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Lab Resource: Multiple Cell Lines

Generation of iPSC lines (UMILi032-A, UMILi033-A, UMILi034-A, UMILi035-A, UMILi036-A) from five Congenital Central Hypoventilation Syndrome patients carrying different poly-alanine expansion mutations in the *PHOX2B* gene

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A B S T R A C T

Congenital Central Hypoventilation Syndrome (CCHS) is a rare, life-threatening genetic disorder of the autonomic nervous system characterized by alveolar hypoventilation and generalized dysautonomia. CCHS is caused by heterozygous *PHOX2B* mutations, predominantly polyalanine repeat expansion (95% of cases) and, less frequently, frameshift mutations (5%). To address the lack of disease models, we generated five human induced pluripotent stem cell (hiPSC) lines derived from patients carrying +5Ala, +6Ala and +11Ala expansion mutations. These hiPSC lines exhibited undifferentiated hPSC phenotype, pluripotency, normal karyotype, and retention of the pathogenic genotype, providing a reliable *in vitro* platform for elucidating CCHS molecular mechanisms and disease pathogenesis.

Resource table

Unique stem cell line identifier	1. UMILi032-A (https://hpscreg.eu/cell-line/UMILi032-A) 2. UMILi033-A (https://hpscreg.eu/cell-line/UMILi033-A) 3. UMILi034-A (https://hpscreg.eu/cell-line/UMILi034-A) 4. UMILi035-A (https://hpscreg.eu/cell-line/UMILi035-A) 5. UMILi036-A (https://hpscreg.eu/cell-line/UMILi036-A)
Alternative name(s) of stem cell line	N/A
Institution	Department of Medical Biotechnology and Translational Medicine (BIOMETRA), Università degli Studi di Milano, Milan, Italy.
Contact information of the distributor	Diego Fornasari diego.fornasari@unimi.it
Type of cell line	iPSCs
Origin	Human
Additional human source info required for human ESC or iPSC	See Table 1
Cell Source	Skin fibroblasts
Clonality	Clonal

(continued on next column)
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(continued on next page)

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(*continued*)

Method of reprogramming	Integration-free Sendai viral vectors
Genetic Feature(s)	See Table 1
Evidence of the reprogramming transgene loss (including genomic copy if applicable)	RT-PCR
Associated disease	Congenital Central Hypoventilation Syndrome (CCHS)
Gene/locus	*PHOX2B*; GRCh38.p14/chr4: 41,744,082–41,748,725
Date archived/stock date	2nd October 2025
Cell line repository/bank	The lines have been registered in the Human Pluripotent Stem Cell Registry (https://hpscreg.eu/)
Ethical approval	This study was approved by the Ethics Committee of the Meyer Children's Hospital, Florence, Italy (study number: 7/2015)

1. Resource utility

Investigation of CCHS pathogenesis has been limited by the unavailability of cellular and animal models. The generation of relevant cell types by differentiation of the generated iPSCs may represent a great potential for disease modelling and screening of new therapeutic approaches.

2. Resource details

The *PHOX2B* gene encodes a transcription factor essential for the development of neural lineages in the autonomic nervous system (ANS) and respiratory control circuits (Pattyn et al., 1999). Polyalanine repeat expansion mutations (PARMs) in exon 3, affecting the 20-alanine tract, account for 90% of congenital central hypoventilation syndrome (CCHS) cases (Amiel et al., 2003).

CCHS is a rare, life-threatening disorder characterized by central hypoventilation and widespread ANS dysfunction. Most patients are diagnosed at birth, although late-onset forms (LO-CHS) also occur. Affected individuals show impaired responses to hypoxia and hypercapnia, particularly during sleep, requiring mechanical ventilation; in severe cases, support is also needed while awake (Trang et al., 2020). Although both *in vivo* and *in vitro* models have been used to investigate pathophysiology and identify therapeutic targets, they only partially recapitulate the human disease (reviewed in Di Lascio et al., 2021). Given the variable expressivity and incomplete penetrance of CCHS (Antic et al., 2006), generating multiple iPSC lines from patients with different *PHOX2B* mutations and clinical onset is crucial to obtain robust disease models, particularly valuable for epigenetic studies and identification of modifier genes that can influence and explain the different phenotypes.

