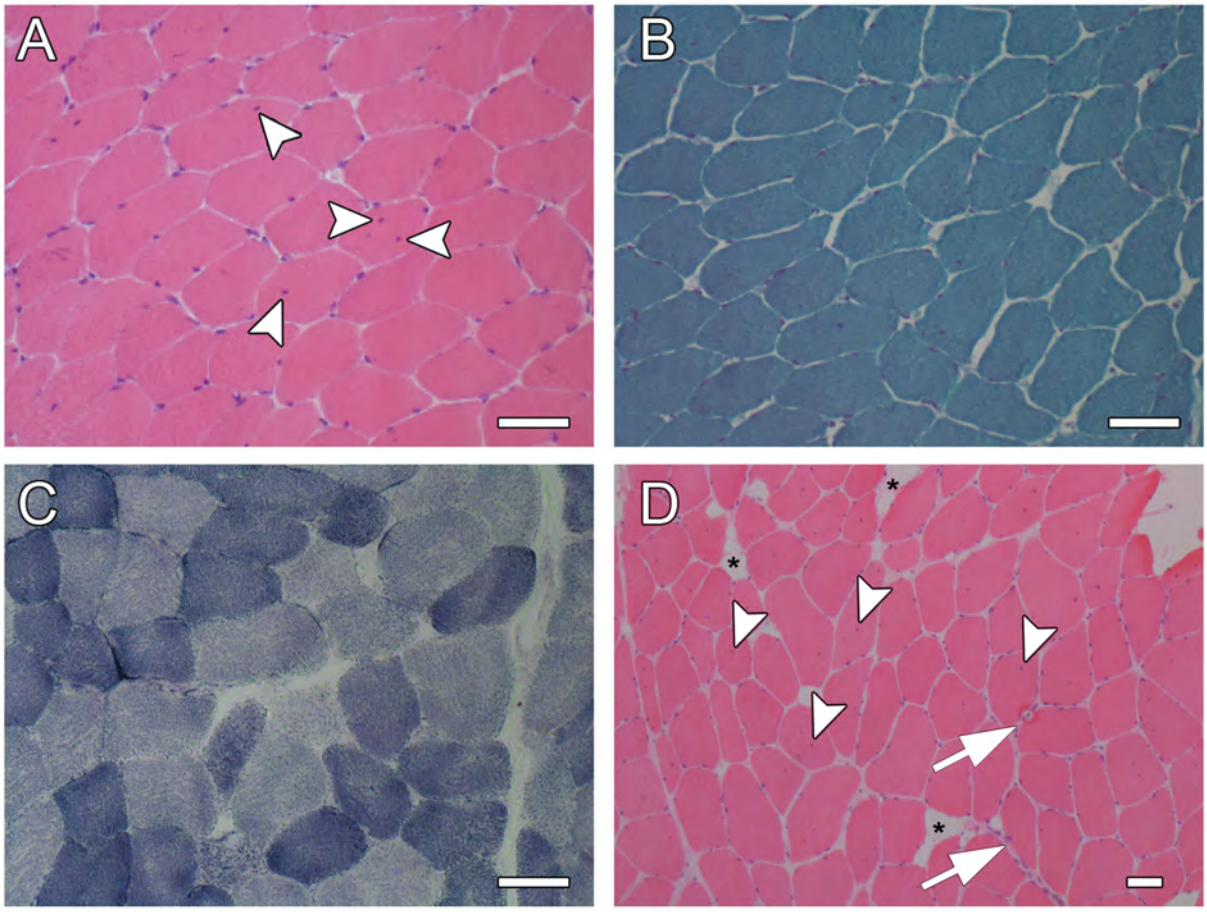
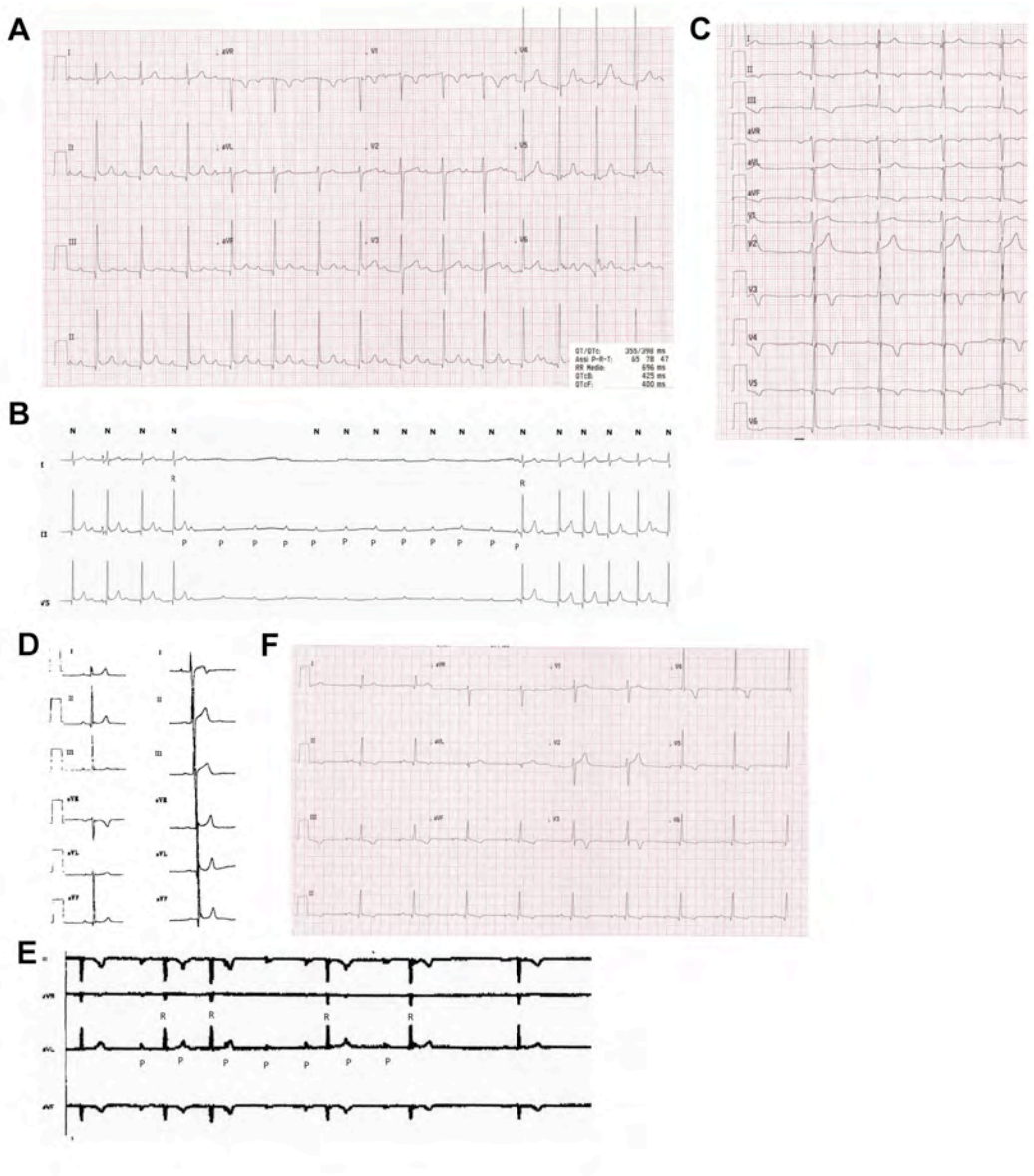
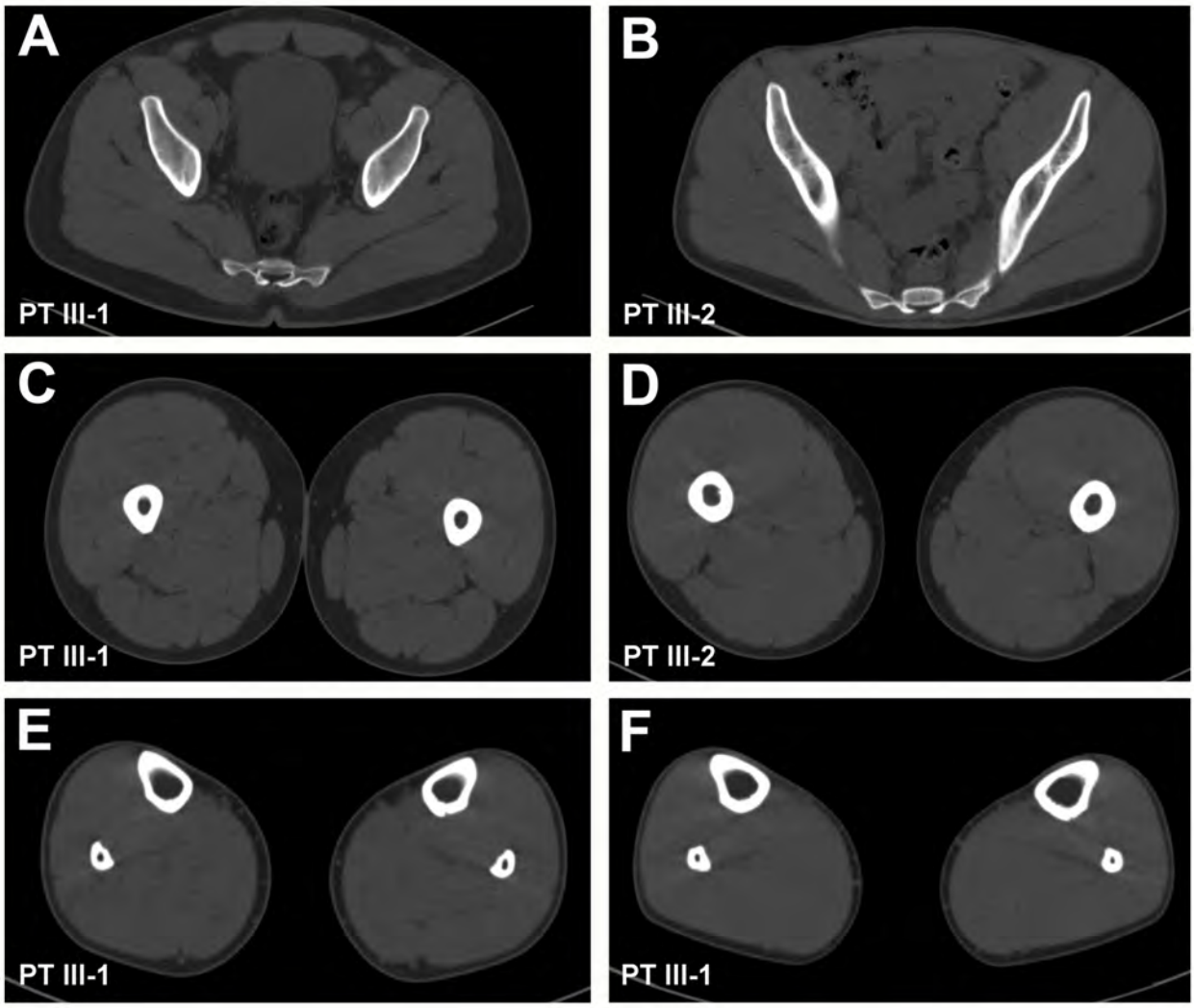
Supplemental Material



