Metabolism Open 16 (2022) 100213

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

Monogenic diabetes variants in Emirati women with gestational diabetes are associated with risk of non-autoimmune diabetes within 5 years after pregnancy

Hinda Daggag [a,1], Anette P. Gjesing [b,1], Alshafi Mohammad [a,*], Lars Ängquist [b], Bindu Shobi [a], Suma Antony [a], Dalia Haj [a], Alia Al Tikriti [a], Adam Buckley [a], Torben Hansen [b], Maha T. Barakat [a]

[a] Research Institute, Imperial College London Diabetes Centre (ICLDC), Abu Dhabi, United Arab Emirates
[b] Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Gestational diabetes
Maturity onset diabetes of the young
Monogenic
Type 2 diabetes mellitus
Gene

ABSTRACT

Aims: To investigate the prevalence of pathogenic variants in monogenic diabetes genes in Emirati women with gestational diabetes (GDM) and examine the risk of developing hyperglycemia during follow-up in carriers and non-carriers.

Methods: Female patients with GDM (n = 370) were identified. Selected monogenic diabetes genes, *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *INS*, *ABCC8* and *KCNJ1I,* were examined by sequencing and identified variants were classified. Anthropometrics and subsequent diagnosis of diabetes were extracted from hospital records. Median follow-up time was 6-years.

Results: A total of 34 variants were detected. Seven women (2%) were carriers of pathogenic variants in *GCK*, *HNF1A*, *INS*, *ABCC8* or *KCNJ11*. A significantly larger fraction of women carrying pathogenic variants were diagnosed with any form of hyperglycemia or diabetes postpartum (risk ratio = 1.8 (1.1–2.9), p = 0.02) or 2.5 (1.3–4.8; p = 0.009), respectively) and they had a shorter disease-free period after GDM compared to women without such variants. There were no significant associations between carrying pathogenic variants and anthropometric measures or C-peptide.

Conclusions: Pathogenic variants were found in known monogenic diabetes genes in two percent of Emirati women with GDM, allowing for precision medicine utilisation in these women both during and outside pregnancy. Carriers were at an increased risk of being diagnosed with hyperglycemia or type 2 diabetes mellitus within 5 years after pregnancy.

1. Introduction

In 2019, the prevalence of diabetes in the United Arab Emirates (UAE) was reported by the International Diabetes Federation (IDF) to be 16.3% for the 20–79 years age group [1]. The number of people with diabetes in the Middle Eastern region is projected to double by 2035 [2]. Women in the Middle East and North Africa have the highest risk globally of developing metabolic diseases [3] and a prevalence of diabetes of 8.6% has been found in a study of Emirati female students [4]. Risk factors like obesity, urbanization, changes in dietary habits, lack of physical activity and genetic factors are likely to play an important role [2].

Little is known about the genetic background of the Emirati population; although, a recent study has shed some light on the genomic architecture of the Emirati population [5]. Furthermore, a study performed whole exome sequencing in two Emirati nationals showed extensive genetic admixture with genetic contribution from the Middle East, Sub-Saharan and North Africa, Central and South Asia as well as Europe and Oceania [6]. In addition, the effect of 101 known type 2 diabetes mellitus (T2DM) loci was examined in Emiratis (422 patients with T2DM and 455 controls) and common SNPs in *HHEX*, *BCL2*,

* Corresponding author.
E-mail addresses: hindadaggag@gmail.com (H. Daggag), anette.gjesing@sund.ku.dk (A.P. Gjesing), alshafimd@yahoo.com (A. Mohammad), lars.angquist@sund.ku.dk (L. Ängquist), bshobi@icldc.ae (B. Shobi), santony@icldc.ae (S. Antony), dhaj@icldc.ae (D. Haj), aaltikriti@icldc.ae (A. Al Tikriti), abuckley@icldc.ae (A. Buckley), torben.hansen@sund.ku.dk (T. Hansen), mbarakat@icldc.ae (M.T. Barakat).
[1] These authors contributed equally to the manuscript.

https://doi.org/10.1016/j.metop.2022.100213
Received 6 September 2022; Received in revised form 18 October 2022; Accepted 18 October 2022
Available online 7 November 2022

Abbreviations

ABCC8	ATP Binding Cassette Subfamily C Member 8
ACMG	American College of Medical Genetics and Genomics
GAD	Glutamic acid decarboxylase
GCK	Glucokinase
GDM	Gestational diabetes
HNF1A	Hepatocyte nuclear factor-1 alpha
HNF1B	Hepatocyte nuclear factor-1 beta
HNF4A	Hepatocyte nuclear factor-4 alpha
HG	Hyperglycemia
IA2	Islet antigen 2
INS	Insulin
IQR	Interquartile range
KCNJ11	Potassium Inwardly Rectifying Channel Subfamily J Member 11
MODY	Maturity-onset diabetes of the young
RR	Risk ratio
T2DM	Type 2 diabetes mellitus
VUS:	Variants of uncertain significance

ADAMTS9, *SLC22A3* and *MTNR1B* associated with T2DM were detected [7]. However, the prevalence of rare variants, detected only by sequencing, has not been examined among Emirati patients with diabetes.

