CLINICAL STUDY

Genetic and clinical characteristics of patients with *HNF1A* gene variations from the German–Austrian DPV database

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Abstract

Objective: To determine prevalence, genetic and phenotype characteristics of patients with hepatocyte nuclear factor-1 α (*HNF1A*) variants in the Diabetes Patienten Verlaufsdokumentation (DPV) multicentre database and to examine the influence of *HNF1A* mutation type, or location on clinical phenotypes.

Patients and methods: Seventy-one DPV patients were labelled as *HNF1A*-MODY (MODY3). Forty-four patients carried *HNF1A* mutations, while 27 patients were found to have *HNF1A* polymorphisms only. Associations between mutation type/position and age at disease onset, HbA_{1c}, body mass index (BMI), diagnosis, family history and treatment modality were analysed using non-parametric statistics (Wilcoxon test).

Results: Patients with *HNF1A* mutations were 36% male, aged 14.1 ± 5.8 years at diagnosis, and slightly overweight (BMI-SDS: $+0.8 \pm 1.1$). Treatment was lifestyle intervention (20.5%), insulin (35.3%), oral anti-diabetic (OAD, 43%) and both insulin + OAD (15.9%). More patients with missense mutations (60%) than patients with nonsense mutations/frameshift (23.8%) did not use insulin ($P=0.03$). No differences were found with regard to mutation types, isoform or domain.

We identified several previously undescribed mutations in the cohort including c.-158insGGTTGG in the promoter region, G31X, E41X, Q130X, L162P, R245I, A269P, S355X, Q398X, Q473X, Q495X, E508X, P588fs-insGCCA and P588fs-delAC. Patients carrying *HNF1A* polymorphisms were significantly younger at diagnosis than patients with *HNF1A* mutations (10.9 ± 4.2 vs 14.19 ± 5.8 years; $P=0.027$), and all carried I27L, S487N and A98V ($n=3$).

Conclusion: *HNF1A*-MODY is the second most frequent MODY diagnosis registered in the DPV database, and previously undescribed *HNF1A* mutations account for about one-third of *HNF1A*-MODY cases. Patients with *HNF1A* polymorphisms documented as *HNF1A*-MODY were misclassified. They may have autoantibody-negative type 1B or type 2 diabetes or may have other MODY types.

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Introduction

Heterozygote mutations in hepatocyte nuclear factor-1 α (*HNF1A*) frequently results in maturity onset diabetes of the young (*HNF1A*-MODY) in many populations. This form of diabetes characterized by autosomal dominant inheritance, usually manifests before the age of 25 years and leads to β cell dysfunction/impaired insulin secretion (1–3). Up to date, over 200 *HNF1A* mutations have been described and account for about 1–2% of all diabetes cases (4, 5).

HNF1A consists of ten exons, coding 631 amino acids and has three different isoforms namely: isoform A (exons 8–10), isoform AB (exon 7) and isoform ABC (exons 1–6) formed by alternative splicing and polyadenylation.

The isoform A has a lower transactivation activity compared with the isoforms AB and ABC. Mutations affecting different isoforms have been associated with age at disease onset in certain studies; thus, isoforms may influence the phenotype of disease differently (6, 7).

The *HNF1A* protein consists of a dimerization domain (amino acids 1–33), a bipartite DNA-binding domain (POU domain: 100–184 and homeodomain: 198–281) and a transactivation domain (amino acids 282–631; Fig. 1). Mutations occurring within different domains may also influence age at manifestation differently, depending on type and location of mutations occurrence (7, 8).

