**HNF1A gene p.I27L is associated with early-onset, maturity-onset diabetes of the young-like diabetes in Turkey**

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**Abstract**

**Background:** The molecular basis of the Turkish population with suspected maturity-onset diabetes of the young (MODY) has not been identified. This is the first study to investigate the association between HNF1A-gene single-nucleotide polymorphisms (SNPs) and having early-onset, MODY-like diabetes mellitus in the Turkish population.

**Methods:** All diabetic patients (N = 565) who presented to our clinic between 2012 and 2015 with a clinical suspicion of MODY were included in the study. Analysis of HNF1A, HNFB, HNF4A, GCK gene mutations was performed using real-time polymerase chain reaction sequencing. After genetic analysis, diabetics (n = 46) with HNF1A, HNF1B, HNF4A, GCK gene mutations (diagnosed as MODY) and diabetics (n = 30) with HNF1B, HNF4A, GCK gene SNPs were excluded. Patients with early-onset, MODY-like diabetes (n = 486) and non-diabetic controls (n = 263) were included. Genetic analyses for the HNF1A gene p.S487N, p.A98V and p.I27L SNPs were performed using Sanger-based DNA sequencing among the control group.

**Results:** p.S487N and p.A98V was similar between the diabetics and controls in dominant and recessive models with no association (each, p > 0.05). p.I27L GT/TT carriers (GT/TT vs. GG, OR = 1.68, 95% CI: [1.21-2.13]; p = 0.035) and p.I27L TT carriers had increased risk of having MODY-like diabetes (GT/GG vs. TT, OR = 1.56, 95% CI: [1.14-2.57]; p = 0.048). Family inheritance of diabetes was significantly more common in patients with the p.I27L TT genotype. The p.I27L SNP was modestly associated with having diabetes after adjusting for body mass index and age (β = 1.45, 95% CI: [1.2-4.2]; p = 0.036).

**Conclusions:** The HNF1A gene p.I27L SNP was modestly associated with having early-onset, MODY-like diabetes in the Turkish population. HNF1A gene p.I27L SNP might contribute to age at diabetes diagnosis and family inheritance.

**Keywords:** P.I27L, P.A98V, HNF1A gene, Diabetes

**Background**

Hepatocyte nuclear factor 1A (HNF1A) is a transcription factor that has a role in the development and function of pancreas β-islet cells. In the developmental stage, both endocrine and exocrine cells of the pancreas have HNF1A expression [1]. HNF1A is necessary for insulin secretion in response to glucose [2–4]. The HNF1A gene has been identified in both monogenic and polygenetic diabetes. Rare mutations of the HNF1A gene cause a monogenic form of diabetes as Type 3 maturity-onset-diabetes of the young (MODY3) [1]. The HNF1A gene contributes to the pathogenesis of Type 2 diabetes mellitus (T2DM). HNF1A gene single nucleotide polymorphisms (SNPs) were modestly associated with Type 2 diabetes mellitus (T2DM) and glycemic features in different populations [5–7]. HNF1A SNPs were associated with impaired insulin secretion [8, 9]. HNF1A gene SNPs (p.I27L, p.A98V and p.S487N) were inconsistently associated with impaired glucose tolerance and having diabetes [8–14]. Some young people with diabetes have atypical features such as insulin resistance or a need for...
insulin treatment. However, these features are not similar to T2DM. These non-obese adults have early-onset, MODY-like diabetes. Monogenic MODY has not been confirmed in patients with early-onset, MODY-like diabetes through genetic analysis [15]. The genetic basis of early-onset, non-monogenic diabetes is not yet known. The aim of this study was to obtain the effects of HNF1A gene SNPs on developing MODY-like diabetes. This is the first study to investigate the association between gene SNPs on developing MODY-like diabetes. The effects of early-onset, non-monogenic diabetes is not yet known.

