology under observation. The neonatal period was characterized by hypotonia, easy fatigability, feeding difficulties. From the first months of life, he presented a marked psychomotor delay. At the age of 12 months, he started to walk with uncertain gait and poor balance. At the time of our observation clinical investigations showed mild intellectual disability, speech impairment, spastic paraparesis, diffuse dyskinesia, severe generalized hyposomia with relative macrocephaly, facial dysmorphisms, generalized muscle wasting. Brain MRI showed white matter abnormal signs (Fig. 1). Electromyography showed mild sensorimotor neuropathy.

Two sequential slices demonstrate diffuse, symmetric hyperintensity of periventricular white matter.

2.2. Genetics studies

2.2.1. WES

Following informed consent, peripheral blood samples were obtained from the proband and both parents. Genomic DNA was extracted using standard protocols. Whole-exome sequencing (WES) was conducted on the trio to identify the genetic basis of the disorder. Library preparation was performed using the Nextera Flex for Enrichment Sample Prep Kit (Illumina, San Diego, CA, USA) following the manufacturer's guidelines. Sequencing was carried out on an Illumina NextSeq500 platform using 2×150 bp paired-end reads. Reads were aligned to the human reference genome (hg19). Variant calling was executed using GATK v4.3 pipeline (McKenna et al., 2010) and changes were annotated with VEP version 95 (McLaren et al., 2016) and filtered using the Genome Mining (GEMINI) software (Paila et al., 2013). Based on phenotype and inheritance, filtering focused on rare variants (allele frequency <1 % in public databases such as 1000 Genomes, EVS, and gnomAD).Variants observed in the homozygous state in healthy individuals were deprioritized. Candidate variants were further assessed for phenotype concordance with the clinical features of the patient.

All retained variants were interpreted and classified according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) 2015 guidelines (Richards et al., 2015), incorporating population data, computational evidence, segregation, and published functional studies. Manual inspection of candidate variants was performed using Integrative Genomics Viewer (IGV) to confirm read quality, zygosity, and segregation.

The genomic region encompassing the SPART c.1120C > T variant was amplified by PCR using custom-designed primers (Table 1), and the resulting amplicons were subjected to bidirectional Sanger sequencing. Segregation analysis of polymorphisms was performed using a custom script adapted from Ting et al. (2007) to process SNP data from WES (Ting et al., 2007) (see Supplementary methods for further details).

2.2.2. SNP-CGH array

SNP-CGH array was carried out on DNA extracted from peripheral blood lymphocytes of the proband and his parents. This analysis used the standard Agilent SurePrint G3 Human Genome CGH + SNP 4×180 K Microarray (Agilent Technologies, Santa Clara, CA, USA), which provides an overall median probe spacing of 25.3 Kb. Labeling and hybridization were performed in accordance with the manufacturer's instructions (Agilent Technologies, Santa Clara, CA, USA). The microarray slide was scanned using an Agilent SureScan Dx Microarray Scanner G5761A (Agilent Technologies, Santa Clara, CA, USA), and the resulting image was analyzed using Agilent CytoGenomics software (v.5.1.2.1). Genomic coordinates were reported based on the GRCh37/hg19 genome assembly. The data were then compared against known copy number variations documented in publicly available databases, including the Database of Genomic Variants (DGV, https://projects.tcag.ca/cgi-bin/variation/gbrowse/ hg19, accessed on 20 December 2024) and DECIPHER (https://decipher.sanger.ac.uk, accessed on 20 December 2024).

3. Results

After alignment, Picard CollectHsMetrics reported a mean on-target depth of 124× for the proband, with 99.4 % of target bases covered at

Table 1
Primers used for Sanger sequencing of the SPART variant.

Gene	RefSeqGene	Primers	intron/exon location
SPART	NG_011559.2	FW 5′-ACTGCCAAACTGACATTCAAACA-3′	IVS3
		RV 5′-TGCACAAGTTGCTTTGCTTTAGT-3′	IVS4

