ORIGINAL ARTICLE

Truncating Variants in OBSCN Gene Associated With Disease-Onset and Outcomes of Hypertrophic Cardiomyopathy

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BACKGROUND: The presence of variants in OBSCN was identified to be linked to hypertrophic cardiomyopathy (HCM), but whether OBSCN truncating variants were associated with HCM remained unknown.

METHODS: Whole-exome sequencing was performed in 986 patients with HCM and 761 non-HCM controls to search for OBSCN truncating variants, and the result was tested in a replication cohort consisting of 529 patients with HCM and 307 controls. The association of the OBSCN truncating variants with baseline characteristics and prognosis of patients with HCM were ascertained.

RESULTS: There were 28 qualifying truncating variants in the OBSCN gene detected in 26 (2.6%) patients with HCM and 6 (0.8%) controls. The OBSCN truncating variants were more prevalent in patients with HCM than controls (odds ratio, 3.4, P=0.004). This association was confirmed in the replication cohort (odds ratio, 3.8, P=0.024). The combined effects of the two cohorts estimated the odds ratio to be 3.58 (P<0.001). Patients with or without OBSCN truncating variants shared similar demographic and echocardiographic variables at baseline. During 3.3±2.4 years (4795 patient-years) follow-up, the patients with OBSCN truncating variants were more likely to experience cardiovascular death (adjusted hazard ratio, 3.1 [95% CI, 1.40–6.70], P=0.005) and all-cause death (adjusted hazard ratio, 2.63 [95% CI, 1.21–5.71], P=0.015).

CONCLUSIONS: Our data indicated that OBSCN truncating variants contributed to the disease-onset of HCM, and increased the risk of malignant events in patients with HCM.

Key Words: cardiomyopathy, hypertrophic ◼ OBSCN ◼ prognosis ◼ truncating variants ◼ whole-exome sequencing

Hypertrophic cardiomyopathy (HCM) is an inherited cardiovascular disease mainly in an autosomal dominant pattern with the genetic transmission, affecting ≈1:500 to 1:200 individuals.1,2 More than 2000 mutations in at least 11 genes, coding for thick, thin, and Z disk protein of sarcomeres, are identified to be responsible for HCM, notwithstanding over 99% mutations in 8 core sarcomeric genes, including MYH7, MYBPC3, TNNT2, TNNI3, MYL2, MYL3, TNNI3, and ACTC1.3,4 Disease-causing variants in sarcomere genes were found in nearly 30% to 60% patients with HCM.5 However, at least 40% of HCM cases are not explained by sarcomeric mutations, suggesting potential genetic factors predispose to patients with established disease.6
Obscurins, encoded by the OBSCN gene, are sarcomeric proteins functioning in myofibrillogenesis and cytoskeletal arrangement. Giant obscurins, including obscurin-A and obscurin-B, modular consisting of a range of immunoglobulin and fibronectin-III domains in addition to an array of singling motifs. The relatively recent study suggested that OBSCN (Obscurins) proteins bound to the thick filament and played structural and regulatory roles, interacting with myosin and myosin-binding protein C. Several missense and truncating variants in the OBSCN gene were reported to be associated with different forms of cardiomyopathy, including HCM, dilated cardiomyopathy, and left ventricular non-compaction. Additionally, the Arg4344Gln variant was found to be linked to the development of HCM and leading to cardiac remodeling and dilation. However, the significance of truncating variants in the OBSCN gene for HCM remained unclear. Here, our study analyzed the spectrum of OBSCN truncating variants in a large HCM case-control cohort and explored the association between OBSCN variants and outcomes of HCM.

METHODS
All data, analytical methods, and study materials supporting this study are available from the corresponding authors on reasonable request. This study was approved by The Ethics Committees of Fuwai Hospital approved this study, which is conducted in conformity to the principles of the Declaration of Helsinki. All subjects provided written informed consent at enrollment. Full methods are available in the Data Supplement.