The clinical phenotype of *HNF1A*-MODY diabetes varies considerably, and studies examining correlations between genotype and phenotype are still rare. In this

Figure 1 Above: *HNF1A* genome structure indicating the three functional domains: black (dimerization domain), mid-grey (DNA-binding domain) and light grey (transactivation domain). Below: *HNF1A* genome structure indicating isoforms: grey (isoform ABC: exons 1–6); white dotted (isoform AB: exon 7) and white (isoform A: exons 8–10). Exons and corresponding isoforms are indicated with arrows (adapted from Bellané-Chantelot *et al.* 2008 (8)).

work, we investigated the clinical characteristics of patients registered as HNF1A-MODY in the multicentre Diabetes Patienten Verlaufsdokumentation (DPV) database, examined frequency/characteristics of the *HNF1A* variants and found out whether mutation type and position (isomer/functional domain of protein affected) influence the phenotype of disease in these patients. We report on a group of patients, whose clinical phenotype resembled HNF1A-MODY diabetes, and who were classified as such by attending physicians, but whose genetic records indicated they carried *HNF1A* polymorphisms.

The aim of our study was to characterize patients classified as HNF1A-MODY in the DPV database and investigate whether mutation type (missense, nonsense and frameshift), mutation isoforms (ABC, AB or A) or functional domain of mutation (dimerization-, DNA-binding- or transactivation domain) was related to clinical phenotype. Patients carrying *HNF1A* mutations were compared with patients misclassified as HNF1A-MODY but who carried common *HNF1A* polymorphisms.

Subjects and methods

The multicentre DPV database which collates data of patients treated for diabetes (currently from 330 health facilities in Germany and Austria) was used to identify subjects for this study. DPV-participating health centres transmit anonymous, standardized, prospective data of patients twice a year to the central administrative unit in Ulm (Germany) for evaluation and benchmarking. In order to guarantee data validity, all inconsistent data are reported back to respective centres for correction every 6 months (9).

If a specific genetic defect in *HNF1A* was found, patients were registered in the database as HNF1A-MODY by the attending physicians. For this investigation, centres who registered HNF1A-MODY patients were contacted and requested (via questionnaires) to specify how HNF1A-MODY diagnosis was confirmed

and to provide detailed genetic data on the *HNF1A* abnormalities detected alongside information on patients' family history of diabetes. When a first or second degree relative was diabetic, additional data on their diabetes phenotype were requested, including current age, age at diagnosis, type of treatment received (insulin, oral anti-diabetic (OAD) agents or lifestyle intervention) and presence of complications (retinopathy and nephropathy) if investigated.

Data analysis was carried out using the Statistical Analysis Software (SAS, 9.2 Cary, NC, USA). Mean and s.d. of variables were computed. Significant differences ($P < 0.05$) between quantitative variables were analysed using Wilcoxon test and reported.

Results

Description of the study cohort

In total, 401 patients documented in the multicentre DPV database were labelled MODY, 17 HNF4A-MODY (MODY1), 248 GCK-MODY (MODY2), 124 HNF1A-MODY (MODY3), 3 IPF-1 (MODY4) and 9 HNF1B (MODY5). HNF1A-MODY was the second most frequently registered MODY form in the database. From the 124 patients classified as HNF1A-MODY, both questionnaires and genetic reports were returned for 71. Genetic findings were not provided for 15 additional subjects whose attending physicians returned questionnaires. Among the 71 patients with genetic data, 44 carried *HNF1A* mutations and 27 were found to carry only common *HNF1A* polymorphisms and silent mutations. Eleven subjects carried both *HNF1A* mutations and *HNF1A* polymorphisms and were analysed under patients with mutations. About half (54.5%) of patients with *HNF1A* mutations were additionally screened for either one or more of the four most frequent genetic causes of MODY, i.e. *HNF4A* ($n = 11$), glucokinase (*GCK* $n = 29$), *HNF1B* ($n = 4$) and *HNF2A* ($n = 6$).