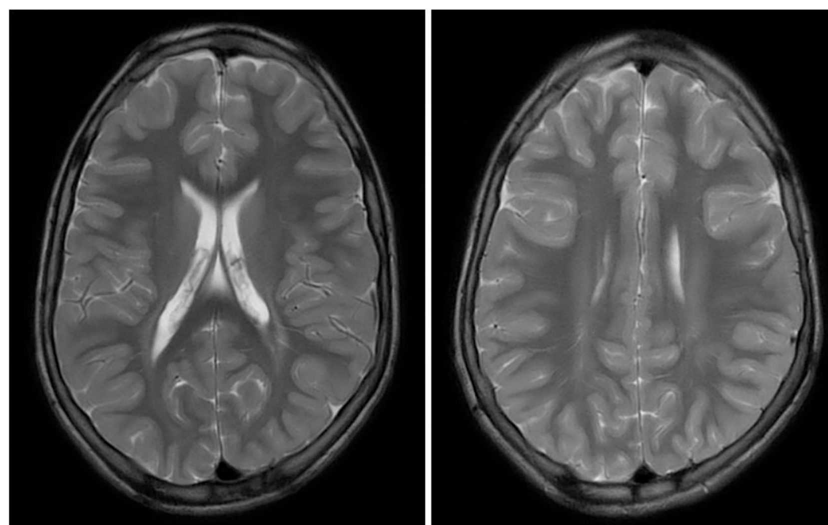

Fig. 1. Axial T2-weighted brain MRI of the proband.

≥10× and 96.1 % at ≥20×; the mean insert size was 217 bp. The parental samples yielded comparable coverage metrics. Upon completion of the bioinformatic pipeline, WES identified a homozygous nonsense variant, (NM_015087.5:c.1120C > T;p.(Gln374Ter)), in exon 4 of the *SPART* gene (Fig. 2). No other rare, pathogenic, or likely pathogenic variants were identified in genes associated with phenotypically similar conditions.

This previously unreported variant introduces a premature stop codon, predicted to result in a truncated transcript likely subject to nonsense-mediated decay. Homozygous or compound heterozygous inactivating variants in *SPART* are known to be associated with Troyer syndrome (Diquigiovanni et al., 2019). According to the ACMG/AMP 2015 guidelines, this variant meets criteria PVS1, PM2, and PP3, supporting its classification as pathogenic.

Unexpectedly, segregation analysis in the patient's parents revealed that the mother was a heterozygous carrier of the *SPART* variant, while the variant was absent in the father (Fig. 2).

Analysis of Mendelian inheritance patterns from WES-derived polymorphisms suggested maternal uniparental inheritance of SNPs on chromosome 13 (Fig. 3).

Subsequent SNP-CGH array analysis in the trio identified a paternally inherited deletion on chromosome 17p12, encompassing the *PMP22* gene, which is associated with hereditary neuropathy with liability to pressure palsies (HNPP), a disorder characterized by incomplete penetrance and variable expressivity (Chrestian et al., 2015; Ivanovic et al., 2020). Additionally, the analysis confirmed the presence of alternating regions of homozygosity and heterozygosity on chromosome 13, indicative of a mixed isodisomy/heterodisomy (UPiD/UPhD) (Fig. 4c). Further segregation analysis of informative SNPs confirmed maternal inheritance of both copies of chromosome 13 [ISCN 2020: arr[GRCh37] 13q12.11q14.11(19584477_40869972) × 2 hmz mat,13q22.2q22.3 (75441715_78681132) × 2 hmz mat,13q31.1q33.1 (85283911_104388683) × 2 hmz mat] (Fig. 4). Notably, the *SPART* variant was located within an isodisomic region of chromosome 13, providing strong evidence that the observed homozygosity for the variant resulted from the inheritance of two identical maternal alleles.

Given the homozygosity surrounding the centromere, the proposed mechanism of uniparental disomy (UPD) involves meiotic recombination events during prophase I, followed by nondisjunction errors in meiosis II (Fig. 4) and a subsequent postzygotic trisomy rescue event leading to the loss of the paternal copy of chromosome 13.

4. Discussion

In this study, we report a 10-year-old boy carrying a homozygous nonsense variant in the *SPART* gene. The patient exhibited a phenotype characterized by mild intellectual disability, speech impairment, spastic paraparesis, diffuse dyskinesia, severe generalized hyposomia with relative macrocephaly, facial dysmorphisms, generalized muscle wasting, and abnormal white matter signals on neuroimaging, consistent with a diagnosis of Troyer syndrome. This previously unreported variant is predicted to introduce a premature stop codon, leading to a truncated transcript likely subject to nonsense-mediated decay, and was classified as pathogenic according to ACMG/AMP 2015 guidelines. Our findings align with previous studies reporting inactivating mutations in *SPART* that disrupt Spartin protein function.

