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Homozygous *SPEG* Mutation Is Associated with Isolated Dilated Cardiomyopathy

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SPEG, a member of the myosin light chain kinase family, is critical for cardiac and skeletal muscle function involved in excitation-contraction coupling. Genetic variants in *SPEG* are associated with centronuclear myopathy (CNM) with or without dilated cardiomyopathy (DCM) [1, 2]. Here we report three individuals from two families who presented with non-syndromic DCM, carrying a homozygous in-frame deletion in *SPEG* (NM_005876.5; c.9028_9030delGAG, p.Glu3010del). This study was approved by an institutional review committee (IRB00010471) and informed consent from the patients or their parents was obtained. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient 1, born at full term to consanguineous parents and currently 5 years old, presented at two years of age with poor feeding, breathing difficulties and metabolic acidosis. Electrocardiogram (ECG) showed normal sinus rhythm and no history of arrhythmia. Echocardiogram revealed severely dilated left ventricle (LV), depressed LV ejection fraction (EF) of 13%, and moderate mitral valve regurgitation (MVR). He was started on anti-failure

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medications with some improvement. Last evaluation at 5 years of age showed dilated left atrium (LA) and LV, moderate MVR, and estimated LVEF of 30.3 % with fractional shortening (FS) of 14.3%. Growth and development were normal with normal tone and muscle strength. At age of 4 years, he started to have unexplained episodes of hypoglycemia of unknown cause despite extensive investigation. He is currently on carvedilol in addition to furosemide, lisinopril, and digoxin. Hypoglycemia secondary to carvedilol, a non-selective both beta- and alpha-adrenergic receptor blocker, cannot be completely excluded.

Patient 2 is the younger sister who also had DCM with moderate LV dilatation, severely impaired LV function (LVEF data unavailable), moderate MVR, and mild tricuspid regurgitation (MTR). At 5 months of age, she was noted to have some developmental delay (not rolling, smiling only) and mild generalized hypotonia. She died at 8 months of age, likely due to heart failure.

Exome sequencing (ES) for both siblings revealed a homozygous in-frame deletion in *SPEG* (c.9028_9030delGAG, p.Glu3010del), parents being carriers for the variant. This variant is absent from the gnomAD database, and the glutamate 3010 residue is highly conserved in vertebrates and invertebrates. No other variants in DCM related genes were reported.

Patient 3 is a two-year-old girl born to consanguineous parents, who was hospitalized at 5 months of age with DCM requiring inotropic support. ECG showed normal sinus rhythm with T-wave inversion in lateral leads and there was no history of arrhythmia. Echocardiogram showed severely dilated LA and LV, depressed LVEF of 22%, mild MVR and moderate TVR. Muscle tone and motor development were normal. Latest echocardiogram at 24 months of age showed moderately dilated LA and LV, mild MVR, and estimated LVEF of 26.9 % with FS of 12.3%. Developmentally she achieved all her gross and fine motor and cognitive milestones at appropriate age and has normal muscle tone and strength.

The father, currently 30-year-old, has history of near syncope due to complete heart block (CHB) needing permanent cardiac pacemaker. Echocardiogram showed normal LV size and function with EF 50-55%, grade 2 LV diastolic dysfunction, normal right ventricle (RV) size with mild RV systolic dysfunction. 24-hour Holter monitoring showed minimum heart rate of 31 beats per minute (BPM) and average 61 BPM with high-grade CHB. The mother and the healthy brother did not have cardiac evaluation yet. The same *SPEG* variant was identified in the proband on quad ES, both parents being carriers, and a healthy brother homozygous for the normal allele. No other variants were reported in the father.

In summary, we report three patients with *SPEG*-associated DCM homozygous for an in-frame deletion (p.Glu3010del). None of them have history of ophthalmoplegia or ptosis, although formal neurologic evaluation or EMG/muscle biopsy were not performed. In Table 1, we summarize the clinical and molecular findings of all 19 patients with *SPEG* mutations [1-3]. While majority of the patients had myopathy with or without DCM, isolated DCM without myopathy was recently described in a family of five members carrying homozygous missense mutation (c.5038G>A, p.Glu1680Lys) in the serine/threonine protein kinase (SK)-1 domain of SPEG [3]. Here we identified three patients with a homozygous in-frame

deletion in the SK-2 domain of SPEG. Structure-based alignment indicated that both residues (glutamate) are highly conserved and may function as nucleotide binding sites. The SK-1 domain of SPEG has been shown to phosphorylate junctophilin-2 in cardiac muscle, while SK-2 phosphorylates sarco-endoplasmic reticulum ATPase-2a [4, 5]. Further investigations are needed to understand how these glutamate residue mutations may specifically affect the role of SPEG in the cardiac muscle.

This study expands the phenotypic heterogeneity associated with *SPEG* mutations with the identification of isolated DCM without myopathy, and further describes genotype-phenotype correlations to guide appropriate clinical diagnosis and management. A better understanding of the underlying mechanism of DCM associated with unique *SPEG* variants could unravel potential therapeutic avenues for the patients.