Building on our previous work, where we generated iPSC lines from two patients carrying a +5-alanine expansion mutation (Cuadros Gamboa et al., 2022), we reprogrammed fibroblasts from five additional patients carrying distinct PARMs (+5, +6 and +11 alanine expansions) (Table 1).

Patient-derived fibroblasts obtained from skin punch biopsies were reprogrammed using the CytoTune™-iPS 2.0 Sendai Reprogramming kit. The resulting iPSC lines (Table 2) displayed typical stem cell morphology, including a high nuclear-to-cytoplasmic ratio and compact colony formation (Fig. 1**A**). Undifferentiated hPSC state was confirmed by immunofluorescence, with all lines positive for OCT4 (nuclear) and SSEA4 (membrane) (Fig. 1**B**). TaqMan real-time PCR further demonstrated induction of *OCT4* and *NANOG* in iPSCs compared to parental fibroblasts (Fig. 1**C**). Antibodies and assays used are detailed in Table 3.

To validate pluripotency functionally, iPSC lines were differentiated into the three germ layers using STEMdiff™ Trilineage Differentiation Kit. Marker expression was evaluated via real-time PCR at T_1 (differentiated) versus T_0 (undifferentiated iPSCs) (Fig. 1**D**). Markers included *PAX6* and *OTX2* (ectoderm), *FOXA2* and *GATA4* (mesoderm), and *NCAM* and *TBXT* (endoderm). Primer sequences are provided in Table 3.

Karyotyping confirmed chromosomal stability (Supplementary Fig. 1A). The absence of residual Sendai virus was verified by RT-PCR (Supplementary Fig. 1B), with primers listed in Table 3. Sanger sequencing confirmed the specific polyalanine expansions (Supplementary Fig. 1C). Short Tandem Repeat (STR) profiling across 16 loci further demonstrated that each iPSC line matched its parental fibroblasts, confirming sample identity (the results are available with authors).

3. Materials and methods

3.1. Patients recruitment and fibroblasts isolation

CCHS patients were recruited at Meyer Hospital (Florence) with informed consent. Primary fibroblast cultures were derived from forearm skin biopsies and maintained in DMEM with 10% fetal bovine serum, 2 mM L-glutamine, and antibiotics (100 U/mL penicillin, 100 µg/mL streptomycin).

3.2. iPSC reprogramming and cell culture

Fibroblasts were reprogrammed using the CytoTune-iPS 2.0 Sendai kit (Thermo Fisher). UMILi032-A, UMILi033-A, UMILi034-A, UMILi035-A, and UMILi036-A were derived by reprogramming fibroblasts at passages p4, p3, p6, p5 and p6, respectively.

Seven days post-transduction, fibroblasts were plated on Matrigel-coated wells (hESC-qualified, Corning) with Essential 8 Flex medium (Thermo Fisher). iPSC colonies were manually picked and expanded on Matrigel-coated dishes. All lines were cultured at 37 °C in 5% CO_2 and passaged twice a week as clumps using 0.5 mM EDTA in DPBS. Routine mycoplasma testing was performed via PCR using primers listed in Table 3.

Table 1
Summary of lines.

Unique cell line ID	Age (yrs)	Sex	Ethnicity	Genotype	GCN repeats	CCHS phenotype
UMILi032-A	19	M	Caucasian	NM_003924.4:c.751_765dup NP_003915.2:p.Ala251_Ala255dup	20/25	Later onset
UMILi033-A	26	F	Caucasian	NM_003924.4:c.751_765dup NP_003915.2:p.Ala251_Ala255dup	20/25	Congenital
UMILi034-A	24	F	Caucasian	NM_003924.4:c.724_741dup NP_003915.2:p.Ala242_Ala247dup	20/26	Congenital
UMILi035-A	21	M	Caucasian	NM_003924.4:c.739_756dup NP_003915.2:p.Ala247_Ala252dup	20/26	Congenital
UMILi036-A	17	F	Caucasian	NM_003924.4:c.733_765dup NP_003915.2:p.Ala245_Ala255dup	20/31	Congenital

Table 2
Characterization and validation.

