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Body clock linked to diabetes and high blood sugar

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Diabetes and high levels of blood sugar may be linked to abnormalities in a person's body clock and sleep patterns, according to a genome-wide association study published today in the journal *Nature Genetics*.

The research suggests that diabetes and higher than normal blood sugar levels could partly be tackled by treating sleep problems, say the researchers, from Imperial College London, the French National Research Institute CNRS, Lille University, McGill University in Canada, Steno Diabetes Centre in Denmark and other international institutions.

People with high blood sugar levels and diabetes have a greatly increased risk of developing a range of conditions, including cardiovascular diseases.

The new study shows that a mutation called rs1387153, near a gene called MTNR1B, is associated with having an increased average blood sugar level and around a 20 percent elevated risk of developing type 2 diabetes.

MTNR1B forms part of a signalling pathway that controls the action of the hormone melatonin. This hormone regulates the body's circadian rhythm - the internal clock that controls sleeping and eating patterns – by responding to daylight and darkness.

The discovery of the rs1387153 mutation provides evidence that high blood sugar and diabetes could be directly linked to an impaired

circadian rhythm.

Professor Philippe Froguel, the corresponding author of the research from the Department of Genomic Medicine at Imperial College London, said: "There is already some research to suggest there are links between sleep problems and conditions such as obesity and depression, both of which are associated with diabetes. For example, we know that obese children tend to sleep badly and that people become more obese if they are not having enough sleep. Our new study demonstrates that abnormalities in the circadian rhythm may partly be causing diabetes and high blood sugar levels. We hope it will ultimately provide new options for treating people."

In healthy people, blood sugar levels are kept under control by insulin, which the pancreas releases in varying amounts at different periods during a 24-hour natural cycle. The researchers suggest that when there is a genetic abnormality that affects melatonin levels and sleep patterns, this may also disturb the levels of insulin in the blood, preventing the body from maintaining control of blood sugar levels.

Insulin is normally secreted in peaks during the daytime, in order to allow blood sugar from meals to be processed properly, and at lower levels at night. In contrast, melatonin levels are low during the daytime and high at night.

The new study is part of a series of discoveries about the genetics of diabetes made by Professor Froguel and his colleagues. In May 2008 they identified a genetic mutation that can raise the amount of sugar in a person's blood to harmful levels and in February 2007 they identified the key genes associated with a risk of developing type-2 diabetes in the first study to map the genes of any disease in such detail.

The new study shows that identifying which people have high numbers

of genetic mutations can reveal who is at most risk of developing high blood sugar levels. On average, the more genetic mutations associated with high blood sugar levels people had, the higher their blood sugar level.

For example, people with five genetic mutations had an average fasting blood sugar level of 5.4, whereas people with one mutation had an average level of 5.12.

Forty three percent of those carrying six or more mutations had levels of fasting blood glucose of 5.6 mmol/l or more. This level is defined as being 'impaired' by the American Diabetes Association, meaning that such people have a very high risk of developing diabetes in the future.

Professor Froguel added: "We have been developing quite a clear picture of the key genes involved with high blood sugar and diabetes and this allows us to better understand them and suggest new avenues for treatment. We are also nearing the stage when we can develop tests that can identify the people at most risk of developing high blood sugar and diabetes later in their lives, so we can intervene to improve their health before they reach that point."

For the new study, the team analysed the genetic makeup of 2,151 non-diabetic French people (comprising 715 lean adults, 614 lean children, 247 obese adults and 575 obese children) and identified the rs1387153 mutation as being associated with high blood sugar levels. They confirmed their findings by looking at the genetic makeup of more than 16,000 non-diabetic people from different groups in France, Denmark and Finland.

The team then determined that the presence of the rs1387153 increased the risk of type 2 diabetes by comparing the genetic makeup of 6,332 French and Danish diabetic subjects with that of a group of 9,132

French and Danish people with normal blood sugar levels. The researchers found the same links between rs1387153 and a risk of diabetes in all the European populations they studied.

Source: Imperial College London