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Rare genetic disorder provides clues to development of the pancreas

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A rare genetic disorder has given researchers at the University of Exeter a surprising insight into how the pancreas develops. The finding provides a clue to how it may be possible to 'programme' stem cells – master cells in the body that can develop into specialised cells – to become pancreatic cells.

Pancreatic agenesis is a rare condition in which the body is unable to produce a pancreas. The pancreas plays an essential role in regulating levels of sugar (glucose) in the blood. It does this by the release of the hormone insulin, which is generated and released by cells known as pancreatic beta cells. It also produces enzymes to help digest and absorb food.

Rare mutations in the genes PDX1 and PTF1A have previously been shown to cause pancreatic agenesis, but have only been identified in a handful of families affected by the condition. Until now, the underlying causes of most cases have been unknown.

In a paper published today in *Nature Genetics*, an international team of researchers led by scientists from the Peninsula College of Medicine and Dentistry at the University of Exeter report a mutation in the gene GATA6 found in fifteen out of twenty-seven individuals with pancreatic agenesis. The study, funded by organisations including the Wellcome Trust, Diabetes UK and the National Institute for Health Research, establishes a key role for GATA6 in the development of pancreatic cells.

The finding was particularly surprising as switching off the GATA6 gene in mouse models appeared to make no difference to the development of the pancreas.

Professor Andrew Hattersley from the Peninsula College of Medicine and Dentistry, said: "This rare genetic condition has provided us with a surprising insight into how the pancreas develops. What is it that programmes cells to become pancreatic beta cells? Our study suggests that GATA6 plays a very important role in this process and we hope this will help the crucial work to try and make beta-cells for patients with type 1 diabetes."

Whilst pancreatic agenesis is an extreme form of pancreatic dysfunction, far more common is diabetes. In type 1 diabetes, which generally develops in childhood, the immune system attacks and destroys pancreatic beta cells and the body is unable to regulate glucose levels, whilst in type 2 diabetes, the beta cells gradually decline until, usually during adulthood, they cease to function.

Professor Sian Ellard, also from Peninsula College of Medicine and Dentistry, added: "This discovery was possible because new sequencing approaches meant we could test all the genetic information in one go and because with the help of doctors throughout the world we were able to study 27 patients with a very rare condition."

More information: Allen, HL et al. GATA6 haploinsufficiency causes pancreatic agenesis in humans. *Nature Genetics*; e-pub 11 Dec 2011

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