OBSERVATIONS

HNF1B Abnormality (Mature-Onset Diabetes of the Young 5) in Children and Adolescents

High prevalence in autoantibody-negative type 1 diabetes with kidney defects

Mature-onset diabetes of the young 5 (MODY5) is characterized by a wide clinical spectrum, including diabetes and kidney disease (1–3). Associated gene defects are either mutations within *HNF1B* or a 1.4–1.5 Mb monoallelic deletion of chromosome 17q12 including *HNF1B* (4,5). Up to now, information on prevalence of MODY5 in children and adolescents with diabetes has been very limited (2). We now report prevalence of MODY5 and associated anomalies of *HNF1B* in a large cohort of children and adolescents with diabetes being followed at our diabetes center.

Analysis of the *HNF1B* gene was performed by DNA sequencing of all exons (including flanking introns), and samples with normal sequence variants were subsequently analyzed for deletions or duplications using quantitative multiplex PCR of short fluorescent fragments, as described previously (3). Presence and size of disease-causing chromosomal rearrangements detected by quantitative multiplex PCR of short fluorescent fragments was completed by array-based comparative genomic hybridization and fluorescence in situ hybridization, as described previously (4). Genetic studies have been approved by the ethical committee of the Charité.

Within our cohort of 623 children and adolescents with diabetes, 95% had type 1 diabetes, 3% monogenic diabetes (with genetic diagnosis), and <1% type 2 diabetes. In terms of autoimmune markers, 84 had no β-cell autoantibodies (GADA, tyrosine phosphatase-like insulinoma antigen 2 [IA-2A], insulin autoantibody [IAA], or islet cell antibody [ICA]) at diabetes onset and were classified as type 1B diabetic. Of these, 37 had at least one of the following features suggesting monogenic diabetes: *1*) parent with diabetes, *2*) associated extrapancreatic features, and *3*) detectable C-peptide outside honeymoon phase. DNA of these patients was tested for defects of the most frequent MODY genes (*GCK, HNF1A, HNF4A,* and *HNF1B*) but also for *HNF1B* deletion. Overall, we found three new cases with a heterozygous *HNF1B* gene deletion but no point mutation of *HNF1B*. In these three cases and a fourth known case with *HNF1B* deletion (4), family history did not indicate MODY5-associated organ disease, and fluorescence in situ hybridization analysis in seven parents tested (except one father) did not show the deletion. Therefore, new deletion of *HNF1B* in these patients is most likely.

Prevalence of MODY5 was 0.6% (4 of 623 subjects) in our cohort but 4.7% (4 of 84 subjects) in all subjects, with autoantibody-negative (type 1B) diabetes. In the subgroup of those with genetic testing for MODY, prevalence was much higher, 11% (4 of 37 subjects). Moreover, in seven cases with known kidney malformations, three had positive autoantibodies, and all four autoantibody-negative cases had the *HNF1B* deletion. Nevertheless, relevance of genetic testing was underlined by the fact that some abnormalities have been found only after genetic diagnosis of *HNF1B* defect, including one case with cystic kidney disease, two cases with pancreas dysplasia, and, finally, one girl with bicornuate uterus. Also, dyslipidemia and liver disease in two cases have been explained by the diagnosis of *HNF1B* deletion.

Overall, prevalence of MODY5 was less than 1% in all patients but between 4.7 and 11% in patients with autoantibody-negative diabetes. Therefore, MODY5 might still be underdiagnosed in cohorts with pediatric and adolescent-onset diabetes. Most importantly, if structural kidney defects are found in these children, MODY5 is a very likely diagnosis.

KLEMENS RAILE, MD[1]
EVA KLOPOCKI, PHD[2]
THEDA WESSEL, MD[1]
DOROTHEE DEISS, MD[1]
DENISE HORN, MD[2]
DOMINIK MÜLLER, MD[3]
REINHARD ULLMANN, PHD[4]
ANNETTE GRÜTERS, MD[1]

From the [1]Institute for Experimental Pediatric Endocrinology and Diabetes, Charité Campus Virchow, Berlin, Germany; the [2]Institute for Medical Genetics, Charité Campus Virchow, Berlin, Germany; the [3]Department of Pediatric Nephrology, Charité Campus Virchow, Berlin, Germany; and the [4]Max Planck Institute for Molecular Genetics, Berlin, Germany.

Corresponding author: Klemens Raile, klemens.raile@charite.de.

DOI: 10.2337/dc08-0920

Acknowledgments— We are very grateful for the very detailed technical work of Fabienne Trotier, including fluorescence in situ hybridization analysis and array-based comparative genomic hybridization analysis at the Department of Medical Genetics.

References

1. Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, Lindner T, Yamagata K, Ogata M, Tomonaga O, Kuroki H, Kasahara T, Iwamoto Y, Bell GI: Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet* 17:384–385, 1997
2. Edghill EL, Bingham C, Ellard S, Hattersley AT: Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. *J Med Genet* 43:84–90, 2006
3. Bellanne-Chantelot C, Clauin S, Chauveau D, Collin P, Daumont M, Douillard C, Dubois-Laforgue D, Dusselier L, Gautier JF, Jadoul M, Laloi-Michelin M, Jacquesson L, Larger E, Louis J, Nicolino M, Subra JF, Wilhem JM, Young J, Velho G, Timsit J: Large genomic rearrangements in the hepatocyte nuclear factor-1β (*TCF2*) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes* 54:3126–3132, 2005
4. Muller D, Klopocki E, Neumann LM, Mundlos S, Taupitz M, Schulze I, Ropers HH, Querfeld U, Ullmann R: A complex phenotype with cystic renal disease. *Kidney Int* 70:1656–1660, 2006
5. Mefford HC, Clauin S, Sharp AJ, Moller RS, Ullmann R, Kapur R, Pinkel D, Cooper GM, Ventura M, Ropers HH, Tommerup N, Eichler EE, Bellanne-Chantelot C: Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes, and epilepsy. *Am J Hum Genet* 81:1057–1069, 2007