

Renal Malformations May Be Linked to Mutations in the Hepatocyte Nuclear Factor-1 α (MODY3) Gene

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Maturity-onset diabetes of the young (MODY) is an autosomal-dominant form of disease characterized by β -cell defects and early age of diagnosis. So far, six MODY genes have been identified (1,2). MODY is sometimes accompanied by extrapancreatic features such as developmental malformations and physiological and biochemical abnormalities (3). The most frequent MODY3 subtype is caused by mutations in the hepatocyte nuclear factor (HNF)-1 α gene, a transcription factor expressed in pancreas, kidney, liver, and gut.

RESEARCH DESIGN AND METHODS

— To dissect the genetic background and to provide clinical characteristics of this form of diabetes in Poland, the Nationwide Registry was established in 2004 at the Department of Metabolic Diseases, Jagiellonian University Medical College in Krakow. So far, 30 families with the early-onset, autosomal-dominant form of diabetes meeting commonly used criteria of MODY (diabetes occurring in at least three generations and at least two individuals diagnosed with diabetes before the age of 25 years) were included in this program. The subjects from those families received a standard questionnaire that contained questions regarding the age of diabetes diagnosis, family history, treatment method, and

other medical issues. Fasting blood was drawn for plasma glucose determinations, other biochemical measurements, and DNA extraction. The study protocol and informed consent procedures were approved by the ethical committee of the Jagiellonian University, Medical College. The project is conducted according to the rules of the Helsinki Declaration.

RESULTS — In the process of screening for HNF-1 α (MODY3) mutations, the 10 exons and promoter region of the gene were analyzed by direct sequencing of the PCR product using DNA from the probands of included families. So far, after screening 20 index cases, six mutations were identified. They segregated with diabetes in the families where they were identified. Four of them were missense mutations: two previously identified (Arg131Gln and Arg271Trp) and two newly discovered (Ser249Pro and Asn257Thr). Two other mutations included a previously published frameshift Pro379fsdelCT mutation in exon 6 and the cryptic splice acceptor site mutation IVS7nt-6G>A. The latter mutation was earlier reported to result in the skipping of exon 7 and a premature termination codon (4).

Interestingly, in two MODY3 families, developmental abnormalities were reported in the questionnaires provided

by the patients. In the index case from family A (Fig. 1A) with the IVS7nt-6G>A mutation, a 28-year-old woman (individual 2) was diagnosed with kidney agenesis and genital malformation (a bicornuate uterus). The kidney abnormalities were discovered in 1993 by ultrasonographic examination and subsequently confirmed by urography. This patient was diagnosed with diabetes at the age of 17 years, and by the time of examination, she developed proliferative retinopathy, massive proteinuria, and diabetic foot syndrome. In spite of developmental malformations and diabetes complications, she delivered a daughter with low birth weight, but otherwise healthy. We identified four more mutation carriers in her family: three of them were diabetic patients, and one, a 12-month-old baby, had normal glucose levels. In all members of Family A included in the study, we performed ultrasonographic examination of the abdomen. In the proband's brother (individual 5), who was an IVS7nt-6G>A mutation carrier, an ectopic (pelvic), dysmorphic, and slightly hypoplastic (96 \times 40 mm) left kidney was described. There was no evidence of developmental abnormalities in other members of this family.

Family B with Arg271Trp amino acid substitution (previously described in a French population) (5) is shown in Fig. 1B. This pedigree included just two mutation carriers: a proband and her daughter (individuals 3 and 6, respectively). Both parents of the proband (individuals 1 and 2) were not mutation carriers. Paternity testing by 16 polymorphic markers indicated that the Arg271Trp mutation in family B have arisen de novo, a phenomenon rarely reported so far in MODY pedigrees. The proband's daughter, who developed diabetes at the age of 15 years, was diagnosed with a single functioning kidney by ultrasonography 6 years before entering this study. Soon after this diagnosis, it was confirmed by urography and renal scintigraphy. In addition, in her mother, the proband from family B, multiple small cysts of the right kidney (the largest 27 \times 31 mm) were described on ultrasonography. No other member of this family was diagnosed with congenital malformations.

