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New Gestational Diabetes Mellitus Risk Algorithm

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BACKGROUND AND OBJECTIVE

Gestational diabetes mellitus (GDM) is a common disorder of pregnancy (14% of pregnancies worldwide), defined by glucose intolerance that begins or is first recognized during pregnancy. It is characterized by carbohydrate intolerance, diagnosed in the second or third trimester of pregnancy and is associated with considerable complications and health risks for both mother and baby [1]. Early risk detection might offer opportunities to improve care for women at high risk of developing Gestational Diabetes Mellitus (GDM) [2, 3]. Predictive models that include genetic susceptibility factors are becoming attractive, and the genetic architecture of GDM predisposition is progressively being considered in the development of predictive algorithms. Our aim was to examine the clinical utility of using genetic variants in a risk assessment model.

METHODS

Study populations. We analyzed a retrospective cohort of 711 women from Hospital Clínico San Carlos (HCSC, Madrid, Spain), with 425 control pregnancies and 286 GDM cases diagnosed per The International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. In addition, we examined a cohort of 157 women (89 controls, 68 cases diagnosed per the criteria of The National Diabetes Data Group (NDDG) from Hospital Cruces (Bilbao, Spain) and a cohort of 416 women (346 controls, 70 cases per IADPSG criteria from the "Mónica Pretelini Sáenz" Maternal Perinatal Hospital, Toluca, State of Mexico, México). All studies were approved by the corresponding institutional ethics committees (ref numbers available upon request) and in compliance with the Declaration of Helsinki). All women signed written informed consent. Information was collected on maternal age, ethnicity, gestational week at the time of the OGTT (Oral Glucose Tolerance Test), body mass index, family history of T2D, past medical history of GDM, past obstetric history and parity, gestational weight gain, associated comorbidities, and the newborn's birth weight. Baseline characteristics of the cohorts are described in Table 1 and de la Torre et al. [4].
Genotyping. A total of 112 SNPs were selected for this analysis after exhaustive exploration of the databases published to date of SNPs associated with GDM [5-9]. Genotyping was performed using iPlex Gold-MassARRAY from Agena Bioscience.
Discrimination and calibration of risk scores were assessed using the receiver operating characteristic (ROC) curve in the internal and the external validation groups.

RESULTS

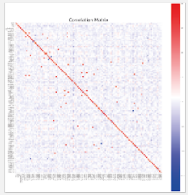
The data quality control process retrieved a total of 286 cases and 425 controls out of the HCSC cohort. Baseline characteristics of study participants are shown in Table 1. Mean age and BMI were higher in cases than in controls (age 33.5 years vs 31.4 years, p=0.00004; BMI 24.04 kg/m2 vs 22.88 kg/m2, p=0.058).

Table 1. Baseline characteristics of the participants, including women from the HCSC, Cruces and HMPMPS cohorts.

HCSC		
Participants	286	425
Age at baseline(years)	33.58 ± 5.13	31.43 ± 5.50
Pre-pregnancy BMI (kg/m²)	24.04 ± 4.20	22.88 ± 3.67
Previous GDM	63 (22.03%)	60 (14.12%)
Family history of DM	22 (7.69%)	44 (10.35%)
Previous gestations	163 (59.85%)	256 (60.71%)
CRUCES		
Participants	68	89
Age at baseline(years)	34.20 ± 4.96	33.83 ± 5.00
Pre-pregnancy BMI (kg/ m²)	25.83 ± 5.27	23.58 ± 4.32
Previous GDM	10 (14.71%)	1 (1.12%)
Family history of DM	28 (41.18%)	8 (8.99%)
Previous gestations	Not available	Not available
HMPMPS		
Participants	57	199
Age at baseline(years)	29.13 ± 6.61	25.60 ± 6.72
Pre-pregnancy BMI (kg/ m²)	30.67 ± 6.10	25.00 ± 4.54
Previous GDM	0	0
Family history of DM	25 (78.13%)	113 (66.83%)
Previous gestations	27 (84.38%)	126 (63.32%)

We examined 112 SNPs previously associated with the risk of T2D, GDM, high BMI and adverse pregnancy traits associated with GDM. A correlation analysis was performed to identify SNPs providing similar information. Of the 112 SNPs, 105 provided unique information and were used for further analysis. The correlation analysis of the SNPs is shown in Figure 1.

Figure 1. Correlation analysis of the 112 SNPs



Sequence Feature Selection analysis showed that 12 attributes provided optimal logistic regression performance, 10 of which are SNPs and 2 are clinical variables (Table 2).

Table 2. Attributes selected by SFS with optimal logistic regression performance.

SNP	Chromosome (GRCh38.p13)	Closest Gene	Effect allele	Trait
rs1387153	chr11:92940867	LOC100128554 /MTNR1B	T	Fasting glucose
rs11605924	chr11:45851540	CRY2	A	Fasting glucose
rs1402060	chr3:185703899	IGF2BP2	T	Fasting glucose, T2D
rs2943634	chr2:226203364	IRS1	C	Fasting insulin, Insulin resistance
rs1801133	chr1:11796321	MTHFR	A	Folate metabolism
rs1106906	chr3:85966222	CCNL2	C	Insulin resistance
rs1805087	chr1:236855200	MTR	G	Folate metabolism
rs11254363	chr10:17088694	CUBN	G	Vitamin B12 metabolism
rs11707792	chr6:136357896	GPSM1	A	Insulin resistance
rs2167270	chr7:128241296	LEP	G	Insulin secretion
Clinical variables	RMI, Age			

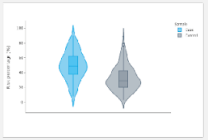
The 10 SNPs identified by SFS and logistic regression analysis reside in genetic loci which have been associated to molecular processes related to fasting glucose (LOC100128554/MTNR1B, CRY2, IGF2BP2), insulin resistance (CCND2, GPSM1, IRS1), insulin secretion (LEP), fasting insulin (IRS1), and folate and vitamin B12 metabolism (MTHFR, MTR, CUBN).
The model showed satisfactory predictive ability with a ROC-AUC of 0.74, sensitivity of 70% and specificity of 69%. The analysis of sensitivity and specificity is shown in Table 3.