Methods

Patients

In our study, none of the control subjects (n = 263) had diabetes. All patients with diabetes (n = 486) met the criteria for the diagnosis of MODY. Subjects with a clinical suspicion of MODY [16] (diagnosis of diabetes age below 25 years, positive family history including autosomal dominant inheritance in at least 2-3 generations, residual insulin secretion with normal C-peptide concentration and absence of B-cell autoimmunity) who presented to our hospital between 2012 and 2015 were included in the study. The inclusion criteria were as follows; patients with T2DM with C-peptide concentrations ≥0.3 nmol/L, negative anti-GAD antibodies, and age-at-onset below 25 years [2]. Patients with suspected MODY did not need insulin treatment for at least first 2 years after diagnosis and had no family history of T1DM [17]. Early or late-onset diabetes was identified by using age 45 years as a cut-off, as described in previous studies [2, 17]. If we selected control subjects from those whose mean age was below 28 years, some of these subjects would develop diabetes later in life. As a way of reducing the possibility of recruiting control subjects who might later develop T2DM, healthy-normoglycemic subjects with fasting glucose below 100 mg/dL and glycated hemoglobin (Hb1Ac) < 5.7%, who were aged ≥45 years and had no first-degree relatives or grandparents with T2DM were included in the control group [17]. Healthy controls without chronic disease such as diabetes, hypertension, renal and hepatic disease, were recruited from the outpatient clinic. Subjects with genetically confirmed MODY or T1DM were excluded [2]. Genetic analysis was performed for all patients (n = 565) in order to diagnose MODY. After genetic analysis, patients with diabetes (n = 46) who had HNF1A, HNF1B, HNF4A, GCK gene mutations were diagnosed as having MODY3, MODY5, MODY1, and MODY2 respectively. Thirty patients with diabetes had HNF1B, HNF4A, had GCK gene SNPs. Patients with diabetes with MODY and HNF1B, HNF4A, and GCK SNPs were excluded from the study. Finally, subjects without HNF1A, HNF1B, HNF4A, and GCK gene mutations and HNF1B, HNF4A, and GCK SNPs (n = 486) were included this study.

Measurements

Fasting glucose, postprandial glucose, creatinine, HbA1C, triglycerides (TG), cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), C-peptide, high-sensitivity (hs-CRP), anti-glutamic acid decarboxylase (GAD) antibody, anti-insulin antibody, anti-islet antibody, and urinary microalbuminuria concentrations were measured. Age and symptoms at onset of diabetes, diabetes treatment, and parental history of diabetes (first-degree relatives, mother or father) were recorded from all patients with diabetes. Body mass index (BMI) was calculated as weight (kg) / height (m)^2. BMI ≥30 kg/m^2 was diagnosed as obesity. T2DM was diagnosed when plasma fasting glucose concentrations were > 125 mg/dL, casual or postprandial glucose levels were > 200 mg/dL or in the presence of current treatment with a hypoglycemic agent, according to the American Diabetes Association criteria [17]. Informed consent was obtained from all participants. This study was approved by Diskapi Yildirim Beyazit Training and Research Hospital Local Ethics Committee.

Genotyping and Statistical analysis is presented in Additional file 1.

Results

The percentage of women (51.5% vs. 58.2%) and BMI value (27.88 ± 5.72 vs. 27.01 ± 3.29 kg/m^2) was similar between the diabetics and controls (p > 0.05). The mean age of the controls was 49.18 ± 3.38 years. The mean age at onset of diabetes was 24.08 ± 4.82 years. The mean C-peptide concentration of the patients with diabetes was 2.47 ± 1.79 nmol/L. Fasting glucose, HbA1c, TG, cholesterol, LDL-C concentrations were higher among the diabetics compared with the controls (p < 0.05, Table 1). HNF1A gene p.I27L rs1169288 and p.A98V rs1800574 SNPs were consistent with the Hardy-Weinberg equilibrium (HWE), and p.S487 N rs2464196 were not consistent with the HWE (Table 2). HNF1A genotypes are shown in Table 3. The frequency of p.S487 N SNPs was similar between the diabetics and controls in the codominant model and dominant model and recessive model (p > 0.05, each). p.A98V SNPs were similar between the diabetics and controls in the dominant model and recessive model (p > 0.05, each). The p.A98V TT genotype was higher in diabetics in the codominant model compared with the controls (TT vs. CC, OR = 1.35, 95% CI: [0.95–3.54]; p = 0.027). HNF1A gene p.I27L TT genotype was increased in diabetes (TT vs. GG, OR = 1.71, 95% CI: [1.25-3.46]; p = 0.024) compared with the controls in the codominant model. p.I27L GT/TT carriers had increased
Table 1 Characteristics of subjects