RESULTS
Study Participants
There were a discovery cohort (986 patients with HCM and 761 non-HCM) and a replication cohort (529 patients and 307 controls) in the final analysis. Of the patients with HCM in the discovery study, the mean (±SD) age was 47.8 (±14.4) years, 64.8% were male, and the maximal ventricular wall thickness was 22.8 (±5.9) mm. There was no significant difference between cases and controls in terms of sex and age distributions (Table I in the Data Supplement). The sarcomere variants were found in 495 (50.2%) patients of the discovery cohort. The information on the subjects in the replication study was previously described. There were 230 (43.5%) patients carrying sarcomere variants in the replication cohort.

OBSCN Truncating Variants Associated With HCM
A total of 28 qualifying truncating variants in the OBSCN gene were found in individuals of discovery cohort, including 8 nonsense variants, 17 frameshift variants, and 3 splice-site variants (Table 1). Among these variants, 11 (39.3%) of them were reported in ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar), whereas 17 (60.7%) truncating variants were novel. In detail, 26 truncating variants were detected in 26 (2.6%) patients with HCM. Comparatively, 6 variants were detected in 6 (0.8%) controls. All these 32 subjects carried one truncating variant. Two variants were found in both patients and controls (Table 1). The OBSCN truncating variants were more prevalent in patients with HCM than controls (odds ratio, 3.4, P=0.004; Table 2).

The association between OBSCN truncating variants and HCM was confirmed in the replication cohort. A total of 20 truncating variants were detected in 19 (3.6%) patients with HCM and 3 variants in 3 (1.0%) controls (Table II in the Data Supplement). The odds ratio was estimated to be 3.8 in the replication cohort (P=0.024; Table 2). The combined effects of the two cohorts estimated the odds ratio to be 3.58 (P<0.001).

Our data found 23 patients with OBSCN truncating variants carried a sarcomere variant. The proportion of patients with OBSCN truncating variants was similar in patients with sarcomere variants (23/725, 3.2%) to those without sarcomere variants (22/790, 2.8%, P=0.657).

Genotype-Phenotype Correlation
We compared clinical characteristics between patients with HCM with and without OBSCN truncating variants in the study population and replication. There were no differences in demographic and echocardiographic findings at baseline between these two groups (Table 3). There were 59 subjects lost to follow-up, including 2 patients with OBSCN truncating variants and 57 without such variants. As 3.3±2.4 years (4795 patient-years) follow-up, there were 99 cases that experienced all-cause death. A total of 85 cases died of cardiovascular causes, including 45 died of sudden cardiac death, 30 of heart failure-related death, and 10 of stroke-related death. In detail, a total of seven patients with OBSCN truncating variants died, and all of them died of cardiovascular death. In detail, a total of seven patients with OBSCN truncating variants died, and all of them died of cardiovascular causes due to sudden cardiac death (n=3) or heart failure-related death (n=4). The OBSCN truncating variants were associated with the cumulative incidence of cardiovascular death (log-rank P=0.015) and all-cause death (log-rank P=0.042) in Kaplan-Meier survival curve analysis from the first enrollment to the last contact (Figure [A] and [B]). Moreover, Kaplan-Meier survival curve analysis from the birth to the last contact displayed the presence of OBSCN truncating variants increased the risk of cardiovascular death (log-rank P=0.013) and
all-cause death (log-rank $P=0.039$; Figure I in the Data Supplement). Univariate analysis showed that \textit{OBSCN} truncating variants significantly increased the risk of cardiovascular death of patients with HCM (hazard ratio, 2.52 [95% CI, 1.16–5.46], $P=0.019$; Table 4). After multivariate adjustment, the \textit{OBSCN} truncating variants were still linked with a higher risk of cardiovascular events (adjusted hazard ratio, 3.1 [95% CI, 1.40–6.70], $P=0.005$; Table 4). Similarly, the \textit{OBSCN} truncating variants increased the risk of all-cause death in patients with HCM (hazard ratio, 2.18 [95% CI, 1.01–4.69], $P=0.048$). After other risk factor–adjusted, the \textit{OBSCN} truncating variants still predicted the risk of all-caused events (adjusted hazard ratio, 2.63 [95% CI, 1.21–5.71], $P=0.015$; Table III in the Data Supplement).

