Supplementary Data

Pathogenic and rare deleterious variants in multiple genes suggest oligogenic inheritance in recurrent exertional rhabdomyolysis

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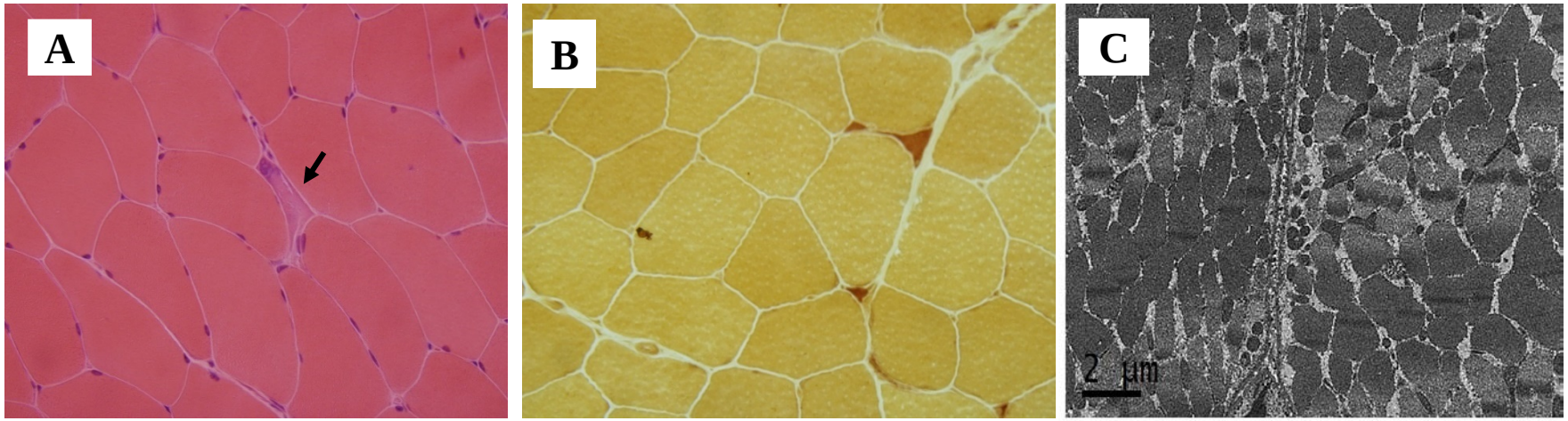


Fig. S1. Histopathological findings in case R410. **A.** Hematoxylin and Eosin stain shows small basophilic regenerating myofiber (an arrow). **B.** Small angular muscle fibers stain dark with non-specific esterase stain. **C.** Electron microscopy shows mitochondria in the subsarcolemmal area. No tubulofilamentous structures or paracrystalline inclusions are identified.

Supplementary Table

ID	Gene	Nucleotide change	AA change	Variant ID*	Freq.**	SIFT	PolyPhen	Mut Taster
R279	NDUFA10	c2_240944654: ins_GGACA	N288RfrTer30	rs764415074	4/123136	Loss of function		DC***
	PYGM	c11_64521431: G>A	R387C	rs926204490	not reported	Deleterious	Damaging	DC
	TIMM50	c19_39978719: C>T	R342W	N.A.	2/122822	Deleterious	Damaging	DC
R302	HMBS	c11_118962147: C>T	R175W	rs756417575	6/90012	Deleterious	Damaging	DC
	GBE1	c3_81635341: C>T	D413N	rs752711257	1/15481	Deleterious	Damaging	DC
	PHKA1	cX_71839141: G>A	L718F	N.A.	not reported	Tolerated	Damaging	DC
	RYR1	c19_39070725: C>T	T4823M	rs148540135	49/138558	Tolerated	Damaging	DC
R410	GBE1	c3_81627124: G>A	R524Ter	rs137852888	9/120346	Loss of function		DC
	PCCB	c13_136046019: ins14del12	G407RfsTer27	rs397507445	not reported	Loss of function		DC
R462	CACNA1S	c1_201047133: C>A	R498L	rs150590855	171/138621	Deleterious	Damaging	DC
	HMBS	c11_118963136: G>A	R225Q	rs142459647	52/138575	Deleterious	Damaging	DC
	NDUFS8	c11_66799622: C>T	R2C	rs150278938	467/138582	Tolerated	Benign	SNP
		c11_67803723: A>G	I126V	N.A.	1/121677	Deleterious	Damaging	DC
R465	CPT2	c1_53676715: A>T	K457Ter	rs756931329	9/123047	Loss of function		DC
	ELAC2	c17_12920410: del_A	Q92RfsTer9	rs748788377	3/123084	Loss of function		DC
R469	ACADVL	c17_7124136: C>A	S133Y	rs757608507	2/123064	Deleterious	Damaging	SNP
	NDUFA6	c22_42482290: del_TTAA	I120KfsTer44	rs768463498	19/123126	Loss of function		DC
R470	NUBPL	c14_32295921: G>A	IVS8DS	rs751631278	4/122943	Loss of function		DC
	OAT	c10_126091499: G>C	Y299Ter	rs121965057	4/123094	Loss of function		DC

