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Obscurin Variants in Patients With Left Ventricular Noncompaction

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Left ventricular noncompaction (LVNC) is a rare type of cardiomyopathy, occurring less frequently than hypertrophic cardiomyopathy (HCM) and dilated CM (DCM). In our patient population, we identified a possible association between LVNC and variants in the obscurin (*OBSCN*) gene. Obscurins are giant sarcomeric proteins (≈700 to 900 kDa) that play key roles in myofibrillogenesis and cytoskeletal arrangement through interaction with several other binding partners, including the proteins titin, myomesmin, and obscurin-like-1 to generate a complex important for myofibrillar M-band function (1). While disrupting these interactions can have severe consequences for normal muscle function, obscurin's pathogenic involvement in cardiomyopathies is unclear.

Two clinical studies previously reported *OBSCN* missense variants associated with cardiomyopathy (2,3). One of these studies reported two *OBSCN* missense variants in HCM patients (with 1 missense variant affecting obscurin's binding to titin and connectin) (2). The other study associated 5 *OBSCN* missense variants with DCM in 4 patients (with decreased levels of obscurin mRNA, potentially indicating haploinsufficiency) (3). A functional cardiac role for obscurin is also supported by animal studies; specifically, zebra-fish *OBSCN* knockdowns have structural and functional abnormalities consistent with congestive heart failure, although mouse knockdown models only have mild myopathy (3). Taken together, the association between *OBSCN* missense variants and either HCM or DCM in 2 clinical studies (2,3), combined with suggestions of cardiac involvement in limited animal studies (3), made obscurin an intriguing target for further exploration in our cardiomyopathy patient cohort.

Using the TruSight One-Sequence panel (Illumina, Redwood City, California), which queries 4,813 genes associated with clinical phenotypes (cardiac and noncardiac), we identified 4 cardiomyopathy probands heterozygous for an *OBSCN* frameshift or splicing variant (4 variants total). These probands were identified from a population of 335 cardiomyopathy patients (325 DCM and 10 LVNC) queried in its entirety, using the panel. Briefly, patient DNA samples had DNA regions of interest captured with the panel, sequenced on a HiSeq 2500 Sequencing System (Illumina, Redwood City, California) with v4 chemistry, and mapped with Genomic Short-read Nucleotide Alignment Program (GSNAP; version 2012-07-20; Thomas Wu, Genentech, San Francisco, California). Variants

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were called with the Genome Analysis Toolkit (GATK; version 2.1-8-g5efb575; Broad Institute, Cambridge, Massachusetts) and classified with Annotate Variation (ANNOVAR, version 2012-07-28, QIAGEN, Hilden, Germany) software. Functional predictions were made with the database for non-synonymous single-nucleotide polymorphism functional predictions (dbNSFP, version 2.0, Xiaoming Liu, University of Texas Health Science Center at Houston, Houston, Texas). All variants were confirmed by Sanger sequencing.

Three of the 4 probands had *OBSCN* frameshift variants, with the remaining 1 having a splicing variant (Table 1). Interestingly, although most patients analyzed had DCM (325 of 335 [97.0%]), only 1 of the 4 *OBSCN* probands had a DCM phenotype. The other 3 probands had LVNC, with a noncompacted-to-compacted myocardium (NC/C) ratio of >2 by echocardiography in end-systole or 2.3 by cardiac magnetic resonance in end-diastole (4,5). LVNC was rare in our population (10 of 335 [3.0%]), and the prevalence of *OBSCN* variants was significantly greater in LVNC (3 of 10) than in DCM (1 of 325) ($p < 0.001$). All 4 *OBSCN* variants identified localized to the C terminus of obscurin-B-like isoform and occurred upstream of the fibronectin type-III 4 and protein kinase 2 domains, which the frameshift variants are predicted to eliminate. The earliest variant (p.Thr7266ArgfsTer53) also occurred upstream of the protein kinase 1 domain. Two variants, specifically a frameshift substitution (p.Thr7266ArgfsTer53) and a splicing variant (c.25367-1G>C), were absent from the Exome Aggregation Consortium (ExAC) browser for each proband's population. Of note, the splicing variant additionally had a Genomic Evolutionary Rate Profiling (GERP) score of >4.2. We screened all 4 probands for variants in 54 other known cardiomyopathy-related genes, but no pathogenic variants were detected. Family members of the probands were unavailable for segregation analysis of the *OBSCN* variants.

Our findings suggest a strong association between *OBSCN* frameshift and splicing variants, all clustering to the C terminus of the same isoform group, with the occurrence of the rare LVNC phenotype. Because LVNC is thought to have a developmental basis, investigating the possible role of obscurin in heart development may warrant further attention.

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TABLE 1

Variants and Clinical Phenotypes of 4 Affected Cardiomyopathy Probands With OBSCN Frameshift or Splicing Variants

CM Type	Variant*	Variant Consequence	ExAC Allele Frequencies†	Conservation (GERP)	Sex/Age‡	Ethnicity	Symptoms	ECG	NYHA Functional Class	LVEF%/ LVEDD (cm)	Imaging
LVNC	1:228552765 ACT/AG	p.Thr7266Arg fs ter53	0/0	1.00	M/56	AF	DOE; CP	SR, LBBB	II–III	21/6	CMR: apical NC/C >2.3 Inferior DE
LVNC	1:228559441 GC/G (rs71180793)	p.Ser7947Pro fs ter82	0.002029/0.003085	1.69	F/30	EU	SOB	SR, QS in V1-2	I–II	56/4.3	ECHO: apical+mid ventricle NC/C >2
DCM	1:228559449 CG/C	p.Ala7950Pro fs ter79	0.00007865/0.00008628	−8.01	F/62	EU	SOB	RS, LBBB	II–III	26/7.08	ECHO: No NC
LVNC	1:228562285 G/C (rs55883237)	c.25367 -1G>C	0.0003921/0	5.16	M/39	AA	SOB; CP; fatigue	SR, QRS 132 msec	III	30–33/6	CMR: apical NC/C = 2.69 Septal DE

*Based on GRCh37(hg19).

†ExAC allele frequencies listed are overall frequency/frequency for proband's population (i.e., African or European [non-Finnish]).

‡Age at enrollment.

AA = African American; AF = African; CM = cardiomyopathy; CMR = cardiac magnetic resonance; CP = chest pains; DCM = dilated cardiomyopathy; DE = delayed enhancement; DOE = dyspnea on exertion; ECG = electrocardiogram; ECHO = echocardiography; EU = European; ExAC = Exome Aggregation Consortium; fs ter = frameshift termination; GERP = Genomic Evolutionary Rate Profiling; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVNC = left ventricular non-compaction; NC/C = noncompacted-to-compacted myocardium ratio; NYHA = New York Heart Association; SOB = shortness of breath.