**DISCUSSION**

Our study for the first time performed whole-exome sequencing in a large case-control cohort consisting of 986

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**Table 1. Qualifying Truncating Variants of OBSCN Detected in Subjects of the Discovery Cohort**

| Transcript effect | Protein | Type | SNP | GnomAD* MAF% | ExAC† MAF% | In-house MAF% | Subject ID (phenotype) | Sarcomere gene variants |
|------------------|---------|------|-----|-------------|------------|--------------|----------------------|------------------------|
| NM_001271223.2   | Gly1150fs | Frameshift | Novel | 0 | 0 | 0.0286 | H1226 (HCM); MYBPC3, p.Leu460fs |
| c.3449delG       | NA | Splicing | Novel | 0 | 0 | 0.0286 | H7026 (HCM); NA |
| c.5611C>T        | Gln1871Ter | Nonsense | rs750858801 | 0.0008 | 0.0017 | 0.0286 | Y5522 (control) | NA |
| c.5826delG       | Trp1942fs | Frameshift | Novel | 0 | 0 | 0.0286 | H7509 (HCM); NA |
| c.6965C>G        | Ser2322Ter | Nonsense | Novel | 0 | 0 | 0.0286 | H7180 (HCM); MYBPC3, p.Gln374Ter |
| c.7823delG       | Gly2608fs | Frameshift | Novel | 0 | 0 | 0.0286 | H8828 (HCM); MYH7, p.Gln1208Lys |
| c.10671G>A       | Trp3557Ter | Nonsense | Novel | 0 | 0 | 0.0286 | H7140 (HCM); MYH7, p.Ala979Thr |
| c.12307C>T       | Gln4103Ter | Nonsense | Novel | 0 | 0 | 0.0286 | H1230 (HCM); NA |
| c.12825C>G       | Tyr4275Ter | Nonsense | rs755214451 | 0.0008 | 0.0004 | 0.0286 | H7029 (HCM); NA |
| c.13428_13429delAT | Cys4479fs | Frameshift | rs748780851 | 0.0357 | 0.0318 | 0.0572 | H9033 (HCM); NA |
| c.13999_14000delAG | Arg4667fs | Frameshift | rs756018529 | 0.0017 | 0.0032 | 0.0286 | H8032 (HCM); MYBPC3, p.Arg845fs |
| c.14484_14485delAT | Val4830fs | Frameshift | rs768971087 | 0.005 | 0.0032 | 0.0286 | H1408 (HCM); NA |
| c.14662dupG      | Ala4888fs | Frameshift | Novel | 0 | 0 | 0.0286 | 7071704AT (control) | NA |
| c.14715dupA      | Gln4906fs | Frameshift | Novel | 0 | 0 | 0.0286 | H1223 (HCM); MYBPC3, p.Glu1050Lys |
| c.14818C>T       | Arg4904Ter | Nonsense | rs766814997 | 0.0032 | 0 | 0.0572 | T0108 (HCM); MYH7, p.Arg403Gln |
| c.15337+1G>T     | NA | Splicing | Novel | 0 | 0 | 0.0286 | A20034 (control) | NA |
| c.17653C>T       | Arg5885Ter | Nonsense | rs758907604 | 0.0008 | 0.0022 | 0.0286 | H8165 (HCM); MYH7, p.Arg1420Trp |
| c.19288_19291delAGAG | Glu6430fs | Frameshift | Novel | 0 | 0 | 0.0286 | H8150 (HCM); MYBPC3, p.Arg977fs |
| c.19603C>T       | Arg5853Ter | Nonsense | rs371757599 | 0.001 | 0.0012 | 0.0286 | H1443 (HCM); NA |
| c.20234dupG      | Val6476fs | Frameshift | Novel | 0 | 0 | 0.0286 | H8311 (HCM); NA |
| c.21646delA      | Arg7216fs | Frameshift | rs753959445 | 0.0082 | 0.0096 | 0.0572 | H7315 (HCM); MYH7, p.Glu379Lys |
| c.21934+1G>T     | NA | Splicing | rs755098840 | 0.0023 | 0.0032 | 0.0286 | H7365 (HCM); NA |
| c.22713_22714insTG | Ile7571fs | Frameshift | Novel | 0 | 0 | 0.0286 | H8313 (HCM); MYH7, p.Leu957Val |
| c.23734delC      | His7912fs | Frameshift | Novel | 0 | 0 | 0.0286 | Y3120 (control) | NA |
| c.23922delT      | Gln7975fs | Frameshift | Novel | 0 | 0 | 0.0286 | Y4866 (control) | NA |
| c.24125delC      | Pro8042fs | Frameshift | Novel | 0 | 0 | 0.0286 | H7175 (HCM); MYH7, p.Met357Val |
| c.26597delG      | Gly8866fs | Frameshift | Novel | 0 | 0 | 0.0286 | H1415 (HCM); MYH7, p.Arg403Gln |
| NM_052843.3      | Arg8395fs | Frameshift | rs767527000 | 0.0042 | 0.0023 | 0.0858 | S130 (HCM); NA |
| c.19185_19188delAGAG | Arg8395fs | Frameshift | rs767527000 | 0.0042 | 0.0023 | 0.0858 | H8284 (HCM); NA |
|                 |         |       |     |             |            |              | H7604 (HCM); NA |