The most common form of monogenic diabetes is maturity-onset diabetes of the young (MODY), characterised by autosomal dominant inherited non-autoimmune diabetes, with early-onset of diabetes (before the age of 25 years in at least one family member) [8]. Rare variants in fourteen genes are so far known to cause MODY and precision medicine-based intervention (involving precise molecular diagnosis and precise path to medical care for an individual) can be applied for the most common of these genetic etiologies [9]. The presence of such variants has been discovered in different populations with diabetes including women with gestational diabetes (GDM) [9–13]. This is of great importance as the identification of such variants in the mother can guide treatment before and during the pregnancy, fetus growth risks, complications during delivery, possible implications for risk of developing diabetes later in life and counselling [12,13]. The aim of the present study was therefore 1) to investigate if pathogenic variants in *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *INS*, *ABCC8* and *KCNJ1I* are present in Emirati women with GDM, 2) to study the associated clinical characteristics of carriers of such variants and 3) to examine if such variants associate with risk of developing hyperglycemia (HG) postpartum.

2. Materials and methods

2.1. Population

Female patients were recruited from Imperial College London Diabetes Centre, Abu Dhabi, UAE. Inclusion criteria were; diagnosis with diabetes for the first time during pregnancy and before the age of 45. Women were excluded if either glutamic acid decarboxylase (GAD) or islet antigen 2 (IA2) autoantibodies were detected. Clinical diagnosis was based on the electronic medical record. The diagnosis of gestational diabetes was based on a ADA guidelines using either the one-step or the two-step diagnostic criteria [14]. The average time from diagnosis with GDM until the study ended in February 2019 was 71 months (approximately 6 years) ranging from 2 to 385 months. In total, 370 women were included in the present study (Supplementary Table S1).

Informed consent was obtained from all participants. The study design was in accordance with the ethical scientific principles of the Helsinki Declaration II and approved by Imperial College London Diabetes Centre Research Ethics Committee (reference number: IREC032).

2.2. Anthropometric and biochemical measurements

Weight (kg) was measured to the nearest 1.0 kg with the participant wearing light clothes and no shoes. Change in weight was calculated as the difference between post-pregnancy weight and pre-pregnancy weight.

GAD and IA2 antibodies were analyzed by Enzyme-Linked Immunosorbent Assay (ELISA) tests using anti-GAD and anti-IA2 commercial kits (EUROIMMUN AG, Germany). C-peptide was measured at the time of recruitment by the electrochemiluminescence immunoassay (ECLIA) method using a Cobas 6000 (Roche, Switzerland).

The hospital records available did not include date of giving birth, thus the time from the registration of GDM to a subsequent registration of either overt T2DM or any form of HG (if either pre-diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or T2DM was recorded in hospital records) was defined as being a minimum of 8 months, in order to ensure that the subsequent diagnosis of diabetes was indeed postpartum, meaning that if follow-up is stated as 2 months, it is 10 months after the first diagnosis of GDM was recorded.

2.3. Targeted sequencing

Targeted regions including the coding regions and exon/intron boundaries of the *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *INS, ABCC8* and *KCNJ11* genes, were captured and sequenced using the Illumina HiSeq2000 Analyzer as previously described [15]. Sequencing data were analyzed for variants using the Annovar software [16] as per the transcripts (*GCK*: NM_000162, *HNF1A*: NM_000545.5, HNF4A: NM_175914, HNF1B: NM_000458.2, NM_001304286 and NM_001304286, INS: NM_000207.2, ABCC8: NM_000352 and KCNJ11: NM_000525).

2.4. Pathogenicity of variants

Variants were classified as being either pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign or benign, as per American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines [17]. This classification was based on: 1) the location and function of variants; 2) minor allele frequency (MAF) in both the Gnomad database [18] and a Middle Eastern reference population [19]; 3) previous information of variants being involved in MODY [20–23]; 4) CADD score (http://cadd.gs.washington.edu/info); 5) ClinVar classification (if available) [24] and 6) information of the prevalence of variants in the *in house* database of approximately 6000 Danish population-based individuals without diabetes (the Inter99 cohort) [25].

In the remainder of the manuscript, variants classified as either likely pathogenic or pathogenic will be denoted pathogenic, variants classified as either likely benign or benign will be denoted benign and variants classified as being of uncertain significance will be denoted VUS.

2.5. Statistical analysis

For all analyses below, we will refer to the non-carrier group – often working as a reference group – which includes individuals with no or only benign variants. The differences in quantitative traits (age at examination and at diagnosis, C-peptide, pre- and post-pregnancy weight, change in weight and age-of-diagnosis) between carriers and non-carriers of pathogenic variants and/or VUS in the investigated genes, were examined using standard linear regression with carrier-status as the explanatory variable and quantitative trait as outcome. All investigated traits (approximately) followed a normal distribution except C-peptide which was log-transformed.

The risk ratio (RR) was calculated as the ratio between the risk of

developing the disease (overt T2DM or any form of HG) after GDM according to carrier-status and was tested for associations between exposure (carrier-status) and disease (developing T2DM or HG).

Median follow-up time was calculated as 1) the time period from the GDM diagnosis noted in the hospital records to the first date of any form of HG (noted in the records as either IFG, IGT or T2DM) or exclusively as T2DM (overt T2DM) or 2) for patients remaining disease free, from the time period from the GDM diagnosis noted in the hospital records until end of study (February 2019). The median follow-up for overt T2DM was 3.7 years (IQR: 2.0–6.7 years) and for any form of HG 3.4 years (IQR: 1.9–6.3 years).