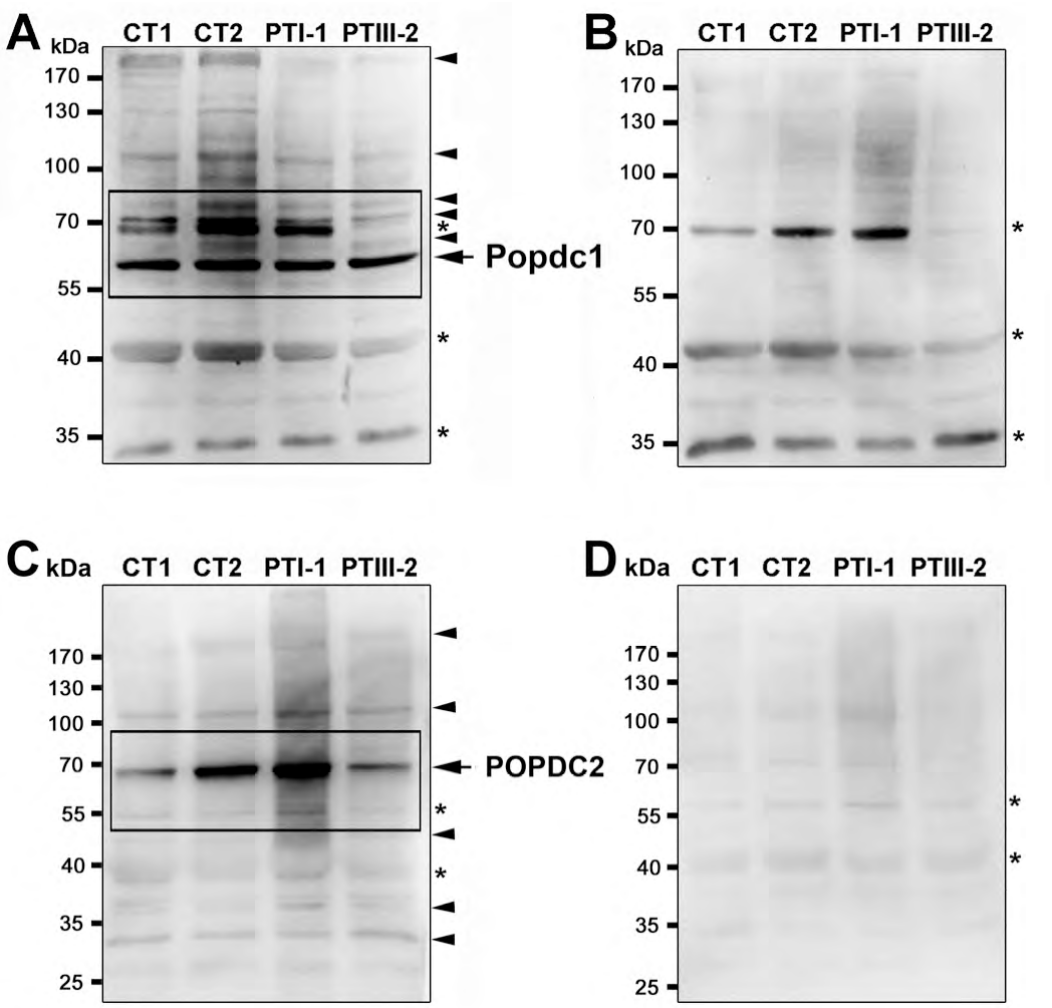
Supplemental Figure 1. Histology of skeletal muscle biopsies. Histological sections of muscle biopsies of patients (**A-C**) III-2 and (**D**) I-1. Biopsies were stained with (**A,D**) hematoxylin/eosin, (**B**) modified Gomori's Trichrome, and (**C**) NADH-tetrazolium reductase (NADH-TR). The biopsy of patient III-2 (**A**) at the age of 19 shows mild myopathic changes such as central nuclei (arrowheads). The biopsy of patient I-1 (**D**) at the age of 60 displays central nuclei (arrowheads), fatty infiltrations (asterisks) and endomysial fibrosis (arrows). Data depicted are representative results obtained from a sinlge skeletal muscle biopsy per patient. Scale bars (A-D): 50 µm.



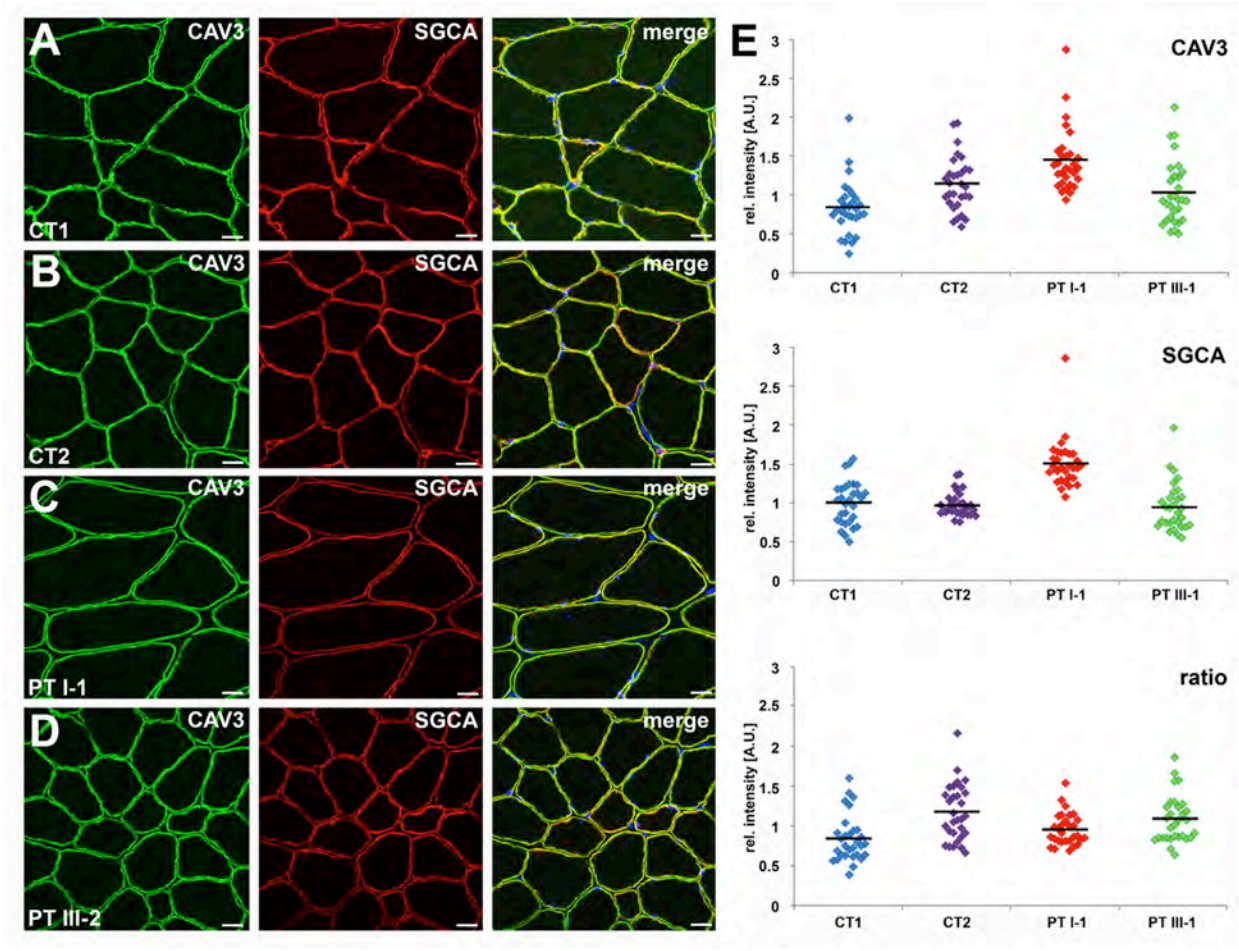
Supplemental Figure 2. Clinical Electrophysiology. ECG analysis of (**A-C**) patient III-1 and (**D-F**) patient III-2. (**A**) Normal pre-implantation electrocardiogram. (**B**) Holter monitoring shows paroxysmal AV block (P-R ratio 12:1) (the same panel is also shown in Figure 1B). (**C**) ECG analysis after double-chamber pacemaker implantation, without pacing. AV-conduction is normal and there are negative t-waves in II, III, AVF, V3, V4, V5 and V6 probably due to electrical memory of repolarization after ventricular pacing interruption. (**D**) Normal pre-implantation electrocardiogram. (**E**) Holter monitoring shows paroxysmal AV block (P-R ratio 3:1). (**E**) ECG analysis after double-chamber pacemaker implantation, with atrial pacing. AV conduction is normal. There are negative t-waves in II, III, AVF, V3, V4, V5 and V6 probably due to electrical memory of repolarization after ventricular pacing interruption.



