Impact of the TCF7L2 rs7903146 type 2 diabetes risk variant on clinical presentation in recently diagnosed patients with type 2 diabetes

A.L. Hansen[1], L.M. Engelhard[2], C. Brøns[3], N. Jessen[4], J.S. Nielsen[5], P. Vestergaard[6], K. Højlund[5], M.K. Andersen[7], T. Hansen[7], M.H. Olsen[8], R.W. Thomsen[9], H.T. Sørensen[9], A. Vaag[10];
[1]Clinical Research, Steno Diabetes Center Copenhagen, Herlev, Denmark, [2]Clinical Research, Lund University, Lund, Sweden, [3]Clinical research, Steno Diabetes Center Copenhagen, Herlev, Denmark, [4]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark, [5]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark, [6]Steno Diabetes Center North Denmark, Aalborg University Hospital, Aalborg, Denmark, [7]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark, [8]Dept. Internal medicine, Steno Diabetes Center Zealand, Holbæk, Denmark, [9]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [10]Lund University Diabetes Centre, Lund University, Lund, Denmark.

Background and aims: The transcription factor 7-like 2 (*TCF7L2*) rs7903146 variant is the most impactful common genetic risk variant for type 2 diabetes (T2D). The risk variant has been associated with lower insulin secretion, inflammation, atherosclerosis, lipid accumulation, and altered body composition. However, it is unknown whether the *TCF7L2* rs7903146-T risk allele is associated with a distinct clinical presentation in recently diagnosed T2D patients.
Materials and methods: In total, 2954 recently diagnosed T2D patients from the Danish Center for Strategic Research in T2D cohort were genotyped. We used a cross-sectional design, to examine the additive impact on anthropometric measures, glucose and -insulin metabolism, blood pressure, lipids, and subclinical inflammation using multivariable linear regression. Associations with medication use and comorbidities were examined using log-binomial and robust Poisson regression.
Results: In total, the risk allele frequency was 0.325. After adjusting for sex, year of birth, and birthweight, the rs7903146 T-allele was associated with 0.58 years (95% CI: -1.20, 0.03) lower age at diagnosis, a 0.57 kg/m^2 (95% CI: 0.25, 0.89) lower BMI and a 1.50 cm (95% CI: 0.73, 2.26) smaller waist circumference. For glucose-insulin metabolism, the per allele effect included a 6% (95% CI: 3.5, 8.5) lower fasting plasma C-peptide, a 5.8% (95% CI: 3.2, 8.3) lower HOMA2-insulin secretion, and a 6.3% (95% CI: 3.5, 9.3) higher HOMA2-insulin sensitivity. In categorical analysis, the additive effect of rs7903146 T-allele was associated with an increased prevalence ratio (PR) of 1.19 (95% CI: 1.03, 1.38) for having microvascular complications at enrolment, primarily driven by diabetic neuropathy (PR = 1.18 [95% CI: 1.01, 1.38]). Carriers of the rs7903146 T-allele were furthermore less likely to be on antihypertensive medication at enrolment (PR = 1.14 [95% CI: 1.05, 1.24]).
Conclusion: The *TCF7L2* rs7903146 T-allele was associated with a slightly younger age at diagnosis, less obesity, lower HOMA2-insulin secretion, and higher HOMA2-insulin sensitivity. Further carriers of the risk allele had a higher risk of being diagnosed with diabetic neuropathy at time of T2D diagnosis. Genotyping of additional 6000 recently diagnosed T2D patients in the DD2 cohort is ongoing, and results for all 8954 T2D patients in the cohort will be presented at the EASD 2023.
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