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Lab Resource: Single Cell Line

Characterisation of the patient-specific induced pluripotent stem cell line UKEi075-A carrying the heterozygous *PRKAG2* frameshift variant c.769_770del (p.E257Kfs*15)

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ABSTRACT

Missense variants in *PRKAG2,* the gene encoding for the γ2-subunit of adenosine monophosphate-activated protein kinase (AMPK), can cause hypertrophic cardiomyopathy, cardiac conduction defects and glycogen storage disorders. Clinical consequences evoked by truncating *PRKAG2* variants are poorly understood. Dermal fibroblasts of a male dilated cardiomyopathy-patient carrying the truncating *PRKAG2* variant c.769_770del (p.E257Kfs*15) at a heterozygous state were reprogrammed by Sendai virus-mediated expression of OCT-4, SOX2, c-Myc and KLF4 to human induced pluripotent stem cells (hiPSCs). HiPSCs displayed a normal karyotype, high pluripotency, mycoplasma-absence and were successfully differentiated into three primary germ layers. This hiPSC-line will enable analysing molecular pathomechanisms underlying *PRKAG2*-cardiomyopathy.

Resource Table:

Unique stem cell line identifier	UKEi075-A, https://hpscreg.eu/cell-line/UKEi075-A
Alternative name(s) of stem cell line	ERC046sv3655, PRKAG2_IEPT
Institution	Institute of Experimental Pharmacology and Toxicology, University Medical

(*continued on next column*)

(*continued*)

Unique stem cell line identifier	UKEi075-A, https://hpscreg.eu/cell-line/UKEi075-A
	Center Hamburg-Eppendorf (UKE), Hamburg, Germany.

(*continued on next page*)

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(*continued*)

Unique stem cell line identifier	UKEi075-A, https://hpscreg.eu/cell-line/UKEi075-A
Contact information of the distributor	Prof. Dr. Friederike Cuello, f.cuello@uke.de, Prof. Dr. Thomas Eschenhagen, t.eschenhagen@uke.de
Type of cell line	Human induced pluripotent stem cell line (hiPSC)
Origin	Human
Additional human source info required for human ESC or iPSC	Age at inclusion: 43, Sex: Male, Ethnicity: Caucasian
Cell Source	Dermal fibroblasts
Clonality	Clonal
Method of reprogramming	Non-integrating Sendai virus vector (CytoTune™-iPS 2.0 Sendai Reprogramming Kit, ThermoFisher, expression of transcription factors OCT-4, SOX2, c-Myc, KLF4)
Genetic Feature(s)	*PRKAG2* c.769_770del, p.E257Kfs*15 (NM_016203.4)
Evidence of the reprogramming transgene loss (including genomic copy if applicable)	Master cell bank (passage 20) negative for Sendai virus by RT-qPCR
Associated disease	Hypertrophic cardiomyopathy (literature); patient presented with severe dilated cardiomyopathy
Gene/locus	*PRKAG2* gene (7q36.1 human hg38)
Date archived/stock date	Skin biopsy 3rd February 2016, generation of master cell bank (passage 20) 3rd December 2017
Cell line repository/bank	hPSCreg.eu – UKEi075-A
Ethical approval	The donor has agreed to the use of cells for research giving written informed consent. Ethical approval for patient recruitment, skin biopsy and analysis of cells following informed consent has been obtained by the local ethics committee at UKE in Hamburg (Reference number: PV4798, 28th October 2014; extended PV4798 27th January 2020).

1. Resource utility

This hiPSC-line was derived from dermal fibroblasts of a male patient carrying a truncating variant in *PRKAG2* diagnosed with severe dilated cardiomyopathy (DCM). The patient-derived hiPSCs and their differentiation to cardiomyocytes represent a versatile tool for unravelling molecular pathomechanisms of cardiomyopathy associated with truncating *PRKAG2* variants.

