Coincidence of a Novel KCNJ11 Missense Variant R365H With a Paternally Inherited 6q24 Duplication in a Patient With Transient Neonatal Diabetes

OBJECTIVE — Neonatal diabetes is a heterogeneous group of disorders with diabetes manifestation in the first 6 months of life. The most common etiology in permanent neonatal diabetes is mutations of the ATP-sensitive K+ channel subunits; in transient neonatal diabetes, chromosome 6q24 abnormalities are the most common cause.

RESEARCH DESIGN AND METHODS — We report a sporadic case of diabetes without ketoacidosis diagnosed on the fourth day of life.

RESULTS — Analysis of the KCNJ11 gene found a novel R365H mutation in the proband and her unaffected father. The functional analysis did not support pathogenicity of this variant. When the patient’s diabetes remitted in the seventh month of life, the 6q42 region was analyzed and a paternally inherited duplication was identified.

CONCLUSIONS — Our case reports a coincidental novel KCNJ11 variant in a patient with transient neonatal diabetes due to a 6q24 duplication, illustrating the difficulty in testing neonates before the clinical course of neonatal diabetes is known.

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Neonatal diabetes is a heterogeneous group of disorders with diabetes manifestation before 6 months of life that most frequently has a monogenic etiology (1). In patients with permanent neonatal diabetes (i.e., without remission) (PND), mutations of the KATP channel subunits (encoded by the KCNJ11 and ABCC8 genes) and mutations of the insulin gene are the most common etiology (1). Transient neonatal diabetes (TND) usually resolves by 6 months of age, but more than 50% of TND patients relapse into diabetes during childhood or adulthood (2). Abnormalities of the imprinted region, 6q24, which encompasses the ZAC and HYMAI genes, cause ~70% of TND cases (3). Mutations of KATP channel subunits are the second most common etiology (3).

RESEARCH DESIGN AND METHODS — We report on a patient who was born with a birth weight of 2,320 g at 38 weeks’ postgestation (<3rd centile). Because of the low birth weight, she required hospitalization at the newborn care unit. She was diagnosed with diabetes without ketoacidosis on the fourth day of postnatal life (blood glucose 19.5 mmol/l). The initial treatment was intravenous insulin (0.04 units · kg⁻¹ · h⁻¹), followed by subcutaneous injections of NPH insulin (0.9 units · kg⁻¹ · day⁻¹).

RESULTS — At the age of 2 weeks and following a clinical diagnosis of neonatal diabetes, analysis of the KCNJ11 gene was undertaken (3). We found a novel, heterozygous missense mutation, R365H (c.1094G>T; p.Arg365His), in the proband. The mutation was present in the unaffected father and paternal grandfather (Fig. 1). Standard oral glucose tolerance tests revealed a normal glucose tolerance with normal insulin and C-peptide values in the parents and paternal grandmother, but the paternal grandfather had impaired fasting glycemia combined with impaired glucose tolerance (0-h glycemia 5.8 mmol/l; 2-h glycemia 9.4 mmol/l).

KATP channel mutations causing TND in the proband and adult-onset diabetes in a parent and/or grandparent have been previously reported (3). The R365H mutation identified in our family was thought likely to be pathogenic because the arginine residue at codon 365 is conserved in dog, rat, and mouse, was not present in 298 control chromosomes, and has not previously been reported in patients with hyperinsulinism. Therefore, in vitro functional studies of this mutation were undertaken. Channels containing the R365H mutation were expressed in Xenopus oocytes and their surface density, activation by the metabolic inhibitor tolbutamide were measured (4). Unexpectedly, there was no difference between the wild-type and mutant channels, which calls into question the pathogenicity of this mutation.

In the meantime, the patient developed hypoglycemia on insulin treatment, and at the age of 7 months, the insulin...
was identified, and family member testing demonstrated that the duplication was also present in the unaffected father and paternal grandmother (Fig. 1).

CONCLUSIONS — We report a novel KCNJ11 variant (R365H) and a 6q24 duplication in a proband with TND and her unaffected father. The paternally inherited 6q24 duplication is likely to be the etiological mutation as a consequence of overexpression of paternal genes within the duplicated chromosome 6q24 region. Expression of genes in this region is regulated by imprinting. The maternal allele is methylated and therefore inactive: only genes on the paternally derived chromosome are transcribed. Normal development depends on normal doses of gene transcripts. The proband’s father is unaffected because his 6q24 duplication is maternally inherited and, therefore, inactive (2). The impaired fasting glycaemia and impaired glucose tolerance in the paternal grandfather may be influenced by his age (53 years), weight (BMI 28.5 kg/m²), and maternal history of type 2 diabetes. We conclude that the R365H is likely to be a rare variant of no clinical significance.

In PND patients, screening of the KCNJ11 mutations is recommended, and if it is negative, mutations in other genes should be investigated (e.g., insulin gene, ABCC8, etc.) (1,6). In the case of TND, KATP channel genes should be tested if the duplication was inherited and, therefore, inactive (2). The impaired fasting glycaemia and impaired glucose tolerance in the paternal grandfather may be influenced by his age (53 years), weight (BMI 28.5 kg/m²), and maternal history of type 2 diabetes. We conclude that the R365H is likely to be a rare variant of no clinical significance.

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