Characteristics of patients with HNF1A mutations

Subjects with *HNF1A* mutations were diagnosed at the age of 14.1 ± 5.8 years. Chronological age was 19.9 ± 8.8 years, and disease duration was 5.8 ± 2.8 years. More females (63.7%) than males (36.3%) were in this group. Patients mostly presented with hyperglycaemia (89.6%) and typical symptoms including polydipsia ($n=9$), polyuria ($n=7$) and glucosuria ($n=3$) at diagnosis were documented (multiple symptoms per patient were possible). These patients were slightly overweight (body mass index (BMI)-SDS: $+0.8 \pm 1.1$), and HbA1c was $6.8 \pm 1.2\%$ at diagnosis. Lifestyle intervention was reported for 20.5%, 36.3% used insulin, 43.2% were treated with OAD and 15.9% of patients received mixed insulin and OAD treatments. Characteristics of subjects with *HNF1A* mutations are presented in Table 1.

A family history (first or second degree relative) of diabetes was reported for 93.2% of subjects with *HNF1A* mutations, and mothers (72.5%) were more often affected by diabetes than fathers (28.6%). Diabetes also affected 22.2% of siblings (Table 2).

Table 1 Characteristics of HNF1A-MODY patients in the DPV database.

Clinical parameters	Patients with <i>HNF1A</i> mutations ($n=44$)	Patients with <i>HNF1A</i> polymorphisms ($n=27$)	P value
Males (%)	36.3	40.7	NS
Chronological age (years)	19.9 ± 8.8	14.1 ± 3.8	0.003
Age at disease onset (years)	14.1 ± 5.8	10.9 ± 4.3	0.027
Duration of disease (years)	5.8 ± 7.1	3.2 ± 2.9	NS
Diagnosis by typical diabetes symptoms (%)	89.7 ($n=29$ examined)	93.3 ($n=15$ examined)	NS
Polydipsia (%)	20.5	7.4	–
Polyuria (%)	15.9	3.7	–
Glucosuria (%)	6.8	7.4	–
Diagnosed by systematic screening (n)	9	5	–
Diagnosed by coincidence (n)	11	7	–
Family history of diabetes (%)	93.2 ($n=42$ examined)	85.6 ($n=21$ examined)	NS
HbA1c	6.8 ± 1.2	6.4 ± 1.5	NS
BMI-SDS (BMI = kg/m ²)	0.8 ± 1.1	0.5 ± 1.2	NS
Oral anti-diabetics (%)	43.2	33.3%	NS
Insulin (%)	36.3	29.6%	NS
Lifestyle (%)	20.5	37.1%	NS
Insulin + OAD	15.9	18.5	NS
1 year after diagnosis with insulin treatment (%)	53.1 ($n=32$)	30.7 ($n=26$)	NS
1 year after diagnosis without insulin treatment (%)	31.2 ($n=16$)	66.6 ($n=9$)	NS

Significance at $P=0.05$; NS, not significant.

Table 2 Family history of diabetes in first degree relatives. Family history of diabetes, indicating first degree relatives of study patients previously diagnosed with diabetes. Genetic reports of family members were not available. Sex differentiation between siblings was not examined.

Family history of diabetes	Number examined (n)	Number of diabetes (n)	Proportion (%)
Patients with <i>HNF1A</i> mutations			
Father	31	10	32.3
Mother	40	29	72.5
Sibling1	27	7	25.9
Patients with <i>HNF1A</i> polymorphisms			
Father	17	6	35.2
Mother	21	11	52.3
Sibling1	15	7	46.7

No abnormalities were found in patients screened for *HNF4A*, *GCK*, *HNF1B* and *HNF2A* mutations in the study sample apart from known silent mutations/polymorphisms, unlikely to be responsible for symptoms of respective patients.

