

# Three Genes Appear to Predict Type 2 Diabetes

The late-breaking data presented at the ADA came from the Malmö Preventive Project.

BY RYAN DUBOSAR, CONTRIBUTING EDITOR

Common variants in three genes may predict development of type 2 diabetes, according to a report presented by lead author Valeriya Lyssenko, MD, PhD, at the American Diabetes Association's 66th Scientific Sessions in Washington, DC.

Each of the three genes can independently predict type 2 diabetes, according to Dr. Lyssenko's presentation of the findings of the Malmö Preventive Project. Each gene also has a unique mechanism that raises the risk for diabetes. People with two or more of the genes have added risk, said Dr. Lyssenko, a fellow in diabetes and endocrinology at Lund University, Malmö, Sweden.

"The identification of the underlying genetic factors has not been an easy task," she said during the late-breaking session. "Many association studies have been underpowered, and cases and controls have not been ascertained in the same way." But the Malmö Preventive Project is a prospective study involving 33,346 individuals followed for a median of 22 years, which offers sufficient power to draw conclusions about the role of genetic variants in the origins of the disease.

The Malmö Preventive Project is a large-scale, long-term, randomized, controlled trial designed to reduce morbidity and mortality related to cardiovascular diseases, alcohol use and breast cancer. Starting in 1974, individuals aged 32 to 51 years were recruited and screened for hypertension, hyperlipidemia, type 2 diabetes and alcohol abuse.

About 25% of study patients received intervention programs such as drug therapy, lifestyle modifications and follow-up visits with physicians and nurses. A subset of 7,061 were randomly selected to participate in a genetic study.

Researchers tested the ability of common variants in nine genes to predict overt type 2 diabetes. Of the 7,061 individuals, 4,392 were men and 2,669 were women. Their average age was  $46 \pm 6$  years, body mass index was  $24 \pm 3$  kg and only 24.5% had impaired fasting glucose or impaired glucose tolerance (ie, when both measures of glucose were above normal but not yet high enough to indicate diabetes).

By the follow-up examination, 1,422 patients or 20.1% of

the group had developed type 2 diabetes.

The scientists identified genes that increased the risk of future type 2 diabetes:

- Two T alleles of TCF7L2 variants contributed to an increased risk with an odds ratio (OR) of 1.40 and 1.52;
- The KCNJ11 K allele contributed to an OR of 1.23; and
- The PPARG PP genotype contributed to an OR of 1.20.

"Despite this relatively modest odds ratio, the *P* values were highly significant given the large number of individuals who converted to type 2 diabetes," Dr. Lyssenko said. "None of the other genes significantly predicted type 2 diabetes.

When researchers examined all the genes together in a multivariate analysis, they found that TCF7L2, KCNJ11 and PPARG variants independently predicted future type 2 diabetes.

"The individual risk for type 2 diabetes compared by genotype was rather modest," Dr. Lyssenko reported. "However, carriers of all three risk genotypes have a clearly increased risk of developing type 2 diabetes, with an odds ratio of 2.79."

The likely mechanism by which these genes lead to type 2 diabetes vary, Lyssenko said.

- TCF7L2 leads to increased insulin secretion and glucose production;
- KCNJ11 causes a modest impairment of insulin secretion, which becomes manifest particularly in overweight individuals; and
- PPARG is associated with insulin sensitivity in nonobese adults and protects against type 2 diabetes predominantly in those whose body weight has not increased over time.

"Our data clearly demonstrate that common variants in the TCF7L2, KCNJ11 and PPARG genes predict future type 2 diabetes and can be considered as true type 2 diabetes susceptibility genes," Lyssenko concluded. ■

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Lyssenko V. Findings of the Malmö Preventive Project. Presented at the American Diabetes Association's 66th Scientific Sessions. Late-breaking sessions. June 9-13, 2006. Washington, DC.