Sequence variants of the sarco(endo)plasmic reticulum Ca2+-transport ATPase 3 gene (SERCA3) in Caucasian Type II diabetic patients (UK Prospective Diabetes Study 48)

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Abstract:

Abstract Aims/hypothesis. Type II (non-insulin-dependent) diabetes mellitus is a common heterogeneous metabolic disorder of largely unknown genetic aetiology. The sarco(endo)plasmic reticulum Ca2+-transport ATPase (SERCA) plays an important part in the glucose-activated beta-cell Ca2+ signalling that regulates insulin secretion. Impaired function and expression of SERCA have been shown in islets of Langerhans from diabetic animal models and have also been associated with beta-cell apoptosis. Thus, the SERCA3 encoding gene is a plausible candidate for a primary pancreatic beta-cell defect. Methods. In this study, the entire coding and the promoter regions of SERCA3 gene were screened by single-strand conformation polymorphism analysis in white Caucasian Type II diabetic patients. Results. We found four rare missense mutations [Exon 4: Gln108MHis (CAGMCAT), Exon 14: Val648 MMet (GTGMATG) and Arg674MCys (CGCM TGC), and Exon 15: Ile753MLeu (ATCMCTC)]. The patients with Gln108MHis, Val648MMet and Arg674MCys mutations, which may affect the E1P-E2P transition of SERCA3 during its enzyme cycle, had normal body weight with marked hyperglycaemia and beta-cell dysfunction. That is an unusual phenotype only found in 6 % of the Type II diabetic patients recruited for the UK Prospective Diabetes Study. In addition, five silent polymorphisms, six intron variants and two polymorphisms in the 3' untranslated region of exon 22 were found with similar frequency in diabetic and control subjects. Conclusion/interpretation. Our result suggests that in white Caucasians, the SERCA3 locus possibly contributes to the genetic susceptibility to Type II diabetes [Diabetologia (1999) 42: 1240-1243].