OBSERVATIONS

Paternally Inherited Proinsulin Mutations May Result in Earlier Onset of Monogenic Diabetes Mutation Identity Effect in Monogenic Diabetes

Mutations within the human proinsulin gene (*INS*) have been reported to cause neonatal, maturity onset diabetes of the young (MODY), and antibody-negative idiopathic type 1 diabetes (1–3). However, because the expression of maternally or paternally transmitted *INS-IGF2* alleles is different as a result of selective methylation (imprinting) (4), we surmised that the effect of *INS* mutations may depend on the origin of the mutated allele.

To verify this hypothesis, pairs comprising an affected child and parent carrying the same heterozygous *INS* mutation were studied. A literature search was performed and yielded eight relevant articles reporting heterozygous *INS* mutations in neonatal, MODY, or antibody-negative type 1 diabetes (supplementary Table 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-1142/DC1). We also included an unpublished case (Pol52 in the Polish Registry of Neonatal Diabetes) with a *Y50C* mutation. The proband presented with diabetes during the 3rd day of life, whereas her father had been diagnosed at 7 years of age and treated as antibody-negative type 1 diabetes.

Altogether, 29 affected parent-child pairs were included from a total of 104 reported *INS* mutation cases. Of these 29 pairs, 16 (55%) of the children had inherited the mutated allele from their mother. In these maternally transmitted cases, 56% of the children developed neonatal diabetes compared with 85% in the paternally transmitted cases ($P = 0.13$). Median age at diagnosis in child/mother pairs was 39.5 months (interquartile range 7.25–162) in children and 48 months (4.13–174) in their mothers. In child/father pairs, median age at diagnosis was 2.5 months (1.75–8.5) and 84 months (36–264), respectively. The difference in age at diagnosis between children and parents was statistically significant for paternally transmitted mutations ($P = 0.0003$) but not for maternally transmitted mutations ($P = 0.82$). Children born with a mutated *INS* allele transmitted from their fathers did not, however, show statistically significant earlier onset than those with maternally transmitted mutations ($P = 0.24$) due to correction for multiple hypothesis testing. Age at diagnosis of parents was similar ($P = 0.89$).

Our analysis of the pooled data seemed to confirm the hypothesis of an allele-identity impact on the course of monogenic diabetes caused by heterozygous *INS* mutations. Maternal transmission of the mutated *INS* allele would then be associated with preferential silencing of the mutated allele, whereas paternal transmission would result in silencing of the functional maternal copy. Clinically, this effect would be manifested in a gap of age at diagnosis between children and their fathers, at least when the father himself has acquired the mutation de novo or inherited it from his mother.

INS mutation results in impaired insulin secretion, disturbed intracellular trafficking, and endoplasmic reticulum stress (5), and the presence of different mutations could explain between-patient differences in age at diagnosis. However, this would not influence the impact of parental allele inheritance because the biological effect of the mutation should be the same in both generations. We therefore conclude that genetic imprinting of the *INS-IGF2* region seems to be a likely explanation of the reported differences in age at onset of monogenic diabetes caused by *INS* mutations. This observation could be used for selection of genes for screening in patients suspected of having monogenic forms of diabetes.

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