Additionally, the patient exhibited mild sensorimotor neuropathy, which could be attributed to a paternally inherited deletion encompassing the *PMP22* gene. Although HNPP is classically characterized by recurrent, transient mononeuropathies triggered by minor trauma or compression, several studies have described cases with a more diffuse sensorimotor polyneuropathy, sometimes mimicking other hereditary neuropathies such as Charcot-Marie-Tooth disease (CMT) (Kleopa et al., 2004; Luigetti et al., 2014). To date, no acute episodes related to mechanical pressure or trauma have been reported in the patient's medical history.

Interestingly, segregation analysis revealed that the *SPART* variant was present in a heterozygous state only in the mother. Subsequent investigations provided evidence of maternal uniparental isodisomy of chromosome 13q, explaining the observed homozygosity.

Uniparental disomy (UPD) refers to a genetic condition in which both copies of a chromosome are inherited from a single parent, with the corresponding contribution from the other parent absent. UPD is further classified into uniparental isodisomy (UPiD) and uniparental heterodisomy (UPhD). In cases of UPiD, the individual receives two identical copies of a chromosome from one parent, whereas UPhD involves the inheritance of both homologs of a chromosome from the same parent (Liehr 2010). Additionally, a combination of these two forms, mixed isodisomy/heterodisomy (UPiD/UPhD), may arise as a result of meiotic recombination events occurring during prophase I. Alternatively, it can occur as segmental UPiD, affecting terminal chromosomal regions, which arises postzygotically often because of chromosomal rearrangement rescue. This mechanism is driven by somatic mitotic recombination between sister chromatids during early embryogenesis followed by subsequent clonal advantage of the recombinant cell. While both UPiD and UPhD may lead to imprinting disorders depending on the chromosome involved, only UPiD or mixed UPiD/UPhD can result in autosomal recessive (AR) disorders through biallelic inheritance of deleterious alleles from a carrier parent. The incidence of UPD was estimated to be approximately 1 in 3500 live births (Yamazawa et al., 2010). However, this figure is likely an underestimation, as most reported cases arise from clinical settings, while UPDs involving non-imprinted chromosomes or

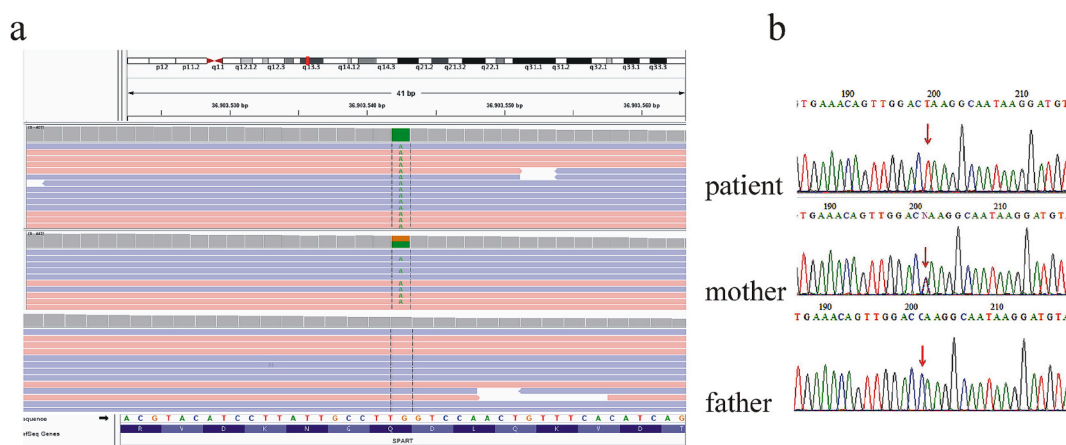

Fig. 2. IGV and Sanger Sequencing Confirmation of SPART c.1120C > T Variant in Family Trio a) IGV screenshot and b) Sanger sequencing electropherogram showing the c.1120C > T variant in *SPART*: homozygous in the patient, heterozygous in the mother, and absent (homozygous for the reference allele) in the father.