2. Resource details

Comprised of a catalytic α-, as well as regulatory β- and γ-subunits, the adenosine monophosphate-activated protein kinase (AMPK) is a cellular energy sensor with particular importance to rewire metabolism during conditions of altered metabolite availability such as nutrient starvation (reviewed in Herzig and Shaw, 2018). The γ-subunit contains binding sites for adenosine monophosphate (AMP) and other adenine nucleotides (Xiao et al., 2007), connecting kinase activity directly to cellular energy demand to ascertain homeostasis. Thereby, AMP binding to the γ-subunit increases the catalytic activity of the α-subunit which phosphorylates key substrates involved in lipid metabolism, mitochondrial biogenesis and autophagy (reviewed in Herzig and Shaw, 2018).

The more frequently occurring missense variants in *PRKAG2* can cause metabolic cardiomyopathy characterised by cardiac hypertrophy, conduction defects and non-lysosomal cardiac glycogen accumulation (Lopez-Sainz et al., 2020). However, information is scarce regarding the impact of truncating variants in this gene classically associated with a phenotype of hypertrophic cardiomyopathy. A recent case report described three infants with homozygous truncating *PRKAG2* variants and heart dilatation who died of a severe neonatal onset form of heart failure a few months after birth (Janin et al., 2023). Heart dilatation was also observed in a male adult patient carrying the heterozygous truncating variant c.769_770del, p.E257Kfs*15 (NM_016203.4) in exon 6 of *PRKAG2* diagnosed with DCM. To further investigate molecular pathomechanisms of truncating *PRKAG2* variants, we generated and thoroughly quality controlled a hiPSC-line derived from this patient by reprogramming of dermal fibroblasts (Table 1). Sendai virus clearance was verified by RT-qPCR before creation of the master cell bank at passage 20 (p20).

HiPSCs displayed a normal colony-forming morphology visualised by brightfield microscopy in both FTDA and TeSR™-E8™ medium (Fig. 1, **panel A**). Mycoplasma PCR tests of hiPSCs conducted during culture confirmed negative results (Fig. 1, **panel B**). Karyotyping by Giemsa-banding (G-banding) revealed a normal male karyotype 46,XY (Fig. 1, **panel C**). Molecular karyotyping shows no evidence for copy number alterations (Fig. 1, **panel D**). Short tandem repeat analysis (STR) was performed as unique identifier for the cell line.

Pluripotency was tested with flow-cytometry analysis of hiPSCs by staining for Stage-Specific Embryonic Antigen 3 (SSEA-3) beside an isotype control, yielding more than 99 % positive cells (Fig. 1, **panel E**). RT-qPCR in triplicates revealed robust expression of pluripotency markers *NANOG* (Nanog homeobox) and *SOX2* (SRY-box transcription factor 2; Fig. 1, **panel F**) in comparison with UKEi001-A.

The variant of uncertain significance in *PRKAG2* was identified in the patient within the course of an EU-funded project by panel sequencing and confirmed by Sanger sequencing of patient-derived hiPSCs genomic DNA (gDNA; Fig. 1, **panel G**).

Mesodermal differentiation potential was assessed after five independent 2D-cardiac differentiation runs yielding between 26 % and 81 % cardiac troponin T (cTnT)-positive cells as determined by flow-cytometry analysis (Fig. 1, **panel H**). Additionally, hiPSCs were differentiated into three primary germ layers for immunofluorescence analysis of endodermal (SRY-box transcription factor 17, SOX17; Hepatocyte nuclear factor 3-beta, HNF-3b), ectodermal (Paired box 6, PAX6; Nestin, NES) and mesodermal (Brachyury) markers (Fig. 1, **panel I**) which confirmed their expression.

3. Materials and methods

3.1. Ethical approval

This study was approved by the local ethics committee (PV4798, 28th October 2014; extended 27th January 2020).