Classification	Test	Result	Data
Morphology	Photography Bright field	Normal	Fig. 1 panel A
Characterization of undifferentiated state	Qualitative analysis by immunocytochemistry	Markers of undifferentiated hPSC state OCT4 and SSEA-4 were expressed by all lines. iPSC line UMILi027-A (Cuadros Gamboa et al., 2022) was added for comparison	Fig. 1 panel B
	Quantitative analysis by RT-qPCR	Markers of undifferentiated hPSC state *OCT4* and *NANOG* were expressed by all lines. iPSC line UMILi027-A (Cuadros Gamboa et al., 2022) was added for comparison	Fig. 1 panel C
Genomic stability	Karyotyping by QFQ-banding	**UMILi032-A**: 46, XY **UMILi033-A**: 46, XX **UMILi034-A**: 46, XX **UMILi035-A**: 46, XY **UMILi036-A**: 46, XX Resolution: 400 bands/haploid set	Supplementary Fig. 1 panel A
mtDNA analysis (IF APPLICABLE)	*Sanger sequencing, Deep sequencing, analysis software (Mitopore https://www.mitopore.de, mtDNA-Server 2, etc)*	Not performed	N/A
Cell line identity verification	Microsatellite PCR (mPCR)	Not performed	N/A
	STR analysis	STR analysis performed. 16 markers tested (CSF1PO, D2S1338, D3S1358, D5S818, D7S820, D8S1179, D13S317, D16S539, D18S51, D19S433, D21S11, FGA, TH01, TPOX, vWA, Amelogenin); matched	Submitted in archive with the journal
Mutation analysis (IF APPLICABLE)	Sanger sequencing	**UMILi032-A**: heterozygous *PHOX2B* +5 Ala expansion (20/25) **UMILi033-A**: heterozygous *PHOX2B* +5 Ala expansion (20/25) **UMILi034-A**: heterozygous *PHOX2B* +6 Ala expansion (20/26) **UMILi035-A**: heterozygous *PHOX2B* +6 Ala expansion (20/26) **UMILi036-A**: heterozygous *PHOX2B* +11 Ala expansion (20/31)	Supplementary Fig. 1 panel C.The duplicated GCN triplets are marked with asterisks.
	Southern Blot OR WGS	Not performed	N/A
Microbiology and virology	Mycoplasma	Mycoplasma testing by RT-PCR. Negative	Not shown
Characterization of the differentiated state	Directed tri-lineage differentiation	Expression of layer-specific markers was tested via qPCR. Ectoderm: *PAX6* and *OTX2* Mesoderm: *NCAM* and *TBXT* Endoderm: *FOXA2* and *GATA4*	Fig. 1 panel D
Donor screening (OPTIONAL)	HIV 1 + 2 Hepatitis B, Hepatitis C	N/A	N/A
Genotype additional info (OPTIONAL)	Blood group genotyping	N/A	N/A
	HLA tissue typing	N/A	N/A

3.3. Variants analysis

Genomic DNA was analyzed by Sanger sequencing of all three *PHOX2B* coding exons and flanking intronic regions (Bachetti et al., 2011). Exon 3 was amplified with oligonucleotides (Table 3). Reaction mixes were run for 35 cycles (95 °C, 1′; 60 °C, 45′′; 72 °C, 1′ 30′′). PCR products were purified using a SapI–ExoIII mix (37 °C, 40′; 80 °C, 15′) and sequenced with the Big Dye Terminator Cycle Sequencing Kit (Applied Biosystem) on an ABI 3100 DNA sequencer. Genomic DNA was extracted from iPSCs at the following passage numbers: UMILi032-A (p9), UMILi033-A (p26), UMILi034-A (p11), UMILi035-A (p20), and UMILi036-A (p23)