|                      | Controls (n = 263) | Diabetics (n = 486) | P    |
|----------------------|-------------------|---------------------|------|
| Women (%)            | 58.2              | 51.5                | 0.081|
| Parent diabetes (%)  | 30.4              | 96.1                | < 0.001|
| Symptoms at the diagnosis (%) | – | – | – |
| Asymptomatic         | 58.1              |                     |      |
| Diabetic symptom     | 32.5              |                     |      |
| Gestational diabetes | 8.1               |                     |      |
| Diabetic complication| 1.3               |                     |      |
| Treatment (%)        | –                 | –                   | –    |
| Diet                 | 20.1              |                     |      |
| Oral antidiabetic    | 32.1              |                     |      |
| Insulin              | 47.8              |                     |      |
| Age at diagnosis (year) | –              | 24.08 ± 4.82        | –    |
| BMI (kg/m²)          | 27.01 ± 3.29      | 27.88 ± 5.72        | 0.109|
| Systolic BP (mmHg)   | 124.70 ± 11.15    | 125.31 ± 11.82      | 0.823|
| Diastolic BP (mmHg)  | 76.64 ± 7.21      | 75.61 ± 7.86        | 0.374|
| Fasting glucose (mg/dl) | 80.68 ± 9.37    | 151.75 ± 74.12      | < 0.001|
| Postprandial glucose (mg/dl) | –               | 252.92 ± 110.97     | –    |
| LDL (mg/dl)          | 96.90 ± 20.75     | 107.99 ± 36.98      | < 0.001|
| TG (mg/dl)           | 99.51 ± 51.64     | 204.46 ± 203.21     | < 0.001|
| Cholesterol (mg/dl)  | 159.18 ± 27.68    | 193.55 ± 87.46      | < 0.001|
| HDL (mg/dl)          | 51.33 ± 16.96     | 44.16 ± 14.07       | < 0.001|
| Creatinine (mg/dl)   | 0.88 ± 0.89       | 1.24 ± 0.91         | 0.018|
| HbA1c (%)            | 5.31 ± 0.10       | 8.21 ± 2.41         | < 0.001|
| TSH (mIU/L)          | 1.74 ± 1.01       | 2.78 ± 8.73         | 0.142|
| hsCRP (µg/ml)        | 3.30 ± 2.98       | 4.08 ± 3.96         | 0.101|
| C-peptide (nmol/L)   | 2.47 ± 1.79       |                     | –    |
| Microalbuminuria (µg/mmol) | 1.96 ± 13.65 | 94.86 ± 348.40 | < 0.001|

BMI: body mass index, HbA1c: hemoglobin A1c, BP: blood pressure
*aStudent’s t test was used for normally distributed continuous variables or log-transformed variables between two groups.
Data are shown as mean ± standard deviation (means ± SD) and percentage (%).
Bold represents the significant p-values.
Categorical variables were analyzed with the Chi-square test or Fisher’s exact test, where appropriate.

1.68 odds of having diabetes (GT/TT vs. GG, OR = 1.68, 95% CI: [1.21-2.13]; p = 0.035) in the dominant model. p.I27L TT carriers had 1.56-fold increased odds of having diabetes (GT/GG vs. TT, OR = 1.56, 95% CI: [1.14-2.57]; p = 0.048) in the recessive model. Clinical and biochemical characteristics did not differ between patients with diabetes with p.I27L, p.S487N, and p.A98V SNPs and diabetics without the SNPs (p > 0.05). Onset of diabetes was 26.17 ± 7.4 years in p.S487N, 25.58 ± 2.7 years in p.A98V, and 24.57 ± 5.2 years in p.I27L (p > 0.05). Parent diabetes (mother or father) was higher in the p.I27L TT genotype compared with the GG genotype (78.5 vs. 98.7%, p = 0.035). Diabetics with p.I27L TT genotype had higher triglyceride concentrations compared with diabetics with the GG genotype (p = 0.041) (Table 4). HNF1A gene p.I27L and p.A98V haplotypes were within Linkage Disequilibrium. p.I27L SNPs was modestly associated with having diabetes after adjusting for BMI and age (β = 1.45, 95% CI: [1.2-4.2]; p = 0.036).

Discussion

This case-control study showed that the HNF1A gene p.I27L SNP was modestly associated with having early-onset, MODY-like diabetes in the Turkish population. Family inheritance of diabetes was significantly more common in patients with the p.I27L TT genotype. The HNF1A gene p.I27L SNP might contribute to age at diabetes diagnosis and family inheritance.