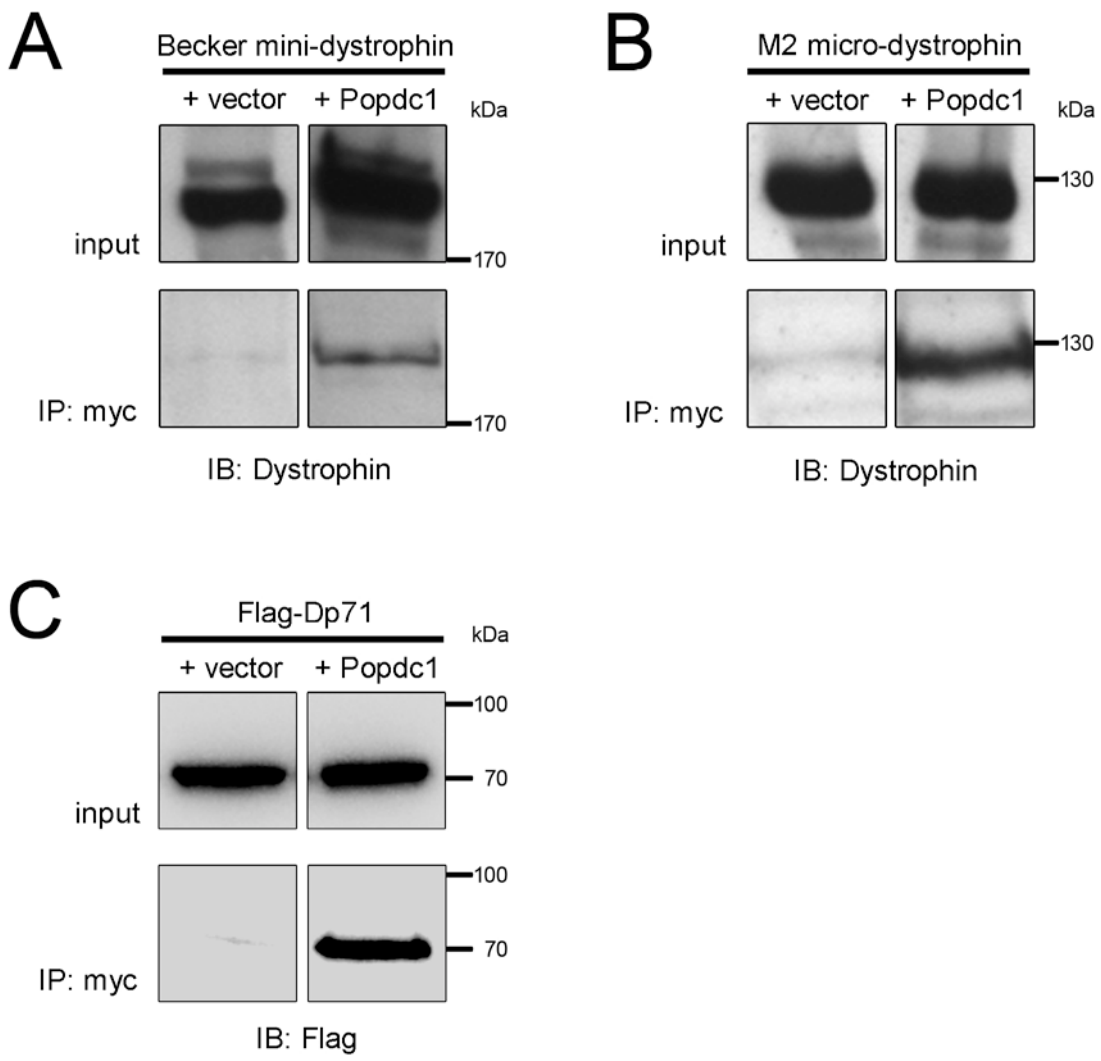
Supplemental Figure 3. Muscular CT imaging. CT scans of the (**A**,**B**) pelvis (**C**,**D**), thigh and (**E**,**F**) lower legs of (A,C,E) PTIII-1 at the age 26 and (B,D,F) PTIII-2 at the age of 19 years. No alterations in muscle structure are observed.



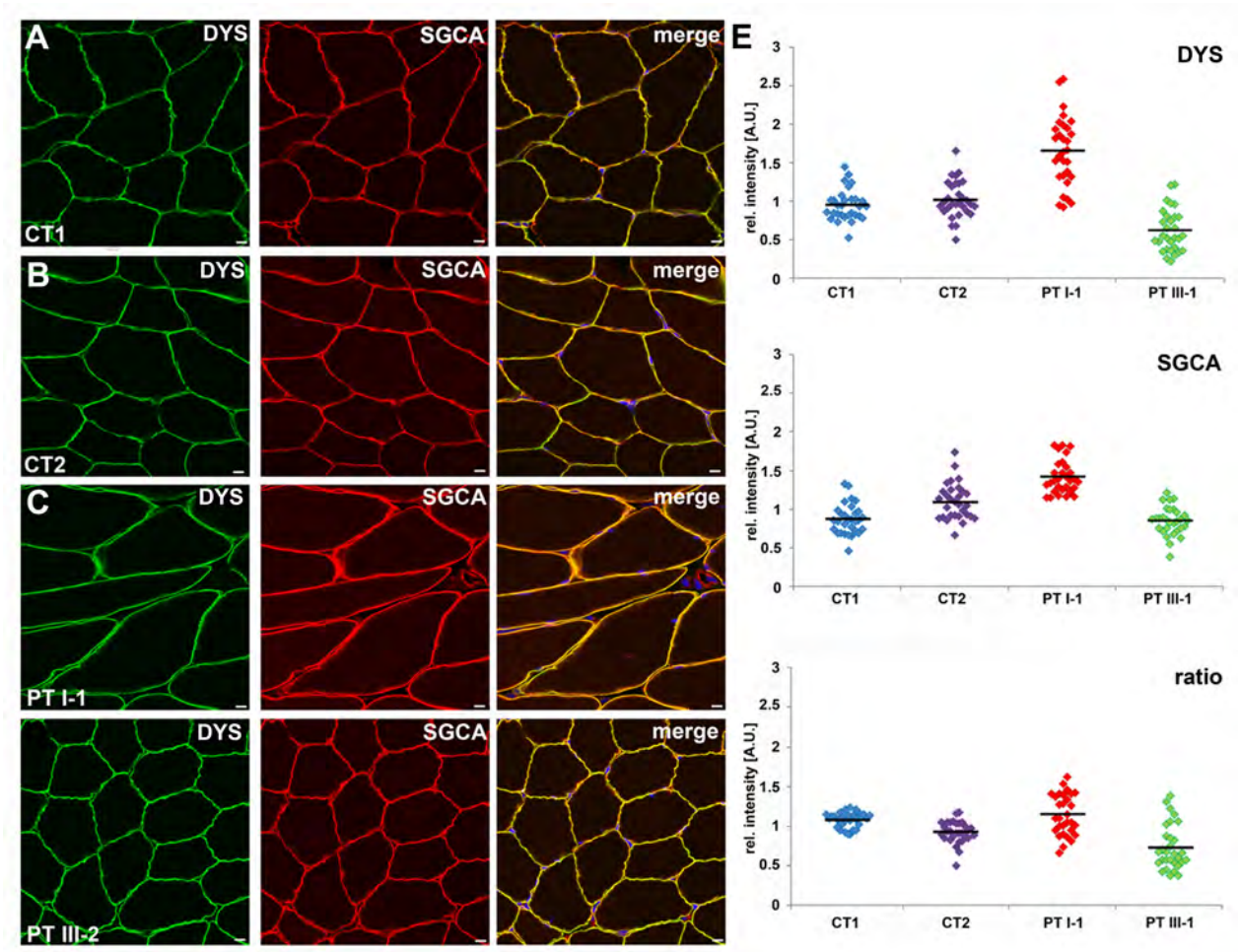
Supplemental Figure 4. Specificity control of the POPDC1 and POPDC2 antibodies. Western blot detection of (**A**,**B**) POPDC1 and (**C,D**) POPDC2 in skeletal muscle biopsies of two controls (CT1 and CT2) and of patients I-1 and III-2. Part of the Western blots (boxed regions in (**A,C**) are also displayed in Figures 2J and 3F of the main paper, respectively. (**B**,**D**) Blots shown in (**A**,**C**) were stripped and reprobed with antibodies directed against (**B**) POPDC1 and (**D**) POPDC2 in the presence of 10-fold excess of the respective competing peptides. The arrows in (**A**,**B**) mark the positions of the main POPDC1 and POPDC2 isoforms, respectively. Arrowheads indicate additional isoforms. Bands in (**B**,**D**), which remain present after peptide competition, are considered to unspecific and labeled by asterisks. Results depicted are representatives of three independent experiments.