3.4. Immunocytochemistry

Cells were fixed with 4% paraformaldehyde, 4% sucrose for 20′ at room temperature (RT), then permeabilized with 0.6% Triton X-100 (except SSEA-4 antibody). After overnight incubation at 4 °C with primary antibodies (Table 3), cells were washed with high salt PBS, incubated with secondary antibodies for 1 h at RT (Table 3), and counterstained with DAPI 0.1 μg/mL. Images were acquired using Leica Stellaris 8 DLS Confocal microscope and processed with LAS X Office (Leica). The following passage numbers were used to assess the expression of markers of undifferentiated hPSC state via immunocytochemistry: UMILi032-A (p6), UMILi033-A (p28), UMILi034-A (p7), UMILi035-A (p15), and UMILi036-A (p24).

3.5. RT-qPCR

Total RNA was isolated using RNeasy Mini Kit (Qiagen). cDNA was synthesized using the GoScript Reverse Transcription system (Promega). qPCR was performed with TaqMan Gene Expression Master Mix (Applied Biosystems) and TaqMan probes (Table 3) on a QuantStudio5™ thermal cycler (Applied Biosystems) as follows: 50 °C for 2′, 95 °C for 10′, followed by 40 cycles at 95 °C for 15′′ and 60 °C for 1′. Gene expression was normalized to *GAPDH* ($2^{-\Delta Ct}$), and fold change was calculated relative to fibroblasts ($2^{-\Delta\Delta Ct}$). The following passage numbers were used to assess the expression of markers of undifferentiated hPSC state via qPCR: UMILi032-A (p10), UMILi033-A (p21), UMILi034-A (p11), UMILi035-A (p15), and UMILi036-A (p19).

3.6. Karyotyping

Karyotype analysis has been performed on iPSCs as follows. The cultures were stopped with 70 ng/mL colcemid (Sigma-Aldrich) at 37 °C for 90′. Chromosome preparations were obtained using standard procedures of the Prenatal and Postnatal Cytogenetics Service of the Department of Medical Biotechnology and Translational Medicine (University of Milan, Italy) and analyzed by QFQ banding (400 bands). Twenty metaphases were examined, and at least five cells were fully karyotyped in accordance with the 2024 International System for Human Cytogenomic Nomenclature (ISCN). The following passage numbers were used for karyotype analysis: UMILi032-A (p19), UMILi033-A (p24), UMILi034-A (p37), UMILi035-A (p18), and

