Supplemental Digital Content 1. *RYR1* Variant Table

***RYR1* Variants in Transcript NM_000540.2 Identified in 870 ClinSeq® Exomes**							
Database Source	**Number of Variants Referenced**	**Total Variants**	***RYR1* Variant Pathogenicity Score**				
HGMD	20 (29% of total)						
Not in HGMD, only LSDB	6 (9% of total)		1	2	3	4	5
No listing	43 (62% of total)	69	6	7	52	0	4

Nucleotide Change	**Predicted Protein Change**	**Associated Disease State**	**ClinSeq® Allele Count**	**NHLBI EVS Allele Count**	**ClinSeq® Pathogenicity Score**
***RYR1* Variants Listed in HGMD (N=20)**					
c.1453A>G	p.Met485Val	Malignant Hyperthermia	2/1,740	1/10,757	2
c.1840C>T	p.Arg614Cys	Malignant Hyperthermia	1/1,740	NF	5^
c.2122G>A	p.Asp708Asn	Congenital Myopathy	2/1,696	1/10,753	3
c.2956C>T	p.Arg986Cys	Myopathy, congenital	1/1,530	4/10,746	3
c.4024A>G	p.Ser1342Gly	Malignant hyperthermia	1/146	386/9608	1
c.4178A>G	p.Lys1393Arg	Malignant Hyperthermia	4/1,202	47/10,703	2

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c.5036G>A	p.Arg1679His	Malignant Hyperthermia	2/1,726	11/10,741	2
c.5183C>T	p.Ser1728Phe	Malignant hyperthermia	1/1,740	1/10,757	5
c.6721C>T	p.Arg2241X	Multi-minicore & Atypical Periodic Paralysis	2/1,740	NF	5
c.6961A>G	p.Ile2321Val	Malignant Hyperthermia	1/1,736	10/10,748	2^
c.7025A>G	p.Asn2342Ser	Malignant Hyperthermia	2/1,734	12/10,746	2
c.7487C>T	p.Pro2496Leu	Malignant hyperthermia	1/1,718	NF	3
c.8327C>T	p.Ser2776Phe	Possible association with Malignant Hyperthermia	1/1,724	10/10,746	2
c.8360C>G	p.Thr2787Ser	Multi-minicore Disease	6/1,716	113/10,645	1
c.9242T>C	p.Met3081Thr	Myopathy, congenital	3/1,738	23/10,735	3
c.10616G>A	p.Arg3539His	Central Core Disease	1/1,666	17/10,741	3
c.10747G>C	p.Glu3583Gln	Possible association with Progressive Axial Muscular Dystrophy	15/1,678	142/10,616	1
c.10747G>C	p.Glu3853Lys	Muscular dystrophy and arthrogryposis	1/1,714	1/10,757	3
c.11958C>G	p.Asp3986Glu	Malignant hyperthermia	1/1,740	NF	5

***RYR1* Variants in Transcript NM_000540.2 Identified in 870 ClinSeq® Exomes**					
c.13513G>C	p.Asp4505His	Possible association with Progressive Axial Myopathy with Cataracts	4/556	36/10,710	3
***RYR1* Variants Not in HGMD, Listed in Other LSDB Sources (N=6)**					
c.4999C>T	p.Arg1667Cys	-?/? (See 1)	4/1,740	21/10,727	3
c.5360C>T	p.Pro1787Leu	-?/?	40/1,704	174/10,578	1^
c.6178G>T	p.Gly2060Cys	-/?	120/1,740	548/10,210	1^
c.6301A>G	p.Met2101Val	NF	1/1,556	NF	3
c.11266C>G	p.Gln3756Glu	-?/?	34/1,728	123/10,635	1
c.12553G>A	p.Ala4185Thr	?/?	2/1,682	6/10,752	3
***RYR1* Variants Not in HGMD or LSDB (N=43)**					
c.89A>T	p.Glu30Val	N/A	1/886	4/10,730	3
c.1099C>T	p.Arg367Trp	N/A	1/1,492	1/10,757	3
c.1384G>A	p.Glu462Lys	N/A	1/1,604	NF	3
c.1474C>T	p.Arg492Cys	N/A	1/1,740	NF	3

