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Genetic study links body clock receptor to diabetes

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A study published in *Nature Genetics* today has found new evidence for a link between the body clock hormone melatonin and type 2 diabetes. The study found that people who carry rare genetic mutations in the receptor for melatonin have a much higher risk of type 2 diabetes.

The findings should help scientists to more accurately assess personal diabetes risk and could lead to the development of personalised treatments.

Previous research has found that people who work night shifts have a higher risk of type 2 diabetes and heart disease. Studies have also found that if volunteers have their sleep disrupted repeatedly for three days, they temporarily develop symptoms of diabetes.

The body's sleep-wake cycle is controlled by the hormone melatonin, which has effects including drowsiness and lowering body temperature. In 2008, a genetic study led by Imperial College London discovered that people with common variations in the gene for MT2, a receptor for melatonin, have a slightly higher risk of type 2 diabetes.

The new study reveals that carrying any of four rare mutations in the MT2 gene increases a person's risk of developing type 2 diabetes six times. The release of insulin, which regulates blood sugar levels, is known to be regulated by melatonin. The researchers suggest that mutations in the MT2 gene may disrupt the link between the body clock and insulin release, leading to abnormal control of blood sugar.

Professor Philippe Froguel, from the School of Public Health at Imperial College London, who led the study, said: "Blood sugar control is one of the many processes regulated by the body's biological clock. This study adds to our understanding of how the gene that carries the blueprint for a key component in the clock can influence people's risk of diabetes.

"We found very rare variants of the MT2 gene that have a much larger effect than more common variants discovered before. Although each mutation is rare, they are common in the sense that everyone has a lot of very rare mutations in their DNA. Cataloguing these mutations will enable us to much more accurately assess a person's risk of disease based on their genetics."

In the study, the Imperial team and their collaborators at several institutions in the UK and France examined the MT2 gene in 7,632 people to look for more unusual variants that have a bigger effect on disease risk. They found 40 variants associated with type 2 diabetes, four of which were very rare and rendered the receptor completely incapable of responding to melatonin. The scientists then confirmed the link with these four variants in an additional sample of 11,854 people.

Professor Froguel and his team analysed each mutation by testing what effect they have on the MT2 receptor in human cells in the lab. The mutations that completely prevented the receptor from working proved to have a very big effect on diabetes risk, suggesting that there is a direct link between MT2 and the disease.

More information: A. Bonnefond et al. 'Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes' *Nature Genetics,* published online 29 January 2012.