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LETTER TO THE EDITOR

Case of aniridia with a heterozygous *PAX6* mutation in which the glucagon response to arginine was evaluated

Pax6 is a highly evolutionally conserved transcription factor involved in the development of the eye and pancreatic islets. In humans, a heterozygous *PAX6* mutation causes aniridia and mild glucose intolerance with impaired insulin secretion[1]. However, there have been no reports evaluating pancreatic α-cell function in aniridia patients with heterozygous *PAX6* mutations. We herein present the first case of an aniridia patient with a heterozygous *PAX6* mutation in which pancreatic α-cell function was evaluated.

A 40-year-old woman with aniridia and obesity (165 cm, 86 kg, body mass index 31.6 kg/m^2) was admitted to the Department of Metabolic Medicine, Osaka Hospital, Suita, Japan, for an endocrine examination. In childhood, she was diagnosed with aniridia, and at 28 years-of-age, it was found that she had a heterozygous *PAX6* mutation (c.969C>T) leading to a truncated protein lacking a transactivation domain. The mutant PAX6 protein in the patient did not exert any transcriptional activity[1]. On admission, a 75-g oral glucose tolerance test showed impaired glucose tolerance (IGT) with impaired insulin secretion (Table 1). On an arginine stimulation test (a 10% L-arginine hydrochloride solution [300 mL] was given intravenously over 30 min), the area under the concentration–time curve for the immunoreactive glucagon (AUC_{IRG}) between time 0 and 120 min was calculated by means of the trapezoidal rule. The serum glucagon concentration was measured by RIA (SRL, Tokyo, Japan) similar to that in non-diabetic Japanese controls[2]. As a result, AUC_{IRG} in the present case was comparable with that in non-diabetic Japanese controls (25.9 pg/mL/min × 10^3 vs 25.20 ± 7.76 pg/mL/min × 10^3)[2].

Recently, the involvement of glucagon in the pathogenesis of diabetes has drawn much attention. Pax6 is a transcription factor involved in the development of pancreatic α- and β-cells. Mice with a targeted disruption of Pax6 die soon after birth with an absence of glucagon-producing α-cells and a marked reduction of insulin producing β-cells. In heterozygous Pax6 mutant mice lacking a transactivation domain similar to the present case, α- and β-cells are reduced to 25 and 40% of wild type[3]. In contrast, aniridia patients with heterozygous *PAX6* mutations had mild glucose intolerance with impaired insulin secretion[1]. However, secretory properties of glucagon in those patients were unclear. The present case showed impaired insulin secretion, whereas her glucagon response to arginine was comparable with those in non-diabetic control subjects. Although we could not conclude, because we failed to assess the glucagon responses to arginine in the control subjects with obese and IGT, and the other subjects with *PAX6* mutation, this result might not necessarily show that her glucagon capacity is normal. This is because it has been shown that glucagon response to arginine in patients with IGT and/or obesity, as well as the present case, is exaggerated. Therefore, the result that her glucagon secretory capacity was not exaggerated despite her obesity and IGT could suggest her impaired glucagon secretory capacity. To the best of our knowledge, the present case is the first report to evaluate pancreatic α-cell function in a patient with a heterozygous *PAX6* mutation. In addition, interestingly, recent studies have shown that blocking glucagon action prevents diabetes[4]. Considering these results, the cause of a mild degree of glucose intolerance in patients with heterozygous *PAX6* mutations might be partially because of decreased glucagon secretion.

In conclusion, we presented the first case of an aniridia patient with a heterozygous *PAX6* mutation in which the glucagon response to arginine was evaluated. Further human studies are required to show the association of *PAX6* mutations with glucagon secretion.

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Table 1 | Results of 75-g oral glucose tolerance test in the patient

Time (min)	0	15	30	60	90	120
PG (mg/dL)	111	149	177	207	194	184
IRI (μU/mL)	10.3	31.7	38.9	58.2	63.8	59.5

IRI, immunoreactive insulin; PG, plasma glucose.

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