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学位論文名	Identification of missense mutations in the hepatocyte nuclear factor-3β gene in Japanese subjects with late-onset Type II diabetes mellitus （日本人2型糖尿病患者におけるHNF-3β遺伝子変異の同定）
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論文内容の要旨

[Aim] Genetic studies found that mutations in the genes encoding hepatocyte nuclear factor (HNF)-4α, HNF-1α and insulin promoter factor-1 (IPF-1) cause diabetes mellitus known as maturity-onset diabetes of the young (MODY), which is characterized by autosomal dominant inheritance and early onset. HNF-3β is a winged-helix transcription factor expressed in pancreatic beta cells, and is involved in the regulation of expression of HNF-4α, HNF-1α and IPF-1 genes. Our previous genetic screening of MODY patients showed that mutations in the HNF-3β gene are not a common cause of MODY in Japanese subjects. However, genetic defects of HNF-3β gene might contribute to the susceptibility to the late-onset diabetes mellitus. In this study, I examined whether mutations in the HNF-3β gene contribute to the susceptibility to late-onset Type II diabetes in Japanese subjects.

[Methods and Results]

(1) Association study. HNF-3β contains a polymorphic TCC repeat in the intron 1. Allele distribution was examined in 112 unrelated Japanese Type II diabetic patients and 96 control subjects. The distribution of the alleles was similar between diabetic and control groups, indicating that this marker is not associated with Type II diabetes.

(2) Mutation screening. DNA sequencing of the coding regions and flanking intros of the HNF-3β gene was performed in 57 unrelated Japanese Type II diabetic patients. Mutation screening of the HNF-3β gene identified 3 silent mutations and 2 missense mutations (A86T and G114E) in the coding region. A86T mutation affects a conserved amino acid in the transactivation domain and this mutation was identified in two out of 57 unrelated Japanese subjects with Type II diabetes. G114E mutation affects an amino acid located in the linker region between transactivation domain and the DNA binding domain. This mutation was found in one out of 57 subjects with Type II diabetes. Neither mutation was found in 225 Japanese control

subjects.

(3) Reporter gene assay. Transactivation activities of wild type and mutant HNF-3β were examined by luciferase reporter gene assay. The transactivation activity of A86T-HNF-3β was significantly decreased (83-86%) compared with that of WT-HNF-3β, but transactivation activity of G114E-HNF-3β was similar with that of WT-HNF-3β.

[Conclusion]

A loss-of-function mutation (A86T) of HNF-3β gene was identified in Japanese subjects with Type II diabetes. The late onset of diabetes observed in subjects with the A86T mutation could be a consequence of the relatively mild nature of the A86T-HNF-3β. These results suggest that HNF-3β is an important transcription factor for the regulation of glucose metabolism and mutations in the HNF-3β gene contributes to the genetic risks of Type II diabetes mellitus.

論文審査の結果の要旨

本研究は、転写因子である hepatocyte nuclear factor (HNF)-3βの遺伝子変異が糖尿病の発症に関与している可能性について報告したものである。膵β細胞に発現している転写因子 HNF-1α、HNF-4α および IPF-1 の遺伝子変異は糖尿病を引き起こすことが知られている。HNF-3βも膵β細胞に発現しており、これら転写因子遺伝子の発現を制御している。申請者は、日本人２型糖尿病患者において HNF-3β遺伝子変異の検索を行い、健常対照者においては認められない２種類のミスセンス変異（A86T および G114E 変異）を同定した。機能解析の結果、A86T 変異 HNF-3βの転写活性は野生体に比して有意に減弱しており、A86T 変異は糖尿病の発症に関与しているものと考えられた。本研究は、HNF-3β遺伝子が糖尿病の発症の遺伝的危険因子の１つである可能性について初めて示したものであり、糖尿病発症の遺伝素因を考える上で極めて意義深く学位に値するものである。