In this study, we suggest that polygenic T2DM may show differences in age-related and family inheritance transmission for an associated monogenic form of diabetes. This is the first study to show the effect of the p.I27L genotype on modifying age at diagnosis in the Turkish population. We excluded monogenic diabetes modifier genes, which often include mutations, because we aimed to examine the influence of variations on polygenic diabetes. In our study, subjects with diabetes were non-obese and the onset of diabetes was early. A previous study showed that non-obese patients with early-onset diabetes were more susceptible to β-cell dysfunction as compared with old and obese individuals [18]. A modest association was found between HNF1A missense SNPs (p.I27L, p.A98V, and p.S487N) and having late-onset T2DM in the European population [2-4]. In European ancestry, no association was shown between HNF1A gene SNPs and having late-onset T2DM [19], but a robust association was found when p.A98V SNPs were included [20]. Similar to our study, European ancestry reported that p.I27L and p.A98V SNPs were associated with having late-onset T2DM [12]. p.I27L GT/TT carriers had 1.68-fold increased odds of having diabetes, and p.I27L TT carriers had 1.5 6-fold increased odds of having diabetes in our study. Only the p.I27L variant was modestly associated with having diabetes and this relationship continued after adjusting BMI and age. There was no association between p.S487N and p.A98V SNPs and early-onset T2DM. Similar to our report, a modest association was shown between p.I27L, p.S487N, and p.A98V and having T2DM in the European population [19]. In agreement with our report, p.I27L was

Table 2 Minor allele frequency of HNF1A gene SNPs

| Risk allele | MAF for study sample |
|-------------|----------------------|
| I27L rs1169288 | T | 0.43 |
| S487N rs2464196 | T | 0.39 |
| A98V rs1800574 | T | 0.09 |

MAF: minor allele frequency
### Table 3: Genotype analysis of HNF1A gene SNPs

| Genotype                  | Controls, n | Diabetes, n | OR (95% CI)     | P     |
|---------------------------|-------------|-------------|-----------------|-------|
| **I27L rs1169288 (%)**    |             |             |                 |       |
| *Co-dominant Wild type GG | 105         | 146         |                 |       |
| Heterozygous GT           | 120         | 233         | 1.02 (0.57–1.78) | 0.984 |
| Homozygous TT             | 38          | 110         | 1.71 (1.25–3.46) | 0.024 |
| Dominant (GT + TT/GG)     | 158 vs 105  | 343 vs 146  | 1.68 (1.21–2.13) | 0.035 |
| Recessive (TT/GG)         | 38 vs 225   | 110 vs 379  | 1.56 (1.14–2.57) | 0.048 |
| **S487N rs2464196 (%)**   |             |             |                 |       |
| *Co-dominant Wild type CC | 102         | 188         |                 |       |
| Heterozygous CT           | 121         | 210         | 0.58 (0.35–1.39) | 0.471 |
| Homozygous TT             | 40          | 91          | 1.25 (0.57–2.75) | 0.638 |
| Dominant (CT + TT/CC)     | 161 vs 102  | 301 vs 188  | 1.01 (0.74–1.38) | 0.938 |
| Recessive (TT/CT + CC)    | 40 vs 223   | 91 vs 398   | 1.27 (0.84–1.91) | 0.241 |
| **A98V rs1800574 (%)**    |             |             |                 |       |
| *Co-dominant Wild type CC | 208         | 411         |                 |       |
| Heterozygous CT           | 52          | 64          | 1.26 (0.48–3.29) | 0.676 |
| Homozygous TT             | 3           | 14          | 1.35 (0.95–3.54) | 0.027 |
| Dominant model (CT + TT/CC)| 55 vs 208  | 78 vs 411   | 0.71 (0.48–1.05) | 0.089 |
| Recessive model (TT/CT + CC)| 3 vs 260 | 14 vs 475 | 2.55 (0.72–8.97) | 0.130 |