The Kaplan-Meier log-rank test was used to compare the estimated disease-free ratio of women who remained free of either any form of HG or T2DM in carriers of, respectively, VUS or pathogenic variants compared to non-carriers.

Statistical analyses were performed using RStudio software version 3.6.1 and 4.0.2 (R Foundation for Statistical Computing, Boston, MA, USA). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Prevalence of identified variants

We identified 34 different variants in the studied genes in 370 women with GDM (Table 1). Eleven of the variants were common (MAF >1%) (*HNF1A*: I27L, A98V and S487 N; *HNF4A*: T117I and I441V; *ABCC8*: A1370S and V1573I; *KCNJ11*: K23E, L270V, V337I and S385C), six were low frequency variants (MAF between 1% and 0.1%) (*GCK*: H318P, *HNF1A*: A239V, P291A, and S574G; *HNF4A*:V147I, and *HNF1B*: F443L) and the remaining 17 were rare (minor allele frequency <0.1%) (*GCK*: Q19H, R64H and T207 M; *HNF1A*: G52A, L254R, S328 N and L389V; *HNF1B*: V25L, S75F, S342F and R435H, *INS*: R55H; *ABCC8*: R285Q, A355T, E612D, and A958V; K*CNJ11*: R365H) (Table 1).

Prevalence of identified variants was compared with available references including a Middle Eastern reference [18,19] and three novel mutations were found (Q19H in *GCK*; L254R and S328 N in *HNF1A*) (Table 1). The remaining 31 variants have previously been described [18,19].

3.2. Pathogenicity of variants

The variants were classified according to pathogenicity, resulting in the identification of six pathogenic variants, 14 VUS and 14 benign variants. All of the common variants were benign.

VUS were present in *GCK*, *HNF1A*, *HNF4A, HNF1B* and *ABCC8* in 25 carriers, resulting in a prevalence of 6.8% (95% CI: 4.6–9.8%) in our samples (Table 2). Seven women were carriers of pathogenic variants located in *GCK*, *HNF1A*, *INS, ABCC8* and *KNJ11*, resulting in a prevalence of 1.9% (0.9–3.9%) (Table 2). It should be noted that two patients carried two rare variants each. One carried the combination of a pathogenic and a benign variant and the other a pathogenic and a VUS. Thus, the combined prevalence was 8.4% (6.0–11.7%).

3.3. Phenotypic characteristics

We did not observe any significant associations between age of examination, age of diagnosis, pre- and post-pregnancy weight or change in weight and carrying either VUS or pathogenic variants (Table 3).

3.4. Risk of developing HG or T2DM

Within the study period a total of 89 out of 370 women developed overt T2DM (24%; 95% CI: 20–29%). Among carriers of pathogenic variants, 57% (25–84%; n = 4) developed T2DM following GDM, 24% (12–43%; n = 6) of the carriers of VUS and 23% (19–28%; n = 79) of the non-carriers (Table 4).

Table 1
Variants identified in 370 Emirati women with GDM.

Variant	Position hg19/rs-number	No. carriers: WT/HE/HO (MAF)	Gnomad (all) [18]	GME [19]	Pathogenicity classification [17]
GCK (NM_033507)					
Q19H	44193054/ NA	369/1/ 0 (0.1%)	0%	0%	VUS
R64H	44192920/ rs746444094	369/1/0[a] (0.1%)	0.001%	0%	Pathogenic
T207 M	44189421/ NA	368/2/ 0 (0.3%)	0.0004%	0%	Pathogenic
H318P	44186131/ NA	369/1/ 0 (0.1%)	0%	0.3%	VUS
HNF1A (NM_000545)					
I27L	121416650/ rs1169288	101/185/ 64 (48%)	36%	43%	Benign
G52A	121416726/ rs142318174	369/1/ 0 (0.1%)	0.02%	0%	VUS
A98V	121416864/ rs1800574	335/33/2 (5%)	3%	4%	Benign
A239V	121431969/ rs587778397	368/2/ 0 (0.3%)	0.02%	0.1%	VUS
L254R	121432014/ NA	369/1/ 0 (0.1%)	0%	0%	Pathogenic
P291A	121432124/ rs151256267	369/1/ 0 (0.1%)	0.0004%	0.1%	VUS
S328 N	121434092/ NA	369/1/ 0 (0.1%)	0%	0%	VUS
L389V	121434401/ rs115080759	367/3/ 0 (0.4%)	0.04%	0%	VUS
S487 N	121435427/ rs2464196	92/173/ 105 (52%)	33%	42%	Benign
S574G	121437382/ rs1169305	369/1/ 0 (0.1%)	0.3%	0.5%	Benign
HNF4A (NM_175914)					
T117I	43042364/ rs1800961	362/8/ 0 (1%)	3%	0.9%	Benign
V147I	43043159/ rs142204928	367/3/ 0 (0.4%)	0.2%	0.3%	VUS
I441V	43058267/ rs147638455	362/8/ 0 (1%)	0.03%	2%	Benign
HNF1B (NM_000458)					
V25L	36104803/ rs139107479	364/5/1[b] (1%)	0.002%	0%	Benign
S75F	36104652/ NA	369/1/ 0 (0.1%)	0.0004%	0%	VUS
S342F	36091606/ rs780035561	363/7/ 0 (1%)	0.003%	0%	VUS
R435H	36047353/ rs200421746	369/1/0[a] (0.1%)	0.005%	0%	VUS
F443L	36047328/ rs8068014	366/4/ 0 (0.5%)	0.7%	0%	Benign
INS (NM_000207.2)					
R55H	2182038/NA	369/1/0[b] (0.1%)	0.0008%	0%	Pathogenic
ABCC8 (NM_001287174)					
R285Q	17482192/ rs199616008	369/1/ 0 (0.1%)	0.01%	0%	VUS
A355T	17474779/ rs145136257	369/1/ 0 (0.1%)	0.05%	0%	VUS
E612D	17450199/ rs764753690	369/1/ 0 (0.1%)	0.0008%	0%	Pathogenic
A958V	17428948/ rs772574110	369/1/ 0 (0.1%)	0.0004%	0%	VUS
A1370S	17418477/ rs757110	32/143/ 195 (72%)	64%	73%	Benign
V1573I	17414570/ rs8192690	303/65/2 (9%)	5%	8.8%	Benign
KCNJ11 (NM_000525)					
K23E	17409572/ rs5219	28/145/ 197 (73%)	65%	73%	Benign
L270V	17408831/ rs1800467	343/27/ 0 (4%)	4%	4%	Benign
V337I	17408630/ rs5215	29/146/ 195 (72%)	65%	73%	Benign