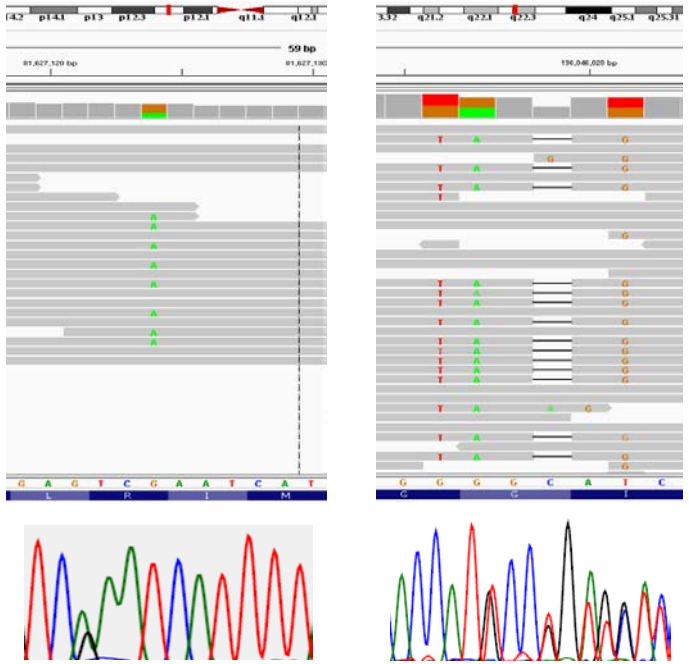
* - N.A., Not Available

** - Genotype frequency from Broad Institute Database of >120,000 genomes

*** - DC, Disease Causing

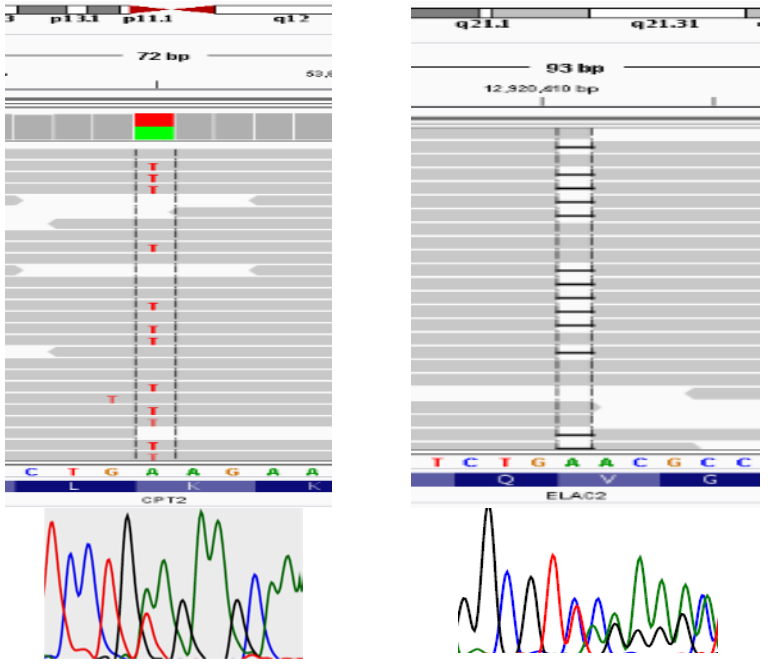
A.

R410:



***GBE1*:** R524Ter ***PCCB*:** G407RfrTer14

R465:

