Telomere shortening affects muscular dystrophy gene

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(Medical Xpress)—Facioscapulohumeral muscular dystrophy (FSHD) is a genetic disorder that causes the muscles of the upper body to waste away. It is unusual in that symptoms do not usually appear until sufferers are in their teens or early 20s, although similar disorders begin to affect victims in early childhood. Moreover, while about one percent of people carry the mutations that cause FSHD, only 1 in 20,000 actually develop the disease. In a study published in *Nature Structural & Molecular Biology*, Woodring Wright of the University of Texas Southwestern Medical Center in Dallas and his team report that telomere shortening, which is associated with age, causes increased expression of the gene associated with FSHD. This could explain why the disease has such a late onset and why so many people with the associated mutations never develop it.

Telomeres are protective DNA sequences at the ends of chromosomes. Normally, genes that are near telomeres are not active. Telomeres shorten with age, and this shortening affects the expression of nearby genes, a phenomenon known as telomere position effect (TPE).

Because DUX4, the gene that is responsible for FSHD, is located next to a telomere, it is normally inactive. To study the effects of telomere shortening on DUX4 expression, Wright and his colleagues cloned muscle precursor cells from people with FSHD and from their siblings, who did not have the disease. The cloned cells had telomeres of different lengths.

The researchers found that expression of DUX4 increased dramatically as telomere length decreased. DUX4 became more than 10 times more active in cells with shortened telomeres.

These results suggest that people with long telomeres or telomeres that shorten slowly may never develop FSHD, despite harboring the disease-causing mutations. Telomere shortening could also explain the disease's late onset. Wright and his team are planning further studies focusing on the relationship between telomere length and FSHD onset and progression.

While DUX4 is close to its telomere, only 25-60 kilobases away, the researchers found that telomere length also affects the expression of a gene known as FRG2, which is as far as 100 kilobases from a telomere.

This indicates that TPE can affect many genes, and telomere length can provide clues about the onset and progression of a number of different age-related inherited diseases.

In the future, doctors could consider telomere length when diagnosing and advising about such diseases. Telomere lengthening could be a way of preventing these diseases from manifesting or of keeping them under control.

More information: Telomere position effect regulates DUX4 in human facioscapulohumeral muscular dystrophy, *Nature Structural & Molecular Biology* (2013) doi:10.1038/nsmb.2571

Abstract

Telomeres may regulate human disease by at least two independent mechanisms. First, replicative senescence occurs once short telomeres generate DNA-damage signals that produce a barrier to tumor progression. Second, telomere position effects (TPE) could change gene expression at intermediate telomere lengths in cultured human cells. Here we report that telomere length may contribute to the pathogenesis of facioscapulohumeral muscular dystrophy (FSHD). FSHD is a late-onset disease genetically residing only 25–60 kilobases from the end of chromosome 4q. We used a floxable telomerase to generate isogenic clones with different telomere lengths from affected patients and their unaffected siblings. DUX4, the primary candidate for FSHD

pathogenesis, is upregulated over ten-fold in FSHD myoblasts and myotubes with short telomeres, and its expression is inversely proportional to telomere length. FSHD may be the first known human disease in which TPE contributes to age-related phenotype.