(*continued on next page*)

Table 1 (*continued*)

Variant	Position hg19/rs-number	No. carriers: WT/HE/HO (MAF)	Gnomad (all) [18]	GME [19]	Pathogenicity classification [17]
R365H	17408545/ rs750689750	369/1/ 0 (0.1%)	0.003%	0%	Pathogenic
S385C	17408485/ rs41282930	344/25/1 (3.6%)	0.5%	3%	Benign

Legend. GME: Greater Middle East.
[a] Carrier of both the *GCK* R64H and the *HNF1B* R435H variant.
[b] Carrier of both the *INS* R55H and the *HNF1B* V25L variant.

Hence, women with pathogenic variants had more than a 2-fold risk of developing overt postpartum T2DM compared to non-carriers, risk ratio (RR) = 2.5 (1.3–4.8; p = 0.009) (Table 4). There were no significant difference in the fraction of women with VUS who developed T2DM when compared to non-carriers (Table 4).

The total number of women who developed any form of HG within the study period was 147 (40%; 35–45%). Among carriers of pathogenic variants 71% (36–92%; n = 5) developed any form of HG compared to 32% (17–52%; n = 8) of the carriers of VUS and 40% (35–45%; n = 134) of the non-carriers. The RR of developing HG among carriers of pathogenic variant was 1.8 (1.1–2.9; p = 0.01) compared to non-carriers (Table 4). The RR was not significant when comparing non-carriers and carriers of VUS (Table 4).

3.5. Length of time from GDM to subsequent development of overt T2DM or any form of HG

The median time from GDM to development of T2DM was 41.2 months (IQR: 28.6; 49.5, n = 4) among carriers of pathogenic variants, 62.1 months (IQR: 53.0; 87.7, n = 6) among carriers of VUS and 43.0 months (IQR: 19.7; 77.3, n = 79) among non-carriers.

The median time from GDM to development of any form of HG was 28.9 months (IQR: 10.8; 35.2, n = 5) among carriers of pathogenic variants, 43.6 months (IQR: 37.3; 75.2, n = 8) among carriers of VUS and 39.3 months (IQR: 17.6; 77.4, n = 134) among non-carriers. The overall follow-up time for all the women was comparable between women who developed either any form of HG or overt T2DM versus those women who remained disease free until end of study according to carrier-status (Supplementary Table S2).

Kaplan-Meier analysis was used to compare time from GDM to development of T2DM or any form of HG between non-carriers vs. carriers of VUS and pathogenic variants. This analysis showed that women with pathogenic variants had a shorter disease-free period until either development of T2DM or HG compared to non-carriers, p = 0.005 and p = 0.0004, respectively (Fig. 1) with all of the women diagnosed with HG within 5 years after GDM (Fig. 1 and Supplementary Table S2). There were no significant differences in the proportion of women who remained disease-free between carriers of VUS and non-carriers (Fig. 1).

4. Discussion

Seven carriers of pathogenic variants in *GCK*, *HNF1A*, *INS, ABCC8* and *KCNJ11* were found in a cohort of 370 Emirati women with GDM, corresponding to a prevalence of two percent. Carrying such variants predisposed the women to develop HG within 5 years after GDM. Moreover, identification of pathogenic variants in selected MODY genes in the Emirati population may be important as precision intervention can be applied. For example, women carrying variants in the *GCK* gene generally do not require treatment outside of the pregnancy [26], however, in women carrying a child who did not inherit the *GCK* mutation, the fetus will increase insulin secretion in response to the slight HG in the mother. This in turn increases the risk of macrosomia. As such, current recommendations state that a mother carrying pathogenic *GCK*

Table 2
Number of carriers of VUS and pathogenic variants among 370 women with GDM.