Classification of HNF1A mutations found in the study sample

Mutations were located throughout the *HNF1A*; mostly affecting exons 1, 4 and 6 but no mutation was detected in exon 10. There were 22 (50%) missense, 12 (27.3%) nonsense and 10 (22.7%) frameshift mutations. Altogether, 35 different *HNF1A* mutations were detected in the sample (Fig. 2), the majority (79.5%) in exons 1–6. Exons 8–10 (9.1%) harboured the least mutations. One frameshift mutation occurred within the promoter region and two (4.5%) in the dimerization domain (one missense and one nonsense). The DNA-binding ($n=23$) and transactivation domains ($n=18$), which both make up the structurally largest domains on the *HNF1A*, were respectively affected by 52.3 and 40.9% of mutations. There were more missense mutations (72.7%) in the DNA-binding domain than nonsense mutations (27.3%). Conversely, more nonsense (55.6%) than missense mutations (44.4%) were found in the transactivation domain. Apart from one frameshift mutation in the 5' UTR promoter region, all others affected the transactivation domain (97.7%; Table 3).

We identified 14 previously undescribed mutations in the DPV study sample. These included three missense mutations (L162P, R245I, and A269P) in the DNA-binding domain; eight nonsense mutations (G31X, E41X, and Q130X) in the DNA-binding domain (S355X, Q398X, E473X, Q495X, and E508X) and in the transactivation domain and four frameshift mutations (5' UTR c.158-insGGGTTGG-promoter region-, P588fs-insGCCA and P588fs-delAC) in the transactivation domain.

Figure 2 *HNF1A* mutations found in patients from the DPV study sample, indicated according to exons and domains affected. *, indicates previously undescribed mutations.

The insertion c.158-insGGGTTGG at the 5' UTR promoter region resulted from a third repetition of the said sequence in that region, where the normal allele has only two repetitions of the said sequence. In the case of G31X, the deletion of two alanine residues in exon 1 codon 68_69 (delAA) led to the introduction of a stop codon at G31 (G31X). Both P588fs-insGCCA and P588fs-.delAC mutations were identified in one individual. All previously undescribed *HNF1A* variants found in the DPV study sample are presented in Table 4.

Eleven patients with *HNF1A* mutations also carried *HNF1A* polymorphism, but their clinical characteristics were not significantly different from other patients with *HNF1A* mutations only.

Mutation type, -isoform, -domain and clinical phenotype

Analysis of patients' clinical phenotype with respect to the mutation type (missense, nonsense, and frameshift) did not reveal any significant difference. However, when patients with nonsense/frameshift mutations (likely to result in premature termination of protein synthesis/disruption in protein structure) were both compared with patients with missense mutations only, there were significant differences with regard to treatment. While 60% of patients with missense mutations did not use insulin, this was the case for 23.8% patients with nonsense or frameshift mutations ($P=0.03$).

In our study, age at disease onset was not significantly different among patients with mutations affecting different isoforms. We also did not find any significant differences among isoforms with respect to BMI, HbA1c, symptoms at diagnosis and type of treatment.

When clinical phenotype was examined with respect to functional domain of *HNF1A* mutation (i.e. dimerization domain, DNA-binding domain and transactivation domain), no significant differences were found in the study sample. Nevertheless, the number of patients who did not use insulin treatment (43.8% patients with mutations in the DNA-binding domain versus 36.8% patients with mutations in the transactivation domain) nearly attained significance level ($P=0.056$). The dimerization domain which only harboured two mutations was not included in this analysis.

Characteristics of patients with *HNF1A* polymorphisms

Twenty-seven patients registered in the DPV database as *HNF1A*-MODY were found to carry only polymorphisms in *HNF1A*. These patients were 40.7% male and aged 10.9 ± 4.3 years at diagnosis. At diagnosis, the majority (93.3%) presented with hyperglycaemia, and some had at least one osmotic symptom: polydipsia (7.4%), polyuria (3.7) or glucosuria (7.8%). HbA1c was on average $6.5 \pm 1.5\%$, and subjects were slightly overweight (BMI-SDS $+0.4 \pm 1.2$). The majority (37%) of these patients used lifestyle interventions, 29.6% received insulin therapy, 33.3% OAD (33.3%) and 18.8% mixed insulin and OAD treatments (Table 1).

