'Jekyll and Hyde' protein linked to type 1 diabetes

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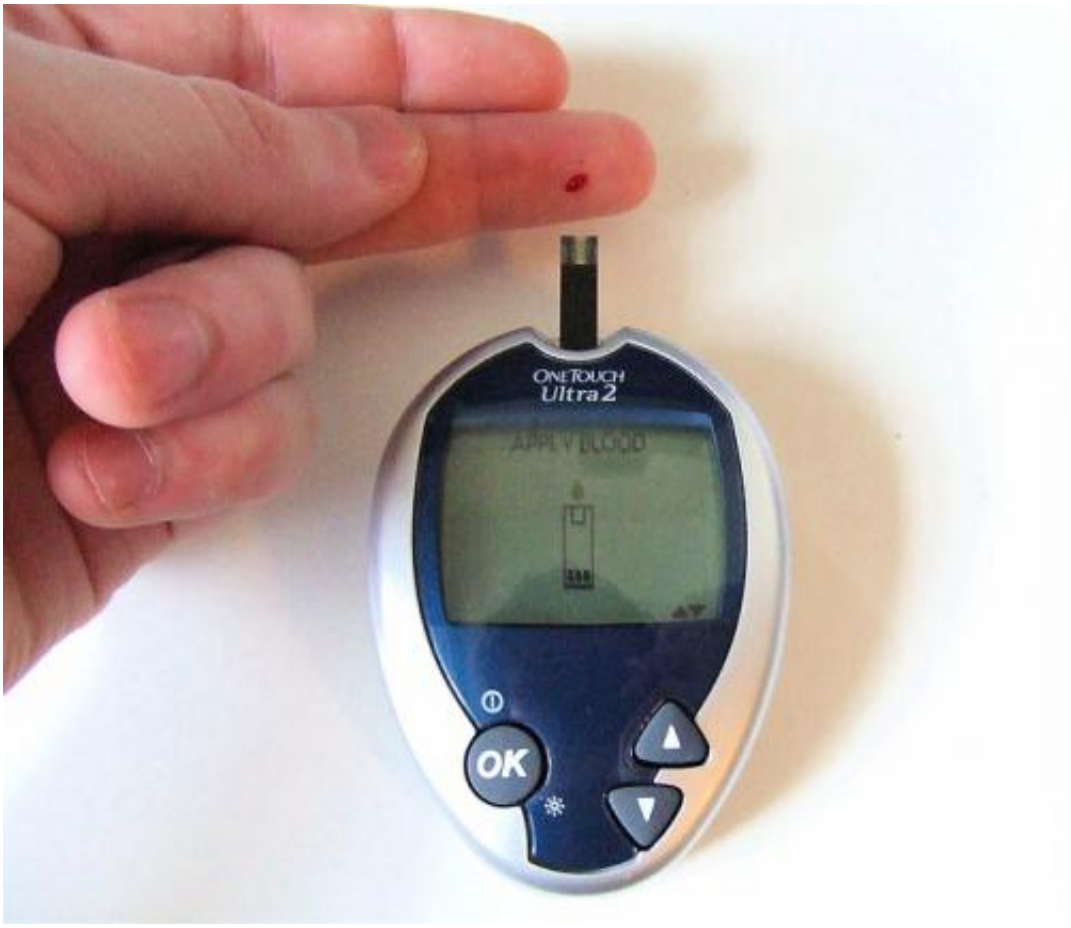

Blood glucose monitoring. Credit: Wikipedia

Researchers are a step closer to establishing the link between a protein with a split personality and type 1 diabetes.

New research, published today in the journal *PNAS*, shows how a protein, called GAD65, changes its shape when it turns itself on and off. Curiously, this characteristic may also link it to type 1 diabetes.

In the human brain, GAD65 performs an essential role: it makes 'neurotransmitters' - chemicals that pass messages between brain cells.

GAD65 is also found in the pancreas. Previous studies linked it to type 1 diabetes because the body makes antibodies against the protein. However the molecular details of what makes GAD65 'sticky' to antibodies has remained a mystery until now.

The new research, led by Monash University, investigated how GAD65 regulates the production of neurotransmitters by changing its shape.

Principal Investigator Associate Professor Ashley Buckle said the findings showed that the normal function of the protein may come at a price.

"GAD65 has an unpredictable, almost Jekyll and Hyde personality when it is turned on and off. When active and making neurotransmitters, it is rigid and rather motionless. Ironically, when switched off, rather than resting as you might expect, it becomes mobile, dancing and jiggling around.

"We suspected that this dual personality might affect how antibodies 'see' it. This turns out to be true - antibodies interact with it very differently depending on whether it's on or off," Associate Professor Buckle said.

GAD65 has previously been used in clinical trials as a vaccine for type 1 diabetes, with limited success. Associate Professor Buckle said the discovery may ultimately lead to the development of better vaccines to

potentially treat and prevent type 1 diabetes.

"The idea to immunise an individual with GAD65 to help the immune system develop a tolerance against it, to stop or at least dampen the immune reaction is a good one. But so far these attempts have not been very successful. This research could change that," Associate Professor Buckle said.

The seven-year study used a combination of experimental and computational methods to understand what GAD65 looks like in its 'off' state and how human antibodies interact with both forms.

Powerful beam lines at the Australian Synchrotron, as well as massive super computers at the Victorian Life Sciences Computation Initiative (VLSCI) and Monash, were used to accelerate the research.

Associate Professor Buckle said access to world-class facilities was critical to the research.

"Techniques like X-ray crystallography produce amazing, detailed pictures of large molecules, but these are often snapshots frozen in time. In order to 'see' the molecules in action we needed to combine other techniques, such as molecular simulation, to produce a movie. The Australian Synchrotron and the VLSCI played a major part in this work," Associate Professor Buckle said.

In the next phase, the research team will visualise GAD65 as it interacts with a human antibody. Understanding why GAD65 is recognised and targeted by antibodies is the next step. In addition to specific insights, it's hoped this work will provide important basic knowledge that could be applied to broader aspects of health and medicine.

More information: Cofactor-dependent conformational heterogeneity

of GAD65 and its role in autoimmunity and neurotransmitter homeostasis, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1403182111