3.2. Reprogramming and hiPSC-culture

Dermal fibroblasts isolated from a skin biopsy were reprogrammed to hiPSCs by Sendai virus-mediated expression of OCT-4, SOX2, c-Myc and KLF4 using the CytoTune™-iPS 2.0 Reprogramming Kit (ThermoFisher, #A16517). HiPSCs were expanded in StemFlex™ medium (ThermoFisher, #A3349401) and switched to FTDA medium (FGF2, TGFbeta1, Dorsomorphin, Activin A; Frank et al. (2012)) for maintenance under hypoxia (37 °C, 5 % CO_2, 5 % O_2) with daily feeding. HiPSCs were passaged with Accutase (Invitrogen, #00–4555-56; 1:2/D-PBS (Gibco, #14190–169)) after washing (D-PBS) every 3 – 4 days, counted with Neubauer hemocytometer and $5x10^4$-$6x10^4$ cells/cm^2 were seeded on Geltrex-coated (Gibco, #A14132-02; 1:100/RPMI-1640 (Gibco, #21875–091)) dishes with Y-27632 (10 μM; Biorbyt, orb1307611). HiPSCs morphology was further validated by culturing cells in TeSR™-E8™ medium (STEMCELL Technologies, #05990) on Vitronectin (Gibco, #A14700) passaged with ReLeSR™ (STEMCELL Technologies, #100–0483). Mycoplasma absence (e.g. p34) was routinely checked by PCR as described by Breckwoldt et al. (2017). Sendai virus clearance was evaluated as described in Shibamiya et al. (2020) by RT-qPCR after RNA extraction from hiPSC (Qiagen, #74106) and cDNA generation by

Table 1
Characterization and validation.

Classification	Test	Result	Data
Morphology	Photography Brightfield	HiPSCs display a normal colony morphology.	Fig. 1, panel A
Characterization of undifferentiated state	Marker expression analysis	Flow-cytometry analysis of hiPSCs revealed > 99 % SSEA-3 positive cells. Expression of pluripotency markers *NANOG* and *SOX2* was confirmed by RT-qPCR.	Fig. 1, panels E and F
Genomic stability	Karyotyping by G-banding, Copy number variation (CNV) array methods	The karyotype 46,XY was confirmed by G-banding. NanoString nCounter® human karyotype panel showed no evidence for copy number variations in the analysed loci.	Fig. 1, panels C and D
mtDNA analysis	*Sanger sequencing, Deep sequencing, analysis software (Mitopore https://www.mitopore.de, mtDNA-Server 2, etc)*	N/A	N/A
Cell line identity verification	Microsatellite PCR (mPCR)	not performed	N/A
	STR analysis	Short tandem repeat (STR) analysis was performed.	submitted and archived by the journal
Mutation analysis	Sequencing	Heterozygous frameshift variant *PRKAG2* c.769_770del, p.E257Kfs*15 (NM_016203.4) was confirmed by Sanger sequencing.	Fig. 1, panel G
	Southern Blot OR WGS	N/A	N/A
Microbiology and virology	Mycoplasma	Mycoplasma PCR tests showed negative results.	Fig. 1, panel B
Characterization of the differentiated state	Embryoid body formation OR Scorecard OR hiPSCore (https://jdobner.shinyapps.io/hipscore/) OR Directed tri-lineage differentiation OR teratoma formation	Mesodermal differentiation was assessed by cardiac differentiation using a 2D-differentiation protocol. Directed trilineage differentiation was performed for endo-, meso- and ectoderm.	Fig. 1, panels H and I
List of recommended differentiated state germ layer markers	Expression of these markers has to be demonstrated at mRNA (RT PCR) or protein (IF) levels, at least 2 markers need to be shown per germ layer	Immunofluorescence staining was conducted for endo- (SOX17 and HNF-3b), ecto- (PAX6 and Nestin) and mesodermal (Brachyury) markers after directed trilineage differentiation. 2D-cardiomyocytes were analysed by flow-cytometry for mesodermal sub-lineage specific marker cardiac troponin T (cTnT).	Fig. 1, panels H and I
Donor screening	HIV 1 + 2, Hepatitis B, Hepatitis C	Screening for HIV 1 + 2, Hepatitis B, Hepatitis C all not detectable in patients fibroblasts	not shown, available with author
Genotype additional info	Blood group genotyping	N/A	N/A
	HLA tissue typing	N/A	N/A

reverse transcription (10 min 25 °C, 120 min 37 °C, 5 min 85 °C; Applied Biosystems, #4368814). Previously Sendai virus positive tested samples were included as positive control.

