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A WINDOW OF AN OPPORTUNITY: REVERSING FRIEDREICH'S ATAXIA

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For the first time ever since its discovery in the 1860s, by Nicholaus Friedreich, a German doctor, there's a potential cure for Friedreich's ataxia (FA). Also called FA or FRDA, it is a disease that causes nervous system damage and movement problems as a result of an inherited, aberrant gene. It usually begins in childhood and leads to impaired muscle coordination (ataxia) that worsens over time.

Now, researchers have found a way to reverse the disease (in cell lines in the lab) using a synthesised molecule which can locate the defective gene and, akin to a prosthetic arm in an amputee, compensate for it.

The India link

The result has made been made possible after nearly two decades of research by a group led by Dr. Aseem Ansari, a scientist based at the University of Wisconsin, Madison, U.S. Scientists from the Delhi-based CSIR-Institute of Genomics and Integrative Biology (IGIB) contributed to the research by testing the efficacy of the molecule in blood cells drawn from a dozen FA patients at the All India Institute of Medical Sciences (AIIMS), Delhi.

"Friedreich's ataxia is present mainly in patients of [an] Indo-European background and absent in people from Africa, China and Japan, for instance. It has been estimated that among Europeans, its prevalence is about 3-4 out of 100,000 people," says Dr. Mohammed Faruq, Senior Scientist from the IGIB who led the Indian group at the IGIB and a co-author of the paper published in *Science* . He adds, "In India we lack statistical estimates of the disease as we do not have a nationwide uniform patient registry. However, it has been noted that approximately 200 families with FA were identified at AIIMS, Delhi, and many others at NIMHANS, Bengaluru."

The disease is more likely when both parents carry defective versions of the gene, and is independent of the child's gender. Symptoms surface around 10-14 years of age; sometimes even earlier. These include a difficulty in walking, slurring of speech, loss of balance and falls due to a loss of muscular co-ordination. In people with this condition, there is a progressive degeneration of nerves of the spinal cord and cerebellum, the part of the brain that controls movement and balance. The disease also affects the heart muscles and some of those affected develop diabetes. This can lead to cardiomyopathy, leading to heart failure.

So far there is no cure, and treatment mainly consists of doctors prescribing medication to tackle the ensuing diabetes or heart conditions and providing braces to support problems of gait, etc.

The genetic origin

Genes, as we know, code for proteins that are responsible for making the cell perform various functions. The FXN gene on chromosome 9, identified in 1996, codes for the protein frataxin. Now, genes are built up by a definite DNA sequence of the four bases A, G, C and T. If the FXN gene is normal, it contains a sequence "GAA" repeated some 7-22 times. In a defective FXN gene, this sequence is repeated hundreds or even thousands of times. This triple-repeat

expansion directly affects the production of a protein called frataxin that is found in the mitochondria of the cell. The mitochondria are also known as the power houses of the cell, and when they become deficient in frataxin, some cells, especially those governing the development of the peripheral nerves, spinal cord, brain and heart muscle cells are affected.

For nearly two decades, Dr. Ansari has been working on targeting genome sites using synthetic genome readers, which are molecules that can read and locate specific sequences in the genome. These molecules seek out specific DNA sequences. In this case, it is the many-times-repeated GAA sequence in the FXN gene. In an e-mail, Dr. Ansari describes this: “The major breakthrough came in 2014 when we developed a ‘COSMIC-seq’ approach that pinpointed the location of our GAA-targeting molecule across the genome from human stem cells.” This is only part of the molecule’s action — that of identifying the location where to bind.

Once it became clear how to bind the molecule, it was easy to design the second half of the molecule. This would engage the cellular machinery needed to help synthesise a copy of the gene and have it translated to the missing protein.

This molecule is a potential future drug and while other methods have been tried, this is the first time such an effective method has been proposed.

Dr. Ansari says that discussions are on with the IGIB, the Indian Council of Medical Research and the Department of Biotechnology to establish a national Friedreich’s ataxia registry that meets international standards.

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