Editorial Board (Comments for the Author):  
  
We are very interested in this manuscript as a research manuscript. However, we would request inclusion of some controls with heart failure. If not, please explain.

We thank the editors for their positive feedback and interest in our study. We have included additional controls in the revised study. To ensure the most proper controls, we chose to include patients with dilated cardiomyopathy caused by likely pathogenic/pathogenic variants in genes not expressed (based on protein expression score) in skeletal muscle tissue. These patients had variants in *RBM20*, *DSP*, and *MYBPC3*. Since our cohort of patients with TTNtv had   
  
  
Reviewer #1 (Comments for the Author):  
  
In this original manuscript by Skriver et al, the authors report a characterization of skeletal muscle structure and function in 25 individuals with TTN truncation variants I-band to M-line that cause dilated cardiomyopathy, but have not been shown to have myopathy previously. The authors have now reported on their cohort of TTNtv individuals with a range of heart failure including some status post transplantation and on a range of heart failure medications. The authors tested their hypothesis that TTNtvs could affect skeletal muscle structure and function given that individuals with muscular dystrophies harbor TTN missense variants mostly localized the m-line structural domain. The authors use MRI to quantify fat content, biopsies to quantify myopathic features including by electron microscopy for a subset of 8 individuals. Finally, muscle strength was assessed by a handheld dynamometer in a make-test. Some muscle groups could not be tested because strength values were above the limits of the assay. The major finding of the study is that TTNtv individuals have increased fat deposition in skeletal muscle, with nominal decrements in muscle strength. The potential for myopathy in TTNtv individuals is of significant clinical interest, but has not been reported previously. The study suffers from major weaknesses particularly the lack of controls including individuals with heart failure but without TTNtvs, and the lack of normal controls particularly for the muscle test portion of the study. The motor strength assay should not rely on historical controls only. Without each variable being tested in the setting of heart failure with normal TTN, the conclusions of the study may be majorly flawed and essentially unsubstantiated. Many of the reported findings could be secondary to heart failure, or other secondary factors such as medications, but independent of TTN functions. As such, the current version of the manuscript is considered to be of low to marginal value for the field.

We thank the reviewer for taking the time to review our manuscript. We agree that the design of our study has its limitations, mostly imparted by its invasive nature and the relatively rarity of the cohort. However, we still

**Reviewer #2 (Comments for the Author):**  
-Please clarify what other variant types were included, such as splice site. Were all pathogenic or likely pathogenic variants in TTN included?

Thank you for this comment. The specific variants in patients included in the project has been listed in Table 1. In total, we included one patient with a splice site variant, while all others were nonsense or frameshift variants. None of the patients were carriers of multiple pathogenic/likely pathogenic variants in *TTN*.   
  
-Given that this was a study of skeletal muscle manifestations in DCM, why were patients with myopathy excluded?

You are correct in highlighting this as counterintuitive. However we   
  
-Are CK values available on the cohort? EMG studies?

Thank you for this clarifying question. We did measure CK and myoglobin concentrations in plasma and have provided information on these in the revised manuscript. EMG studies were not performed in patients.  
  
-Would manual muscle testing be more sensitive in identifying small differences in ankle flexion and extension strength?

Manual muscle testing is not likely to identify small differences in muscle strength in persons with (relatively) normal strength. Evaluation of ankle flexion and extension using an isokinetic dynamometer, such as a Biodex system, could potentially identify small differences in strength. However, in patients, with mild (perhaps even subclinical) affection of skeletal muscle, a range of other factors (sex, age, body habitus, coordination/ability to recruit muscle fibers for a maximal effort) are likely to make the identification of these differences unlikely.  
  
-The data on fat content in muscle are interesting but authors do not speculate on the reason for this. They note similar observations in other muscular dystrophies; is this simply a nonspecific dystrophic process?

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-The authors compare the muscle biopsy findings in this cohort to those of recessive titinopathies, but dominant skeletal muscle titinopathies, such as Udd distal myopathy and HMERF may be better comparators since they share the dominant mechanism and milder skeletal muscle disease.

We thank the reviewer for this comment and have added information on the dominant titinopathies in the revised manuscript.

-In the discussion, authors note that "In dilated cardiomyopathy, allele dropout and haploinsufficiency caused by TTNtv is an accepted disease mechanism 18, 38, 39, found in 14-20% of DCM patients" but note that recent work by Linke and others suggests a dominant negative mechanism may be (also) at play.

Thank you for bringing our attention to this very interesting paper. We have revised the discussion, to reflect this finding.  
  
-In the introduction it is stated that "the presence and degree of muscle involvement in individuals with familial dilated cardiomyopathy caused by heterozygous TTNtv have not been investigated", but at least one other paper reports on the presence of skeletal muscle features in carriers of TTNtv, specifically Rich et al 2020 (DOI: 10.1002/mgg3.1460) found that 18% of of DCM patients with TTNtv or other pathogenic variants also had skeletal muscle manifestations. Authors should review this publication, which reaches similar conclusions regarding the need for multisystem evaluation of persons with TTNtv and other pathogenic variants.

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-Were the three transplanted patients on corticosteroids during this study (which are known to cause myopathy)? If so the analysis for fat content should be censored for these 3 to ensure that they were not the cause of the positive outcomes.

Thank you for this question. All three transplanted patients received corticosteroids. As suggested by the reviewer, we have performed a sensitivity analysis excluding these patients (they did not affect the results).  
  
In light of use of transplanted patients, please confirm that no other drugs known to cause myopathy were used by any of the patients used in this study.

Thank you for this comment. Supplementary table 1 contains all information on cardiac medications of the patients, included in this project.