GDM (n = 370)	NC or benign, n	Carriers of VUS, n	Carriers of pathogenic variants, n	Prevalence of carriers of VUS, % (95% CI)	Prevalence of carriers of pathogenic variants, % (95% CI)
GCK	365	2	3	0.5 (0.2–2.0)	0.8 (0.3–2.4)
HNF1A	361	8	1	2.2 (1.1–4.2)	0.3 (0.05–1.5)
HNF4A	367	3	0	0.8 (0.3–2.4)	0
HNF1B	361	9	0	2.4 (1.3–4.6)	0
INS	369	0	1	0	0.3 (0.05–1.5)
ABCC8	366	3	1	0.8 (0.3–2.4)	0.3 (0.05–1.5)
KCNJ11	369	0	1	0	0.3 (0.05–1.5)
Total, specific	**340**	**25**	**7**	**6.8 (4.6–9.8)**	**1.9 (0.9–3.9)**
Total, combined	**339**[a]	**31**[a]		**8.4% (6.0–11.7)**	

Legend. NC: Non-carrier. VUS: Variant of uncertain clinical significance. CI: Confidence interval.
[a] One individual carried a pathogenic and a VUS and one carried a pathogenic and a benign variant.

Table 3
Phenotypical characteristics among women with GDM with and without pathogenic variants in *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *INS*, *ABCC8* and *KCNJ11*.

GDM (n = 370)	N	NC or benign (n = 339)	Carriers of VUS (n = 24[a])	Carriers of pathogenic variants (n = 7)	*p*-value (non-carriers vs. carriers of VUS)	*p*-value (non-carriers vs. carriers of pathogenic variants)
Age at examination (years)	370	39.0 (34.5; 44.0)	36.5 (34.5; 4050)	39.0 (33.0; 41.00)	0.3	0.5
Age of diagnosis (years)	370	33.0 (30.0; 38.0)	32.5 (30.0; 35.0)	34.0 (26.0; 35.0)	0.3	0.5
C-peptide (nmol/l)	367	1.0 (0.75; 1.34)	0.89 (0.72; 1.20)	1.16 (0.99; 1.48)	0.2	0.5
Pre-pregnancy weight (kg)	139	74.9 (65.0; 85.4)	79.2 (66.4; 93.0)	74.2 (65.8; 83.7)	0.6	0.8
Post-pregnancy weight (kg)	218	78.3 (66.6; 91.0)	77.8 (62.9; 84.5)	71.8 (63.2; 77.9)	0.6	0.3
Change in weight (kg)	116	1.5 (−1.68; 5.25)	6.2 (4.3; 6.6)	−0.4 (−2.2; 1.9)	0.3	0.7

Legend. Data is presented as median (interquartile range (IQR)). GDM: Gestational diabetes. NC: Non-carrier. VUS: variant of uncertain significance.
[a] Carrier with both a VUS and a pathogenic variant is included among carriers of pathogenic variants.

Table 4
Number of women with and without post-partum development of T2DM or HG.

	Without T2DM	With T2DM	Proportion T2DM (95% CI)	RR vs. reference (non-carriers)
Non-carriers (n = 339)	260	79	23% (19–28%)	
Carriers of VUS (n = 24[a])	19	6	25% (12–45%)	1.0 (0.5–2.1), p = 0.9
Carriers of pathogenic variants (n = 7)	3	4	57% (25–84%)	2.5 (1.3–4.8), p = 0.009
	Without HG	With HG	Proportion with HG (95% CI)	
Non-carriers (n = 339)	202	137	40% (35–46%)	
Carriers of VUS (n = 24[a])	17	8	33% (18–53%)	0.8 (0.45–1.4), p = 0.4
Carriers of pathogenic variants (n = 7)	2	5	71% (36–92%)	1.8 (1.1–2.9), p = 0.02

Legend. HG: Hyperglycemia. RR: Risk ratio. T2DM: type 2 diabetes mellitus. VUS: variant of uncertain significance.
[a] Carrier with both a VUS and a pathogenic variant is included among carriers of pathogenic variants.

variants is followed closely during pregnancy and that C-section is performed at signs of macrosomia [12].

Women carrying pathogenic variants in the transcription factor *HNF1A* as well as the two genes (*ABCC8* and *KCNJ11*) encoding a beta-cell K-ATP channel are sensitive to sulphonylurea treatment [26–28]. Yet, due to the risk of *trans*-placental transfer of sulphonylurea, carriers of pathogenic *HNF1A*, *ABCC8* or *KCNJ11* variants are recommended to be transferred onto insulin before the third trimester in order to reduce the risk of fetal hyperinsulinism and macrosomia [12,13].

Women with a pathogenic variant in *INS* gene often require insulin treatment regardless of pregnancy as their insulin production is significantly reduced [29].

In our cohort of women with GDM, carriers of pathogenic variants had a higher risk of developing any form of HG and T2DM after delivery. A previous study on Danish women with a history of GDM, found that 71% of the women with pathogenic MODY variants had glucose levels corresponding to diabetes at follow-up after approximately 10 years [10]. This is in line with the current study, stating that 71% of women carrying pathogenic variants developed HG postpartum with a median follow-up time of 6 years. Thus, in addition to tailoring treatment during and post-pregnancy, identification of women with pathogenic MODY mutations can aid the identification of women in need of more frequent control visits postpartum.

Previous studies in women from other ethnic groups with GDM, have found prevalence of pathogenic *GCK* variants between 2 and 6% [10,11,30,31] and pathogenic *HNF1A* variants between 1 and 2% [10,11,30], thus, slightly higher than seen in our study. This could be due to ethnic differences or a more strict pathogenicity classification of identified variants in recent studies. More extensive variant information is now available, including prevalence of variants in individuals without diabetes, resulting in fewer variants classified as pathogenic.

