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Genetic disease which causes recurrent respiratory infections discovered

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Cambridge scientists have discovered a rare genetic disease which predisposes patients to severe respiratory infections and lung damage. Because the scientists also identified how the genetic mutation affects the immune system, they are hopeful that new drugs that are currently undergoing clinical trials to treat leukaemia may also be effective in helping individuals with this debilitating disease.

For the study, led by the University of Cambridge in collaboration with the Babraham Institute and the MRC Laboratory for Molecular Biology, the researchers first examined genetic information from individuals who suffer from immunodeficiency and are predisposed to infections. From this group, the scientists identified a unique genetic mutation in 17 patients that suffer from severe respiratory infections and rapidly develop lung damage.

The researchers, who were primarily funded by the Wellcome Trust, MRC, BBSRC and the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre, found that the mutation increases activity of an enzyme called Phosphoinositide 3-Kinase δ (PI3Kδ). The enzyme is present in immune cells and regulates their function. However, constantly activated PI3Kδ impairs work of these immune cells, preventing them from responding efficiently to infection and providing long-lasting protection. Consequently, patients with this mutation have severe and recurrent infections.

"Patients with this mutation have a defect in the immune cells, so their

protection from infections is weak and inefficient," said Sergey Nejentsev, Wellcome Trust Senior Research Fellow from the University of Cambridge who led the research. "We called this newly identified disease Activated PI3K- δ Syndrome (APDS) after the enzyme in the immune system that is affected by the genetic mutation."

The researchers believe that it may be possible to treat APDS in future. There are currently drugs in clinical trials for leukaemia that were designed specifically to inhibit the PI3Kδ enzyme. The researchers have already shown that these drugs reduce activity of the mutant protein.

Alison Condliffe, joint senior author on the paper from the University of Cambridge, said: "We are very excited by the prospect of using these drugs to help patients with APDS. We believe that they may be able to restore functions of immune cells, thereby reducing infections and preventing lung damage."

Although the prevalence of the disease is not yet known, the scientists believe that it is relatively frequent compared to other immunodeficiencies and may underpin immunodeficiencies and chronic lung disorders in a substantial fraction of patients.

"It is very important that doctors consider a possibility of APDS in their patients," said Dr Nejentsev. "A simple genetic test can tell if the patient has the mutation or not. We believe that now many more APDS patients will be identified all over the world."

More information: 'Phosphoinositide 3-Kinase δ Gene Mutation Predisposes to Respiratory Infection and Airway Damage' *Science Express*, 2013.