

## **Protein's well-known cousin sheds light on its gout-linked relative**

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Johns Hopkins scientists have found out how a gout-linked genetic mutation contributes to the disease: by causing a breakdown in a cellular pump that clears an acidic waste product from the bloodstream. By comparing this protein pump to a related protein involved in cystic fibrosis, the researchers also identified a compound that partially repairs the pump in laboratory tests.

The mutation in question, known as Q141K, results from the simple exchange of one amino acid for another, but it prevents the protein ABCG2 from pumping uric acid waste out of the bloodstream and into urine. A buildup of uric acid in the blood can lead to its crystallization in joints, especially in the foot, causing excruciatingly painful gout.

"The protein where the mutation occurs, ABCG2, is best known for its counterproductive activity in <u>breast cancer patients</u>, where it pumps anti-<u>cancer drugs</u> out of the <u>tumor cells</u> we are trying to kill," says William Guggino, Ph.D., professor and director of the Department of Physiology at the Johns Hopkins University School of Medicine. "In kidney cells, though, ABCG2 is crucial for getting uric acid out of the body. What we figured out is exactly how a gout-causing genetic mutation inhibits ABCG2 function."

A description of the work with Q141K's effects at the <u>cellular level</u> were published online March 14 in the *Proceedings of the National Academy of Sciences*.



Gout affects 2 to 3 percent of Americans, approximately 6 million people. It usually involves sudden attacks of severe pain, often in the joint at the base of the big toe and frequently in the wee hours of the morning, when body temperature is lowest. It has been nicknamed the "disease of kings," because it usually results from high-purine diets, food that only kings and other noblemen could afford in large quantities in bygone years: red meat, organ meats, oily fishes and some vegetables like asparagus and mushrooms.

While most gout can be remedied by <u>dietary changes</u>, about 10 percent of Caucasians get the disorder because their ABCG2 protein contains the Q141K mutation. This number is lower (around 3 percent) for African-Americans and much higher (31 percent) for Asians.

Guggino notes that the ABCG2 Q141K mutation was first connected with gout in 2008 through a large genomic study directed, in part, by Josef Coresh, M.D., a biostatistician and epidemiologist at the Johns Hopkins University School of Public Health. At the time, Guggino's laboratory was studying a protein frequently found mutated in cystic fibrosis patients: cystic fibrosis transmembrane conductance regulator, or CFTR. The structure of ABCG2 is quite similar to CFTR's, so Coresh suggested that Guggino's team apply their knowledge of CFTR to characterize ABCG2.

The team first genetically engineered several standard mammalian cell types to make regular or mutant versions of ABCG2. Cells with the mutated ABCG2 gene contained much less of the ABCG2 protein than cells making the regular form. Additionally, the researchers found that the mutation made it difficult for ABCG2 molecules to get to their proper place on the cell surface. Since ABCG2 pumps molecules from the inside of the cell to the outside, it is not functional anywhere but the cell surface.



The team then lowered the temperature at which the ABCG2-making cells were growing, and found more mutant ABCG2 at the cell surface. Guggino says this finding suggested that the lower temperature had stabilized ABCG2 and helped it achieve its proper 3-D conformation, because proteins that don't assume the right shape are likely to be broken into pieces for reuse, preventing them from reaching their final destinations.

When ABCG2 and CFTR are lined up, their structures are very similar. In fact, one of the most common <u>cystic fibrosis</u> mutations, a CFTR deletion of amino acid F508, lines up next to the Q141K mutation in ABCG2 and causes similar results in the protein's location and processing.

Knowing that the F508 deletion in CFTR creates instability in a certain part of the protein, the researchers introduced additional mutations intended to stabilize the wobbly region of the Q141K mutant ABCG2. As predicted, they found that this stabilization increased the amount of ABCG2 on the cell surface, suggesting again that ABCG2 had been saved from the recycling bin.

To confirm the involvement of the recycling process, the team fed the cells several small molecules known to help malformed proteins avoid degradation. One molecule, VRT-325, partially restores CFTR's activity. The same molecule was also able to increase the amount of mutant ABCG2 found in the cells and on their surfaces, and to decrease the amount of <u>uric acid</u> in the cells, bringing it within the normal range.

"Though there are many more lab tests needed before clinical trials can even be designed, our results represent an important step forward in both understanding how gout results from this mutation and finding a treatment," says Guggino.



## Provided by Johns Hopkins University School of Medicine

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