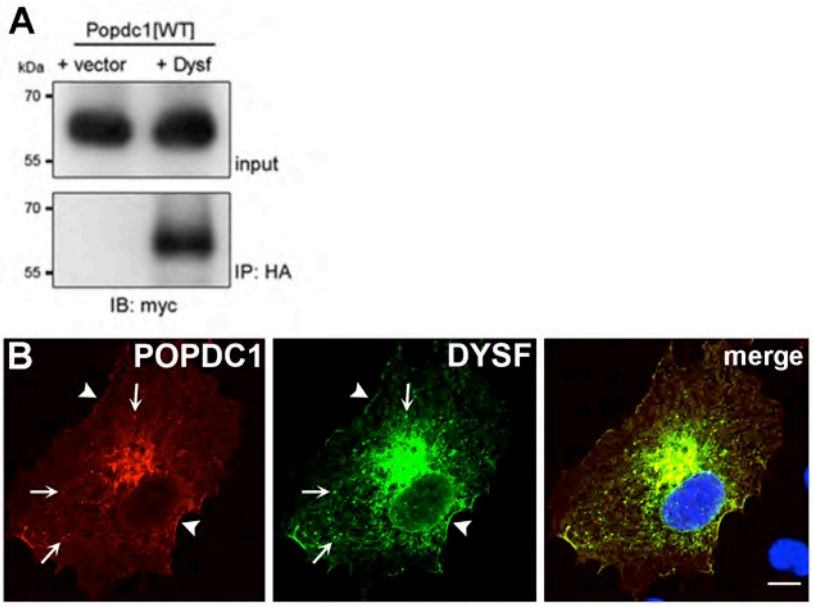
Supplemental Figure 5. Membrane localization of Caveolin 3 in biopsy material. Frozen sections of skeletal muscle biopsies of (**A**) control 1 (CT1), (**B**) control 2 (CT2), (**C**) PT I-1, and (**D**) PT III-2 were subjected to immunostaining with antibodies against Caveolin 3 (CAV3) and alpha-sarcoglycan (SGCA). (**E**) Quantification of the relative intensities of the plasma membrane staining of CAV3 and SGCA in 10 fibres each of three sections per biopsy. Signals of CAV3, SGCA and the ratio of both, were plotted relative to the means of both controls, which were set as 1. The normalized intensities revealed no difference between control and patient material. Scale bars: 20 µm.



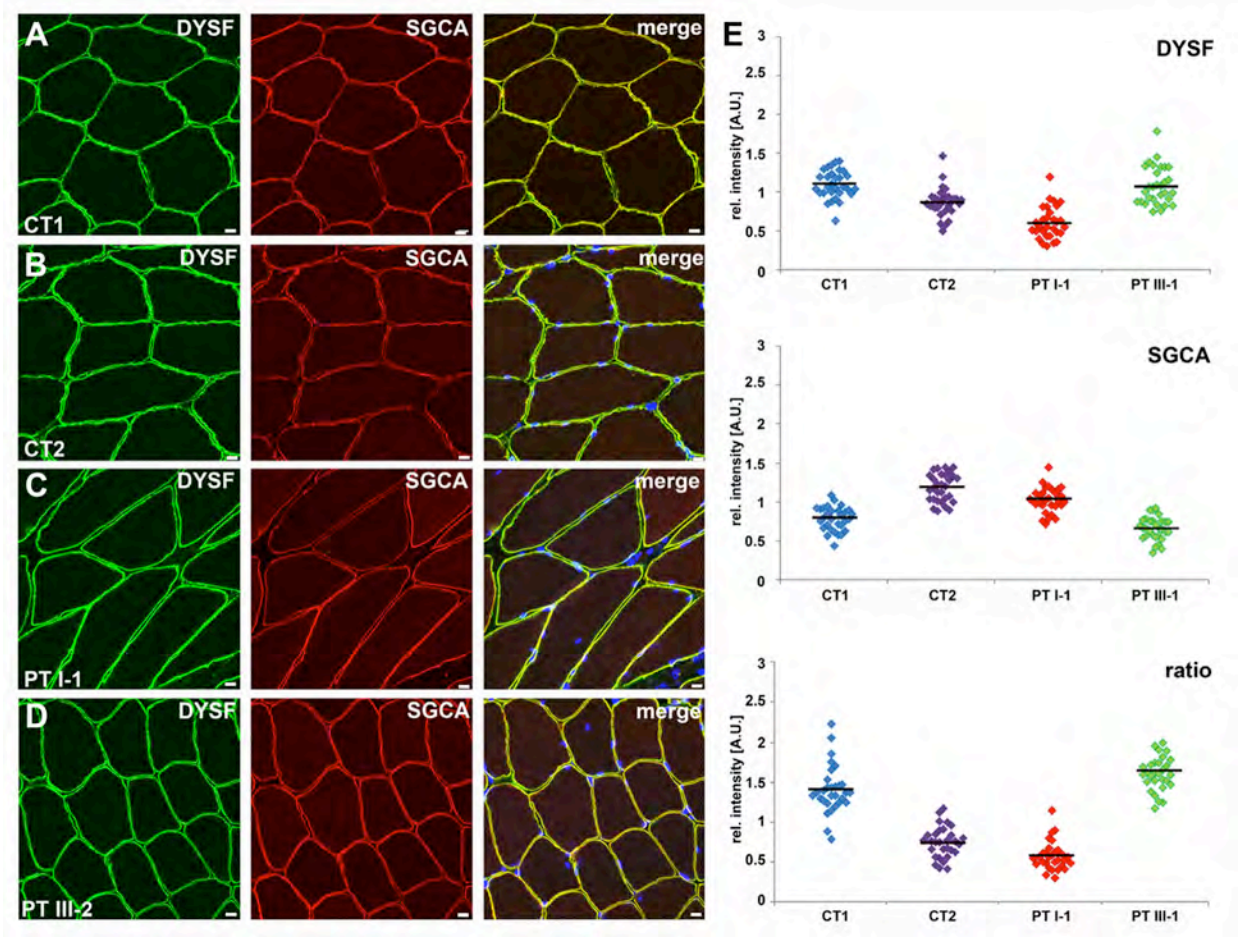
Supplemental Figure 6. Co-precipitation analysis of Popdc1 and Dystrophin. Immunoprecipitation of Dystrophin constructs with Popdc1. Co-transfection of myc-tagged Popdc1 and (**A**) Becker mini-Dystrophin. (**B**) M2 micro-Dystrophin and (**C**) Flag-tagged Dp71 in Cos-7 cells followed by co-immunoprecipitation. All three Dystrophin constructs display robust interaction with Popdc1. Results depicted are representatives of at least three independent experiments.



