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Shape-shifting mutants: one rare nucleotide change causes alpha 1-antitrypsin deficiency

Scientists from Daegu University identify how a rare mutation affects the structure of alpha 1 antitrypsin, linked to various lung and liver diseases.

(Tokyo, XX Month)

Low alpha 1-antitrypsin (A1AT) levels are linked to serious lung and liver diseases, including liver cirrhosis and asthma. Although scientists think that mutations in the gene coding for A1AT are responsible for the deficiency, it is not clear exactly how. Now, a new article by Dr. Hong-Nhung Trinh and colleagues from Daegu University, published in *Molecular Genetics and Genome Medicine*, elucidates this question. These researchers explore the structure and properties of one specific mutation, "F51S" to see if its differences from the normal gene cause A1AT deficiency.

A1AT is the most common serine protease inhibitor in human blood, meaning its job is to stop a group of enzymes (serine proteases) from breaking down other proteins. When defective A1AT is produced because of genetic mutations, the liver cannot properly release the protein into the bloodstream, leading to an A1AT-deficient condition. As a result, lung damage occurs due to build-up of other proteins A1AT is supposed to break down, and because defective A1AT remains in the liver, that accumulation also causes liver problems. Scientists have identified hundreds of mutations that affect A1AT levels. However, Dr. Trinh explains, "Only a few of these mutations have been fully explored to pinpoint whether they decrease A1AT through affecting the secretion process, or if they actually affect A1AT's ability to inhibit enzymes. This lack of understanding means it is difficult to perform targeted therapies that can fix the different causes of the same symptom, which is A1AT deficiency." The F51S mutation examined by Dr. Trinh and colleagues changes the make-up of A1AT, adding a new region for interacting with other proteins. The scientists hypothesized that this addition could make the protein more sensitive to heat and less stable.

Dr. Trinh and colleagues produced the F51S mutant protein and normal A1AT in hamster cells (widely used in scientific research for generating proteins). Through a series of experiments, scientists found that the F51S mutant could inhibit the serine protease trypsin like normal A1AT could, but had lower thermal stability, meaning that the protein lost its shape and became more flexible at higher temperatures. The latter characteristic appeared to significantly reduce secretion levels (in other words, the F51S mutant protein mostly remained inside hamster cells while the wild-type A1AT found its way into the surrounding culture medium). Interestingly, this increased flexibility also prevented protein polymerization, meaning that the F51S mutant remained mostly as monomers instead of forming dimers and trimers.

When A1AT polymerization increases, the protein's concentrations decrease. However, A1AT polymerization has actually been linked to liver disease and is mechanistically similar to Alzheimer's. Thus, researchers believe that identifying a mutation stopping A1AT polymerization is potentially useful for treating patients. Obviously, any attempts to harness the decreased polymerization potential of F51S for therapy would also have to account for the corresponding risks of A1AT deficiency.

Nevertheless, Dr. Trinh feels that their work provides important empirical evidence showing some of the mechanisms that cause the F51S mutation to result in A1AT deficiency, opening the door for research that can then focus on validating the findings clinically. "Not only that," Dr. Trinh states, "but a lot of research has shown that rare SNPs may actually be more important for predicting the risk of some common diseases. But by dint of being rare, they are hard to study traditionally without using millions of people. Here, the biochemical methods we used, like gel electrophoresis to check polymerization, allowed us to examine the effects of a rare allele in a cost-effective and less effort-intensive way. With careful development, our approach could help doctors identify at-risk patients through the presence of a rare mutation."