ExAC indicates Exome Aggregation Consortium; GnomAD, Genome Aggregation; HCM, hypertrophic cardiomyopathy; MAF, minor allele frequency; NA, not available; and SNP, single nucleotide polymorphism.

*GnomAD: https://gnomad.broadinstitute.org/
†ExAC: http://exac.broadinstitute.org
patients with HCM and 761 controls to search for OBSCN variants and identified that the prevalence of OBSCN truncating variants was nearly 3% in patients with HCM and 0.8% in controls. Our data showed OBSCN truncating variants enriched in HCM cases, suggesting that these variants are predisposed to HCM. Furthermore, we found carrying OBSCN truncating variants might be an independent predictor for malignant events in patients with HCM.

Obscurin is one member of the family of giant sarcomeric proteins acting as structural and signaling mediators in muscle cells.\(^{15,16}\) The OBSCN gene contains 117 exons and its large size gives rise to multiple protein isoforms which may deter the variants in OBSCN from linking to cardiomyopathies.\(^{17,18}\) Benefiting from the advanced sequencing technology, the OBSCN gene was included in genetic screens for familial heart diseases, and at least 15 variants were identified to be linked to HCM.\(^{9,19}\) However, it is the first time to explore the relationship of OBSCN truncating variants with HCM in large-size HCM control cohort, and the prevalence was nearly 3-fold in patients with HCM than controls, indicating that OBSCN truncating variants contributed to HCM. The observed prevalence of OBSCN truncating variants were nearly 3% in patients with HCM and 0.8% in controls. Xu et al\(^{19}\) reported the presence of four OBSCN truncating variants in 4 (5.4%) cases of a Chinese HCM cohort consisting of 74 patients with HCM. The prevalence of OBSCN truncating variants in patients of our study was lower than Xu et al\(^{19}\) reported, which might be caused by different sizes of the study population.

