

Variant near ADAMTS9 Known to Associate with Type 2 Diabetes Is Related to Insulin Resistance in Offspring of Type 2 Diabetes Patients—EUGENE2 Study

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Abstract

Background: A meta-analysis combining results from three genome-wide association studies and followed by large-scale replication identified six novel type 2 diabetes loci. Subsequent studies of the effect of these variants on estimates of the beta-cell function and insulin sensitivity have been inconclusive. We examined these variants located in or near the *JAZF1* (rs864745), *THADA* (rs7578597), *TSPAN8* (rs7961581), *ADAMTS9* (rs4607103), *NOTCH2* (rs10923931) and the *CDC123/CAMK1D* (rs12779790) genes for associations with measures of pancreatic beta-cell function and insulin sensitivity.

Methodology/Results: Oral and intravenous glucose stimulated insulin release ($n = 849$) and insulin sensitivity ($n = 596$) estimated from a hyperinsulinemic euglycemic clamp were measured in non-diabetic offspring of type 2 diabetic patients from five European populations. Assuming an additive genetic model the diabetes-associated major C-allele of rs4607103 near *ADAMTS9* associated with reduced insulin-stimulated glucose uptake ($p = 0.002$) during a hyperinsulinemic euglycemic clamp. However, following intravenous and oral administration of glucose serum insulin release was increased in individuals with the C-allele ($p = 0.003$ and $p = 0.01$, respectively). A meta-analysis combining clamp and IVGTT data from a total of 905 non-diabetic individuals showed that the C-risk allele associated with decreased insulin sensitivity ($p = 0.003$) and increased insulin release ($p = 0.002$). The major T-allele of the intronic *JAZF1* rs864745 conferring increased diabetes risk was associated with increased 2nd phase serum insulin release during an IVGTT ($p = 0.03$), and an increased fasting serum insulin level ($p = 0.001$). The remaining variants did not show any associations with insulin response, insulin sensitivity or any other measured quantitative traits.

Conclusion: The present studies suggest that the diabetogenic impact of the C-allele of rs4607103 near *ADAMTS9* may in part be mediated through decreased insulin sensitivity of peripheral tissues.

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