Cause of genetic disorder found in 'dark matter' of DNA

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For the first time, scientists have used new technology which analyses the whole genome to find the cause of a genetic disease in what was previously referred to as "junk DNA". Pancreatic agenesis results in babies being born without a pancreas, leaving them with a lifetime of diabetes and problems digesting food. In a breakthrough for genetic research, teams led by the University of Exeter Medical School and Imperial College London found that the condition is most commonly caused by mutations in a newly identified gene regulatory element in a remote part of the genome, which can now be explored thanks to advances in genetic sequencing.

In a study published today (November 10 2013) in *Nature Genetics*, the team discovered that the condition is caused by mutations in genomic "dark matter", the vast stretches of DNA that do not contain genes that accounts for 99 per cent of the human genome. Instead, it is responsible for making sure that genes are "switched on" at the right time and in the right part of the body. The effects of this region on human development is only beginning to be understood, thanks to technologies which allow scientists to analyse the whole genome – all 3 billion letters in our DNA codes.

The research was funded through the Wellcome Trust, the European Community's Seventh Framework Programme and the National Institute for Health Research (NIHR) Exeter Clinical Research Facility.

Dr Mike Weedon, lead researcher and Senior Lecturer at the University

of Exeter Medical School, said: "This breakthrough delves into the 'dark matter' of the genome, which until recently, was very difficult to systematically study. Now, advances in DNA sequencing technology mean we have the tools to explore these non-protein coding regions far more thoroughly, and we are finding it has a significant impact on development and disease."

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.

Pancreatic agenesis means babies have diabetes from birth and problems with digesting food which prevents weight gain. The disease is rare, but its study also helps scientists gain a better understanding of how the pancreas works, which helps shed light on research into diabetes.

Professor Andrew Hattersley, a Wellcome Trust Senior Investigator who led the Exeter team said: "This finding gives a deeper understanding to families affected by this disorder, and it also tells us more about how the pancreas develops. In the longer term, this insight could have implications for regenerative stem cell treatments for Type 1 Diabetes."

The team found six different mutations in a newly discovered PTF1A regulatory region in eleven people affected by pancreatic agenesis from across the world.

More information: Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis, *Nature Genetics*, DOI: 10.1038/ng.2826

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