Polymorphisms found in the study sample were previously described amino acid substitutions, SNP and silent mutations affecting *HNF1A* exons 1, 4, 7 and 8 and introns 1, 2, 7, 8 and 9. They included I27L, S487N, S487D, A98V L17L, G228G, L459L (c.1375C>T), L459L (c.1377G>A), T515T, VS1-42G>A, IVS2+66G>C, IVS2-51T>A, intron 6 G237A, IVS7+7G>A, IVS8+29C>T, IVS24T>C and intron 9 211C. All subjects in this group carried the I27L variant (dimerization domain) and S487N (transactivation domain). Three individuals in this group additionally carried the A98V (dimerization domain) polymorphism.

Patients with *HNF1A* mutations versus patients with *HNF1A* polymorphisms

Patients with *HNF1A* mutations were significantly older at diagnosis than patients with *HNF1A* polymorphisms

Table 3 Frequency of *HNF1A* mutations: type, isoform and domain. Frequency of mutation according to type, isoform and domain of the *HNF1A* gene affected.

Mutation	Mis sense (n)	Non sense (n)	Frame shift (n)
Isoform ABC (n=35)	19	8	8
Isoform AB (n=5)	1	4	—
Isoform A (n=4)	2	—	2
Dimerization domain (n=2)	1	1	—
DNA-binding domain (n=23)	17	6	—
Transactivation domain (n=18)	4	5	9
5' UTR promoter region			1

Table 4 Previously undescribed *HNF1A* mutations found in the DPV database. Mutations of HNF1A-MODY patients in the DPV database, not previously described in accessible literature.

Location	Change at DNA level	Change at protein level	Mutation type	Occurrence
Promoter/ 5' UTR	c.-158ins- GGGTTGG	–	Frameshift	1
Exon 1	c.68_69 del AA	p.Lys23ArgfsX9– p.Gly31X	Nonsense	1
Exon 1	c.121G>T	p.Glu41X	Nonsense	4
Exon 2	c.388C>T	p.Gln130X	Nonsense	1
Exon 2	c.486T>C	p.Leu162Pro	Missense	1
Exon 4	c.731G>T	p.Arg244Ile	Missense	1
Exon 4	c.807G>C	p.Ala269Pro	Missense	1
Exon 5	c.1004C>G	p.Ser335X	Nonsense	1
Exon 6	c.1192C>T	p.Gln398X	Nonsense	1
Exon 7	c.1417C>T	p.Gln473X	Nonsense	1
Exon 7	c.1483C>T	p.Gln495X	Nonsense	1
Exon 8	c.1522G>T	p.Glu508X	Nonsense	2
Exon 8	c.1563A>G	p.Thr521Ala	Missense	1
Exon 9	c.1764ins- GCCA	p.588ins- GCCA	Frameshift	1
Exon 9	c.1764del AC	p.588fsdelAC	Frameshift	1

(14.1 ± 5.8 vs 10.9 ± 4.3 years, $P=0.027$). This was also true for chronological age (19.9 ± 8.8 vs 14.1 ± 3.8 years, $P=0.003$, Table 1). Family history showed that more mothers of patients in both groups had also been diagnosed with diabetes than fathers, or siblings. While 72.5% of mothers were affected when patients carried *HNF1A* mutations, this was the case for 52.1% when patients carried *HNF1A* polymorphism. Siblings of patients with *HNF1A* polymorphisms were more often diabetic (*HNF1A* polymorphisms: 46.7% versus *HNF1A* mutations: 22.2%). In the study sample, twice as many maternal grandparents had also been diagnosed with diabetes as paternal grandparents (50.6 vs 23.3%) where data were provided.

Disease duration, gender, BMI-SDS, HbA1c and type of treatment received did not differ significantly between patients with *HNF1A* mutations and *HNF1A* polymorphisms.