*Co-dominant model was compared wild type, homozygous variant and heterozygous variant were compared
DM Diabetes mellitus, OR odds ratio, CI confidence interval
Data are shown as mean ± standard deviation (means ± SD) and percentage (%)
Bold represents the significant p-values
Categorical variables were analyzed with Chi-square test or Fisher’s exact test, where appropriate
Multiple logistic regression analysis and Fisher’s exact test were tested using models: dominant (major allele homozygotes vs heterozygotes + minor allele homozygotes), recessive (major allele homozygotes + heterozygotes vs minor allele homozygotes) and codominant (major allele homozygotes vs heterozygote and minor allele homozygotes vs major allele homozygotes)

### Table 4: HNF1A gene p.I27L SNPs and clinical features in diabetics patients

| Feature                  | GG (wild) | GT      | TT      | P<sup>a</sup> GG/GT | P<sup>b</sup> GG/TT | P<sup>c</sup> GT/TT |
|--------------------------|-----------|---------|---------|----------------------|---------------------|---------------------|
| Age at the diagnosis (year)<sup>a</sup> | 23.36 ± 9.51 | 20.89 ± 6.54 | 21.29 ± 9.78 | 0.845 | 0.653 | 0.958 |
| Parent diabetes (%)      | 78.5      | 89.2    | 98.7    | 0.427                | 0.035               | 0.852               |
| BMI (kg/m<sup>2</sup>)<sup>a</sup> | 26.78 ± 6.02 | 27.81 ± 3.85 | 28.42 ± 4.70 | 0.871 | 0.852 | 0.990 |
| Fasting glucose (mg/dl)<sup>a</sup> | 151.12 ± 75.89 | 175.01 ± 98.35 | 154.01 ± 68.13 | 0.895 | 0.836 | 0.127 |
| Postprandial glucose (mg/dl)<sup>a</sup> | 239.43 ± 114.53 | 264.18 ± 100.37 | 276.18 ± 125.38 | 0.625 | 0.327 | 0.785 |
| HbA1c (%)                | 7.85 ± 3.45 | 8.20 ± 6.75 | 8.47 ± 2.29 | 0.427 | 0.324 | 0.913 |
| LDL (mg/dl)<sup>a</sup>   | 112.30 ± 37.61 | 106.09 ± 30.98 | 136.09 ± 45.65 | 0.358 | 0.339 | 0.249 |
| TG (mg/dl)<sup>a</sup>    | 174.31 ± 175.80 | 197.91 ± 186.34 | 218.91 ± 276.52 | 0.258 | 0.041 | 0.377 |
| Cholesterol (mg/dl)<sup>a</sup> | 185.35 ± 96.84 | 189.27 ± 35.63 | 197.87 ± 44.90 | 0.957 | 0.924 | 0.847 |
| HDL (mg/dl)<sup>a</sup>   | 46.22 ± 11.37 | 49.32 ± 17.93 | 43.28 ± 20.85 | 0.542 | 0.627 | 0.332 |
| C-peptide (nmol/L)<sup>a</sup> | 2.82 ± 2.28 | 2.15 ± 1.32 | 2.32 ± 1.51 | 0.246 | 0.351 | 0.513 |
| Microalbuminuria         | 91.30 ± 357.93 | 96.42 ± 349.35 | 106.50 ± 320.85 | 0.792 | 0.650 | 0.838 |

<sup>a</sup>GG genotype vs GT genotype  <sup>b</sup>GG genotype vs TT genotype  <sup>c</sup>GT genotype vs TT genotype
Data are shown as mean ± standard deviation (means ± SD) and percentage (%)
Bold represents the significant p-values
BMI body mass index, HbA1c hemoglobin A1c
Student’s t test was used for normally distributed continuous variables or log-transformed variables between two groups
Categorical variables were analyzed with the Chi-square test or Fisher’s exact test, where appropriate
associated with having T2DM in non-obese French [21] and Finnish subjects [13]. A Chinese and Japanese meta-analysis reported that p.I27L was associated with having T2DM [18]. HNF1A gene p.I27L was associated with having late-onset T2DM in Brazilian [22] and Western Indian [23] overweight/obese subjects aged 51–60 years; however, this association was found in normal-weight Japanese subjects [11]. In line with our report, Holmkvist et al. determined that p.I27L was associated with having late-onset T2DM in overweight Scandinavian subjects aged over 60 years, and p.A98V was reported to decrease in vivo glucose-responsive to insulin secretion [2]. Chi et al. demonstrated that p.I27L has a modest role in β-cell dysfunction [10] and in insulin resistance [8, 24]. Consistent with our study, European population studies found a modest association between only p.A98V and having T2DM [3, 4]. A Danish study of Caucasians found p.A98V to be associated with decreased insulin secretion in healthy individuals [9], but this effect was balanced by increased insulin sensitivity [25]. HNF1A gene p.A98V was associated with having early-onset T2DM in Scandinavian [26] and Asian-Indian [27] individuals. HNF1A p.A98V was associated with having late-onset T2DM in Finnish but not in Chinese individuals [14]. Our study reported that the p.A98V TT genotype was higher compared with the GG genotype in diabetics, nevertheless, with no association.

