MedicalXpress

Mayo Clinic discovers mutation causing protein misfolding remission

May 11 2010

Light chain amyloidosis, a deadly protein misfolding disease, is caused by multiple mutations in cells that are intended to protect the body. Instead, the mutations send misfolded bundles of proteins through the bloodstream, potentially destroying the heart, kidneys, liver or other organs. Mayo Clinic researchers have identified one of these mutations and have shown that the molecule's shifting position is as important as its unique shape. The findings appear in the current issue of the journal *Structure*.

"This is a condition that often is misdiagnosed because it could appear as many other common conditions and can affect different organs," says Marina Ramirez-Alvarado, Ph.D., Mayo Clinic biochemist and senior author of the study. "It can be initially identified by a simple blood test and a fat aspirate analysis. After that, we can only treat symptoms as there is currently no cure."

About 2,000 patients are diagnosed with amyloidosis annually in the United States. Survival after diagnosis averages about three years. Immunoglobulin molecules made in cells from the bone marrow are subject to mutations that can cause the proteins to misfold. In essence, what should be a set configuration of amino acids becomes chaotic, appearing in models as a twisted ball of "spaghetti" that then accumulates more fibrous threads called fibrils. These misfolded proteins travel in the bloodstream accumulating fibrils that clog osmotic and other filtering processes in the liver, kidneys and heart, ultimately causing other organ-based diseases.

Mayo researchers studied light chains that normally are made in plasma B cells as part of the protective immune mechanism, found in bone marrow. Through a combination of crystallography, nuclear magnetic resonance spectroscopy, and bioinformatics, they were able to determine the surface shape of the molecule involved with one mutation and also deduce that it was constantly shifting its position, from 90 degrees to 180 degrees off the normal position of the comparable functional protein.

Because of the realignment, the protective nature of the molecule is lost and its new molecular contacts promote amyloid formation. This process is what happens in 85 percent of amyloidosis patients. In this specific case, the researchers were able to identify that the mutation called the Tyr-to-His substitution in the reconfiguration at position 87 on the protein was the alteration that promoted fibril development. Researchers say that while this is just one of many possible mutations, it is a beginning towards identifying targets for future drug development in a condition that is otherwise fatal.

Provided by Mayo Clinic