The mechanisms of OBSCN truncating variants contributed to HCM might be through several pathways. First, the protein of obscurins functions in thick filament assembly and stabilization, and the truncating protein may result in failure of myosin to assemble into periodic A-bands.\(^{20,21}\) Second, truncating protein lost the multiple adhesion motifs which may play a role for myomesin, titin, and myosin-binding protein C as binding sites. The variants in MYH7 and MYBPC3 accounted for the most genetic HCM.\(^{22-24}\) Third, obscurins interact with signaling proteins, such as a member of the rho family of small GTPases, by rho-guanine nucleotide exchange factor motifs.\(^{25}\) The truncated variants could decrease the number of motifs, and modulate contractility by affecting the activity of a member of the rho family of small GTPases.\(^{25}\) The authentic mechanism of OBSCN truncating variants causing HCM remained to be determined.

There is wide phenotypic heterogeneity observed in the age of onset, disease severity, and prognosis among patients with HCM.\(^{26}\) This heterogeneity in HCM phenotypes may be explained in part by the effects of genetic

### Table 2. Association of OBSCN Truncating Variants With Hypertrophic Cardiomyopathy

| Study       | With truncating variant | Without truncating variant | OR   | \(P\) value |
|-------------|-------------------------|---------------------------|------|------------|
| Discovery   | n=45                    | 6 (0.8)                   | 755 (99.2) | 3.41       | 0.004     |
| Replication | n=1515                  | 3 (1.0)                   | 304 (99.0) | 3.77       | 0.024     |
| Combined    | n=1515                  | 9 (0.8)                   | 1059 (99.2) | 3.58       | <0.001    |

\(N\) indicates number of individuals; and OR, odd ratio.

### Table 3. Demographic and Clinical Characteristics of Patients With HCM With or Without OBSCN Truncating Variants

| Variables                        | Overall cohort; \(n=1515\) | With truncating variants; \(n=45\) | Without truncating variant; \(n=1470\) | \(P\) values* |
|----------------------------------|-----------------------------|-----------------------------------|------------------------------------|---------------|
| Male, n (%)                      | 1010 (66.7)                 | 32 (71.1)                         | 978 (66.5)                        | 0.521         |
| Age at enrollment, y             | 48.9±14.5                   | 48.2±17.9                        | 48.9±14.4                         | 0.733         |
| Family history of HCM, n (%)     | 323 (21.3)                  | 9 (20.0)                          | 314 (21.4)                        | 0.826         |
| Family history of SCD, n (%)     | 190 (12.5)                  | 5 (11.1)                          | 185 (12.6)                        | 0.769         |
| Left atrium diameter, mm         | 41.3±7.1                    | 40.5±8.5                         | 41.3±7.0                          | 0.443         |
| LVEDD, mm                        | 44.4±6.3                    | 44.6±5.5                         | 44.3±6.4                          | 0.768         |
| MVT, mm                          | 22.1±5.7                    | 21.4±6.0                         | 22.2±5.7                          | 0.401         |
| LVEF, %                          | 67.2±8.4                    | 67.9±7.7                         | 67.2±8.4                          | 0.594         |
| Maximum LVOT gradient, mmHg      | 43.7±41.7                   | 41.5±48.1                        | 43.7±41.6                         | 0.740         |
| Unexplained syncope, n (%)       | 177 (11.7)                  | 7 (15.6)                          | 170 (11.6)                        | 0.412         |
| Atrial fibrillation at baseline, n (%) | 177 (11.7)             | 6 (13.3)                          | 171 (11.6)                        | 0.726         |
| NYHA class III or IV, n (%)      | 277 (18.3)                  | 5 (11.1)                          | 272 (18.5)                        | 0.206         |

Continuous variables are presented as mean±SD; the categorical variables were presented as number (percentage). HCM indicates hypertrophic cardiomyopathy; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MVT, maximal left ventricular wall thickness; NYHA, New York Heart Association; and SCD, sudden cardiac death.