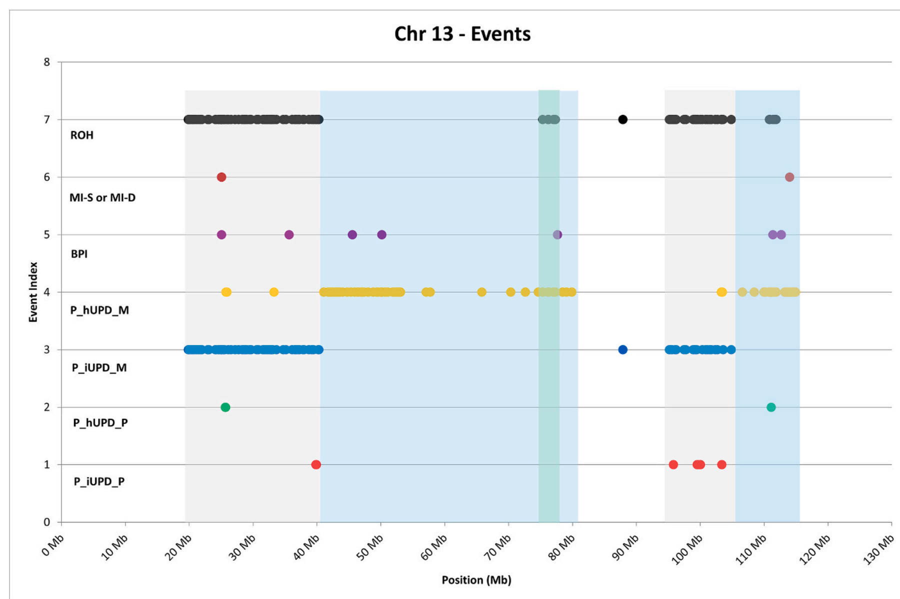

Fig. 3. Scatter plot of statistically significant inheritance and UPD-related events along chromosome 13. The x-axis shows genomic position (Mb); the y-axis separates seven event classes: 1–4, UPD (by subtype); 5, informative biparental inheritance (BPI); 6, meiotic errors (MI-S/MI-D); 7, runs of homozygosity (ROH). For each 20-SNP sliding window (step 10 SNPs), only the UPD class with the lowest significant p-value ($p < 0.001$) is plotted. ROH windows with $P_ROH < 0.001$ are plotted in lane 7; individual informative SNPs (BPI) and MI-S/MI-D SNPs in lanes 5–6. Light grey (i_UPD_M) and blue (h_UPD_M) shaded bands mark regions where significant windows cluster densely, as opposed to isolated events. Band boundaries enclose stretches where significant windows are consecutive or closely spaced. A dark-green sub-band at ~75–78 Mb highlights a child ROH due to biallelic inheritance from a homozygous mother. The depletion of BPI markers supports uniparental inheritance; isolated BPI calls here likely reflect genotyping artifacts. The ~82–95 Mb region lacks significant events due to low marker density (15 SNPs).

