The Type and the Position of HNF1A Mutation Modulate Age at Diagnosis of Diabetes in Patients with Maturity-Onset Diabetes of the Young (MODY)-3

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Résumé en anglais	**OBJECTIVE**—The clinical expression of maturity-onset diabetes of the young (MODY)-3 is highly variable. This may be due to environmental and/or genetic factors, including molecular characteristics of the hepatocyte nuclear factor 1-α (*HNF1A*) gene mutation. **RESEARCH DESIGN AND METHODS**—We analyzed the mutations identified in 356 unrelated MODY3 patients, including 118 novel mutations, and searched for correlations between the genotype and age at diagnosis of diabetes. **RESULTS**—Missense mutations prevailed in the dimerization and DNA-binding domains (74%), while truncating mutations were predominant in the transactivation domain (62%). The majority (83%) of the mutations were located in exons 1- 6, thus affecting the three *HNF1A* isoforms. Age at diagnosis of diabetes was lower in patients with truncating mutations than in those with missense mutations (18 vs. 22 years, $P = 0.005$). Missense mutations affecting the dimerization/DNA-binding domains were associated with a lower age at diagnosis than those affecting the transactivation domain (20 vs. 30 years, $P = 10-4$). Patients with missense mutations affecting the three isoforms were younger at diagnosis than those with missense mutations involving one or two isoforms ($P = 0.03$). **CONCLUSIONS**—These data show that part of the variability of the clinical expression in MODY3 patients may be explained by the type and the location of *HNF1A* mutations. These findings should be considered in studies for the search of additional modifier genetic factors.
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