Reference

Authors:	Hong-Nhung Trinh, Sei-Heon Jang, and ChangWoo Lee
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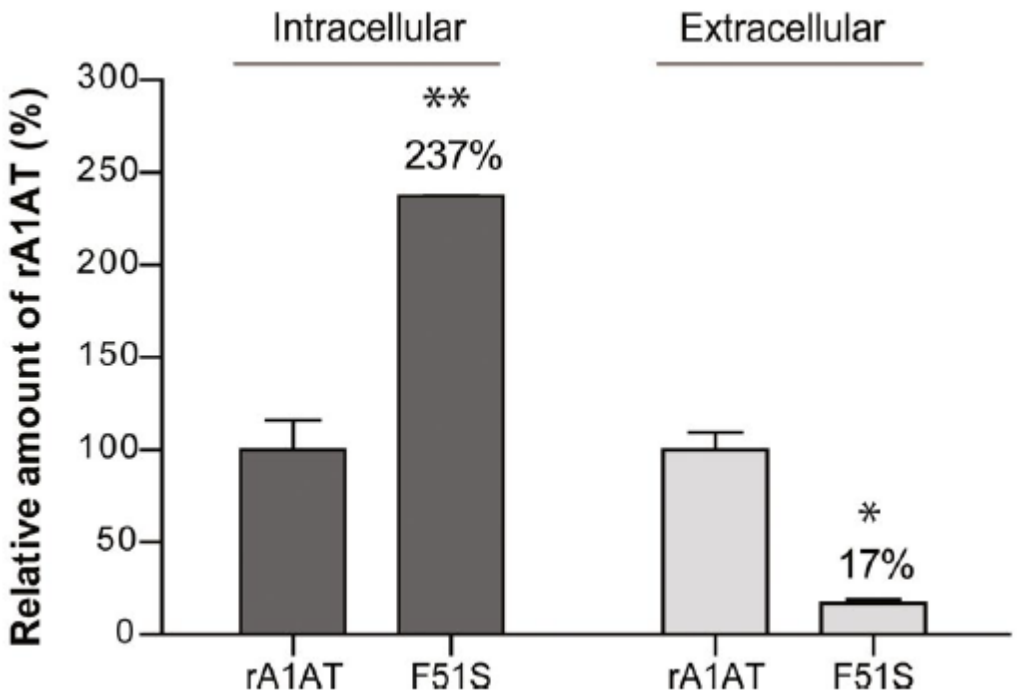

Figure 1. Protein secretion

Wild-type A1AT was secreted by cells into the surroundings, whereas F51S mutant remained inside cells.

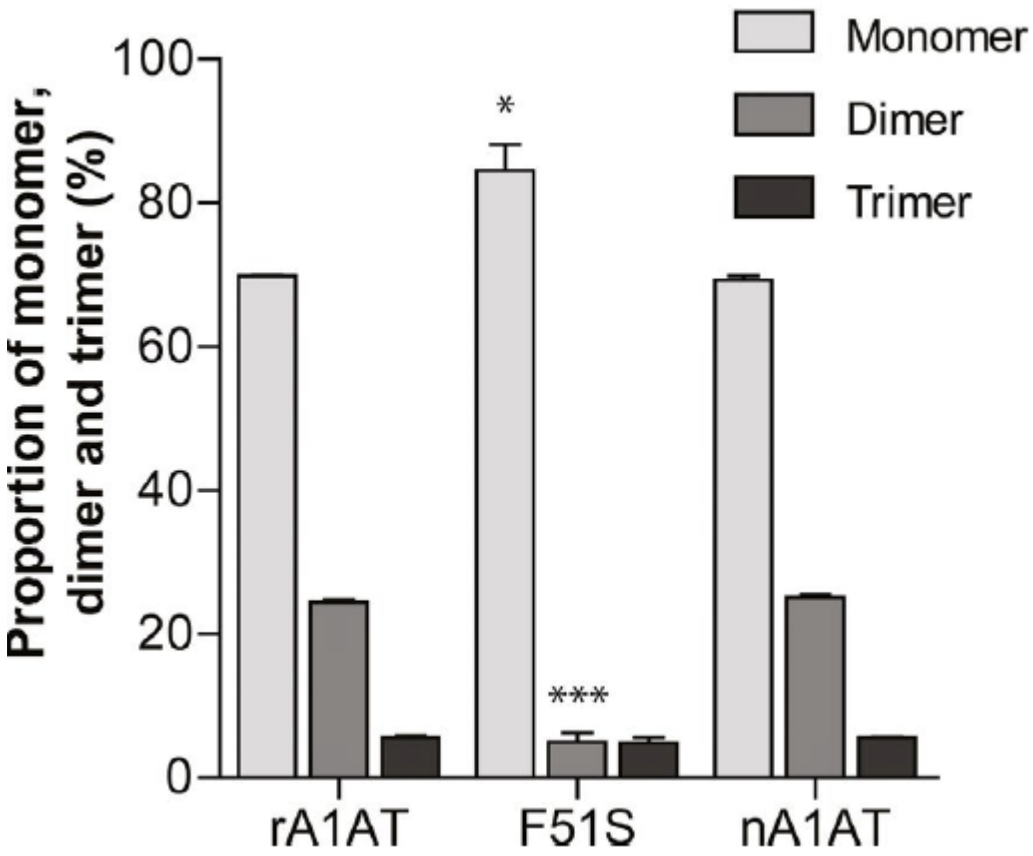

Figure 2. Protein polymerization

Wild-type A1AT formed significantly more dimers and trimers than the F51S protein.