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Abbreviations: HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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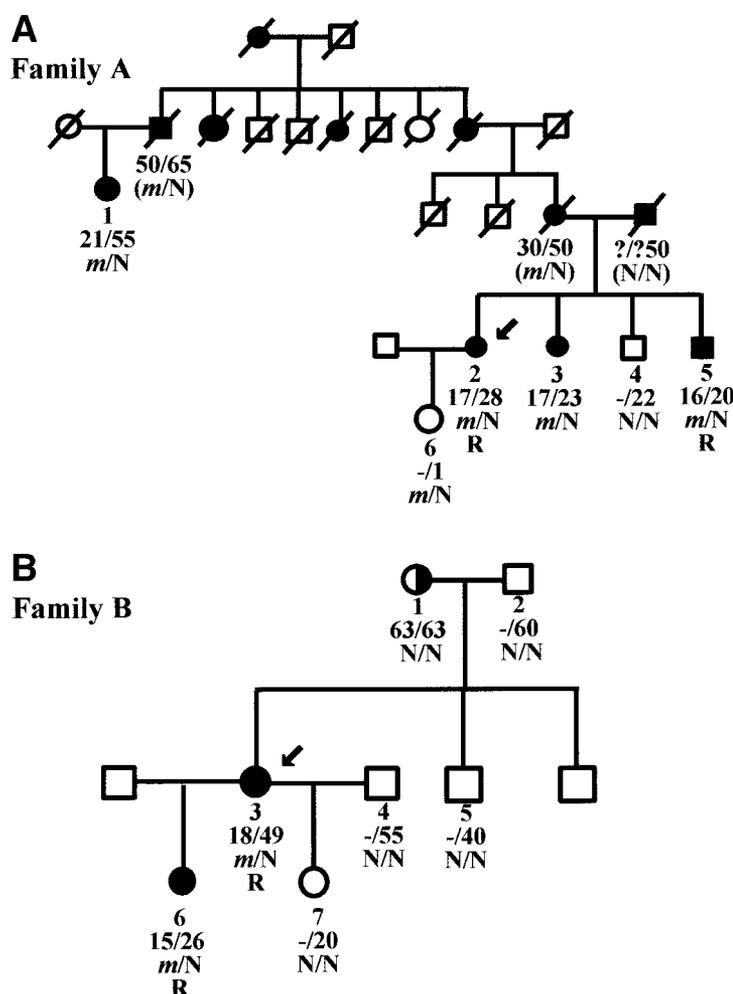


Figure 1—A: Pedigree, genotypes, and clinical characteristics of family A. The segregation of IVS7nt-6G>A mutation is shown. At the time of examination, individuals 1, 2, and 3 were taking insulin, and individual 5 was on sulfonylurea agent. An arrow indicates the index case. Closed, half-closed, and open symbols represent subjects with diabetes, impaired glucose tolerance, and normal glucose tolerance, respectively. The first line under the symbols is the identification number of the examined individual. The second line is the age at diabetes diagnosis for affected members, age at death for deceased members, and age at examination for others. The third line is the genotype at -6 bp in intron 7 of the gene. In the last line, the information about renal phenotype was provided where appropriate. The genotype in parentheses has been inferred for two deceased subjects. N, normal allele; m, mutant allele; R, presence of renal malformations. B: Pedigree, genotypes, and clinical characteristics of family B. The symbols and the data are the same as in A. The genotype applies to codon 271 of the gene. At the time of examination, individuals 3 and 6 were taking insulin.

Since there were earlier reports on mutations in the HNF-1 β gene resulting in disorders of renal and genital development and early-onset diabetes (MODY5) (6), we performed a screening by direct sequencing for HNF-1 β mutations in both diabetic individuals with major congenital defects of a single functioning kidney (individual 2 from family A and individual 3 from family B, respectively). This search, however, produced negative results.

CONCLUSIONS— Our report constitutes the first observation suggesting

that mutations in HNF-1 α may, although probably more rarely than in HNF-1 β , produce the phenotype of renal malformations. HNF-1 α is expressed in the early development of the kidney, although later than in HNF-1 β (7). In spite of a large number of MODY3 families reported worldwide, including one with IVS7nt-6G>A mutation and one with Arg271Trp substitution, no renal abnormalities were described in mutation carriers, the only renal HNF-1 α -related phenotype reported being an altered tubular glucose reabsorption (8). Interestingly, we observed them in two families in this rela-

tively modest-in-size collection from the Polish population. One possible explanation is that the expression of this phenotype in affected individuals is influenced by unidentified polygenic or environmental factors. It should also be admitted that one cannot entirely rule out that renal abnormalities in MODY3 mutation carriers from both families were caused by other inherited factors unrelated to diabetes causing sequence differences. We postulate that MODY families with renal developmental abnormalities that were negatively screened for HNF-1 β mutations should be first in line to be screened for sequence differences in the HNF-1 α gene. We also suggest the reevaluation of MODY3 families from other collections in search for these kind of defects. The occurrence of a single case of genital abnormalities (bicornuate uterus) in one woman with HNF-1 α mutation might well be an incidental finding and should be considered with caution.

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