One carrier of an *INS* variant was identified in a previous study [10], but none of the previous studies investigated the prevalence of rare *ABCC8* and *KCNJ11* pathogenic variants in patients with GDM. A

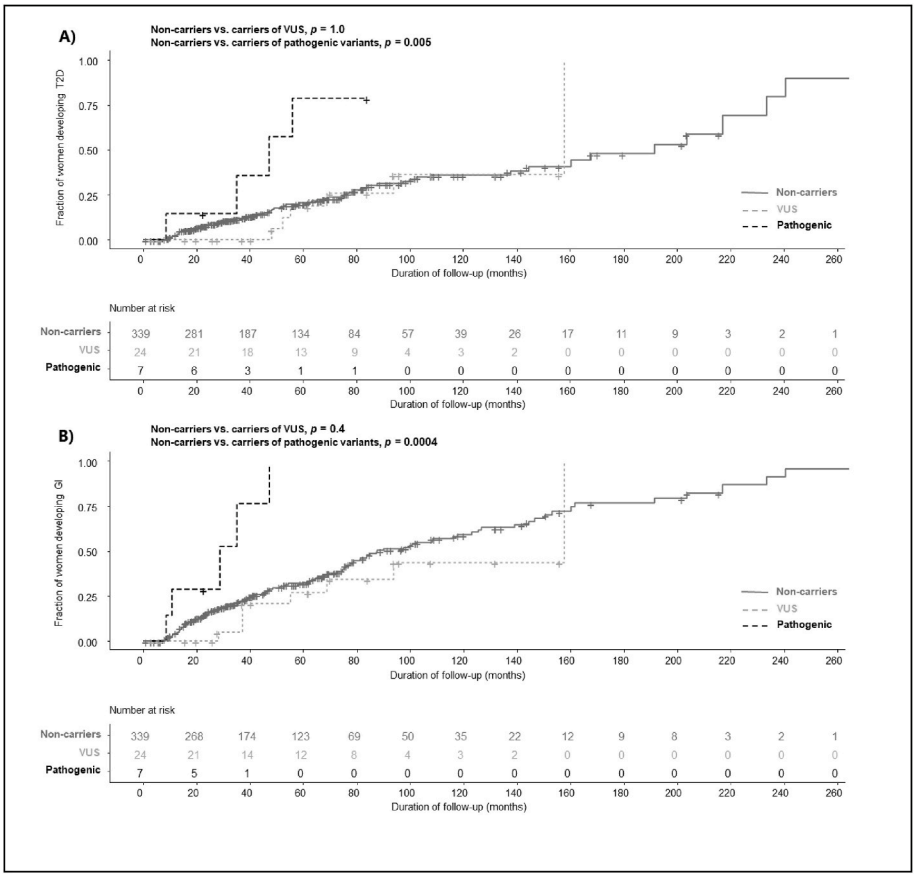

Fig. 1. Kaplan-Meier curves of the time from GDM to development of overt T2DM (A) or any form of HG (B) for non-carriers and carriers of VUS and pathogenic variants.
Legend. HG: Hyperglycemia. T2DM: Type 2 diabetes mellitus. VUS: Variants of uncertain clinical significance.

systematic review investigated the effect of a polymorphism (rs5219) in *KCNJ11*, and found a slight association with elevated risk of GDM [32].

In the current study we identified three novel variants in the Emirati population (*GCK*: Q19H and *HNF1A*: L254R; S328 N). Two *HNF1B* variants (V25L and S342F) found to be rare in other populations, had a MAF of 1% in the Emirati population [18,19]. However, in order to validate whether these variants are more frequent in the Emirati population, a local reference genome is needed. The remaining variants were found in allele frequencies comparable to the ones published online [18,19].

One limitation of the study is the small sample size due to which we were not able to extrapolate the estimated prevalence in the overall population. Additionally, the number of patients developing HG subsequent to GDM is connected to the length of follow-up and it can be expected that a larger number of women would develop HG with increased follow-up time. Yet, follow-up time was longer for non-carriers and carriers of VUS compared to carriers of pathogenic variants, thus the lower number of events among non-carriers and carriers of VUS is likely not a consequence of follow-up time. However, median follow-up time for carriers of pathogenic variants without any events was shorter than the median follow-up for the pathogenic events group. This could perhaps indicate that even more events would have been observed, if follow-up times were lengthened. Finally, a limitation of the study is the lack of a healthy control group to which results could have been compared. Nevertheless, our study does show that pathogenic variants in MODY genes are present in the Emirati population and may be the cause of diabetes in women with GDM. In addition, the majority of carriers have developed HG within a few years after their pregnancy. Thus, accurate genetic diagnosis enables better treatment, early detection of complication related to fetal growth and a better follow-up after delivery.

5. Conclusions

In the present study, two percent of Emirati women with GDM carry pathogenic variants in genes known to be involved in monogenic diabetes. Correct diagnosis of women with GDM due to the presence of pathogenic variant in MODY genes, enables the application of precision medicine both during and outside of pregnancy and also allows for screening of family members, with early detection leading to earlier diagnosis and adequate treatment.

Data availability

The data supporting the results of this research paper is included within this article and its additional supplementary files.

