Low Prevalence of *HNF1A* Mutations After Molecular Screening of Multiple MODY Genes in 58 Italian Families Recruited in the Pediatric or Adult Diabetes Clinic From a Single Italian Hospital

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Maturity-onset diabetes of the young (MODY; MIM# 606391) is a genetically and clinically heterogeneous form of diabetes, accounting for 1–2% of all diabetes cases (1). MODY is characterized by mild hyperglycemia or overt diabetes usually detected in three consecutive generations, with onset before the age of 25 years and absence of type 1 diabetes autoantibodies. Among the thirteen MODY genes identified, two subtypes, *GCK*-MODY and *HNF1A*-MODY, account for most of cases (1). The prevalence of *GCK*-MODY has been reported higher in Southern Europe (2), while *HNF1A*-MODY is the most common MODY subtype in Northern Europe (3). This difference might be attributable to the clinical setting in which genetic screening is performed, especially when pediatric and adult diabetes clinics are distinct entities. We addressed this issue by investigating MODY patients identified in the pediatric or in the adult diabetes clinics of the same research-based hospital in Southern Italy to obtain data from a homogeneous geographic and genetic background. We selected 58 probands of Italian ancestry fulfilling stringent MODY criteria: *1*) blood glucose >100 mg/dL (confirmed), *2*) no type 1 diabetes autoantibodies, and *3*) three consecutive generations with hyperglycemia before age 25 years. Forty-three patients were recruited at the pediatric clinic (age 1–18 years) and 15 at the adult clinic (age >18 years). We screened by DNA sequencing six "classic" MODY genes (*HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*) (1) in both groups and *INS* (MODY 10) and *KCNJ11* (MODY 13) genes in the pediatric group.

In the pediatric group, we identified 29 *GCK* (67.4%), 6 *HNF1A* (14%), 2 *HNF4A* (4.6%), and 2 *HNF1B* (4.6%) mutations, with only 4 children (9.3%) remaining without a genetic diagnosis (MODY X). In the adult group, we detected 2 *GCK* (13.3%) ($P < 0.001$ vs. pediatric group), 3 *HNF1A* (20%), and 1 *HNF4A* (6.7%) mutations. Nine adult patients were classified as MODY X (60%, $P < 0.001$ vs. pediatric group) (Table 1).

We thus confirmed that *GCK* mutations represent the most common MODY defect in the pediatric setting, whereas they are rare in patients from the adult diabetes clinic. *HNF1A* mutations ranked second (14%) in the pediatric clinic but accounted for a similar proportion (20%) among adults. This result was in keeping with previous data (14%) obtained in a total of 42 Italian families with autosomal dominant diabetes recruited in Central (Tuscany, Sardinia) and Northern (Piedmont) Italy (4,5), and it was in sharp contrast with results obtained in Northern Europe (3). The major strength of our investigation is that the two groups of patients were recruited from the same geographic area and screened in the same laboratory. Conversely, we acknowledge that the small number of families in the adult group represents a study limitation. Thus, these results need to be replicated before one can firmly conclude that there is a "latitude" of MODY across Europe. In all, our study confirms that *HNF1A* mutations are much less prevalent in Italy compared with Northern Europe and that this does not depend on ascertainment bias.

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Table 1—MODY gene mutations found in our sample

MODY gene mutated	Patients	Nucleotide change	Mutations (probands)	Age at clinical diagnosis (years)	Age at molecular screening (years)	Blood glucose (mg/dL)	HbA_{1c} (%)	Treatment at molecular diagnosis
HNF4A (NM_175914.4)	2 pediatric patients (4.6%)	c.932G>A c.340C>T	p.Arg311Hist (1) p.Arg114Trp (1)	9.2–11.8	9.9–12	103–119	5.5–6.7	None
	1 adult patient (6.7%)	c.340C>T	p.Arg114Trp (1)	20.1	66	167	9.2	OAD
GCK (NM_000162.3)	29 pediatric patients (67.4%)	c.49G>T c.146C>T§ c.175C>T c.218A>G c.401T>C c.571C>T c.667G>A c.676G>A c.683C>T c.704T>C c.793G>A c.866A>G c.1112delG§ c.1114G>T	p.Glu17Term (2) p.Thr49Ile@ (1) p.Pro59Ser (6) p.Asp73Gly (1) p.Leu134Pro (1) p.Arg191Trp (2) p.Gly223Ser (7) p.Val226Met (1) p.Thr228Met (2) p.Met235Thr (1) p.Glu265Lys (1) p.Tyr289Cys (2) p.Cys371Serfs31# (1) p.Glu372Term (1)	0.8–13.9	0.9–14.3	106–131	5.8–7.4	1 patient: diet; 28 patients: none
	2 adult patients (13.3%)	c.175C>T c.775G>A	p.Pro59Ser (1) p.Ala259Thr (1)	17.9–18.6	44–45	113–132	5.4–5.7	1 patient: diet; 1 patient: OAD
HNF1A (NM_000545.5)	6 pediatric patients (14%)	c.160C>T c.392G>A c.686G>A c.814C>T c.1061C>T c.1330_1331delCA	p.Arg54Term (1) p.Arg131Gln (1) p.Arg229Gln (1) p.Arg272Cys (1) p.Thr354Met (1) p.Gln444Glufs*104 (1)	14.1–17.8	14.2–19.1	109–149	5.9–8.1	3 patients: none; 2 patients: insulin; 1 patient: OAD
	3 adult patients (20%)	c.787C>T c.864dupG c.1859C>T	p.Arg263Cys (1) p.Pro291Glnfs*51 (1) p.Thr620Ile (1)	17.9–19.6	21.5–61	124–219	7.2–9.5	1 patient: none; 2 patients: insulin
HNF1B (NM_000458.2)	2 pediatric patients (4.6%)	c.443 C>T c.827 G>A	p.Ser148Leu (1) p.Arg276Gln (1)	7.5–15.4	9.6–16.9	Not available	Not available	Insulin
Unknown (MODY X)	4 pediatric patients (9.3%)	—	—	4.5–12.8	7.8–16.5	106–252	5.6–7.8	1 patient: insulin; 3 patients: none
	9 adult patients (60%)	—	—	16.1–24.8	24–57.9	112–258	6.6–9.8	4 patients: insulin; 3 patients: insulin + OAD; 2 patients: OAD

OAD, oral antidiabetes drug. Reference sequences together with mutations nomenclature are reported according to the Human Gene Mutation Database Professional 2014.2. §Novel mutations cosegregating with hyperglycemia in each family not found in 396 alleles of nondiabetic individuals and 276 alleles of patients with type 2 diabetes. @Mutation predicted to be probably damaging by PolyPhen-2. #Deletion predicted to be probably damaging by MutationTaster.

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