

SNP rs7754840 of *CDKALI* is associated with impaired insulin secretion in non-diabetic offspring of Type 2 diabetic subjects (the EUGENE2 study) and in a large sample of men with normal glucose tolerance

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Abstract

Context: *CDKALI* is a recently discovered susceptibility gene for type 2 diabetes.

Objective: To investigate the impact of rs7754840 of *CDKALI* on insulin secretion, insulin sensitivity and risk of type 2 diabetes.

Design and Settings: Study I (the EUGENE2 study): Cross-sectional study including subjects from five white populations in Europe (Denmark, Finland, Germany, Italy and Sweden). Study II: Ongoing prospective study of Finnish men.

Participants: Study I: 846 non-diabetic offspring of type 2 diabetic patients (age 40 ± 10 years; BMI 26.7 ± 5.0 kg/m²). Study II: 3900 middle-aged men (533 type 2 diabetic and 3367 non-diabetic subjects).

Interventions: Study I: intravenous glucose-tolerance test (IVGTT), oral glucose-tolerance test (OGTT), euglycemic hyperinsulinemic clamp. Study II: OGTT.

Main outcome measures: Parameters of insulin secretion, insulin resistance, and glucose tolerance status.

Results: Study I: Carriers of the GC and CC genotypes of rs7754840 had 11% and 24% lower first-phase insulin release in an IVGTT compared to that in carriers of the GG genotype ($P=0.002$). The C allele was also associated with higher glucose area under the curve in an OGTT ($P=0.016$). Study II: rs7754840 was significantly associated with type 2 diabetes ($P=0.022$), and markers of impaired insulin release (insulinogenic index, $P=0.012$) in 2405 men with normal glucose tolerance.

Conclusions: rs7754840 of *CDKALI* was associated with markers of impaired insulin secretion in two independent studies. Furthermore, rs7754840 was associated with type 2 diabetes in Finnish men (Study II). Therefore, *CDKALI* is likely to increase the risk of type 2 diabetes by impairing insulin secretion.