Langmuir. 2021 Oct 7. doi: 10.1021/acs.langmuir.1c02006. Online ahead of print.

# Single-Molecule Force Spectroscopy Studies of Missense Titin Mutations That Are Likely Causing Cardiomyopathy

Jiacheng Zuo [1], Denghuang Zhan [1], Jiahao Xia [1], Hongbin Li [1]

Affiliations

PMID: 34618459 DOI: 10.1021/acs.langmuir.1c02006

## Abstract

The giant muscle protein titin plays important roles in heart function. Mutations in titin have emerged as a major cause of familial cardiomyopathy. Missense mutations have been identified in cardiomyopathy patients; however, it is challenging to distinguish disease-causing mutations from benign ones. Given the importance of titin mechanics in heart function, it is critically important to elucidate the mechano-phenotypes of cardiomyopathy-causing mutations found in the elastic I-band part of cardiac titin. Using single-molecule atomic force microscopy (AFM) and equilibrium chemical denaturation, we investigated the mechanical and thermodynamic effects of two missense mutations, R57C-I94 and S22P-I84, found in the elastic I-band part of cardiac titin that were predicted to be likely causing cardiomyopathy by bioinformatics analysis. Our AFM results showed that mutation R57C had a significant destabilization effect on the I94 module. R57C reduced the mechanical unfolding force of I94 by ~30-40 pN, accelerated the unfolding kinetics, and decelerated the folding. These effects collectively increased the unfolding propensity of I94, likely resulting in altered titin elasticity. In comparison, S22P led to only modest destabilization of I84, with a decrease in unfolding force by ~10 pN. It is unlikely that such a modest destabilization would lead to a change in titin elasticity. These results will serve as the first step toward elucidating mechano-phenotypes of cardiomyopathy-causing mutations in the elastic I-band.

## LinkOut - more resources

**Full Text Sources**

American Chemical Society

**Miscellaneous**

NCI CPTAC Assay Portal