3.3. Differentiations and immunofluorescence

HiPSCs (p34) were differentiated under normoxic conditions (37 °C, 5 % CO_2, 21 % O_2) for five days in trilineage media (STEMCELL Technologies, #05230) in Matrigel-coated (Corning, #354263; 1:60/RPMI-1640) ibidi-dishes (#80801). Cells were fixed (10 min ROTI®Histofix; Roth, #A146), permeabilised (5 min Triton®X-100; Roth, #3051.3; 0.2 %/D-PBS) and blocked in 5 % goat-serum (20 min; Sigma-Aldrich, #G9023) in immunofluorescence-buffer (10 mM Tris, 155 mM NaCl, 2 mM EGTA, 2 mM $MgCl_2$, 1 % (w/v) BSA, pH 7.5). After primary antibody incubation overnight (4 °C), incubation with secondary antibodies was performed for 3 h (20 °C) followed by 4′,6-diamidino-2-phenylindole (DAPI) and phalloidin (F-actin) for 15 min (Table 2). Images were acquired with a Zeiss LSM800 confocal microscope. Five 2D-cardiac differentiation runs of hiPSCs (p29-p34) were performed using the protocol described by Mosqueira et al. (2018) with a time interval of 14 – 15 h until adding Activin A and BMP4 to the culture medium.

3.4. Pluripotency analysis

RNA was isolated from hiPSCs (p37) with TRIzol™ (Invitrogen, #15596026), RNA concentration measured (NanoDrop, ND-1000) and cDNA synthesised (10 min 25 °C, 120 min 37 °C, 5 min 85 °C; Applied Biosystems, #4368814). RT-qPCR was performed with SYBR Green (ThermoFisher, #K0221) in a QuantStudio 5 (Applied Biosystems). UKEi001-A (RRID:CVCL_A8PR, see hPSCreg.eu) provided by the Institute of Experimental Pharmacology and Toxicology at UKE served as control hiPSC-line.

3.5. Karyotyping, genotyping and STR analysis

G-banding of 15 metaphases (p31) and NanoString nCounter® human karyotype panel analysis (p28) were performed. To confirm the *PRKAG2*-variant, we isolated hiPSC-gDNA (Qiagen, #69506) and amplified the locus by PCR (35 cycles; 10 s 98 °C, 20 s 68 °C, 30 s 72 °C; Eppendorf-Mastercycler pro S; primers in Table 2) using Q5® Master Mix (New England Biolabs, M0492S) to analyse the purified (Roche, #11732676001) PCR product by Sanger sequencing (Eurofins). For STR analysis of patient́s blood buffy coat and hiPSCs, DNA was amplified with the PowerPlex® ESI17 Fast Kit (Promega, #DC1720) using an ABI 7500 RealTime PCR System. The resulting fragments were analysed with an AB 3130 Genetic Analyzer and GeneMapper ID 3.2 software (all from Applied Biosystems).

3.6. Flow-cytometry

Flow-cytometry data were acquired using a NovoCyte Quanteon (Agilent) with NovoExpress 1.6.2 software and analysed using FlowJo 10.10.0. For cTnT-yield determination, hiPSC-cardiomyocytes were fixed (ROTI®Histofix), permeabilised (5 % fetal bovine serum (FBS; PAN, #P40-37500), 0.5 % (w/v) saponin, 0.05 % (w/v) sodium azide/D-PBS) and stained with cTnT and isotype control antibodies. To assess SSEA-3 expression, hiPSCs (p34) were blocked in FBS before staining with SSEA-3 and isotype control antibodies (see Table 2).