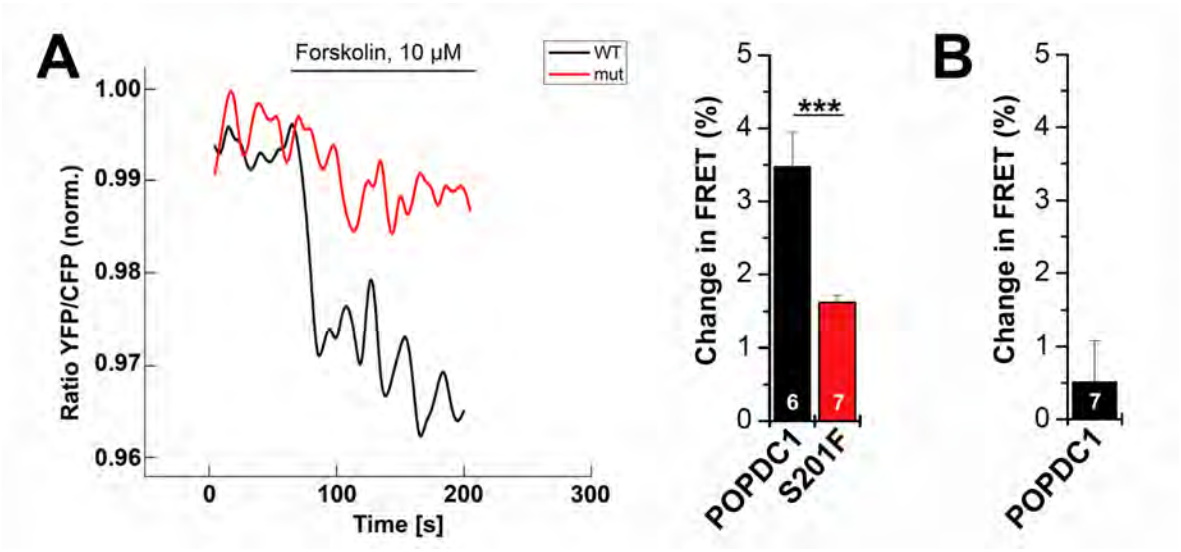
Supplemental Figure 7. Membrane localization of Dystrophin in biopsy material. Frozen sections of skeletal muscle biopsies of (**A**) control 1 (CT1), (**B**) control 2 (CT2), (**C**) PT I-1, and (**D**) PT III-2 were subjected to immunostaining with antibodies against Dystrophin (DMD) and alpha-sarcoglycan (SGCA). (**E**) Quantification of the relative intensities of the plasma membrane staining of DYS and SGCA in 10 fibres each of three sections per biopsy. Signals of DYS, SGCA and the ratio of both, were plotted relative to the means of both controls, which were set as 1. The normalized intensities revealed no difference between control and patient material. Scale bars: 10 µm.



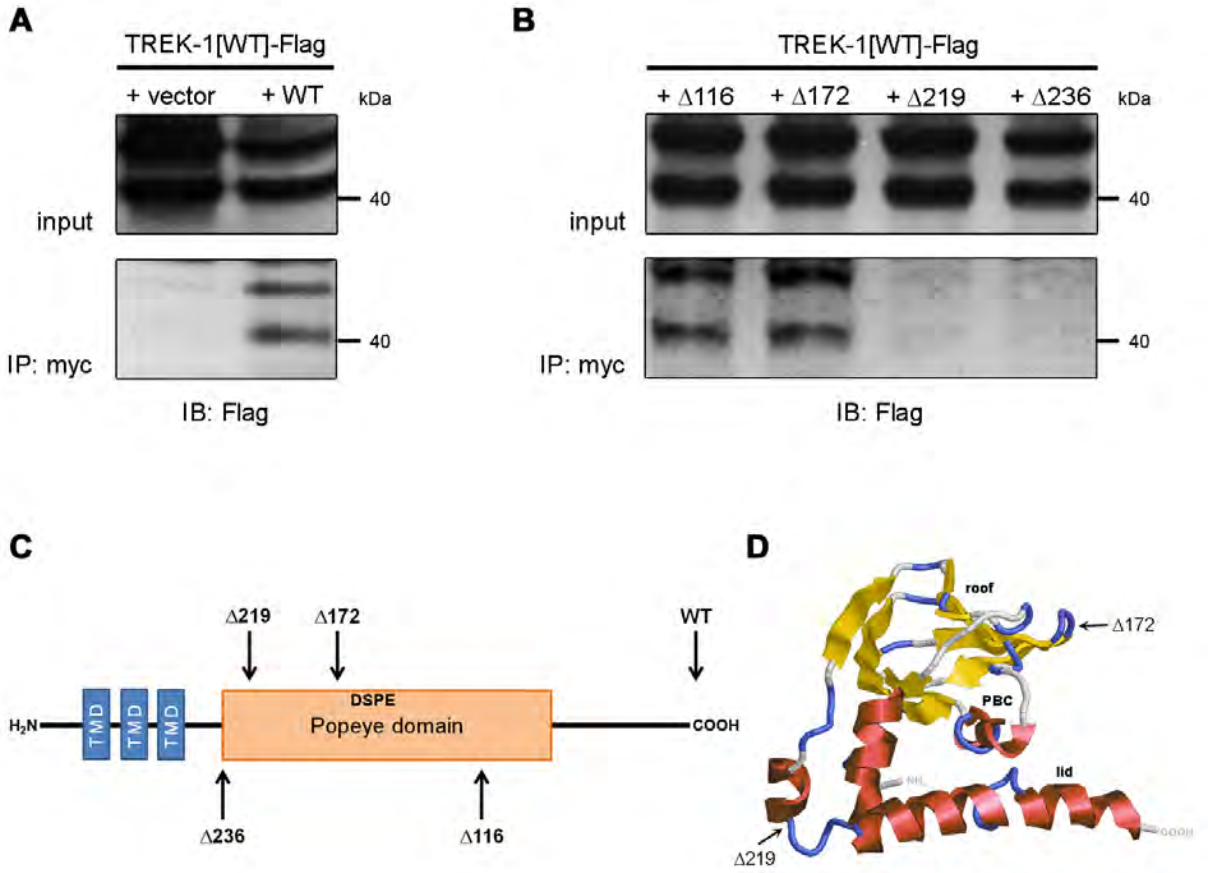
Supplemental Figure 8. Popdc1 and Dysferlin display protein-protein interaction and co-localisation. (**A**) Co-immunoprecipitation analysis of Dysferlin (DYSF) and POPDC1 after co-transfection of myc-epitope tagged Popdc1 and HA-tagged Dysferlin in Cos-7 cells. (**B**) Both proteins are co-localized at the plasma membrane (arrowheads) and in intracellular vesicles (arrows). Results depicted are representatives of two independent experiments. Scale bar in (B): 10 µm.



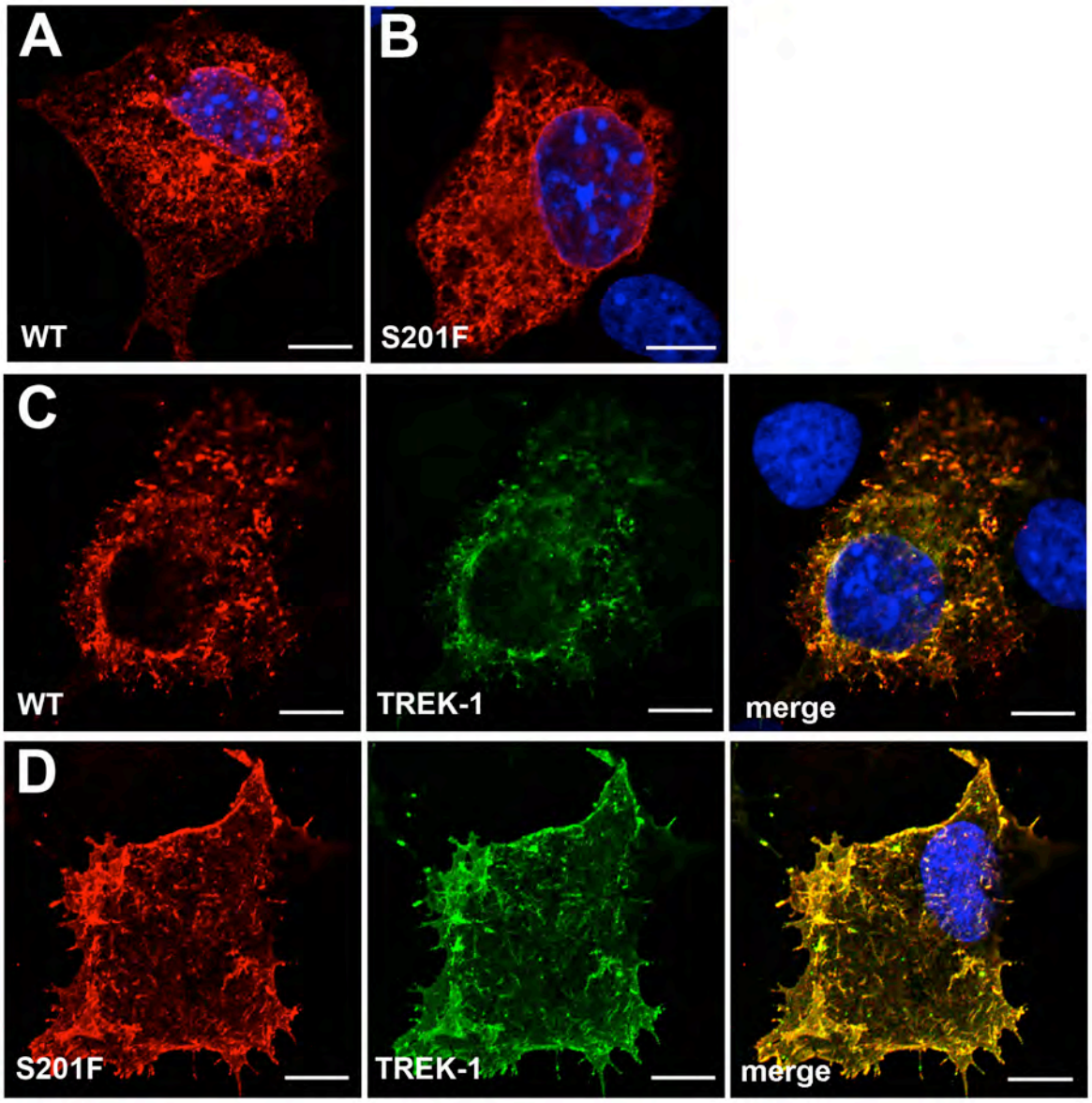
Supplemental Figure 9. Membrane localization of Dysferlin in biopsy material. Frozen sections of skeletal muscle biopsies of (**A**) control 1 (CT1), (**B**) control 2 (CT2), (**C**) PT I-1, and (**D**) PT III-2 were subjected to immunostaining with antibodies against Dysferlin (DYSF) and alpha-sarcoglycan (SGCA). (**E**) Quantification of the relative intensities of the plasma membrane staining of DYSF and SGCA in 10 fibres each of three sections per biopsy. Signals of DYSF, SGCA and the ratio of both, were plotted relative to the means of both controls, which were set as 1. The normalized intensities revealed no difference between control and patient material. Scale bars: 10 µm.



