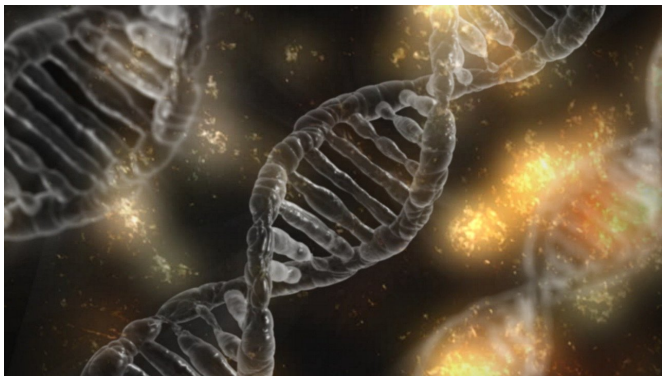
Gene therapy for gamma-sarcoglycanopathy moves toward a clinical trial

27 May 2019



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Isabelle Richard's team, a CNRS researcher in an Inserm unit at Genethon, the AFM-Telethon laboratory, has demonstrated the efficacy of gene therapy and determined the effective dose for treating a rare muscle disease, gamma-sarcoglycanopathy, in mouse models of the disease. Based on these encouraging results, published in *Molecular Therapy: Methods and Clinical Development*, the researchers are preparing a clinical trial.

Gamma-sarcoglycanopathy (LGMD2C) is one of the most common limb-girdle myopathies. It affects less than 10 people per 1,000,000 and is characterized by progressive muscle weakness in the pelvis (pelvic girdle) and shoulders (scapular girdle), linked to mutations in the SGCG gene encoding gamma-sarcoglycan. There is currently no cure for this neuromuscular disease.

In this study, Isabelle Richard's team:

- demonstrated the concept of systemic gene therapy treatment: an AAV8 drug vector expressing deficient gamma-sarcoglycan allowed the protein to be reexpressed in the treated muscle after injection in mouse models of the disease,
- determined the effective treatment dose: Three different doses were tested. The drug vector restored, with the highest dose, an almost complete expression of the deficient SGCG gene. The researchers observed that the proportion of corrected muscle fibers is less than 5% with the lowest dose, between 25% and 75% with the intermediate dose and between 75% and 100% with the highest dose (see figure)

In addition, the researchers also observed the consequences of physical exercise on muscle fibers and found that at the highest dose the treatment allows the treated muscle fibers to resist stress.

"This study is the result of several years of work. Indeed, we had already tested another vector that proved to be well tolerated but with limited gene expression. Thanks to this work, we have determined the vector and dose that would be effective in patients and today we have the means to work on a clinical trial," enthuses Isabelle Richard, lead author of the work.

In 2006, a first phase I gene therapy clinical trial, lead by Genethon, tested the efficacy of an AAV1 vector injected intramuscularly in nine patients. One month after injection, the researchers found that the product was well tolerated and that the therapeutic gene was present in patients treated at the highest dose but in limited quantities (Results published in *Brain*, January 11, 2012).

More information: David Israeli et al, A dose response study in ?–sarcoglycanopathy mouse model in the context of mechanical stress, *Molecular Therapy - Methods & Clinical Development* (2019). DOI: 10.1016/j.omtm.2019.04.007

Provided by AFM-Téléthon