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A TITIN-eGFP KNOCK-IN MOUSE MODEL TO STUDY CARDIAC AND SKELETAL MUSCLE DISORDERS

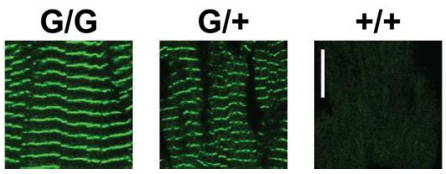
Keywords: titin, knock-in mouse, cardiac disorders, skeletal disorders

INVENTION NOVELTY

Provided is a unique fluorescence knock-in mouse model for visualization of titin during remodeling and regeneration of the myofilament structure. This titin-eGFP knock-in mouse and the independent titin-DsRed counterpart (TO 03-00495), are the only available rodent models that allow live visualization of titin dynamics and remodeling.

VALUE PROPOSITION

Titin is a giant sarcomeric protein with a size of up to 3.7 MDa. It is therefore not readily available for overexpression, gain-of-function studies, or the generation of a tagged full-length protein. Titin-eGFP mice circumvent these issues and facilitate the analysis of titin and sarcomere dynamics in development, remodeling at physiological expression levels and normal regulation.
Titin is involved in a variety of cardiac and skeletal muscle disorders such as dilated cardiomyopathy, diastolic heart failure and tibial muscular dystrophy. The animal model enables research on these diseases as well as studies on how muscles grow and rebuild in response to exercise, and on how cardiomyocytes remodel after myocardial infarction. It also allows tracking of implanted cells to monitor the efficiency of cell therapies.



The eGFP-tagged titin protein was integrated into the sarcomere as seen by confocal imaging in cardiac tissue from both hetero- and homozygotes.
Scale bar, 10 µm.

TECHNOLOGY DESCRIPTION

The targeting strategy to generate this mouse model was designed to integrate eGFP into titin's M-band exon 6 with a Neo resistance gene inserted into the 3'-untranslated region. Heart and skeletal muscle cells express titin-eGFP at physiological levels and eGFP-tagged sarcomeres assemble properly, as there was no apparent adverse phenotype in homozygous or heterozygous animals.

COMMERCIAL OPPORTUNITY

Breeder pairs are available under a Tangible Property License Agreement.

DEVELOPMENT STATUS

By crossing homozygous titin-eGFP(M) mice with the homozygous titin-DsRed(Z) mice, the double heterozygous animals with titin labeled at the Z-disk and M-band are obtained. This dual fluorescent model has allowed discriminating titin's N and C termini and has been used to study sarcomere dynamics.

PATENT SITUATION

No patent application has been filed.

FURTHER READING

Titin visualization in real time reveals an unexpected level of mobility within and between sarcomeres. J Cell Biol (2011) 193 (4): 785–798.
Resolving titin's lifecycle and the spatial organization of protein turnover in mouse cardiomyocytes. Proc. Natl. Acad. Sci. U.S.A. (2019) 116, 25126–25136.

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