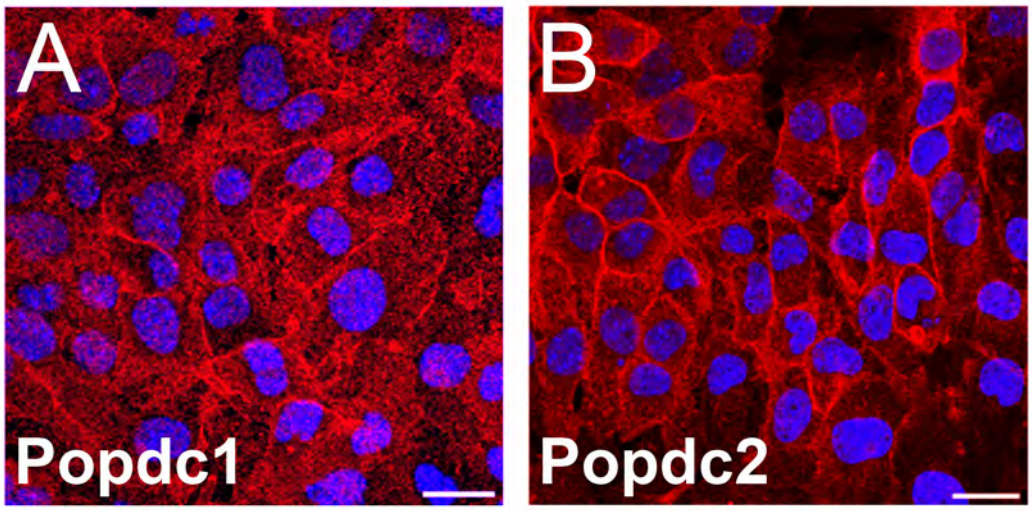
Supplemental Figure 10. POPDC1^{S201F} displays a reduction in cAMP sensitivity. FRET measurements of 293A cells transfected with YFP–TREK-1 together with POPDC1-CFP or POPDC1^{S201F}-CFP. (**A**) Left: example of a FRET experiment. The time at which 10µM Forskolin was added to the medium is indicated by a bar. Right: Percentage change in FRET signal in cells transfected with WT or mutant POPDC1 constructs. (**B**) In this set of experiments cells were pre-incubated with 5µM propranolol before 10µM isoproterenol was added and the FRET signal was measured. The number of observations is indicated in each bar. Results are presented as mean ± SEM. One-way ANOVA was used to compare the data. Statistical significance was defined as $P < 0.05$. *** $p < 0.01$.



Supplemental Figure 11. Mapping of the TREK-1 interaction domain of Popdc1. (**A**) Popdc1 interacts with TREK-1. Myc epitope-tagged murine Popdc1 and Flag epitope-tagged human TREK-1c (WT) or an empty plasmid (vector) as control were co-transfected into Cos-7 cells and subjected to co-immunoprecipitation analysis using myc antibody for precipitation and a Flag antibody for Western blot detection of TREK-1. (**B**) Mapping of the interaction domain by co-immunoprecipitation analysis of deletion constructs of Popdc1. From the carboxyl terminus of Popdc1 116 (Δ116), 172 (Δ172), 219 (Δ219), and 236 (Δ236) amino acids were deleted. The data suggest that the interaction domain is located between amino acid 139 and 186. Thus the TREK-1 interaction domain in Popdc1 lies upstream of the DSPE motif. (**C**) Schematic representation of the domain structure of Popdc1. The approximate positions of the different deletion sites are demarcated by arrows. (**D**) Localisation of the TREK-1 interaction domain using a 3D model of the Popeye domain. Results are representatives of three independent experiments.



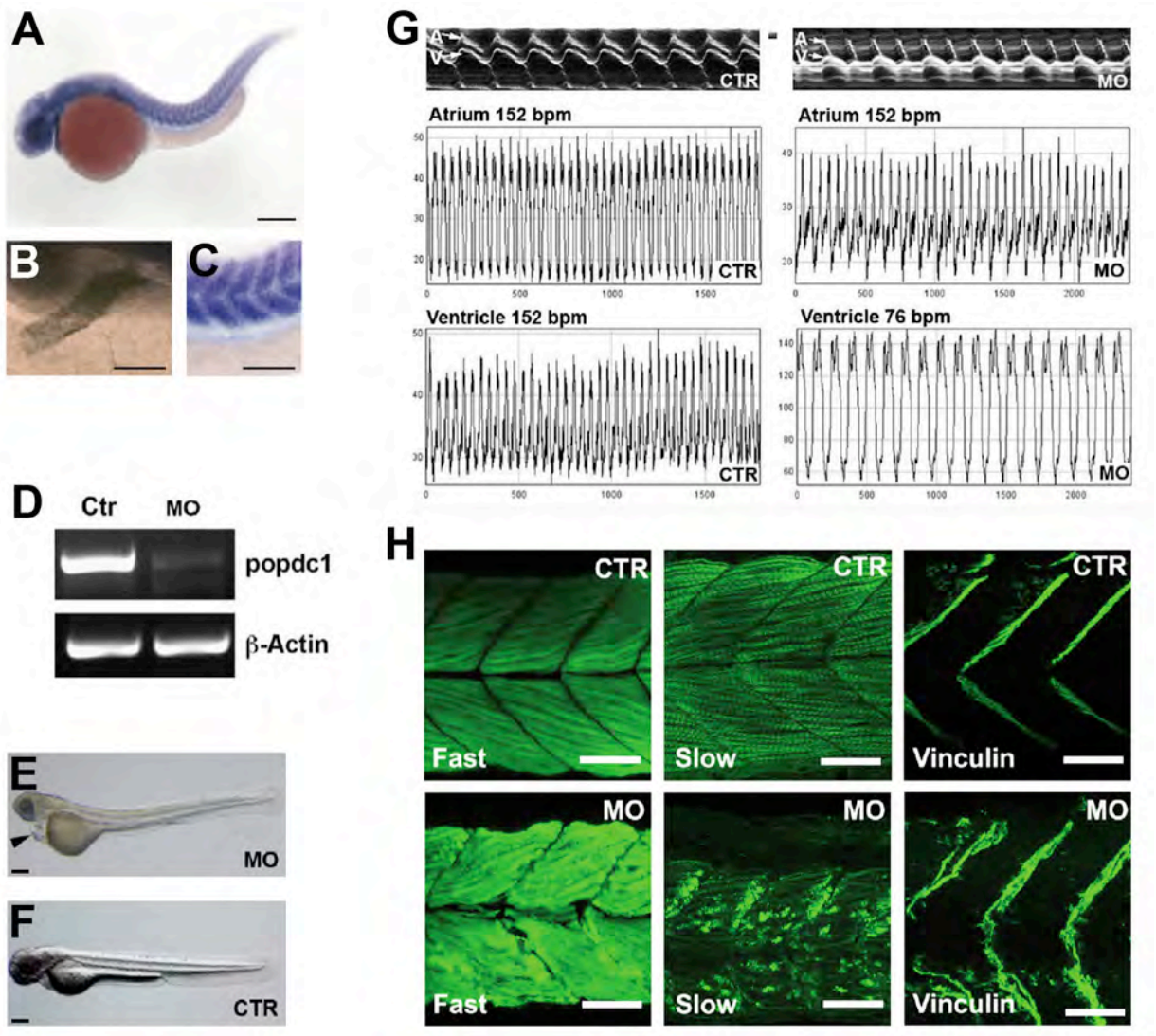
Supplemental Figure 12. Subcellular localization of wildtype Popdc1 (WT) and S201F mutant proteins. (A) WT and (**B**) S201F mutant HA-epitope-tagged POPDC1 constructs were transfected into Cos-7 cells. Immunostaining reveals similar subcellular distribution of WT and S201F mutant proteins. (**C,D**) Co-transfection of HA-epitope-tagged (**C**) WT and (**D**) S201F POPDC1 cDNAs together with a FLAG epitope-tagged TREK-1c cDNA into Cos-7 cells. Both WT and mutant proteins display co-localisation with TREK-1, suggesting that the mutant protein retains the ability to interact with TREK-1. Results are representatives of two independent experiments. Scale bars: 10 µm.



