Press Release

SAN RAFFAELE / TELETHON – FSHD MUSCULAR DYSTROPHY

Study published in *Cell* discovers

**new mechanism of disease and potential therapeutic target.**

Milan, May 7, 2012 - A new defect in gene regulation, never before seen in a human disease is the cause of one of the most common forms of muscular dystrophy: Facio-Scapulo-Humeral muscular dystrophy (FSHD). Describe this, in paper published in the journal *Cell*, is Davide Gabellini, a researcher of the Dulbecco Telethon Institute at the IRCCS San Raffaele Hospital in Milan, Italy where he Direct the Gene Expression and Muscular Dystrophy Unit. The discovery gives hope to people affected by the disease and may help explain other enigmatic diseases, including some forms of diabetes or cancer.

For **at least 500,000 people around the world**, FSHD causes progressive loss of facial muscles, shoulders and upper arms, making it difficult to walk, lift the arms or even smile. For years, the mechanism underlying the disease has eluded scientists, but this study sheds light describing an entirely new, complex mechanism: FSHD occurs because a non-coding RNA allows neighbors genes to become hyperactive.

In 1992, the cause of FSHD had been traced to the deletion in a region of chromosome 4 which consists of repeating units of DNA called D4Z4. At that time, many scientists had assumed that the FSHD would follow the classic mechanism of other genetic diseases: mutation of a gene within the D4Z4 with loss of its ability to produce a protein. Subsequent research, conducted when Davide Gabellini was in the U.S., however, have found the opposite: FSHD is not caused by the loss of a protein, but by an excess of protein production. The next step was to understand how D4Z4 is able to regulate protein production from the FSHD region. With the new study, the group directed by Gabellini has shown that the loss of repeated sequences D4Z4 allows the production of a new non-coding RNA, that researchers have called DBE-T. It is DBE-T to be directly responsible for the activation of the expression of genes in the region FSHD and therefore of the increased protein production.

"The mechanism we described is new and represents an interesting model to address other complex diseases in which the classical candidate gene approach has not been successful," says Davide Gabellini.

Examining muscle biopsies, Gabellini and his colleagues Daphne Cabianca and Valentina Casa have found that DBE-T is produced exclusively in FSHD patients, but not in healthy subjects. They also demonstrated experimentally that, by blocking the production of DBE-
T, one obtains a normalization of gene expression in the region FSHD: this suggests that DBE-T may be a valid therapeutic target for disease control.

The repetitive DNA sequences (regions repeated thousands of times in our genome and that, not coding for proteins, are the mostly ignored) represent over 50% of human genetic material.

"There is a good chance that alterations in other repetitive sequences in our genome are responsible for bad gene regulation in other diseases," said Gabellini. For example, regions of DNA are repeated near the insulin gene and their alteration may predispose to diabetes.

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A Long ncRNA Links Copy Number Variation to a Polycomb/Trithorax Epigenetic Switch in FSHD Muscular Dystrophy, April 26 2012, Cell

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