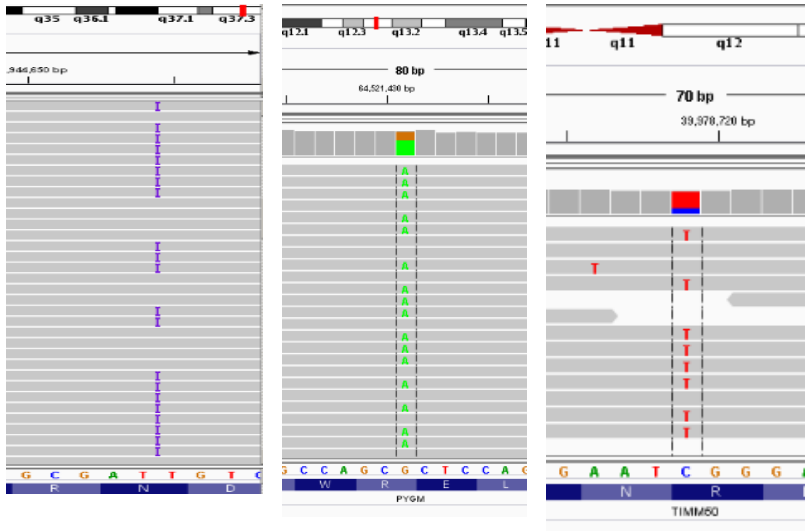


CPT2: K457Ter ***ELAC2:*** Q92frTer9

Fig. S2. Representative images of exome sequencing results. **A.** Integrated view of exome sequencing results presented below subjects ID. Sequence alignments are shown as grey polygons. Variants mismatching the reference sequences indicated by color in the integrated view. Genes and variants are given below aligned sequence reads. Conventional Sanger sequencing was used to confirm exome sequencing results.

Continuation of Fig. S2.

R279:

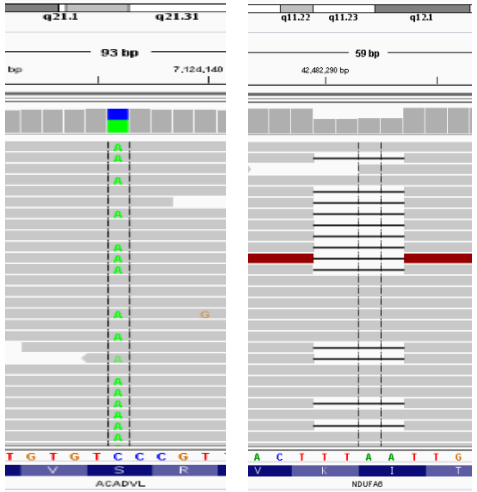


NDUFA10: N288RfsTer20

PYGM: R387C

TIMM50: R342W

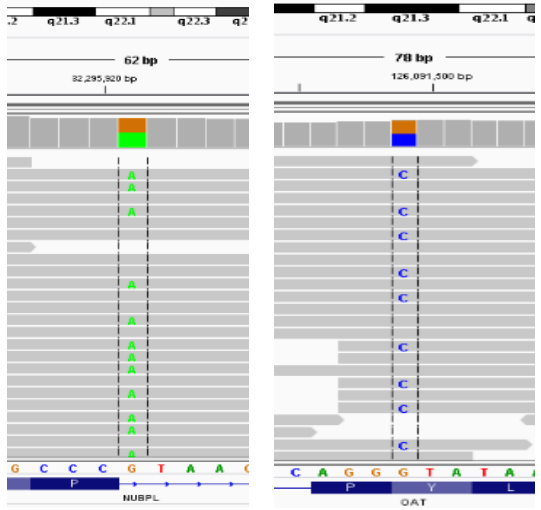
R469:



ACADVL: S110Y

NDUFA6: I120KfrTer44

R470:

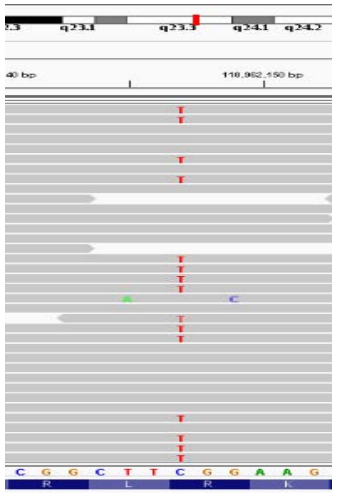


NUBPL: IVC8DC

OAT: Y299Ter

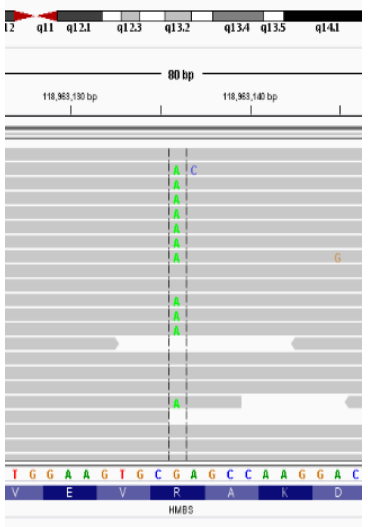
Continuation of Fig. S2.

R302:



***HMBS*: R175W**

R462:



***HMBS*: R229Q**

B.

HMBS Protein alignment:

Mutant	TRLWKLD...VEVQAKD
Human	TRLRKLD…..VEVRAKD
Dog	TRLRKLD...VEVRAKD
Rat	TRLRKLD…..VEVRAKD
Mice	TRLRKLD…..VEVRAKD
Zebra fish	TRLRKLD…..VEVRARD
Fruit fly	TRLAKLD…..VECRAND

B. Alignment of Hydroxymethylbilane Synthase (HMBS) Protein show that *HMBS* variants found in subjects R302 and R462 change residues that are highly conserved between species.