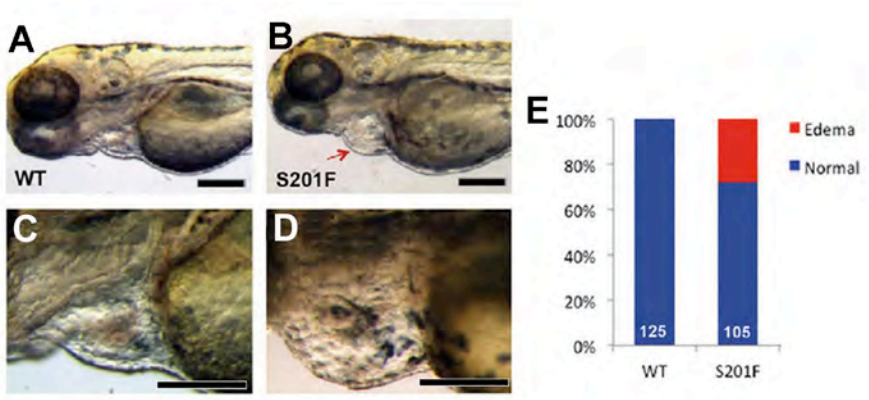
Supplemental Figure 13. Endogenous expression pattern of Popdc1 and Popdc2 in HL-1 cells. Immunodetection of (A) Popdc1 and (B) Popdc2. Both proteins are localized at the plasma membrane and in intracellular vesicular structures. Results are representatives of two independent staining experiments. Scale bars in (A,B): 20 µm.



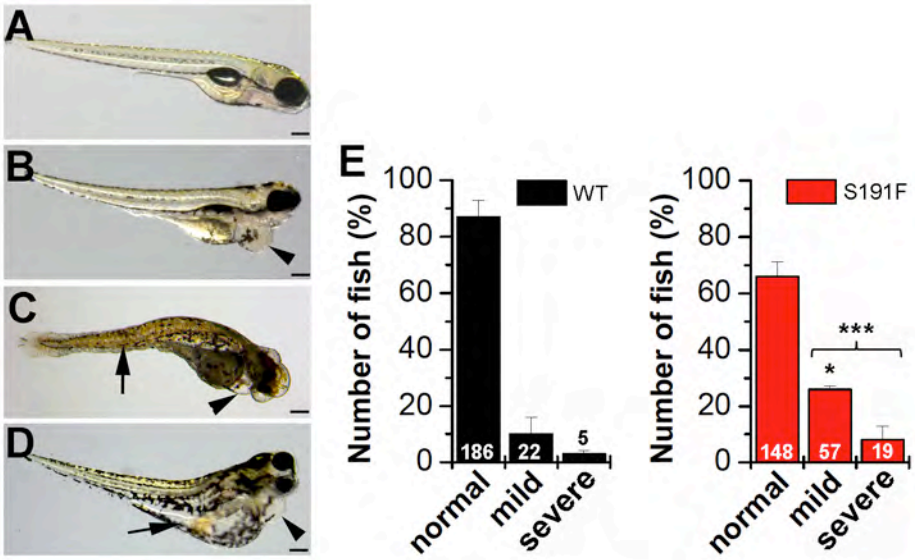
Supplemental Figure 14. Expression of TREK-1 in HL-1 cells. RT-PCR analysis of TREK-1 expression in HL-1 cells. For control purpose, GAPDH was also amplified. Non-reverse transcribed mRNA was used as negative control.



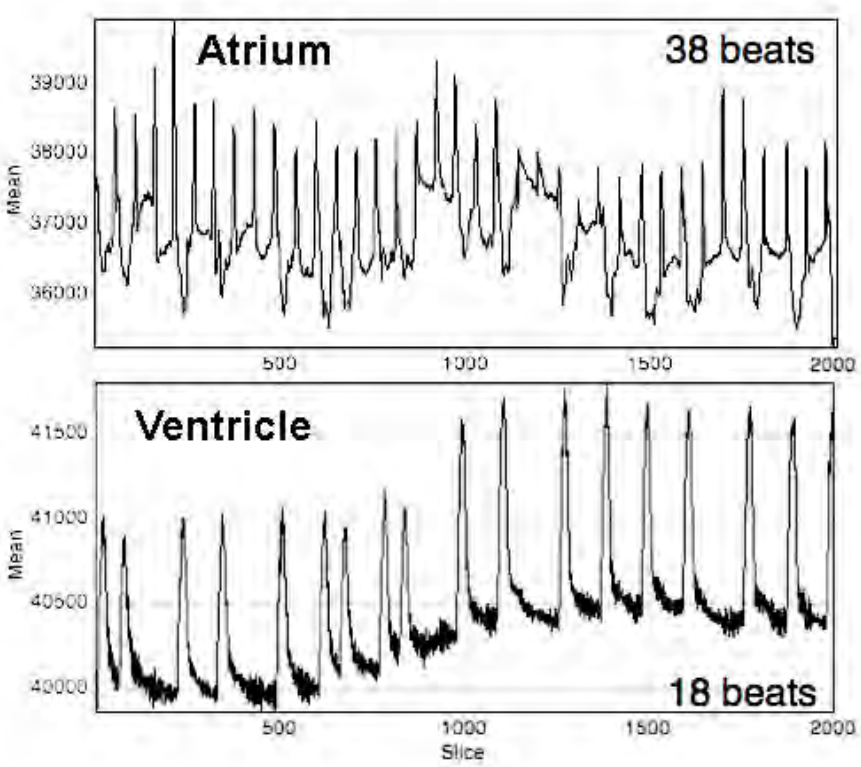
Supplemental Figure 15. *popdc1* is essential for striated muscle development in the zebrafish embryo. (A-C) Expression analysis of *popdc1* in the zebrafish embryo at 30 hpf. (A) whole mount; (B) heart tube; (C) tail muscles. Results are representatives of two independent staining experiments. (D) Morpholino-mediated knockdown of *popdc1.* RT-PCR analysis of *popdc1* expression in control (Ctr) and *popdc1* (MO) morpholino-injected embryos. (E,F) Morphological analysis revealing (E) cardiac edema (arrowhead) in the *popdc1* (MO) morpholino-treated embryos in comparison to (F) the control embryo. Results are representatives of multiple independent experiments. (G) M-mode (top) and heart rate analysis (below) of atrium and ventricle revealing the presence of a 2:1 AV-block in 48 hpf morphants (MO). See also Supplemental Video 1 and 2. Results are representatives of multiple independent experiments. (H) *popdc1* morphants display impaired muscle fiber alignment and detachment. The slow muscles appear to be affected more severely. The myotendinous junctions (vinculin staining) are structurally aberrant in the morphants. Results are representatives of three independent staining experiments. Scale bars: A,E,F: 200 µm, B,C: 100 µm, E: 50µm.



Supplemental Figure 16. Forced expression of POPDC1^{S201F} causes cardiac edema formation. Zebrafish embryo at 3 dpf injected with cRNA encoding (**A**) wildtype POPDC1 and (**B**) POPDC1^{S201F} mutation. (**C,D**) enlarged view of the hearts of the embryos depicted in (**A**,**B**) revealing a pericardial edema. (**E**) Quantification of embryos displaying cardiac edema after forced expression of mutant and WT POPDC1. Scale bars in (A-D): 200 µm.