CRediT authorship contribution statement

Benedict Hoffmann: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tim Knochenhauer:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Julian Schlobohm:** Methodology, Investigation. **Konstantina Stathopoulou:** Writing –

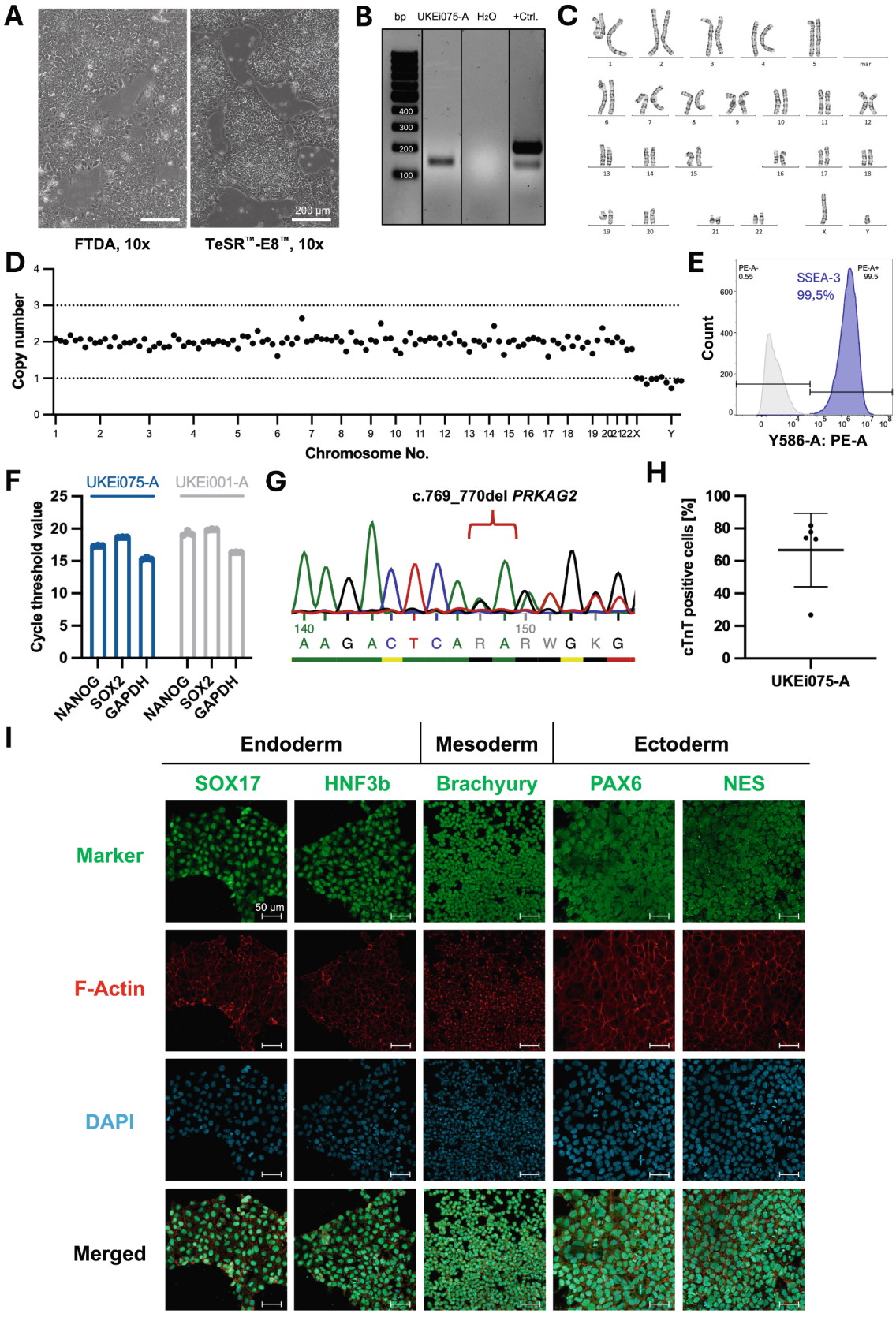


Fig. 1. Quality control of the patient-derived hiPSC line UKEi075-A carrying the *PRKAG2* variant c.769_770del (p.E257Kfs*15).

Table 2
Reagent details.