Early-onset diabetes (19 years) was observed in Chinese p.I27L + p.S487N carriers [28]. Yorifuji et al. reported that patients who were MODY-mutation–positive were younger and had a lower BMI percentile at diagnosis compared with mutation-negative patients in Japan [29]. A German-Austrian study reported that age at onset of diabetes (10.9 years) was found to be younger in p.I27L + p.S487N ± p.A98V carriers, as compared with HNF1A mutation (14 years). Locke et al. reported that each p.I27L allele was associated with a 1.6-year decrease in age at diagnosis in patients with HNF1A–MODY [30]. Our study reported early onset of diabetes (24.08 ± 4.82 year) with no differences between HNF1A gene SNPs. Similar to our report, paternal diabetes was higher in HNF1A gene SNP carriers [31]. This study found that diabetes was higher in first-degree relatives (mother or father) of p.I27L homozygous TT carriers, suggesting a probability of significant familial transmission.

The HNF1A locus p.I27L is localized in the dimerization domain, p.S487N is localized in the trans-activation domain, and the p.A98V is localized in the DNA-binding domain [1, 22, 28]. HNF1A gene p.I27L, p.A98V, and p.S487N variants reduce transcriptional activities of genes that have a role in glucose metabolism [2]. It was reported that p.I27L + p.A98V variations decreased transactivation activity on GLUT2 in HeLa cells more than p.I27L alone and p.A98V alone [2]. Decreased insulin secretion and β-cell dysfunction was observed in p.I27L coexisting with p.487 N carrier (when p.A98V carrier included). This leads to developing diabetes [1, 2, 4, 24, 25, 31]. HNF1A controls β-cell function by regulating target genes such as glucose transporter 2 (GLUT2), HNF 4A, collectrin, liver pyruvate kinase, and hepatocyte growth factor activator. HNF1A activity dysfunction causes a reduction β-cell mass and induces onset of diabetes [1]. Gene expression regulation among diabetic subjects with HNF1A variation can be explained by environmental factors together with epigenetic factors [22, 31].

This study had a case-control design and small sample size. p.I27L and p.A98V were consistent with the HWE whereas p.S487 was not consistent with HWE. HNF1A gene p.I27L and p.A98V haplotypes were within LD. These are the limitations of this study.

Conclusions
We report a genetic modifier of the HNF1A gene age at diagnosis that shows an effect of genetic variation on diabetes phenotype. The HNF1A variant p.I27L was associated with having early-onset, MODY-like diabetes in the Turkish population. Enlightening the role of HNF1A in β-cells would be helpful in understanding the molecular mechanism of both T2DM and MODY and would guide new therapeutic approaches.

Additional file

Additional file 1: Genotyping and Statistical analysis. (DOCX 14 kb)

Abbreviations
BMI: Body mass index; HbA 1c: Hemoglobin A 1c; HNF1A: Hepatocyte nuclear factor 1α; SNPs: Single nucleotide polymorphisms; T2DM: Type 2 diabetes mellitus

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Authors’ contributions
SB, contributions to conception and design, or acquisition of data, or analysis and interpretation of data, involved in drafting the manuscript and approved the manuscript; NE and FAP, contributions to conception and design, or acquisition of data, or analysis and approved the manuscript; EC, revising it critically for important intellectual content; and have given final approval of the version to be published.