Funding

The study was partially performed at the Novo Nordisk Foundation Center for Basic Metabolic Research, an independent research centre at the University of Copenhagen, partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk). The study was also partially performed at the Research Institute at Imperial College London Diabetes Centre (ICLDC) and partially funded by ICLDC (www.icldc.ae). The study was also supported by Augustinus Foundation (16–2922) and the Novo Nordisk Foundation through the Challenge Program (NNFOC0033950) and the Steno Collaborative Grants (NNF17OC0028328). Funders did not have any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

Hinda Daggag: were responsible for, Conceptualization, were responsible for design of the study, were involved in, Funding acquisition, critically revised the manuscript and contributed to the discussion, The final version of the paper was read and approved by all authors. **Anette P. Gjesing:** were responsible for, Conceptualization, were responsible for design of the study, took part in the, Formal analysis, were involved in, Funding acquisition, Writing – original draft, the article, critically revised the manuscript and contributed to the discussion, The final version of the paper was read and approved by all authors. **Alshafi Mohammad:** was involved in, Writing – review & editing, electronic medical records and, Data curation, critically revised the manuscript and contributed to the discussion, The final version of the paper was read and approved by all authors. **Lars Ängquist:** took part in the, Formal analysis, critically revised the manuscript and contributed to the discussion, The final version of the paper was read and approved by all authors. **Bindu Shobi:** were responsible for DNA extraction and, Data curation, collection. **Suma Antony:** were responsible for DNA extraction and, Data curation, collection. **Dalia Haj:** was responsible for recruitment. **Alia Al Tikriti:** was involved in extracting phenotypic, Data curation. **Adam Buckley:** critically revised the manuscript and contributed to the discussion, The final version of the paper was read and approved by all authors. **Torben Hansen:** were responsible for conception, were responsible for design of the study, took part in the, Formal analysis, were involved in, Funding acquisition, Writing – original draft, the article, critically revised the manuscript and contributed to the discussion, The final version of the paper was read and approved by all authors. **Maha T. Barakat:** were responsible for, Conceptualization, were involved in, Funding acquisition, critically revised the manuscript and contributed to the discussion. The final version of the paper was read and approved by all authors.

Declaration of competing interest

None.

Acknowledgement

From Novo Nordisk Foundation Centre for Basic Metabolic Research, University of Copenhagen, Denmark, we wish to thank A. Forman, T. H. Lorentzen and G. J. Klavsen for laboratory assistance, P. Sandbeck for data management, and C. Verdich and L. Ryborg for grant management. From ICLDC Research Institute, we wish to thank H. Al-Karbi for patient recruitment and T. Ghulam for laboratory assistance. Authors have no relevant conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2022.100213.

References

[1] Federation ID. IDF diabetes atlas. ninth ed. 2019 2019 https://www.diabetesatlas.org/en/resources.
[2] Abuyassin B, Laher I. Diabetes epidemic sweeping the Arab world. World J Diabetes 2016;7:165–74. https://doi.org/10.4239/wjd.v7.i8.165.
[3] Azizi F, Hadaegh F, Hosseinpanah F, Mirmiran P, Amouzegar A, Abdi H, Asghari G, Parizadeh D, Montazeri SA, Lotfaliany M, et al. Metabolic health in the Middle East and north Africa. Lancet Diabetes Endocrinol 2019;7:866–79. https://doi.org/10.1016/S2213-8587(19)30179-2.
[4] Mohamad MN, Ismail LC, Stojanovska L, Apostolopoulos V, Feehan J, Jarrar AH, Al Dhaheri AS. The prevalence of diabetes amongst young Emirati female adults in the United Arab Emirates: a cross-sectional study. PLoS One 2021;16:e0252884. https://doi.org/10.1371/journal.pone.0252884.
[5] AlSafar HS, Al-Ali M, Elbait GD, Al-Maini MH, Ruta D, Peramo B, Henschel A, Tay GK. Introducing the first whole genomes of nationals from the United Arab Emirates. Sci Rep 2019;9:14725. https://doi.org/10.1038/s41598-019-50876-9.
[6] Osman W, Hassoun A, Jelinek HF, Almahmeed W, Afandi B, Tay GK, Alsafar H. Genetics of type 2 diabetes and coronary artery disease and their associations with twelve cardiometabolic traits in the United Arab Emirates population. Gene 2020;750:144722. https://doi.org/10.1016/j.gene.2020.144722.

