

## 小児期発症糖尿病の病因の解明に進展が見られました（小児ゲノム医療研究室）

1型糖尿病の多くは膵β細胞に対する自己免疫反応により、インスリン分泌が枯渇することで起こります（1A型）。自己免疫が証明されない場合、1B型と分類されます。1B型と分類された小児1型糖尿病の中に、単一遺伝子異常による糖尿病、特にインスリン遺伝子変異による糖尿病が混在していることを見いだしました。（*Pediatr Diabetes*. 14:112-20, 2013）

### Identification of *INS* and *KCNJ11* gene mutations in type 1B diabetes in Japanese children with onset of diabetes before 5 years of age.

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#### Abstract

**BACKGROUND:** The etiology of type 1 diabetes (T1D) is heterogeneous and is according to presence or absence of pancreatic autoantibodies divided into two subtypes: type 1A (autoimmune-mediated) and type 1B (non-autoimmune-mediated). Although several genes have been linked to type 1A diabetes, the genetic cause of type 1B diabetes in Japanese individuals is far from understood.

**OBJECTIVE:** The aim of this study was to test for monogenic forms of diabetes in auto antibody-negative Japanese children with T1D.

**METHODS:** Thirty four (19 males and 15 female) unrelated Japanese children with glutamate decarboxylase (GAD) 65 antibodies and/or IA-2A-negative T1D and diabetes diagnosed at < 5 yr of age were recruited from 17 unrelated hospitals participating in the Japanese Study Group of Insulin Therapy for children and adolescent diabetes (JSGIT). We screened the *INS* gene and the *KCNJ11* gene which encode the ATP-sensitive potassium channel by direct sequencing in 34 Japanese children with T1D.

**RESULTS:** We identified three novel (C31Y, C96R, and C109F) mutations and one previously reported mutation (R89C) in the *INS* gene in five children, in addition to one mutation in the *KCNJ11* gene (H46R) in one child. These mutations are most likely pathogenic and therefore the cause of diabetes in carriers.

**CONCLUSION:** Our results suggest that monogenic forms of diabetes, particularly *INS* gene mutations, can be detected in Japanese patients classified with type 1B. Mutation screening, at least of the *INS* gene, is recommended for Japanese patients diagnosed as autoantibody negative at <5 yr of age.

3 世代にわたって若年発症しているような家族性糖尿病を MODY といい、特定の遺伝子の変異で起こることが報告されています。学校糖尿病検診で診断される小児非肥満 2 型糖尿病の中に高率にグルコキナーゼ遺伝子変異による糖尿病 (MODY2) が存在することを示し、従来日本人には少ないとされてきた MODY2 が実は多いことを見いだしました。( *Endocr J.* 58:741-6, 2011)

**Detection of glucokinase gene defects in non-obese Japanese children diagnosed with diabetes by school medical examinations.**

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**Abstract**

We examined children who were diagnosed with asymptomatic type 2 diabetes by school medical examinations to investigate the existence of glucokinase (GCK) gene defects in this group. Among 20 children diagnosed with asymptomatic type 2 diabetes by school medical examinations between 2003 and 2009 at our 2 hospitals, 8 were classified as non-obese type. Among them, we screened 5 children (2 boys and 3 girls; age: 8-13 years) who had mild elevation of fasting plasma glucose (108-134 mg/dL) with slightly high internationally standardized HbA1c levels (6.3-6.9%) at first close examination. Written informed consent was obtained and all families agreed to participate in this study. We found 4 different mutations (G223S, G81C, S336X and T228M) in 4 of the examined children. The blood glucose control levels had not become worse in any children during the 2-6 years follow-up period. The inheritance of diabetes with GCK gene defect was later confirmed in 1 family. These results suggest that GCK gene defects exist in non-obese children who are diagnosed with asymptomatic diabetes by school medical examinations. Cases of diabetes that are caused by GCK mutations may not be as rare in Japanese subjects as previously described and could be found in patients tentatively diagnosed as type 2 diabetes