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Ethics approval and consent to participate
This study was approved by Diskapi Yildirim Beyazit Teaching and Research Hospital Ethics Board (Number 24.01.2015–17/25). Written informed consent was obtained from all subjects.
Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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References
1. Balaraman K, Bjerkhage L, Mahajan S, Kannthimathi S, Njalstad PR, Srinivasan N, Mohan V, Radha V. Structure-function studies of HNF1A (MODY3) gene mutations in South Indian patients with monogenic diabetes. Clin Genet. 2016;90:486–95.
2. Holmkvist J, Cervin C, Lyssenko V, Winckler W, Anesvi D, Cilio C, Almgren P, Berglund G, Nilsson P, Tuomi T, et al. Common variants in HNF-1 alpha and risk of type 2 diabetes. Diabetologia. 2006;49:2882–91.
3. Weedon MN, Owen KR, Shields B, Hitman G, Walker M, McCarthy MI, Hattersley AT, Frayling TM. A large-scale association analysis of common variation of the HNF1alpha gene with type 2 diabetes in the UK Caucasian population. Diabetes. 2005;54:2487–91.
4. Winckler W, Burt NP, Holmkvist J, Cervin C, de Bakker PIW, Sun M, Almgren P, Tuomi T, Gaudet D, Hudson TJ, et al. Association of common variation in the HNF1alpha gene region with risk of type 2 diabetes. Diabetes. 2005;54:2336–42.
5. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luu SY, Aycan Z, Cetinkaya S, Bas VN, Önder A, Petek Keciordii HN, Doğan H, Ceylaner S. Maternity onset diabetes of youth (MODY) in Turkish children: sequence analysis of 11 causative genes by next generation sequencing. J Pediatr Endocrinol Metab JFPM. 2016;29:487–96.
6. Gambooa-Melendez MA, Huerta-Chagoya A, Moreno-Macias H, Vazquez-Cardenas P, Ordoñez-Sánchez ML, Rodriguez-Guillén R, Ribas L, Rodriguez-Torres M, Guerra-Garcia MT, Guillén-Pineda LE, et al. Contribution of common genetic variation to the risk of type 2 diabetes in the Mexican mestizo population. Diabetes. 2012;61:3314–21.
7. Chen T, Cao X, Long Y, Zhang X, Yu H, Xu J, Yu T, Tian H. I27L polymorphism in hepatocyte nuclear factor-1A gene and type 2 diabetes mellitus: a meta-analysis of studies about orient population (Chinese and Japanese). Int J Diabetes Mellit. 2010;2:28–31.
8. Winckler W, Weedon MN, Graham RR, McCarroll SA, Purcell S, Almgren P, Tuomi T, Gaudet D, Boström KB, Walker M, et al. Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes. Diabetes. 2007;56:685–93.
9. Saxena R, Elbers CG, Guo Y, Peter I, Gaunt TR, Jiange L, Lanktree MB, Tare A, Castillo BA, Li YR, et al. Large-scale gene-centric meta-analysis across 39 studies identifies type 2 diabetes loci. Ann J Hum Genet. 2012;90:1410–25.
10. Gauchi S, Nead KT, Choquet H, Horber F, Potocnac N, Balkau B, Marre M, Charpentier G, Froguel P, Meyre D. The genetic susceptibility to type 2 diabetes may be modulated by obesity status: implications for association studies. BMC Med Genet. 2008;9:45.
11. Bonatto N, Nogarato V, Svidnicki PV, Milileio FO, Grassioli S, Almeida MC, Vicari MR, Artoni RF. Variants of the HNF1A gene: a molecular approach concerning diabetic patients from southern Brazil. Genet Mol Biol. 2012;35:73–73.
12. Deobagkar D, Randase S, Deobagkar D. Identification of I27L polymorphism in the HNF1-Agene in Western Indian population with late-onset of diabetes. Int J Diabetes Dev Ctries. 2013;30:226.
13. Chiu KC, Chang LM, Ryu JM, Tsai GP, Saad MF. The I27L amino acid polymorphism of hepatic nuclear factor-1alpha is associated with insulin resistance. J Clin Endocrinol Metab. 2000;85:1718–83.
14. Bergman BC, Howard D, Schauer IE, Maahs DM, Snell-Bergeon JK, Eckel RH, Perreault L, Rewers M. Features of hepatic and skeletal muscle insulin resistance unique to type 1 diabetes. J Clin Endocrinol Metab. 2012;97:1663–72.
