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Major step towards personalised medicine against hereditary autoimmune deficiency

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Researchers at Karolinska Institutet in Sweden have found a method to repair the gene mutation causing agammaglobulinemia, an autoimmune deficiency disease that almost exclusively affects boys and in which the body lacks the ability to produce immunoglobulins (gamma globulin). The disease is characterised by recurring bacterial infections, mainly in the respiratory system, and persons who suffer from the illness currently need life-long gamma globulin treatment.

"Although there is a lot of research left to be done, the findings indicate that we may be able to treat some patients in the future," says Edvard Smith, Professor at the Department of Laboratory Medicine at Karolinska Institutet and one of the researchers behind the study that is presented in the *Journal of Clinical Investigation*.

Agammaglobulinemia is a rare, hereditary disease that is caused by a mutation which results in a lack of the enzyme BTK. BTK plays an important role in the signalling of white blood cells and thus in developing and maintaining an effective autoimmune system. In the new study, the researchers show that it is possible to repair faulty RNA and recreate BTK in lymphocytes, white blood cells. The new study emanates from the same research group at Karolinska Institutet that previously identified the predisposition for sex-linked agammaglobulinemia (XLA).

It is previously known that synthetic building blocks in our genetic make-up (known as oligonucleotides) can modify the RNA and recreate

truncated forms of the protein that is missing in severe muscular dystrophy. The new study shows that it is possible to experimentally correct the defect and recreate an intact BTZ enzyme for a Swedish family with XLA. The therapy has been customised for this particular mutation and is thereby a genuine example of "personalised medicine". The researchers utilised molecular biological methods and created a mouse which carries the gene in question. The mice also lacked enzymes of their own, as their genes were inactivated.

"We have been able to show how synthetic oligonucleotides can correct RNA both in patient cells in a test tube, and in living animals," says Edvard Smith.

The number of new cases of agammaglobulinemia is estimated at 6 in one million births, which means that there is roughly one boy born with the disease in Sweden every other year. BTK has received renewed attention as it has been discovered that the protein also plays an important role in various types of blood cancer that have their origin in immune cells. A new medicine that blocks the function of the BTK enzyme was recently approved for the treatment of leukaemia and lymphoma in the USA.

The study has been financed using funds from the Swedish Cancer Society, the Swedish Research Council and Stockholm County Council (ALF), among others.

More information: 'Splice-correcting oligonucleotides restore BTK function in X-linked agammaglobulinemia model' Burcu Bestas, Pedro M.D. Moreno, K. Emelie M. Blomberg, Dara K. Mohammad, Amer F. Saleh, Tolga Sutlu, Joel Z. Nordin, Peter Guterstam, Manuela O. Gustafsson, Shabnam Kharazi, Barbara Piatosa, Thomas C. Roberts, Mark A. Behlke, Matthew J.A. Wood, Michael J. Gait, Karin E. Lundin, Samir EL Andaloussi, Robert Månsson, Anna Berglöf, Jesper Wengel,

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