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PRESS RELEASE (2015/05/20)

Identification of human virus-induced diabetes susceptibility gene!
—Prospective to the discovery of diabetogenic viruses and vaccine development—

Abstract

Professor Seiho Nagafuchi, at Kyushu University Graduate School of Medical Sciences, in cooperation with Kyushu University Hospital, Matsuyama Red Cross Hospital, Fukuoka Red Cross Hospital, Minami Naika Clinic, Okada Naika Clinic, Saga University Hospital, and other study groups, has succeeded in identifying the virus-induced diabetes susceptibility gene as *TYK2* in humans. This finding will lead to the discovery of diabetogenic viruses and to the development of anti-diabetogenic virus vaccine. His research group has already discovered natural virus-induced susceptibility gene in mice and clarified the exact mechanisms (Nature Communications 2015). In this study, based on previous murine study, the observations could extend to humans, and they found that human *TYK2* promoter variant; a *TYK2* promoter haplotype with multiple genetic polymorphisms, which are in complete linkage disequilibrium, serves an increased risk not only in type 1 diabetes, most highly in patients with flu-like syndrome at the onset, but also in non-obese type 2 diabetes.

The finding has been published in EBioMedine (group journal of Lancet) on 15 May as online in press condition.

■ **Background:** Although accumulating evidence has suggested a viral origin of type 1 diabetes, the susceptibility genes to virus-induced diabetes have not yet been clarified. Recently, natural mutation of *Tyrosine kinase 2 (Tyk2)* gene has been shown to determine susceptibility to murine virus-induced diabetes (Nature Communications 2015). In addition, a previous human genome-wide study suggested the type 1 diabetes susceptibility region to be (Mein, C.A., Esposito, L.,Dunn, M.G., et al. 1998. Nat. Genet. 19:297-300), where the human *TYK2* gene is located (Firmbach-Kraft, I., Byers, M., Shows, T., et al. 1990. Oncogene 5:1329-1336.).

■ **Methods:** Polymorphisms of *TYK2* gene at the promoter region and exons were analyzed focusing on the type 1 diabetes associated with flu-like syndrome at diabetes onset by polymerase chain amplification, followed by the direct sequencing of the target gene. Statistical analyses of frequency study for identified polymorphisms were studied among 331 healthy controls, and 302 patients with type 1 and 314 with type 2 diabetes in the Japanese.

■ **Findings:** A *TYK2* promoter haplotype with multiple genetic polymorphisms, which are in complete linkage disequilibrium, named *TYK2* promoter variant, presenting decreased promoter activity, is associated with an increased risk not only in type 1 diabetes (odds ratio (OR), 2.4; 95% confidence interval (CI), 1.2 to 4.6; P=0.01), but also in type 2 diabetes (OR, 2.1; 95% CI, 1.1 to 4.1; P=0.03). Especially non-obese (BMI<26kg/m^2) people (OR, 2.4; 95% CI, 1.2 to 4.8; P=0.01). The risk is high in patients with type 1 diabetes associated with flu-like syndrome at diabetes onset (OR, 3.6; 95% CI, 1.5 to 8.5; P=0.005) and also in those without anti-glutamic acid decarboxylase autoantibody (OR, 3.3; 95% CI, 1.6 to 7.2; P=0.002).

■ **Interpretation:** The *TYK2* promoter variant is associated with an overall risk for diabetes, most highly in type 1 diabetes associated with flu-like syndrome at the onset, and also in patients with non-obese type 2 diabetes, thus serving a good candidate as a virus-induced diabetes susceptibility gene in humans.

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