Supplemental Figure 17. Gross appearance of the *popdc1*^{S191F} mutant. (**A-D**) Zebrafish *popdc1*$^{S191F/S191F}$ mutants at 5 dpf showing (**A**) normal appearance, (**B**) cardiac edema (arrowhead, mild phenotype), (**C**) pericardial edema and defective tail muscle structure (arrow, severe phenotype), (**D**) massive edema, affecting the entire body of the larvae (severe phenotype). Arrowheads in (A-D) - cardiac edema. Arrow in (C) – aberrant structure of the tail musculature. Arrow in (D) – yolk sac edema. (**E**) Distribution of zebrafish embryos at 5dpf with normal, mild, and severe phenotype in WT (left) and in the homozygous *popdc1*^{S191F} mutant (right). Significant differences (analyzed by paired Two-tailed Student's t-test) of the number of embryos with mild or severe phenotype in *popdc1*$^{S191F/S191F}$ mutants compared to WT. * $p \leq 0.05$ and *** $p \leq 0.01$. A total of three spawns were morphologically evaluated at 3dpf and the numbers of normal, mildly and severely affected embryos were counted. Scale bars in (A-D): 200 µm.



Supplemental Figure 18. The zebrafish popdc1S191F mutant displays cardiac arrhythmia. Example of a luminescence periodograms of atrial and ventricular chambers of a popdc1^{S191F} homozygote at 7dpf. The heart displays 2:1 and 3:1 AV-block. The same sequence is also available as supplemental video 3. Results depicted are representatives of three independent litters.

Supplemental Movies

Supplemental Movie 1. Heart of a Tg(myl7:GFP) larvae at 48hpf. Consecutive rhythmic contractions of atrium and ventricle. Ventral view, anterior to the top. Ventricle on the left and atrium on the right.

Supplemental Movie 2. Heart of a Tg(myl7:GFP) *popdc1* morphant at 48hpf displaying a 2:1 AV block. Ventral view, anterior to the top. Ventricle on the left and atrium on the right.

Supplemental Movie 3. The zebrafish *popdc1*^{S191F} mutant displays cardiac arrhythmia. Lateral view, anterior to the top. Atrium at the top and ventricle at the bottom. The heart displays 2:1 and 3:1 AV-block.

Supplemental Table 1. Patients with muscle phenotype/high CK and/or cardiomyopathy and rhythm disturbances screened by Sanger for *POPDC1* mutations.

Patients' details, phenotypes and gene variations are reported. No homozygous or compound heterozygous pathogenic *POPDC1* mutations were identified.

Abbreviations: DCM - dilated cardiomyopathy; AVB – atrioventricular block ; CMH - cardiomyopathy hypertrophic, hCK - high Creatine Kinase; LQT - long QT syndrome; LGMD – limb-girdle muscular dystrophy.

	CODE	GENDER	CLINICAL PHENOTYPE	POPDC1 SNPs
1.	KAV	F	DCM	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
2.	VAR	M	DCM	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
3.	CAC	F	DCM	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom
4.	SAC	M	DCM	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
5.	PIA	M	DCM	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
6.	PES	M	CMH	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
7.	TM1489/07	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
8.	CR1503/10	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

9.	CG1377/11	M	DCM, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom
10.	RV256/12	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
11.	DO515/07	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
12.	GM1964	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
13.	PF886/09	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom
14.	BG2376/11	F	DCM, AVBI, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
15.	FM1285/08	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
16.	MA782/11	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
17.	RD2414/09	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
18.	MR367	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

19.	IG1062/09	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
20.	MC528/10	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom
21.	DP19/12	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom
22.	NM1046/10	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
23.	MB162/05	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
24.	GD1090/08	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
25.	BA7557	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
26.	FC1623	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
27.	BM558	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
28.	PJ225/12	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom

29.	AP1105/06	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
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31.	MC1128/08	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
32.	BF161/09	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
33.	BM552/10	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C het
34.	PA564	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
35.	RS6530	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
36.	CF191/05	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
37.	SG25/11	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

38.	PV2094/08	M	DCM, AVB	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C het
39.	CS852	M	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
40.	CT1276/09	F	DCM, AVB, hCK	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C het
41.	LR1139/10	M	DCM, Arrhythmias, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
42.	TL1173/11	M	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
43.	TA1174/11	F	LQT	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
44.	CA2518/09	M	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
45.	PM515/10	F	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C het
46.	PN1754/10	F	Arrhythmias	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

47.	IA351/10	F	DCM	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
48.	MC1416/10	F	Sudden death	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
49.	CA1353/10	M	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
50.	GD2/11	M	DCM, Arrythmias	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
51.	VA731/12	M	Sudden death	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
52.	PG1888/11	M	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
53.	TP1775/11	M	CMH, LQT	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
54.	LM974/11	F	LQT	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
55.	DA979/10	M	Arrhythmias	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

56.	CA999/10	M	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom
57.	LA621/10	M	Arrhythmias	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
58.	CV866/09	M	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
59.	BF2390/08	F	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
60.	ZM342/13	M	Brugada syndrome	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
61.	PIP	M	CMH, hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C hom
62.	BEX	F	hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
63.	MOM	M	MYOPATHY	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
64.	MIM	M	hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
65.	COF	M	hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

66.	OUI	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A hom intron 2 rs9404603 g.105577172 T/C hom
67.	BAE	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
68.	PAD	M	MYOPATHY, AVB	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
69.	GAG	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
70.	BER	F	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
71.	BOF	F	MYOPATHY	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
72.	TRG1	M	AVB	intron 1 rs4946656 g.105577401 G/A hom
73.	MRA2	F	AVB	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
74.	SPL3	M	AVB	Intron1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

75.	PLE4	F	AVB	Intron1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
76.	MRG5	F	AVB	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
77.	RSE6	F	AVB	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
78.	BTV7	F	AVB	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
79.	MFM8	F	AVB	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
80.	BNE10	M	hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
81.	PND11	M	hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
82.	L62571	M	DCM	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
83.	PEM	F	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
84.	RIMP	F	MILD MYOPATHY, hCK	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C het

85.	RIA	F	MILD MYOPATHY, hCK	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C het
86.	RID	M	MYOPATHY	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
87.	BIG	F	MYOPATHY	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
88.	KOLE	M	LGMD	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
89.	CIHO	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
90.	WUDO	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
91.	VARI	M	MYOPATHY	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C hom
92.	RAAN	F	DCM	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
93.	NUIM	F	MYOPATHY	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

94.	LIMA	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
95.	FAOR	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
96.	DBAN	F	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
97.	HOCA	F	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
98.	PIDA	F	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
99.	MZGI	M	LGMD	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
100.	MOBE	M	LGMD	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs9404603 g.105577172 T/C het
101.	BALI	F	hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
102.	CODA	M	hCK	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom
103.	MADA	M	hCK, MILD MYOPATHY	intron 1 rs4946656 g.105577401 G/A het intron 2 rs9404604 g.105577224 T/G het intron 2 rs72932419 g.105577199 G/A het intron 2 rs9404603 g.105577172 T/C het

104.	CRFR	M	MILD MYOPATHY	intron 1 rs4946656 g.105577401 G/A hom intron 2 rs9404604 g.105577224 T/G hom intron 2 rs9404603 g.105577172 T/C hom

The genotyping of the following POPDC1 SNPs are reported.

rs4946656 NC_000006.11:g.105577401C>T
Allele frequency.
All C:0.147/T:0.853
African C:0.377/T:0.623
American C:0.049/T:0.951
European C:0.041/T:0.959
East Asian C:0.064/T:0.936
South Asian C:0.098/T:0.902

rs9404604 NC_000006.11:g.105577224A>C
Allele frequency.
All A:0.230/C:0.770
African A:0.610/C:0.390
American A:0.086/C:0.914
European A:0.087/C:0.913
East Asian A:0.090/C:0.910
South Asian A:0.109/C:0.891

rs72932419 NC_000006.11:g.105577199C>T
Allele frequency.
All C:0.896/T:0.104
African C:0.795/T:0.205
American C:0.951/T:0.049
European C:0.931/T:0.069
East Asian C:0.946/T:0.054
South Asian C:0.906/T:0.094)

rs9404603 NC_000006.11:g.105577172A>G
Allele frequency.
All A:0.147/G:0.853
African A:0.377/G:0.623
American A:0.049/G:0.951
European A:0.041/G:0.959
East Asian A:0.064/G:0.936
South Asian A:0.098/G:0.902

Supplemental Table 2. List of primer sequences used for exon amplification and sequencing of *POPDC1* in patients with cardiac and skeletal muscle disease listed in Supplemental Table 1.

Exon	Primer Forward	Primer Reverse	Product (bp)
1	TGGATTTGAATCTGGGTCTGTC	TTGCTATGGGCCTGACAAAG	483
2	CACCCAGTGATTGCTTATTAGCTG	ATGTAAACAGAAAGCCTAAACTTCAGAG	490
3	CTATTGGCCTAAATACAGAAGGGTG	TCTCCATTCATTGGCAACATTTC	426
4	AAATACTTGTGCCTCAAGAAGTGC	CCCCCAATAATTCATAGCAGTG	370
5	TCATTGCTATGATAATGTCCACTAAATC	CCCCAGTACATTTAACATATGGCTAGT	394
6	GGAAAAGTACATGCTGCTTAAATGG	AGGTTGCCTTTCAAATAGTTACCTG	338
7	GAGATGCTGGATTGAAATAGAATGG	AAGCAGAATAACCTAAAAGCCATGA	387