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References:

1. Agrawal PB, Pierson CR, Joshi M, Liu X, Ravenscroft G, Moghadaszadeh B, Talabere T, Viola M, Swanson LC, Haliloglu G, Talim B, Yau KS, Allcock RJ, Laing NG, Perrella MA and Beggs AH. SPEG interacts with myotubularin, and its deficiency causes centronuclear myopathy with dilated cardiomyopathy. Am J Hum Genet. 2014;95:218–26. [PubMed: 25087613]
2. Tang J, Ma W, Chen Y, Jiang R, Zeng Q, Tan J, Jiang H, Li Q, Zhang VW, Wang J, Tang H and Luo L. Novel SPEG variant cause centronuclear myopathy in China. J Clin Lab Anal. 2020;34:e23054. [PubMed: 31625632]
3. Levitas A, Muhammad E, Zhang Y, Perea Gil I, Serrano R, Diaz N, Arafat M, Gavidia AA, Kapiloff MS, Mercola M, Etzion Y, Parvari R and Karakikes I. A Novel Recessive Mutation in SPEG Causes Early Onset Dilated Cardiomyopathy. PLoS Genet. 2020;16:e1009000. [PubMed: 32925938]
4. Quick AP, Wang Q, Philippen LE, Barreto-Torres G, Chiang DY, Beavers D, Wang G, Khalid M, Reynolds JO, Campbell HM, Showell J, McCauley MD, Scholten A and Wehrens XH. SPEG (Striated Muscle Preferentially Expressed Protein Kinase) Is Essential for Cardiac Function by Regulating Junctional Membrane Complex Activity. Circ Res. 2017;120:110–119. [PubMed: 27729468]
5. Quan C, Li M, Du Q, Chen Q, Wang H, Campbell D, Fang L, Xue B, MacKintosh C, Gao X, Ouyang K, Wang HY and Chen S. SPEG Controls Calcium Reuptake Into the Sarcoplasmic Reticulum Through Regulating SERCA2a by Its Second Kinase-Domain. Circ Res. 2019;124:712–726. [PubMed: 30566039]

Table 1.

Clinical and molecular findings in individuals carrying *SPEG* mutations

Family-Patient	Gender /age	Genotype	Variant type	Variant location	Isoforms affected
DCM with no or mild myopathy					
I-1, I-2	M/5 years; F/died at 8 months	Homozygous: c.9028_9030delGAG, p.Glu3010del	In-frame deletion	SK2	SPEGβ & SPEGα
II-1	F/ 2 years	Homozygous: c.9028_9030delGAG, p.Glu3010del	In-frame deletion	SK2	SPEGβ & SPEGα
III-1, III-2, III-3, III-4, III-5	M/died between 2 months and 12 years; F/died at 16 years	Homozygous: c.5038G>A, p.Glu1680Lys	Missense	SK1	SPEGβ & SPEGα
Myopathy with no DCM					
IV-1	M/3 years	Homozygous: c.1626_1627insA, p.Thr544fs	Small indel	Between Ig-like 1 and Ig-like 2	SPEGβ
V-1	F/10 years	Compound heterozygous: c.1071_1074dup, p.Lys359fs; c.4399C>T, p.Arg1467Ter	Small indel and nonsense	Between Ig-like 1 and Ig-like 2; Ig-like 7	SPEGβ & SPEGα (partial)
VI-1	F/6.5 years	Compound heterozygous: c.2183delT, p.Leu728fs; c.8962_8963ins25, p.Val2997fs	Small indels	Ig-like 2; SK2	SPEGβ & SPEGα (partial)
Myopathy and DCM					
VII-1	F/died at 3 weeks	Homozygous: c.6697C>T, p.Gln2233Ter	Nonsense	Between SK1 and Ig-like 9	SPEGβ &SPEGα
VIII-1	M/died at 19 weeks	Homozygous: c.7119C>A, p.Tyr2373Ter	Nonsense	Between SK1 and Ig-like 9	SPEGβ & SPEGα
IX-1	M/8 years	Homozygous: c.9586C>T, p.Arg3196Ter	Nonsense	SK2	SPEGβ & SPEGα
X-1, X-2	F/died at 3 and 5 days	Homozygous: c.8710A>G, p.Thr2904Ala	Missense	Between Fn type III-2 and SK2	SPEGβ & SPEGα
XI-1	M/died at 17 years	Homozygous: c.9185_9187delTGG, p.Val3062del	In-frame deletion	SK2	SPEGβ & SPEGα
XII-1	F/6 years	Compound heterozygous: c.3709_3715+29del36, p.Thr1237fs; c.4276C>T, p.Arg1426Ter	Small indel and nonsense	Ig-like 6; Ig-like 7	SPEGβ & SPEGα
XIII-1	M/19 months	Compound heterozygous: c.2915_2916delCCinsA, p.Ala972fs; c.8270G>T, p.Gly2757Val	Small indel and missense	Ig-like 4; Fn type III-2	SPEGβ & SPEGα

Abbreviations: Ig-like, immunoglobin-like; Fn type III, Fibronectin type III; SK, serine/threonine protein kinase; ASD, atrial septal defect; CHF, congestive heart failure; CM, congenital myopathy; CNM, centronuclear myopathy; DCM, dilated cardiomyopathy; ECG, echocardiogram; LV, left ventricular; LVEF, left ventricular ejection fraction; LVNC, left ventricular non-compaction; LVFS, left ventricular fractional shortening; VSD, ventricular septal defect. SPEGβ (amino acids 1-3267), the longest SPEG isoform and SPEGα (missing amino acids 1-854), the shorter isoform.

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