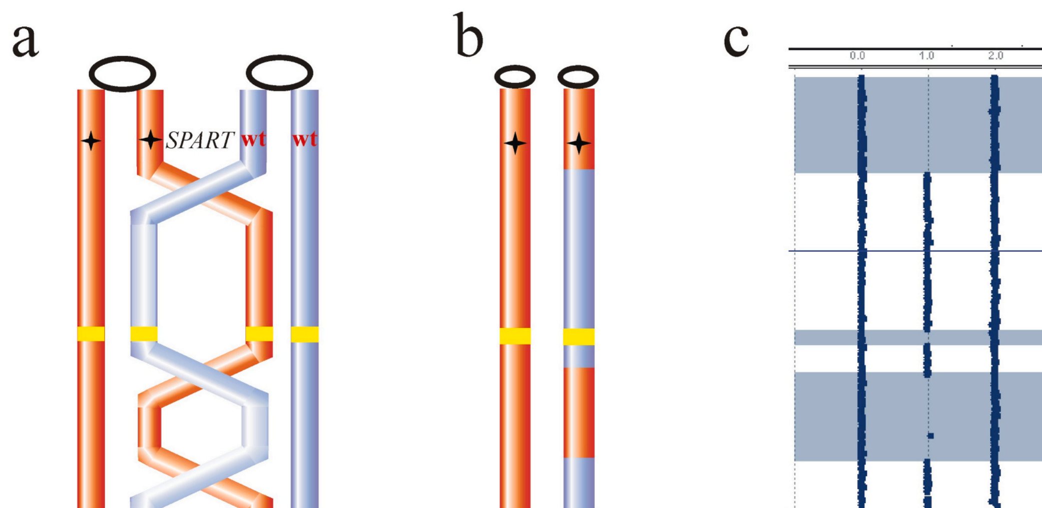

Fig. 4. Schematic representation of the proposed mechanism underlying the origin of mixed UPD. a) Meiotic recombination events during meiosis I between maternal homologous chromosomes 13, one carrying the wild-type *SPART* allele and the other carrying the mutated *SPART* allele (indicated by a black star). The yellow box represents a 3.2 Mb region of homozygosity in the maternal cells. b) Following normal segregation in meiosis I, a nondisjunction error in meiosis II leads to a gamete containing both sister chromatids, which are distinct due to recombination events in meiosis I. c) SNP-array profile of chromosome 13 in the patient (Agilent CGH/SNP platform). The plot shows the number of uncut alleles per SNP: heterozygous SNPs have one uncut allele, while homozygous SNPs have zero or two. Regions lacking SNPs with one uncut allele (shadowed boxes) indicate extended homozygosity, consistent with alternating segments of uniparental isodisomy (UPiD) and heterodisomy (UPhD).

UPiD affecting genomic regions without pathogenic variants can occur in healthy individuals and often go undetected. Additionally, many UPDs are detected by SNP-array which cannot identify pure heterodisomy without parental SNP segregation analysis. In this context, it is important to note that all types of UPD can be suspected by analyzing Mendelian inheritance patterns of polymorphisms extracted from WES data in a trio (King et al., 2014). Recent studies, both utilizing whole-exome sequencing data from large cohorts, have refined our understanding of UPD prevalence. Nakka et al. (2019) reported that UPD occurs in approximately 1 in 2000 births in the general population (Nakka et al., 2019). Similarly, a WES-based investigation by Moch et al. (2024) found that UPD is present in roughly 0.16 % (or 1 in 625) of pediatric cases, particularly among individuals with seizures and neurodevelopmental disorders (Moch et al., 2024).

The first report of UPiD contributing to an AR disorder was described in a case of cystic fibrosis, which resulted from UPiD involving

chromosome 7 (Spence et al., 1988). Since then, multiple reports have documented both segmental and complete chromosome UPiD as causative mechanisms in recessive diseases. These cases span a variety of chromosomes and AR conditions, with approximately 60 % involving complete UPiD and the remaining 40 % presenting as combined UPiD/UPhD (Niida et al., 2018). Several instances of maternal or paternal UPD affecting chromosome 13 have also been identified (Slater et al., 1994; Berend et al., 1999; Tsai et al., 2004). Most individuals in these cases displayed no apparent phenotype, supporting the notion that chromosome 13 does not contain imprinted genes (Slater et al., 1995). However, pathogenic roles for UPiD involving chromosome 13 have been described in two individuals with prelingual hearing impairment (Alvarez et al., 2003) and two others with spastic ataxia of the Charlevoix-Saguenay type (Anesi et al., 2011).

In summary, we describe the first SPG20 case with a novel homozygous *SPART* variant resulting from maternal UPiD/UPhD13. This finding underscores the importance of parental segregation analysis in homozygous recessive cases, as UPD carries major implications for genetic counseling and typically indicates a low recurrence risk.

UPD is a chromosomal anomaly that is recognized as a significant, yet often overlooked, cause of neurodevelopmental disorders and should not be considered rare in this context. While SNP-array often remains the standard method for UPD detection, it is inherently unable to identify pure heterodisomy unless parental genotypes are included. Given that many neurodevelopmental disorders are routinely investigated using WES in a trio-based approach, we recommend the integration of bioinformatics tools that can suggest the occurrence of both isodisomy and heterodisomy by analyzing Mendelian inheritance patterns of polymorphisms derived from WES data. Incorporating these tools into routine clinical diagnostics would enhance detection rates, improve diagnostic accuracy, and ultimately lead to better patient management.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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CRediT authorship contribution statement

Eugenia Borgione: Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Ornella Galesi:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Sandro Santa Paola:** Investigation, Formal analysis, Data curation. **Mariangela Lo Giudice:** Investigation, Formal analysis. **Marika Giuliano:** Investigation, Data curation. **Lucia Saccuzzo:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Nunzio Testa:** Investigation. **Marco Fichera:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Carmela Scuderi:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments, and the protocol was approved by the Ethics Committee of the Oasi Research Institute–IRCCS of Troina (Italy) on 5 April 2022 (approval code: 2022/04/05/CE-IRCCS-OASI/52).

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2025.149646.

Data availability

Data will be made available on request.

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