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LETTER TO THE EDITOR

Case of a novel *PAX6* mutation with aniridia and insulin-dependent diabetes mellitus

PAX6 is a transcription factor involved in ocular and neural development, and *PAX6* mutations result in ocular anomalies, one of which is aniridia[1]. PAX6 is also expressed in the pancreas, and pancreatic islet cells showed dysplasia in a *PAX6* homozygous mutation mouse model[1]. In humans, one patient with a *PAX6* heterozygous mutation presented with aniridia and early-onset diabetes mellitus with a relatively low insulin secretory capacity[2]. However, most *PAX6* mutations are associated with mild glucose intolerance[3].

A 63-year-old man with diabetes was admitted to Osaka University Hospital, Suita, Japan. At the age of 12 years, he was diagnosed with aniridia. At the age of 31 years, his fasting plasma glucose and hemoglobin A1c levels were 279 mg/dL and 14.8%, respectively. He was diagnosed with diabetes, and biphasic insulin therapy was started immediately (12 U/day); intensive insulin therapy was started by the age of 40 years. On admission, his body mass index was 22.9 kg/m^2. His hemoglobin A1c was 9.7%, and both fasting serum C-peptide level and that at 6 min after an intravenous injection of 1 mg of glucagon were undetectable. The patient was negative for antibodies against glutamic acid decarboxylase, insulinoma-associated antigen 2 and zinc transporter 8. He continued to receive basal–bolus insulin therapy and was discharged with a total daily dose of 26 units of insulin.

His eldest son also had aniridia, but was not diagnosed with diabetes until his death at the age of 26 years. His mother was diagnosed with diabetes at an older age, and she did not receive insulin therapy. His eldest daughter was diagnosed with acute-onset type 1 diabetes at the age of 35 years, her anti-glutamic acid decarboxylase antibody was positive and she is currently treated with continuous subcutaneous insulin infusion. She had been diagnosed with congenital glaucoma in childhood, but does not have any symptom nor sign suggesting aniridia now. The pedigree tree is shown in Figure 1.

The patient had a heterozygous 4-bp duplication in exon 7 of the *PAX6* gene (c.483_486dupTTGG); this mutation has previously been reported[4]. This duplication led to a frameshift and a subsequent premature stop codon in exon 8. There were no mutations in any other exons. The patient's eldest daughter did not have this mutation. These genetic analyses were carried out with the approval of the Clinical Genetics Unit in our hospital. Written informed consent was obtained after genetic counseling.

This is the first case of *PAX6* mutation with aniridia and diabetes with the complete loss of insulin secretory capacity. The gradual decrease in insulin secretory capacity and negative islet autoimmunity suggests that the patient

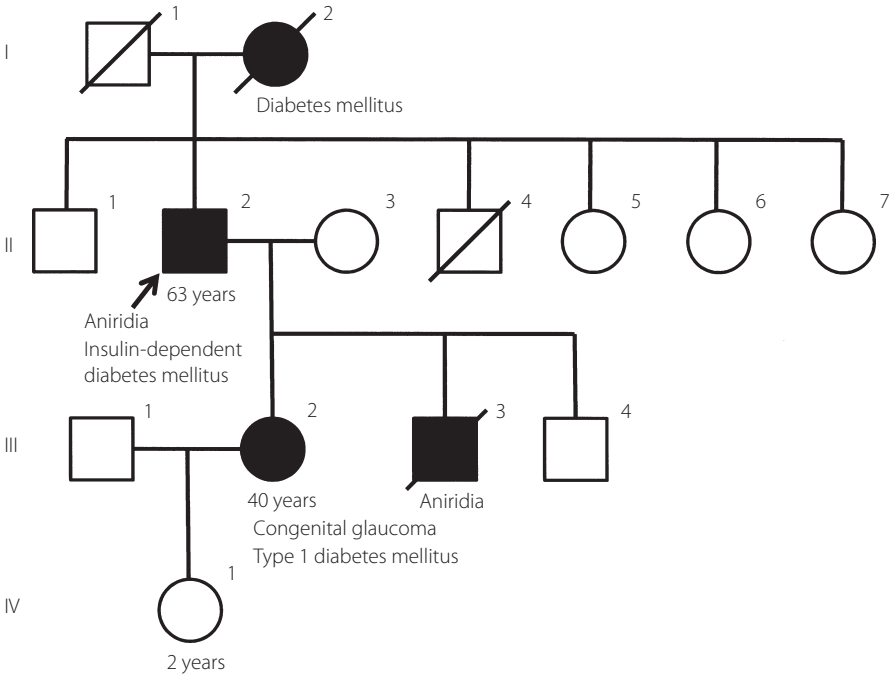

Figure 1 | Pedigree tree of the patient. Black arrow indicates the proband. His eldest son had also aniridia and was not diagnosed with diabetes until his death at the age of 26 years. His eldest daughter was diagnosed with congenital glaucoma when she was a child and was diagnosed with autoimmune type 1 diabetes mellitus at the age of 35 years. His mother was diagnosed with diabetes mellitus at an older age.

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does not have typical type 1 diabetes. Considering that the function of PAX6 in the present case might be kept at half, though the messenger ribonucleic acid with premature stop codon is degraded by nonsense-mediated messenger ribonucleic acid decay and that heterozygous *PAX6* mutations usually cause mild glucose intolerance[3], other genetic factors, which might have been involved in the onset of diabetes of his mother or his eldest daughter, in addition to the *PAX6* mutation, might affect his insulin secretory capacity, leading to complete loss of insulin.

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DISCLOSURE

The authors declare no conflict of interest.

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