Discussion

In this study, we examined 71 diabetes patients labelled HNF1A-MODY in the German–Austrian multicentre DPV database. Genetic reports indicated that 44 patients carried *HNF1A* mutation and 27 patients carried *HNF1A* polymorphisms. The latter were misclassified, since no *HNF1A* mutations were detected.

Like in other studies (10, 11), disease phenotype was highly variable in the cohort. The majority of patients presented with hyperglycaemia at disease onset and specific symptoms including polydipsia, polyuria or glucosuria were reported for one fifth of patients. Another one-fifth was diagnosed through systematic screening, usually after a first degree relative had been

identified as HNF1A-MODY. No other specific symptom at diagnosis was provided for the rest of the patients presenting with hyperglycaemia. The variability of HNF1A-MODY clinical phenotype is further reflected by the fact that one quarter of patients with mutations were asymptomatic and coincidentally diagnosed while consulting for another condition.

We found 35 different HNF1A mutations in the study sample, distributed throughout the gene. Most frequently affected were exons 1, 4 and 6 in the study sample. The distributions indicated that missense mutations were more abundant in the DNA-binding domain and that nonsense and frameshift mutations were predominant in the transactivation domain. This distribution is consistent with other studies, which show that the transactivation domain is more accommodating of mutations causing minor changes in protein structure than the DNA-binding domain (4, 12, 13).

We investigated the effects of *HNF1A* mutation type, isoform and domain occurrence on age at disease onset and clinical phenotype of HNF1A-MODY. Since patients were recruited from a paediatric database, they were usually in the early teens at disease onset and comparatively younger than patients examined in other similar studies. Patient's age at onset of disease did not vary depending on mutation type, isoform or domain in our sample. Similar results regarding genotype–phenotype correlation have been reported for mutation type (8); mutation type and location in other studies (13). An association was only found with regard to treatment, i.e. 60% of patients with missense mutations did not use insulin 1 year after diagnosis as opposed to 23.8% of patients with nonsense or frameshift mutations ($P=0.03$). Previous studies indicate that *HNF1A* mutations generating mRNA harbouring premature termination codons are likely to cause significant reduction in protein levels due to nonsense-mediated decay unlike missense mutations with milder functional consequences (8, 14). Our result could therefore indicate that insulin secretion was more severely or earlier compromised in patients with nonsense and frameshift mutations than in patients with missense mutations leading to more likely use of insulin. Additionally, more patients with mutations affecting the DNA-binding domain, than the transactivation domain, did not use insulin (43.8 vs 36.8%; $P=0.056$). This difference only nearly attained statistical significance, but supports the fact that mutations found in the transactivation domain were mostly nonsense or frameshift as well as the possibility that these patients may have had more severe clinical phenotypes, requiring insulin more often. Others studies also found a fairly high proportion of patients with more severe clinical phenotypes resulting from HNF1A mutations to use insulin treatment and that with disease progression,

more HNF1A-MODY patients would use insulin treatment (15, 16).

Mutation isoform and domain of occurrence associated with age at disease onset in certain studies examining larger numbers and older subjects. Truncating mutations affecting the transactivation domain were associated with a lower age at diagnosis, but not missense mutations. Age at diagnosis was lower when missense mutations occurred in exon 1–6 compared with truncating mutations affecting the same exons (8). Other comparable studies did not find these associations (7). Our results are in line with the latter. However, the number of patients we examined were much fewer and younger (on average pubertal) at disease onset. Other clinical features also did not differ significantly with respect to mutation type, isoform or domain of occurrence in the study sample. In over 65% of study patients with *HNF1A* mutations, other MODY genes were additionally examined and no pathological variants were found.