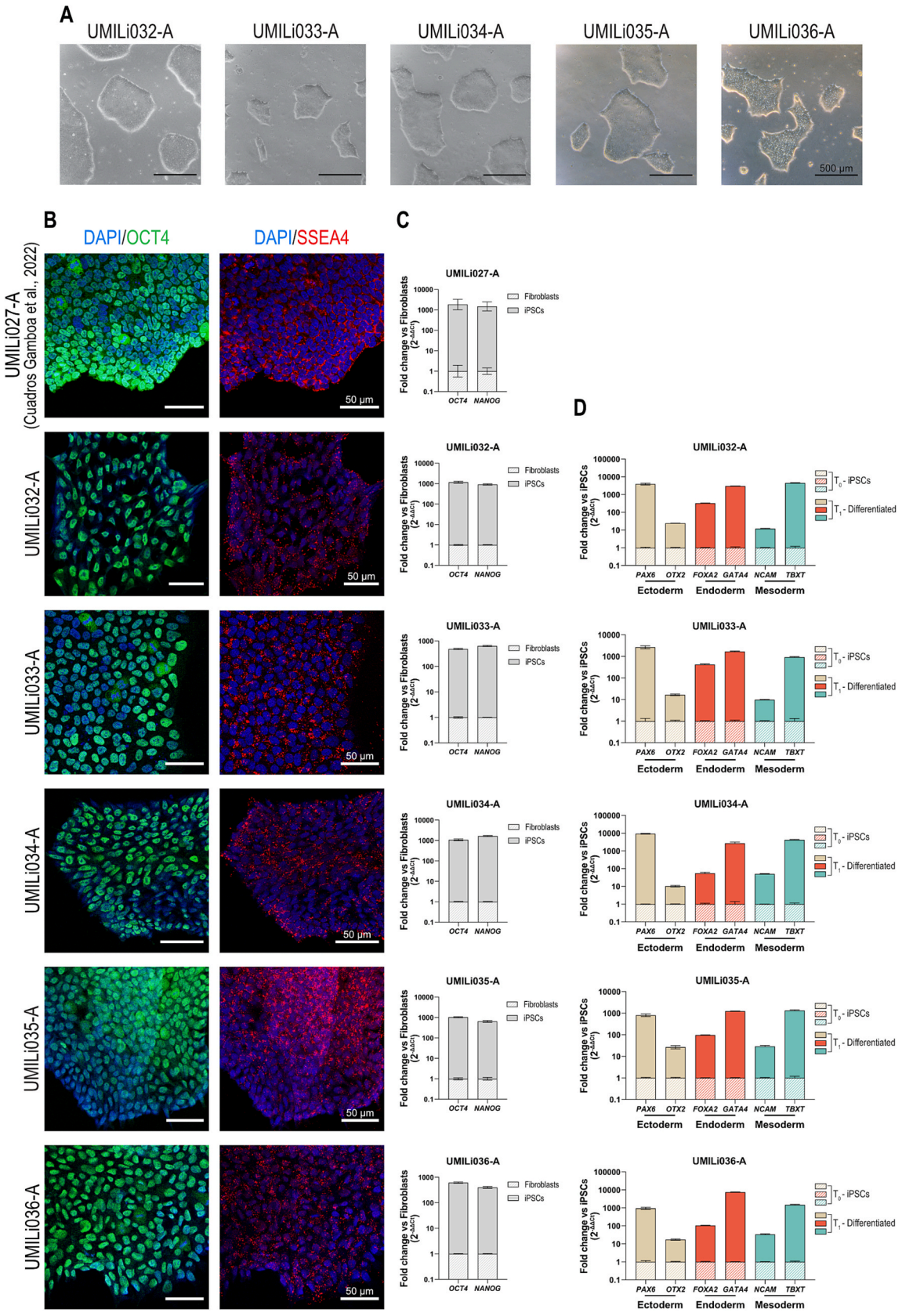

Fig. 1. Characterization of generated iPSC lines.

Table 3
Reagent details.

	Antibodies used for immunocytochemistry/flow-cytometry			
	Antibody	**Dilution**	**Company Cat #**	**RRID**
Markers of undifferentiated hPSC state	Rabbit anti-OCT4	1:40	Cell Signaling Technology Cat# 2840	AB_2167691
	Mouse anti-SSEA-4	1:250	Cell Signaling Technology Cat# 4755	AB_1264259
Secondary antibodies	DyLight 549-conjugated goat anti-mouse IgG (H + L)	1:200	Jackson ImmunoResearch Cat#115–505-146	AB_2341133
	Alexa Fluor® 488-conjugated donkey anti-rabbit IgG (H + L)	1:400	Jackson ImmunoResearch Cat#711–545-152	AB_2313584