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c.1753A>G	p.Ile585Val	N/A	1/1,740	NF	3
c.2075C>T	p.Thr692Ile	N/A	1/1,724	NF	3
c.2173G>A	p.Val725Met	N/A	1/1,716	NF	3
c.2255C>T	p.Pro752Leu	N/A	1/1,740	NF	3
c.2275A>G	p.Asn759Asp	N/A	1/1,740	2/10,756	3
c.2461C>A	p.His821Asn	N/A	1/1,740	NF	3
c.2533C>T	p.Leu845Phe	N/A	1/1,732	NF	3
c.2697C>A	p.Asn899Lys	N/A	1/1,720	NF	3
c.2812G>A	p.Val938Met	N/A	2/982	1/10,735	3
c.2824G>A	p.Asp942Asn	N/A	1/1,040	NF	3
c.3431C>T	p.Pro1144Leu	N/A	1/1,740	NF	3
c.5317C>T	p.Pro1773Ser	N/A	1/1,740	NF	3

***RYR1* Variants in Transcript NM_000540.2 Identified in 870 ClinSeq® Exomes**					
c.5980C>T	p.Arg1994Cys	N/A	1/1,736	1/10,757	3
c.6191T>G	p.Met2064Arg	N/A	1/1,740	1/10,757	3
c.6607A>G	p.Met2203Val	N/A	1/1,738	NF	3
c.6670C>T	p.Arg2224Cys	N/A	1/1,738	NF	3
c.6688A>T	p.Thr2230Ser	N/A	1/1,738	NF	3
c.6700C>T	p.Arg2234Cys	N/A	1/1,740	NF	3
c.7902C>A	p.Asn2634Lys	N/A	1/1,740	2/10,756	3
c.7958A>G	p.Lys2653Arg	N/A	1/1,642	NF	3
c.8113G>A	p.Ala2705Thr	N/A	1/1,740	NF	3
c.8155T>C	p.Tyr2719His	N/A	1/1,740	NF	3
c.8231+1G>A	Splicing IVS#+G>A	N/A	1/1,740	NF	3
c.8305G>A	p.Asp2769Asn	N/A	1/1,740	NF	3

***RYR1* Variants in Transcript NM_000540.2 Identified in 870 ClinSeq® Exomes**					
c.9347C>T	p.Ser3116Leu	N/A	1/1,738	NF	3
c.9800C>T	p.Pro3267Leu	N/A	3/1,664	NF	3
c.10046C>G	p.Ala3349Gly	N/A	1/1,700	NF	3
c.10183C>T	p.Arg3395Trp	N/A	1/978	NF	3
c.10492C>G	Arg3498Gly**+**	N/A	1/1,714	NF	2
c.10664A>T	p.Asn3555Ile	N/A	1/1,740	NF	3
c.11061_11063del	p.Glu3689del	N/A	2/1,056	NF*****	3
c.11599C>T	p.Arg3867Cys	N/A	1/1,520	3/10,755	3
c.11731A>G	p.Thr3911Ala	N/A	1/1,740	NF	3
c.14167C>T	p.Arg4723Cys	N/A	1/1,740	NF	3
c.14189G>T	p.Gly4730Val	N/A	1/1,740	NF	3
c.14901C>G	p.Asp4967Glu	N/A	1/1,740	NF	3

***RYR1* Variants in Transcript NM_000540.2 Identified in 870 ClinSeq® Exomes**					
c.14915C>T	p.Thr4972Ile	N/A	1/1,740	NF	3
c.14929G>C	p.Glu4977Gln	N/A	1/1,740	NF	3
c.15098A>G	p.Tyr5033Cys	N/A	1/1,738	NF	3
Variant total: **Variant Type:** 1 stopgain_SNV (2241X) 1 splicing (IVS#+G>A) 1 nonframeshift_substitution (Glu3689del) 1 exonic; splicing (Asp4505His) 65 Missense			=69	NF =40 (58% of total variants)	

Pathogenicity scores were determined as described in the Methods. HGMD =Human Gene Mutation Database (Professional 2012.2 from BIOBASE). LSDB =Locus Specific Database. LOVD =Leiden Open Variation Database (v.3.0). NHLBI ESP EVS =The National Heart, Lung, and Blood Institutes, Exome Sequencing Project, Exome Variant Server. NF =Not Found.

1 –These symbols are used in the LOVD variant pathogenicity rating, as reported on Leiden Muscular Dystrophy webpages. The first symbol indicates the conclusion of the publication cited in that publication entry. The second symbol indicates the conclusion of the database curator. Reported/Concluded; '+' indicating the variant is pathogenic, '+?' probably pathogenic, '-' no known pathogenicity, '-?' probably no pathogenicity, '?' effect unknown. **^ =**on European Malignant Hyperthermia Group's list of 31 approved diagnostic (causative) mutations, or 156 non-pathogenic variants (as of 01/2013). **+** =Proband with family history of MHS over 3 generations. * =The NHLBI exome variant server does not include any insertions or deletions.