Several mutations found in the study sample have not been previously described. Some of these were found at codons where other mutations had been previously identified, e.g. we found nonsense mutations where missense mutations have been described, e.g. Q130X at Q130H (17) and G31X at G31D (18) as well as missense mutations where others have been reported, e.g. T521A at T521I (19). A previously undescribed frameshift variant was also found in the 5' UTR promoter region; here, a third insertion of c.158-insGGGTTGG occurred, where only two repetitions of the said sequence are known to exist. These variants at the said positions may indicate hotspots for mutation occurrence on *HNF1A*. It is unclear whether these new *HNF1A* mutations are pathologic and directly responsible for HNF1A-MODY symptoms in the affected patients. However, it is very likely that the nonsense and frameshift mutations caused HNF1A-MODY in affected subjects. Diagnosing laboratories classified these mutations as the most likely cause of patients' symptoms. The mutations G31X, R54X, S355X, A269P, and G495X, which have not been previously described before, were also detected in relatives (mothers) of the affected study participants as physicians noted in the genetic reports. This was also true for the previously reported variants S142F, Y218insC and 291insC found in the sample. We, however, did not have genetic reports of parents and investigations to conclusively classify previously undescribed variants, as novel mutations would go beyond the scope of this work.

Patients labelled HNF1A-MODY in the database, who carried polymorphisms only in *HNF1A*, were misclassified. They were significantly younger at diagnosis than patients carrying *HNF1A* mutations. More often, they also used oral medication and lifestyle interventions and less often used insulin treatment than patients with *HNF1A* mutations. Even though these differences were non-significant, they may indicate that β cell

deterioration was less severe among these patients. These patients were nonetheless comparable with those carrying *HNF1A* mutations in other clinical parameters, and this similarity may have fostered misclassification as HNF1A-MODY. Genetic analysis revealed that among other silent mutations, all subjects carried I27L and S487N (three additionally A98V) variants which have been associated with reduced glucose-stimulated insulin secretion/insulin resistance, compromised β cell function/reduced transcription activity and increased risk of type 2 diabetes (20, 21–23). Misclassified subjects may be suffering auto-antibody-negative type 1B or type 2 diabetes. Other MODY causing genes were not analysed in this group; thus, it is also possible that these patients maybe suffering other MODY types.

Family history, given for over 80% of all subjects in this study, indicated that mothers of both patients with *HNF1A* mutations and *HNF1A* polymorphisms were more likely to also have diabetes than other first degree relatives. Predominance of maternal diabetes among patients with diabetes has been previously reported (24, 25). In this study sample, mothers were more often diabetic when patients carried *HNF1A* mutations than when they carried *HNF1A* polymorphism (72.5 vs 52.2%). Data on diabetes during pregnancy were, however, not available for further analysis of possible links to predominance of diabetic mothers in this group. There were twice as many diabetic siblings when patients carried *HNF1A* polymorphisms than when they carried *HNF1A* mutations (42.7 vs 22.2%). Apart from genetic predisposition, environmental factors (diet and physical activity) may play more influential roles in disease manifestation when patients carry *HNF1A* polymorphisms than when they carry *HNF1A* mutations.

Conclusion

To date, specific genes which modify the phenotype of HNF1A-MODY have not been completely clarified. Patients classified as HNF1A-MODY in the multicentre DPV database were in early teenage, symptomatic or asymptomatic at disease onset, and majority had family history of diabetes. No associations were found between age at disease onset and *HNF1A* mutation type in the study sample contrary to a previous study, but likewise, no age association with domain of mutation occurrence was found (8). We found previously undescribed *HNF1A* variations, which were most likely to be responsible for the clinical phenotype, in one-third of patients carrying *HNF1A* mutations.

Patients with *HNF1A* polymorphisms labelled as HNF1A-MODY in the database were misclassified, though clinically similar to HNF1-MODY patients. Considering that majority of patients were not

additionally tested for other MODY causing genes, it is possible that they could have had other common MODY types like GCK-MODY. It is also possible that they may be antibody-negative type 1B diabetes or type 2 diabetes patients or that unknown factors may account for their HNF1A-MODY-like clinical phenotype.

Declaration of interest

The authors declare that there is no conflict of interest that can be perceived as prejudicing the impartiality of the research reported.

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