

Advanced stem cell models of a severe childhood muscle disease help test gene therapies

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What is LMNA-related congenital muscular dystrophy (L-CMD)?

LMNA-related congenital muscular dystrophy (L-CMD) is one of the most severe forms of muscular dystrophy in children. It's caused by changes (mutations) in a gene called LMNA, which provides the instructions for making proteins known as Lamin A and C. These proteins help support and protect the cell's nucleus, the control centre of the cell, and play an important role in regulating how cells function. Babies with L-CMD develop severe muscle weakness very early in life, often can't hold up their head ("dropped head syndrome"), and many don't survive past childhood because the heart and breathing muscles fail. There is currently no cure, which is exactly why building better research tools, like the one in this study, matters so much.

What did the researchers do?

The standout achievement of this study is the creation of a realistic 3D model of L-CMD, using human muscle tissue grown in the laboratory. Until now, researchers have lacked a reliable way to study this condition in human muscle. Using stem cells (iPSCs) derived from patients, or genetically altered to carry the same disease-causing changes, the team grew realistic, engineered muscle tissue that goes far beyond flat dishes of cells and mirrors the architecture of real muscle.

This 3D model reproduced many of the key features seen in people with L-CMD. This showed that the model accurately reflects what happens in affected muscle and provides researchers with a powerful new tool for studying the condition.

This is a significant advance in itself because L-CMD research has often relied on mouse models, cell lines, or scarce patient biopsies that don't fully capture human muscle biology. Having a robust, human, tissue-like system that recreates the disease so faithfully opens the door to far more meaningful preclinical research.

Encouragingly, the team also found that muscle cells carrying the L-CMD mutations formed normally at first, with no obvious defect in early muscle development. This suggests that the disease process may begin later, after muscle cells have formed. This finding could help researchers identify the best time to intervene with future treatments, with the aim of slowing, preventing or reversing disease progression.

What did the research show?

The researchers found that muscle cells carrying the L-CMD gene changes formed normally at first, and didn't struggle to become muscle cells in the lab. This suggests the disease may take hold after muscle cells have formed, rather than preventing muscle from developing in the first place.

However, once formed, these muscle cells showed the classic hallmarks of the disease. These problems were most severe in cells carrying the most damaging genetic changes (the more severe mutations).

The team then tested two different gene-editing strategies (both using CRISPR, a “molecular scissors” tool for editing DNA) to try to fix the problem:

- Cutting out the faulty piece of the gene (removing exon 5, similar to “exon skipping” approaches used in other muscle diseases) – this let cells make Lamin protein again, but it didn’t fix the abnormal nuclear shape or calm down the inflammatory gene signature.
- Precisely correcting the exact mutation back to the healthy DNA sequence – this worked much better: nuclear shape returned to near-normal, DNA damage was reduced, and the harmful inflammatory gene activity was calmed.

Putting the model to work: testing gene therapies

With this validated 3D model in hand, the researchers used it to directly compare two CRISPR-based gene-editing strategies for correcting the LMNA mutation:

- Removing the faulty section of the gene (exon removal) – this restored Lamin protein production, an encouraging proof that the editing approach can work at the molecular level.
- Precisely correcting the mutation back to the healthy DNA sequence – the researchers went a step further, restoring normal nuclear shape, reducing DNA damage, and calming the disease-associated inflammatory gene signature, bringing cells close to a healthy state.

A major strength of this study is that it demonstrates how a realistic, human 3D muscle model can be used to directly compare different treatment approaches. By showing that precise correction of the mutation produced better results than removing part of the gene, the researchers have identified a particularly promising strategy for future therapy development. This type of testing platform could help accelerate the search for effective treatments for L-CMD and other rare muscle diseases.

Why it matters

This study provides two important advances for the L-CMD and broader laminopathy research community. First, it has created a realistic 3D model of human muscle that accurately recreates many of the key features of the disease. Second, it provides early evidence that precisely correcting the disease-causing genetic change can restore healthy cell behaviour. Together, these achievements give researchers a powerful new tool for studying L-CMD and testing potential treatments. The model can be used to evaluate and improve future gene-editing approaches before they are considered for clinical trials, helping researchers identify the most promising and safest strategies.

While more research is still needed, these findings represent an encouraging step towards the development of effective genetic treatments for this devastating childhood muscle disease.