	Primers		
	Target	**Size of the band**	**Forward/Reverse primer (5′-3′)**
Markers of undifferentiated hPSC state (qPCR)	*NANOG*		Taqman probe ID: Hs02387400_g1
	OCT4		Taqman probe ID: Hs00999634_gH
House-keeping genes (qPCR)	*GAPDH*		Taqman probe ID: Hs99999905_m1
	HPRT1	103 bp	TTTGCTGACCTGCTGGATTACA/GGTCATTACAATAGCTCTTCAGTCTGAT
Trilineage differentiation markers (qPCR)	*PAX6*	88 bp	CGCCTATGCCCAGCTTCAC/GGCAGCATGCAGGAGTATGAG
	OTX2	153 bp	AGTCGAGGGTGCAGGTATG/GGCCACTTGTTCCACTCTCT
	TBXT	96 bp	GGGTCCACAGCGCATGAT/ATTTTAAGAGCTGTGATCTCCTCGTT
	NCAM	107 bp	TCCTGGGAACTGCAGTTTCTCT/TTTGGCATCTCCTGCCACTT
	FOXA2	60 bp	TTCAGGCCCGGCTAACTCT/ACCCCCACTTGCTCTCTCACT
	GATA4	69 bp	AGCTGGGTAGTTTAGCCAAACG/TGTGTGACACGGTGAACGAA
Mycoplasma testing (PCR)	*GPO-1/MGSO*	700 bp	ACTCCTACGGGAGGCAGCAGTA/TGCACCATCTGTCACTCTGTTAAC
Sendai viral genome (PCR)	*SeV*	181 bp	GGATCACTAGGTGATATCGAGC/ACCAGACAAGAGTTTAAGAGATATGTATC
	KOS	528 bp	ATGCACCGCTACGACGTGAGCGC/ACCTTGACAATCCTGATGTGG
	Klf4	410 bp	TTCCTGCATGCCAGAGGAGCCC/AATGTATCGAAGGTGCTCAA
	c-Myc	532 bp	TAACTGACTAGCAGGCTTGTCG/TCCACATACAGTCCTGGATGATGATG
Sanger sequencing	*PHOX2B*	678 bp	TTGGGCCACCCTAACCGG/TACCCGCTCGCCCACTCG

UMILi036-A (p21).

3.7. Analysis of differentiation potential

STEMdiff™ Trilineage Differentiation Kit (Stem Cell Technologies) was used according to manufacturer's instructions. RNA was isolated using RNeasy Mini Kit and reverse transcribed using High-Capacity RNA-to-cDNA™ Kit (Thermo Fisher). Layer-specific markers were analyzed by qPCR using SYBR™ Select Master Mix (Thermo Fisher) and primers (Table 3), on a 7500 Real-Time PCR System (Applied Biosystem). The following protocol was applied: 95 °C for 10′, followed by 40 cycles at 95 °C for 15'' and 60 °C for 1′. Data were normalized to *HPRT1* ($2^{-\Delta Ct}$) and fold-change was calculated relative to undifferentiated iPSCs ($2^{-\Delta\Delta Ct}$). Trilineage differentiation was performed on iPSCs at the following passage numbers: UMILi032-A (p17), UMILi033-A (p31), UMILi034-A (p22), UMILi035-A (p31), and UMILi036-A (p27)

3.8. STR analysis

Genomic DNA from iPSCs and fibroblasts was extracted using the QIAamp DNA Mini Kit (Qiagen). Short tandem repeat (STR) profiling of 16 loci was performed by Eurofins Genomics (Germany) for cell line authentication.

CRediT authorship contribution statement

Ana Lucia Cuadros Gamboa: Writing – original draft, Methodology, Investigation, Formal analysis. **Filippo Chiesa:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Paride Pelucchi:** Writing – review & editing, Investigation, Formal analysis. **Martina Bertocchi:** Validation, Resources. **Anna Ripepi:** Investigation, Formal analysis. **Eleonora Piscitelli:** Writing – review & editing, Resources. **Marta Peruzzi:** Resources, Data curation. **Niccolò Nassi:** Resources, Data curation. **Cinzia Arzilli:** Resources, Data curation. **Monica Annunziata:** Resources, Data curation. **Amelia Morrone:** Writing – review & editing, Resources, Investigation, Data curation. **Viviana Tritto:** Resources, Investigation, Formal analysis. **Paola Riva:** Resources, Investigation, Formal analysis. **Giuseppe Santamaria:** Resources, Investigation, Formal analysis. **Isabella Ceccherini:** Writing – review & editing, Resources, Investigation, Formal analysis. **Roberta Benfante:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Simona Di Lascio:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Diego Fornasari:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Diego Fornasari reports financial support was provided by A.I.S.I.C.C. Diego Fornasari reports a relationship with Telethon Foundation that includes: funding grants. Diego Fornasari reports a relationship with CCHS Family Network that includes: funding grants. If there are other authors, they 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.scr.2025.103888.

Data availability

Data will be made available on request.

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