

The common *SLC30A8* Arg325Trp variant is associated with reduced first-phase insulin release in 846 non-diabetic offspring of type 2 diabetes patients—the EUGENE2 study

T. W. Boesgaard · J. Žilinskaitė · M. Vanttinen ·
M. Laakso · P.-A. Jansson · A. Hammarstedt ·
U. Smith · N. Stefan · A. Fritsche · H. Häring ·
M. Hribal · G. Sesti · D. P. Zobel · O. Pedersen ·
T. Hansen · for the EUGENE 2 Consortium

Received: 3 October 2007 / Accepted: 18 January 2008 / Published online: 7 March 2008
© Springer-Verlag 2008

Abstract

Aims/hypothesis A recent genome-wide association study identified the *SLC30A8* rs13266634 polymorphism encoding an Arg325Trp polymorphism in the zinc transporter protein member 8 (ZnT-8) to be associated with type 2 diabetes. Here,

Electronic supplementary material The online version of this article (doi:10.1007/s00125-008-0955-6) contains supplementary material, which is available to authorised users.

T. W. Boesgaard (✉) · D. P. Zobel · O. Pedersen · T. Hansen
Steno Diabetes Center,
Niels Steensens Vej 1, NLC2.12,
DK-2820 Gentofte, Copenhagen, Denmark
e-mail: tweb@steno.dk

J. Žilinskaitė · M. Vanttinen · M. Laakso
Department of Medicine, University of Kuopio,
Kuopio, Finland

P.-A. Jansson · A. Hammarstedt · U. Smith
The Lundberg Laboratory for Diabetes Research,
Department of Internal Medicine, Sahlgrenska University Hospital,
Gothenburg, Sweden

N. Stefan · A. Fritsche · H. Häring
Department of Internal Medicine,
Division of Endocrinology, Diabetology, Nephrology,
Vascular Medicine and Clinical Chemistry,
University of Tübingen,
Tübingen, Germany

M. Hribal · G. Sesti
Department of Experimental and Clinical Medicine,
University Magna Graecia of Catanzaro,
Catanzaro, Italy

O. Pedersen
Faculty of Health Science, University of Aarhus,
Aarhus, Denmark

we investigate whether the polymorphism is related to altered insulin release in response to intravenous and oral glucose loads in non-diabetic offspring of type 2 diabetic patients.

Methods We genotyped *SLC30A8* rs13266634 in 846 non-diabetic offspring of type 2 diabetic patients from five different white populations: Danish ($n=271$), Finnish ($n=217$), German ($n=149$), Italian ($n=109$) and Swedish ($n=100$). Participants were subjected to both IVGTTs and OGTTs, and measurements of insulin sensitivity.

Results Homozygous carriers of the major type 2 diabetes C risk-allele showed a 19% decrease in first-phase insulin release (0–10 min) measured during the IVGTT (CC $3,624 \pm 3,197$; CT $3,763 \pm 2,674$; TT $4,478 \pm 3,032$ pmol l⁻¹ min⁻¹, mean \pm SD; $p=0.007$). We found no significant genotype effect on insulin release measured during the OGTT or on estimates of insulin sensitivity.

Conclusions/interpretation Of European non-diabetic offspring of type 2 diabetes patients, 46% are homozygous carriers of the Arg325Trp polymorphism in ZnT-8, which is known to associate with type 2 diabetes. These diabetes-prone offspring are characterised by a 19% decrease in first-phase insulin release following an intravenous glucose load, suggesting a role for this variant in the pathogenesis of pancreatic beta cell dysfunction.

Keywords Beta cell dysfunction · Genetics · Insulin · Offspring · Polymorphism · *SLC30A8* · Type 2 diabetes · Zinc transporter protein member 8 · ZnT-8

Abbreviations

HOMA-IR homeostasis model assessment of insulin resistance
ZnT-8 zinc transporter protein member 8