[7] Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metabol 2008;4:200–13. https://doi.org/10.1038/ncpendmet0778.ncpendmet0778 [pii].
[8] Anik A, Catli G, Abaci A, Bober E. Maturity-onset diabetes of the young (MODY): an update. J Pediatr Endocrinol Metab : JPEM (J Pediatr Endocrinol Metab) 2015;28:251–63. https://doi.org/10.1515/jpem-2014-0384.
[9] Monsonego S, Clark H, Karovitch A, O'Meara P, Shaw T, Malcolm J. Management and outcomes of maturity-onset diabetes of the young in pregnancy. Can J Diabetes 2019;43:647–54. https://doi.org/10.1016/j.jcjd.2019.07.004.
[10] Gjesing AP, Rui G, Lauenborg J, Have CT, Hollensted M, Andersson E, Grarup N, Sun J, Quan S, Brandslund I, et al. High prevalence of diabetes-predisposing variants in MODY genes among Danish women with gestational diabetes mellitus. Journal of the Endocrine Society 2017;1:681–90. https://doi.org/10.1210/js.2017-00040.
[11] Weng J, Ekelund M, Lehto M, Li H, Ekberg G, Frid A, Aberg A, Groop LC, Berntorp K. Screening for MODY mutations, GAD antibodies, and type 1 diabetes–associated HLA genotypes in women with gestational diabetes mellitus. Diabetes Care 2002;25:68–71.
[12] Dickens LT, Naylor RN. Clinical management of women with monogenic diabetes during pregnancy. Curr Diabetes Rep 2018;18:12. https://doi.org/10.1007/s11892-018-0982-8.
[13] Shepherd M, Brook AJ, Chakera AJ, Hattersley AT. Management of sulfonylurea-treated monogenic diabetes in pregnancy: implications of placental glibenclamide transfer. Diabet Med : a journal of the British Diabetic Association 2017. https://doi.org/10.1111/dme.13388.
[14] American Diabetes A. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44:S15–33. https://doi.org/10.2337/dc21-S002.
[15] Gao R, Liu Y, Gjesing AP, Hollensted M, Wan X, He S, Pedersen O, Yi X, Wang J, Hansen T. Evaluation of a target region capture sequencing platform using monogenic diabetes as a study-model. BMC Genet 2014;15:13. https://doi.org/10.1186/1471-2156-15-13.
[16] Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res 2010;38:e164. https://doi.org/10.1093/nar/gkq603.
[17] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical genetics and genomics and the association for molecular Pathology. Genet Med : official journal of the American College of Medical Genetics 2015;17:405–24. https://doi.org/10.1038/gim.2015.30.
[18] Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536:285–91. https://doi.org/10.1038/nature19057.
[19] project GV. The greater Middle East (GME) variome project. 2020.
[20] De Franco E, Saint-Martin C, Brusgaard K, Knight Johnson AE, Aguilar-Bryan L, Bowman P, Arnoux JB, Larsen AR, May S, Greeley SAW, et al. Update of variants identified in the pancreatic beta-cell KATP channel genes KCNJ11 and ABCC8 in individuals with congenital hyperinsulinism and diabetes. Hum Mutat 2020;41:884–905. https://doi.org/10.1002/humu.23995.
[21] Osbak KK, Colclough K, Saint-Martin C, Beer NL, Bellanne-Chantelot C, Ellard S, Gloyn AL. Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. Hum Mutat 2009;30:1512–26. https://doi.org/10.1002/humu.21110.
[22] Colclough K, Bellanne-Chantelot C, Saint-Martin C, Flanagan SE, Ellard S. Mutations in the genes encoding the transcription factors hepatocyte nuclear factor 1 alpha and 4 alpha in maturity-onset diabetes of the young and hyperinsulinemic hypoglycemia. Hum Mutat 2013;34:669–85. https://doi.org/10.1002/humu.22279.
[23] Bonnefond A, Boissel M, Bolze A, Durand E, Toussaint B, Vaillant E, Gaget S, Graeve F, Dechaume A, Allegaert F, et al. Pathogenic variants in actionable MODY genes are associated with type 2 diabetes. Nat Metab 2020;2:1126–34. https://doi.org/10.1038/s42255-020-00294-3.
[24] Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, Gu B, Hart J, Hoffman D, Jang W, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res 2018;46:D1062–7. https://doi.org/10.1093/nar/gkx1153.
[25] Glumer C, Jorgensen T, Borch-Johnsen K, Inter s. Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. Diabetes Care 2003;26:2335–40.
[26] Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. JAMA 2014;311:279–86. https://doi.org/10.1001/jama.2013.283980.
[27] Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet 2003;362:1275–81. https://doi.org/10.1016/S0140-6736(03)14571-0.
[28] Hansen T, Eiberg H, Rouard M, Vaxillaire M, Moller AM, Rasmussen SK, Fridberg M, Urhammer SA, Holst JJ, Almind K, et al. Novel MODY3 mutations in the hepatocyte nuclear factor-1alpha gene: evidence for a hyperexcitability of pancreatic beta-cells to intravenous secretagogues in a glucose-tolerant carrier of a P447L mutation. Diabetes 1997;46:726–30. https://doi.org/10.2337/diab.46.4.726.
[29] Harris AG, Letourneau LR, Greeley SAW. Monogenic diabetes: the impact of making the right diagnosis. Curr Opin Pediatr 2018;30:558–67. https://doi.org/10.1097/MOP.0000000000000643.
[30] Zurawek M, Wender-Ozegowska E, Januszkiewicz-Lewandowska D, Zawiejska A, Nowak J. GCK and HNF1alpha mutations and polymorphisms in Polish women with gestational diabetes. Diabetes Res Clin Pract 2007;76:157–8. https://doi.org/10.1016/j.diabres.2006.08.001.
[31] Stoffel M, Bell KL, Blackburn CL, Powell KL, Seo TS, Takeda J, Vionnet N, Xiang KS, Gidh-Jain M, Pilkis SJ, et al. Identification of glucokinase mutations in subjects with gestational diabetes mellitus. Diabetes 1993;42:937–40.
[32] Zhang C, Bao W, Rong Y, Yang H, Bowers K, Yeung E, Kiely M. Genetic variants and the risk of gestational diabetes mellitus: a systematic review. Hum Reprod Update 2013;19:376–90. https://doi.org/10.1093/humupd/dmt013.