Siblings with unique genetic mutation help scientists progress drug search for type 1 diabetes

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Two siblings who have the only known mutations in a key gene anywhere in the world have helped scientists gain new insights that could help progress the search for new treatments in type 1 diabetes.

Type 1 diabetes (also known as autoimmune diabetes) is a devastating and life-long disease, in which the patient's immune cells wrongly destroy the insulin producing beta cells in the pancreas. People living with autoimmune diabetes need to test their blood sugar and inject insulin throughout their lives to control their blood sugars and prevent complications.

Autoimmune diabetes with clinical onset in very early childhood is rare and can result from a variety of genetic variants. However, there are many cases of early onset diabetes without known genetic explanation. In addition, some cancer patients treated with a category of immunotherapy known as immune checkpoint inhibitors—which target the same pathway that the mutation was found in—are prone to developing autoimmune diabetes.

The reason why only this category of cancer immunotherapy can trigger autoimmune diabetes is not well understood. Like type 1 diabetes, genetic or immunotherapy-associated autoimmune diabetes requires life-long insulin replacement therapy—there is currently no cure.

The new research, published in the *Journal of Experimental Medicine*, began when researchers studied two siblings who were diagnosed with a rare genetic form of autoimmune diabetes in the first weeks of life. The paper is titled "Human inherited PD-L1 deficiency is clinically and immunologically less severe than PD-1 deficiency."

The University of Exeter offers free genetic testing worldwide for babies diagnosed with diabetes before they are nine months old. For most of these babies, this service provides a genetic diagnosis and in around half of these babies, it allows for a change in treatment.

When researchers tested the two siblings in the study, no mutation in any of the known causes was identified. The Exeter team then performed

whole genome sequencing to look for previously unknown causes of autoimmune diabetes. Through this sequencing, they found a mutation in the gene encoding PD-L1 in the siblings and realized it could be responsible for their very-early-onset autoimmune diabetes.

Study author Dr. Matthew Johnson, from the University of Exeter, UK, said, "PD-L1 has been particularly well studied in animal models because of its crucial function in sending a stop signal to the immune system and its relevance to cancer immunotherapy. But, to our knowledge, nobody has ever found humans with a disease-causing mutation in the gene encoding PD-L1.

"We searched the globe, looking at all the large-scale datasets that we know of, and we haven't been able to find another family. These siblings therefore provide us with a unique and incredibly important opportunity to investigate what happens when this gene is disabled in humans."

The PD-L1 protein is expressed on many different cell types. Its receptor, PD-1, is expressed exclusively on immune cells. When the two proteins bind together it provides a stop signal to the immune system, preventing collateral damage to the bodies tissues and organs.

Researchers from the Rockefeller Institute in New York and King's College London joined forces with Exeter to study the siblings. After contacting the family's clinician in Morocco, the Exeter team visited the siblings where they were living to collect samples and return them to King's College London, within the crucial 10-hour window for analysis while the immune cells were still alive. The London and New York teams then performed extensive analysis on the siblings' cells.

Study co-author Dr. Masato Ogishi, from the Rockefeller University in New York, said, "We first showed that the mutation completely disabled the function of PD-L1 protein. We then studied the immune system of

the siblings to look for immunological abnormalities that could account for their extremely early-onset diabetes.

"As we previously described another two siblings with PD-1 deficiency, both of whom had multi-organ autoimmunity including autoimmune diabetes and extensive dysregulation in their immune cells, we expected to find severe dysregulation of the immune system in the PD-L1-deficient siblings.

"To our great surprise, their immune systems looked pretty much normal in almost all aspects throughout the study. Therefore, PD-L1 is certainly 'indispensable' for preventing autoimmune diabetes but is 'dispensable' for many other aspects of human immune system.

"We think that PD-L2, another ligand of PD-1, albeit less well-studied than PD-L1, may be serving as a back-up system when PD-L1 is not available. This concept needs to be further investigated in the context of artificial blockade for PD-L1 as cancer immunotherapy."

Study co-author Professor Timothy Tree, from King's College London, said, "Through studying this one set of siblings—unique in the world to our knowledge—we have found that the PD-L1 gene is essential for avoiding autoimmune diabetes, but is not essential for 'everyday' immune function.

"This leads us to the grand question; 'what is the role of PD-L1 in our pancreas making it critical for preventing our immune cells destroying our beta cells?' We know that under certain conditions beta cells express PD-L1. However, certain types of immune cells in the pancreas also express PD-L1. We now need to work out the 'communication' between different cell types that is critical for preventing autoimmune diabetes.

"This finding increases our knowledge of how autoimmune forms of

diabetes such as type 1 diabetes develop. It opens up a new potential target for treatments that could prevent diabetes in the future. Simultaneously, it gives new knowledge to the cancer immunotherapy field by uniquely providing the results of completely disabling PD-L1 in a person, something you could never manipulate in studies. Reducing PD-L1 is already effective for cancer treatment, and boosting it is now being investigated as a type 1 diabetes treatment—our findings will help accelerate the search for new and better drugs."

Dr. Lucy Chambers, Head of Research Communications at Diabetes UK, said, "Pioneering treatments that alter the behavior of the immune system to hold off its attack on the pancreas are already advancing type 1 diabetes treatment in the U.S., and are awaiting approval here in the UK.

"By zeroing in on the precise role of an important player in the type 1 diabetes immune attack, this exciting discovery could pave the way for treatments that are more effective, more targeted and more transformational for people with or at risk of type 1 diabetes."

Helmsley Program Officer Ben Williams said, "New drugs often fail in development because scientific discoveries made in animal models don't translate into humans. As such, drug developers strongly prefer to pursue new drugs where human genetic evidence supports the drug's target. This study provides such compelling evidence that PD-L1 is a high-priority target to treat T1D, and should be pursued with the ambition of eventually reducing the burden of this difficult to manage disease."

More information: Human inherited PD-L1 deficiency is clinically and immunologically less severe than PD-1 deficiency, *Journal of Experimental Medicine* (2024).