	Antibodies used for immunocytochemistry/flow-cytometry			
	Antibody	Dilution	Company Cat #	RRID
Pluripotency Markers (flow-cytometry)	anti-SSEA-3, rat IgM, PE	1:5	BD Pharmingen™ #560237	RRID:AB_1645542
	k Isotype Control, rat IgM, PE	1:80	BD Pharmingen™ #553943	RRID: AB_10056839
Differentiation Marker (flow-cytometry)	anti-cardiac troponin T, human IgG1, APC, REAfinity™	1:100	Miltenyi Biotec #130–120-403	RRID:AB_2783887
	REA Control (I), human IgG1, APC, REAfinity™	1:100	Miltenyi Biotec #130–120-709	RRID:AB_2784399
Differentiation Markers (immunofluorescence)	anti-human SOX17, polyclonal goat IgG	1:10	R&D Systems #AF1924	RRID:AB_355060
	anti-human HNF–3 beta/FoxA2, polyclonal goat IgG	1:10	R&D Systems #AF2400	RRID:AB_2294204
	anti-human Pax6, polyclonal sheep IgG	1:10	R&D Systems #AF8150	RRID:AB_2827378
	anti-Nestin (10C2), monoclonal mouse IgG	1:500	Cell Signaling Technology	RRID:AB_2799037
	anti-Brachyury, polyclonal goat IgG	1:10	#33475	RRID:AB_2200235
Secondary antibodies and dyes	Alexa Fluor™ 488 donkey anti-goat IgG	1:100	R&D Systems #AF2085	
	Alexa Fluor™ 488 donkey anti-sheep IgG	1:100	Invitrogen #A-32814	RRID:AB_2762838
	Alexa Fluor™ 488 goat anti-mouse IgG	1:100	Invitrogen #A-11015	RRID:AB_2534082
	Alexa Fluor™ 633 Phalloidin (F-actin)	1:100	Invitrogen #A-11029	RRID:AB_2534088
	DAPI (nuclei)	1:100	Invitrogen #A-22284	N/A
	Primers		Sigma-Aldrich #D9542	N/A
	Target	**Size of the band**	**Forward/Reverse primer (5′-3′)**	
Pluripotency Marker (RT-qPCR)	*NANOG*	155 bp	GATTTGTGGGCCTGAAGAAA /	
	SOX2	189 bp	AAGTGGGTTGTTTGCCTTTG	
			AGTCTCCAAGCGACGAAAAA /	
			TTTCACGTTTGCAACTGTCC	
Housekeeping gene (RT-qPCR)	*GAPDH*	189 bp	CCTCAAGATCATCAGCAATGCC /	
			ATGTTCTGGAGAGCCCCGC	
Genotyping (PCR)	*PRKAG2* Exon 6	388 bp	GAATTAGTGAGAGTGAGCATCCTTGC /	
			CCCGATAGTGCAAAGGACTCA	
Sendai virus clearance (RT-qPCR)	Sendai virus	181 bp	GGATCACTAGGTGATATCGAGC /	
			ACCAGACAAGAGTTTAAGAGATATGTATC	

review & editing, Supervision, Conceptualization. **Bärbel M. Ulmer:** Methodology, Investigation. **Aya Shibamiya:** Methodology, Investigation. **Sandra D. Laufer:** Writing – review & editing, Methodology, Investigation. **Sarina Schäfer:** Resources, Methodology. **Elisabeth Krämer:** Methodology, Investigation. **Sigrid Fuchs:** Methodology, Investigation. **Christa Augustin:** Methodology, Investigation. **Evaldas Girdauskas:** Writing – review & editing. **Till J. Demal:** Writing – review & editing. **Sabine Klaassen:** Writing – review & editing, Methodology, Conceptualization. **Tanja Zeller:** Writing – review & editing, Conceptualization. **Stefan Blankenberg:** Writing – review & editing. **Thomas Eschenhagen:** Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Friederike Cuello:** Writing – review & editing, Supervision, Project administration, Conceptualization.

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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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Data availability

Data will be made available on request.

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