15. Lehto M, Wipemo C, Ivanson SA, Lindgren C, Lipsanen-Nymans M, Weng J, Wibell L, Widen E, Tuomi T, Groop L. High frequency of mutations in MODY and mitochondrial genes in Scandinavian patients with familial early-onset diabetes. Diabetologia. 1994;37:1311–7.
16. Anuradha S, Radha V, Deepa R, Hansen T, Carstensen B, Pedersen O, Mohan V. A prevalent amino acid polymorphism at codon 98 (Ala58Val) of the hepatocyte nuclear factor-1alpha gene is associated with reduced serum C peptide and insulin responses to an oral glucose challenge. Diabetes. 1997;46:912–6.
17. I27L polymorphism of the hepatocyte nuclear factor-1alpha on estimated and measured beta cell indices. Eur J Endocrinol. Eur Fed Endocr Soc. 2003B;148:641–7.
18. Urhammer SA, Fridberg M, Hansen T, Rasmussen SK, Møller AM, Clausen JO, Pedersen O. A prevalent amino acid polymorphism at codon 98 in the hepatocyte nuclear factor-1alpha gene is associated with reduced serum C peptide and insulin responses to an oral glucose challenge. Diabetes. 1997;46:912–6.
19. Chiu KC, Chang LM, Chu A, Wang M. Comparison of the impact of the I27L polymorphism of the hepatocyte nuclear factor-1alpha on estimated and measured beta cell indices. Eur J Endocrinol. Eur Fed Endocr Soc. 2003B;148:641–7.
20. Urhammer SA, Fridberg M, Hansen T, Rasmussen SK, Møller AM, Clausen JO, Pedersen O. A prevalent amino acid polymorphism at codon 98 in the hepatocyte nuclear factor-1alpha gene is associated with reduced serum C peptide and insulin responses to an oral glucose challenge. Diabetes. 1997;46:912–6.
21. Chiu KC, Chang LM, Ryu JM, Tsai GP, Saad MF. The I27L amino acid polymorphism of hepatic nuclear factor-1alpha is associated with insulin resistance. J Clin Endocrinol Metab. 2000;85:1718–83.
22. Bergman BC, Howard D, Schauer IE, Maahs DM, Snell-Bergeon JK, Eckel RH, Perreault L, Rewers M. Features of hepatic and skeletal muscle insulin resistance unique to type 1 diabetes. J Clin Endocrinol Metab. 2012;97:1663–72.
23. Lehto M, Wipemo C, Ivanson SA, Lindgren C, Lipsanen-Nymans M, Weng J, Wibell L, Widen E, Tuomi T, Groop L. High frequency of mutations in MODY and mitochondrial genes in Scandinavian patients with familial early-onset diabetes. Diabetologia. 1994;37:1311–7.
24. Anuradha S, Radha V, Deepa R, Hansen T, Carstensen B, Pedersen O, Mohan V. A prevalent amino acid polymorphism at codon 98 (Ala58Val) of the hepatocyte nuclear factor-1alpha gene is associated with maternal inheritance of type 2 diabetes in Asian Indians. Diabetes Care. 2005;28:2430–5.
25. Yang Y, Zhou T-C, Liu Y-Y, Li X, Wang W-X, Irwin DM, Zhang Y-P. Identification of HNF1A mutation p.T130I and HNF1A mutations p.I27L and p.S487N in a Han Chinese family with early-onset maternally inherited type 2 diabetes. J Diabetes Res. 2016;2016:3582616.
26. Nordin T, Hugosson S, Kavalrita R, Hrixokova Y, Aysama T, Murakami A, Kawa Y, Hatake K, Nagasaka H, Tamagawa N. Genetic basis of early-onset, maturity-onset diabetes of the young-like diabetes in Japan and features of patients without mutations in the major MODY genes: dominance of maternal inheritance. Pediatr Diabetes. 2018;19:164–72.
27. Locke JM, Stain-Martin C, Laver TW, Patel KA, Wood AR, Sharp SA, Eillard S, Bellanné-Chantelot C, Hattersley AT, Harries LW, et al. The common HNF1A
variant I27L is a modifier of age at diabetes diagnosis in individuals with HNF1A-MODY. Diabetes. 2018;67:1903–7.

31. Awa WL, Thon A, Raile K, Grulich-Henn J, Meissner T, Schöber E, Holl RW, DPV-Wiss. Study Group. Genetic and clinical characteristics of patients with HNF1A gene variations from the German-Austrian DPV database. Eur J Endocrinol Eur Fed Endocr Soc. 2011;164:513–20.