"Continuous variables were compared by Student t test; the categorical variables were compared by \(\chi^2\) test."
modifiers, as recent studies have found pathogenic variants in genes or pathways associated with left ventricular hypertrophy that can function as modifier genetic variants that influence HCM phenotypes. In our study, the frequency of **OBSCN** truncating variants was similar in patients with HCM with or without sarcomere variants, which indicated the function of **OBSCN** truncating variants were not associated with sarcomere variants. Therefore, our data suggested **OBSCN** truncating variants might be genetically modified factors to increase the risk of HCM and the outcomes in patients with HCM, but the mechanism remained unknown.

Some limitations remained to be noticed in our study. First, the pathogenicity of **OBSCN** truncating variants requires to be confirmed by further studies. Second, all subjects were recruited from one center, and the

Table 4. Univariable and Multivariable Cox Regression Analysis of the Association Between **OBSCN** Truncating Variants and Cardiovascular Death in Patients With HCM

| Variables                      | Crude HR (95% CI) | Crude P value | Adjusted HR (95% CI) | Adjusted P value |
|-------------------------------|-------------------|---------------|----------------------|------------------|
| **OBSCN** truncating variants | 2.52 (1.16–5.46)  | 0.019         | 3.06 (1.40–6.70)     | 0.005            |
| Sarcomere variants            | 1.22 (0.79–1.89)  | 0.378         |                      |                  |
| Male                          | 1.37 (0.89–2.12)  | 0.155         |                      |                  |
| Age at enrollment             | 1.01 (0.99–1.02)  | 0.456         |                      |                  |
| Family history of HCM         | 1.05 (0.98–1.17)  | 0.135         |                      |                  |
| Family history of SCD         | 2.02 (1.22–3.34)  | 0.006         | 1.53 (0.91–2.56)     | 0.107            |
| Left atrium diameter          | 1.06 (1.04–1.09)  | <0.001        | 1.03 (1.00–1.06)     | 0.034            |
| LVEDD                         | 1.06 (1.03–1.09)  | <0.001        | 1.02 (0.99–1.05)     | 0.245            |
| MVT                           | 1.04 (1.01–1.08)  | 0.034         | 1.05 (1.01–1.09)     | 0.016            |
| LVEF                          | 0.95 (0.93–0.97)  | <0.001        | 0.97 (0.95–0.99)     | <0.001           |
| Maximum LVOT gradient         | 1.00 (0.99–1.00)  | 0.413         |                      |                  |
| Unexplained syncope           | 1.62 (0.93–2.83)  | 0.091         |                      |                  |
| Atrial fibrillation at baseline| 1.61 (0.90–2.86) | 0.106         |                      |                  |
| NYHA class III or IV          | 3.90 (2.52–6.06)  | <0.001        | 2.87 (1.79–4.60)     | <0.001           |

Variants in 8 core sarcomere genes (**MYH7**, **MYBPC3**, **MYL2**, **MYL3**, **TNNT2**, **TNNI3**, **TPM1**, and **ACTC1**) classified as pathogenic, likely pathogenic, or unknown significance according to the criteria of American College of Medical Genetics and Genomics were defined as sarcomere gene variants. HCM indicates hypertrophic cardiomyopathy; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MVT, maximal left ventricular wall thickness; NYHA, New York Heart Association; and SCD, sudden cardiac death.
findings in present study needed to be tested in other populations. Third, the mechanism of **OBSCN truncating variants** for the disease-onset and malignant outcomes of HCM and remained to be explored. Fourth, the risk score recommended by the European Society of Cardiology and late gadolinium enhancement of patients were not included in the adjusted model because of missing data.

**CONCLUSIONS**

Our study was the first report that revealed the relationship between **OBSCN truncating variants** and HCM. The **OBSCN truncating variants** might be a predictor for malignant outcomes of patients with HCM and are considered to be included in genetic testing and management of HCM.

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**Disclosures**

None.

**Supplemental Materials**

Expanded Materials and Methods

Supplemental Tables I–III

Supplemental Figure I

References 7–10

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