Gene finding provides new insights into pancreas development and helps search for type 1 diabetes cure

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Understanding how the human pancreas develops is crucial to allow scientists to make insulin producing–beta cells in the quest to cure type 1

diabetes. Now, scientists have made a unique and surprising discovery—a gene that is essential for making the pancreas in humans is not present in almost all other animals.

Beta cells within the pancreas produce insulin that regulate blood sugar. Every mammal needs the pancreatic beta-cells to survive. In established type 1 diabetes there are no, or very few, working beta-cells.

The paper, entitled "Primate-specific ZNF808 is essential for pancreatic development in humans," and published in *Nature Genetics* challenges assumptions about how the regulation of development evolves.

Until now, scientists had assumed that genes essential for development of key organs and functions were highly conserved through evolution, meaning the genetic pathway remains the same between different species, from fish to humans. However, the gene, called ZNF808, is only found in humans, other apes such as chimpanzees and gorillas, and in some monkeys, such as macaques.

The research was carried out by researchers at the University of Exeter Medical School, the University of Cambridge and the University of Helsinki in Finland. The study shows just how different humans can be to other animals often used in research, such as mice, emphasizing the importance of studying the human pancreas.

Lead author Dr. Elisa De Franco, of the University of Exeter Medical School, said, "Our finding is really surprising—this is the only example we know of where a gene that is fundamental to the development of an organ in humans and primates is not present in other animals."

"You'd expect a gene only found in primates to regulate a feature that is specific to primates, such as brain size, but it is not the case for this gene, which instead is involved in development of an organ shared by all

vertebrates! We think this shows that there must have been an evolutionary shift in higher primates to serve a purpose."

Senior author Professor Andrew Hattersley, of the University of Exeter Medical School, said, "One hypothesis that we are exploring is that the evolutionary benefit is to the pancreas in the fetus. Human babies are born through the pelvis, so they cannot stay in the uterus for a longtime as they would grow too large for birth."

"Instead to cope with being born early and needing to survive without continual feeding they need to be born with more fat than any other animal. This fat is laid down when the fetus' pancreas produces more insulin. Our research has shown that human fetuses have more insulin-related growth than other animals."

Dr. Nick Owens, of the University of Exeter Medical School, said, "This research really emphasizes the importance of studying the human pancreas in order to understand and find new treatments for diabetes. Animal research is important, but it can only tell us so much. We know there are fundamental differences between humans and other animals, such as mice which are often the subject of research in this field. The human pancreas is different in how it looks, works and develops. Our genetic finding could help us understand why that's the case."

ZNF808 belongs to a family of recently evolved proteins which bind and "switch off" specific regions of the DNA which have also developed recently in evolutionary terms. These DNA regions were among the regions considered "junk" DNA with no meaningful purpose for decades, but new technology have recently allowed us to discover their functions. Our findings confirm that these regions of our DNA are playing important roles during human development.

Dr. Michael Imbeault, from the University of Cambridge, said "These

findings show that genes like ZNF808, even if relatively 'recent' in evolution, can have a crucial role in human development. ZNF808 is a member of the largest, but also least studied family of proteins that regulate our genome. There are hundreds of genes like ZNF808 in our DNA, many primate or even human specific, and our results demonstrate how these can be key players in human health."

The identification of ZNF808 as being involved in human pancreas development occurred after researchers at the University of Exeter examined genetic samples from patients recruited across the world who were born without a pancreas and found that they all had genetic changes resulting in loss of ZNF808.

They then teamed up with colleagues at the University of Cambridge and Helsinki University to study the effect of ZNF808 loss using stem cells in the lab. The results showed that ZNF808 plays an important function early during human development when cells need to 'decide' whether to become pancreas or liver.

Among those who shared their genetic samples was Tania Bashir, aged 12, from Luton. Her father Imran Bashir welcomed the Exeter team's progress. "Having an answer to why this happened is important. We've always wanted to know—now we do. The next important step is to understand what this means to the future of science. My dream is that one day, scientists will be able to genetically modify a stem cell and grow a human pancreas, and implant that into Tania, and potentially cure her. I don't know if that will ever be possible, but I do know that this understanding is a crucial step forward."

Professor Timo Otonkoski from University of Helsinki said, "The input of people born without a pancreas was fundamental to this discovery. Nobody would have ever thought that ZNF808 played a role in pancreatic development if we hadn't found the changes in this gene in

these patients."

"The ultimate goal of our research is for this knowledge to be translated into being able to manipulate stem cells to produce beta cells that can produce insulin in the laboratory. That could be the key to curing type 1 diabetes. Our finding is a significant step in understanding what makes the human pancreas unique, which could help progress this area."

Dr. Elisa de Franco, of the University of Exeter Medical School, said, "Our findings really show the importance of studying the DNA of people with rare diseases to understand how organs develop and function. We are immensely grateful to people like Tania and her family, without them none of this would be possible."

More information: Primate-specific ZNF808 is essential for pancreatic development in humans, *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01565-x

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