Cystic fibrosis study offers new understanding of silent changes in genes

May 17 2017

Credit: University of Bristol

Researchers studying the root cause of cystic fibrosis have made a major advance in our understanding of silent gene changes with implications for the complexity of cystic fibrosis. The findings are published today in [16 May] *PLoS Biology*.

Cystic fibrosis is a common life-shortening inherited disease that affects over 70,000 people worldwide, the majority of whom are children and young adults. Individuals living with cystic fibrosis carry faults in a single gene that disables or destroys a protein called CFTR (cystic fibrosis transmembrane conductance regulator). CFTR plays a crucial

role in cells by forming a gated pathway for chloride ions, one part of salt, to stream across cell membranes. However, loss of CFTR leads to ducts and tubes in the body becoming blocked by thick, sticky mucus, causing breathing difficulties in the lungs and problems digesting and absorbing food in the gut.

Since 1989, when CFTR was first identified more than 2,000 changes have been reported in its gene; 1,700 of these changes lead to cystic fibrosis. Among the remaining 300 replacements are a group of silent changes, so called because they alter the gene without changing the composition of the CFTR protein. Such silent changes have long been considered without effect on how proteins are made and how they work in cells.

The team led by Professor Zoya Ignatova from the University of Hamburg and Professor David Sheppard at the University of Bristol, working with colleagues in the Netherlands (Professor Ineke Braakman, Utrecht University) and the USA (Dr Lynda Ostedgaard, University of Iowa), have investigated the impact on the CFTR protein of a silent change in its gene called T2562G.

T2562G changes how the CFTR protein is made by cells. At the University of Bristol, Dr Zhiwei Cai discovered that T2562G causes the CFTR pathway for chloride ions to become narrowed, slowing chloride movement across cell membranes. At the University of Hamburg, Dr-Sebastian Kirchner and Robert Rauscher found that the change in how CFTR is made is the result of how the cell reads genetic information. T2562G causes protein producing machines called ribosomes to slow down the speed with which CFTR is made, resulting in an altered protein with impaired chloride transport. This finding reveals a new unexpected way by which silent changes in genes alter how proteins are made and how they work in cells.

The findings, published in *PLoS Biology*, provide new understanding of the impact of silent changes in genes and highlight the genetic complexity of cystic fibrosis which in turn affects disease severity and an individual's response to treatments targeting the root cause of cystic fibrosis.

More information: Sebastian Kirchner et al. Alteration of protein function by a silent polymorphism linked to tRNA abundance, *PLOS Biology* (2017). DOI: 10.1371/journal.pbio.2000779