# Trembling hands and molecular handshakes

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The heritable Fragile X tremor/ataxia syndrome is a common neurodegenerative disease. It is assumed to result from a relative lack of the protein Pur-alpha. A new study by a German team under the leadership of Dr. Dierk Niessing of the Helmholtz Zentrum Munchen and the Gene Center at Ludwigs-Maximilians-Universitaet in Munich provides important insights into the structure and function of this protein, which may lead to the development of a therapy.

The Fragile X tremor/ataxia syndrome (FXTAS) is a recently recognized condition, which is actually one of the most prevalent heritable neurodegenerative diseases. It is assumed that the condition is caused by deficiency for the protein Pur-alpha, which is essential for normal neural function. Structural studies undertaken by a team under the leadership of Dr. Dierk Niessing of the Helmholtz Zentrum München and the Gene Center at Ludwigs-Maximilians-University (LMU) have now determined the three-dimensional structure of Pur-alpha, and gained insights into the molecular function of the protein. The findings provide a possible basis for the development of an effective therapy for the disease.(*PNAS Early Edition*, 21 Oktober 2009)

Most FXTAS patients are males, and symptoms of the condition become manifest around the age of 55. As the disease progresses, patients develop tremor in their hands and also show ataxia, i.e. they have difficulty maintaining their balance when they move, and therefore have a tendency to fall. Quite often these deficits are accompanied by cognitive defects and dementia.

The underlying cause of FXTAS is a mutation in the gene for FMRP (Fragile X Mental Retardation Protein). This mutation is found on the X chromosome in one out of 800 men, and involves abnormal expansions of a DNA sequence composed of repeats of the base triplet CGG. Healthy people have between 5 and 54 copies of this sequence, while those who will develop FXTAS are born with between 55 and 200 repeats. Expansion of the triplet sequence beyond 200 copies leads to Fragile X Syndrome (FXS), which is the second most common cause of hereditary mental retardation after Down's syndrome. FXTAS itself is apparently triggered by a lack of the protein Pur-alpha. This protein binds to the CGG sequences in FMR messenger RNAs (mRNA). The excessive numbers of CGG triplets found in the mutant FMRP mRNA essentially bind so much Pur-alpha that insufficient amounts are available for its normal cellular function.

Dr. Niessing's team reports in the online Early Edition of the journal *Proceedings of the National Academy of Sciences USA (PNAS)* that the Pur-alpha protein itself consists of three copies of a structural unit called the PUR repeat. "The crystal structure of Pur-alpha will make it possible to understand the protein's function in detail, and this could contribute to the development of a therapy for FXTAS", says Dierk Niessing, who leads a junior research group that is jointly funded by the Helmholtz Zentrum München, the Helmholtz Association and LMU's Gene Center. "With the treatment options we have at the moment, we can only alleviate the symptoms but cannot attack the real cause of the disease."

"A PUR repeat looks like a hand: four so-called beta-strands, corresponding to four fingers, form a beta-sheet, and an adjacent alpha-helix resembles a thumb", explains Almut Graebsch, the first author from Niessing's group. Pairs of PUR repeats bind to each other in a particular configuration that is reminiscent of a handshake, forming a functional unit. In addition to X-ray diffraction, the researchers have used a technique called small angle X-ray scattering, which revealed that

the Pur-alpha protein forms dimers - two molecules of the protein bind stably to one another. This probably occurs when PUR repeats in separate molecules interact, in a similar way to the repeats within a molecule, to form the handshake structure.

Experiments in animals have shown that the symptoms of FXTAS disappear if extra Pur-alpha is supplied. "Perhaps the condition can be cured if one can find a way of stopping Pur-alpha from binding to long stretches of CGG in mRNA", says Niessing. By mutating the protein, his group has already obtained clues to how Pur-alpha binds to the CGG repeats. The next step is to find out precisely how Pur-alpha binds to RNA. This in turn could suggest ways of preventing the interactions that cause the disease. (HHZM)

More information: "X-ray structure of Pur-alpha reveals a Whirly-like fold and an unusual nucleic-acid binding surface" Almut Graebsch, Stephane Roche, and Dierk Niessing. *PNAS* online, 21 October 2009

Source: Ludwig-Maximilians-Universität München