Supplemental Digital Content 2. *CACNA1S* Variant Table

***CACNA1S* Variants In Transcript NM_000069.2 Identified in 870 ClinSeq® Exomes**								
Database Source	**Number of Variants Referenced**	**Total Variants**	***CACNA1S* Variant Pathogenicity Score**					
HGMD	1 (2% of total)							
Not in LSDB, only LSDB	6 (12% of total)		1	2	3	4	5	
Not listing	44 (86% of total)	51	10	--	41	--	--	

Nucleotide Change	**Predicted Protein Change**	**Associated Disease State**	**ClinSeq® Allele Count**	**NHLBI EVS Allele Count**	**ClinSeq® Pathogenicity Score**
***CACNA1S* Variants Listed in HGMD (N=1)**					
c.4060A>T	p.Thr1354Ser	Malignant Hyperthermia	9/1,740	48/12,958	3
***CACNA1S* Variants Not in HGMD, Listed in Other LSDB Sources (N=6)**					
c.206C>G	p.Ala69Gly	PMID 19825159; benign	70/1,738	510/12,496	1
c.773G>A	p.Gly258Asp	PMID 19825159; benign	14/1,710	101/12,903	1
c.1373T>A	p.Leu458His	PMID 19825159; benign	518/1,732	3,572/9,434	1
c.1493G>A	p.Arg498His	+/+ (See1)	1/1,740	NF	3

***CACNA1S* Variants In Transcript NM_000069.2 Identified in 870 ClinSeq® Exomes**					
c.1817G>A	p.Ser606Asn	PMID 19825159; benign	16/1,740	113/12,893	1
c.5399T>C	p.Leu1800Ser	PMID 12636044; benign and PMID 20010423; VUS	266/1,724	3,509/9,497	1
***CACNA1S* Variants Not Listed in HGMD or LSDB (N=44)**					
c.900+1G>A	*Splice-site*	N/A	1/1,682	NF	3
c.262A>G	p.Lys88Glu	N/A	1/1,740	3/13,003	3
c.502C>T	p.Arg168*	N/A	1/1,584	NF	3
c.530C>T	p.Ser177Leu	N/A	3/1,444	7/12,999	3
c.743C>T	p.Thr248Met	N/A	1/1,652	NF	3
c.773G>T	p.Gly258Val	N/A	2/1,710	NF	3
c.862T>G	p.Cys288Gly	N/A	1/1,728	NF	3
c.895T>C	p.Tyr299His	N/A	2/1,700	91/ 12,915	1
c.1112C>T	p.Thr371Met	N/A	1/1,740	3/ 13,003	3

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c.1166A>T	p.Asp389Val	N/A	1/1,740	4/13,002	3
c.1301T>C	p.Phe434Ser	N/A	5/1,740	8/12,998	3
c.1313T>G	p.Val438Gly	N/A	1/1,650	NF	3
c.1348G>A	p.Ala450Thr	N/A	1/1,740	1/13,005	3
c.1519G>A	p.Gly507Ser	N/A	1/1,740	NF	3
c.1547C>T	p.Ser516Leu	N/A	3/1,738	8/12,998	3
c.1745G>C	p.Gly582Ala	N/A	1/1,740	NF	3
c.1903A>G	p.Met635Val	N/A	2/1,740	4/13,002	3
c.2047C>T	p.Arg683Cys	N/A	1/1,738	127/ 12,879	1
c.2440G>A	p.Ala814Thr	N/A	2/656	20/12,976	3
c.2467C>T	p.Arg823Trp	N/A	1/852	NF	3
c.2630C>T	p.Ala877Val	N/A	1/1,556	1/13,005	3
c.2957G>A	p.Arg986His	N/A	1/1,694	4/13,002	3

***CACNA1S* Variants In Transcript NM_000069.2 Identified in 870 ClinSeq® Exomes**					
c.2992G>A	p.Asp998Asn	N/A	1/1,728	17/ 12,989	3
c.3026C>T	p.Thr1009Met	N/A	1/1,730	2/3,004	3
c.3190G>A	p.Val1064Ile	N/A	1/1,740	2/ 13,004	3
c.3364T>C	p.Tyr1122His	N/A	1/1,740	NF	3
c.3733A>C	p.Lys1245Gln	N/A	1/1,736	NF	3
c.3811G>A	p.Ala1271Thr	N/A	1/1,608	93/ 12,913	1
c.3905G>A	p.Arg1302Gln	N/A	1/1,740	1/13,005	3
c.4415G>A	p.Arg1472His	N/A	1/1,726	NF	3
c.4483_4485del	p.Lys1496del	N/A	1/1,740	NF	3
c.4615C>T	p.Arg1539Cys	N/A	184/1,740	1,161/11,845	1
c.4718C>T	p.Thr1573Met	N/A	1/1,740	1/13,005	3
c.4731C>G	p.Asp1577Glu	N/A	1/1,740	1/13,005	3

***CACNA1S* Variants In Transcript NM_000069.2 Identified in 870 ClinSeq® Exomes**					
c.4747G>A	p.Glu1583Lys	N/A	3/1,740	4/13,002	3
c.4885_4886del	p.Gln1629Valfs*3	N/A	1/1,728	NF*	3
c.4954C>T	p.Arg1652Cys	N/A	1/1,734	5/13,001	3
c.4973G>A	p.Arg1658His	N/A	123/1,726	1,572/11,434	1
c.4984A>T	p.Asn1662Tyr	N/A	1/1,720	NF	3
c.5005G>A	p.Ala1669Thr	N/A	1/1,678	NF	3
c.5299C>T	p.Pro1767Ser	N/A	1/1,628	NF	3
c.5510A>C	p.Glu1837Ala	N/A	2/1,740	NF	3
c.5515C>T	p.Pro1839Ser	N/A	7/1,740	33/12,973	3
c.5570G>A	p.Ser1857Asn	N/A	3/1,740	33/12,973	3
Variant total: **Variant Type:** 1 frameshift_deletion 1 nonframeshift_substitution 1 splicing 48 missense			=51	NF =20	

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. PMID =PubMed unique identifier.

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 30 approved diagnostic (causative) mutations, or 158 non-pathogenic variants (as of 01/2013). * =Insertion and deletion variants are not included in the NHLBI exome variant server.