Table 3. Specificity, sensitivity, and predictive values analysis at different thresholds.

Threshold	Specificity	Sensitivity	PPV	PNV
0.30	0.50	0.84	0.52	0.83
0.35	0.61	0.79	0.57	0.82
0.37	0.64	0.76	0.58	0.81
0.40	0.69	0.70	0.59	0.78
0.45	0.79	0.62	0.65	0.76

We obtained violin plots where the number of samples in each risk percentage is represented in terms of density. Control and cases were discriminated, as the area with major density in controls (median: 30.02%) is smaller than the one of the cases (median: 49.62%).

Figure 2. Genetic Risk Score (GRS) distribution violin plots for controls vs. cases. The distribution of the risk values for the group control/case is displayed.



In the training dataset the AUC was 0.74, sensitivity of 77% and specificity of 64%. AUCs in the HCSC, UAEM and Cruces validation sets were 0.71, 0.70 and 0.62 respectively.

Table 4. Performance of GDM prediction algorithm in development and validation cohorts.

Cohort	HCSC (70%)	HCSC (30%)	HMPMPS	Cruces
Cases	194	92	32	68
Controls	303	122	199	89
Location	Madrid, Spain	Madrid, Spain	Mexico	Bilbao, Spain
Diagnostic criteria	IADPSG	IADPSG	IADPSG	NDDG
AUC	0.7423	0.7000	0.7220	0.6224

CONCLUSIONS

The utilization of genetic markers in combination with clinical characteristics may improve GDM risk evaluation and can help the clinician identify women at high risk for GDM before pregnancy and early in pregnancy to accelerate preventive interventions.

Our study also highlights the importance of applying consensus criteria for the diagnosis of GDM.

We have made progress in understanding the potential metabolic functions underlying GDM risk. This will potentially support moving towards personalized recommendations and treatments for each of them. However, the study of the metabolic pathways that underlie GDM susceptibilities is still limited and warrants further investigation.

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1. Buchanan TA et al. Diabetes Care 2007; 30 Suppl 2, S105–11
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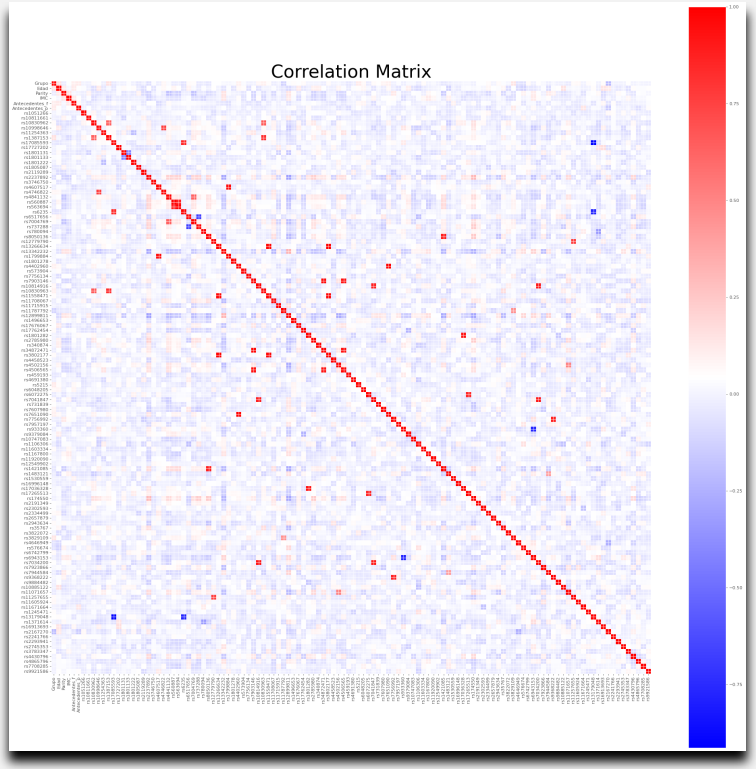

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RESULTS (4)

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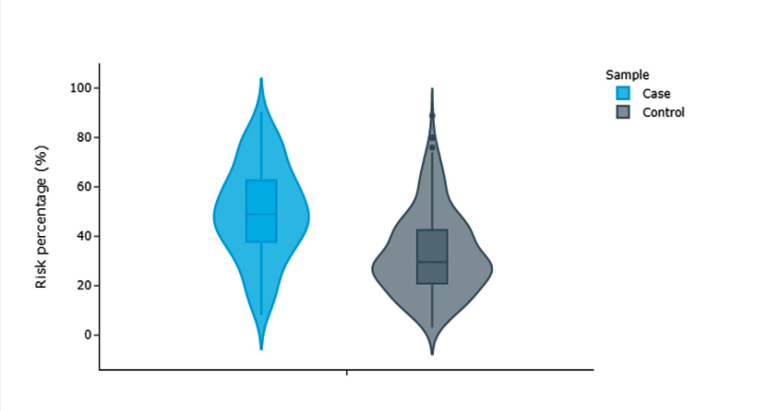

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- ✔ The utilization of genetic markers in combination with clinical characteristics may improve GDM risk evaluation and can help the clinician identify women at high risk for GDM before pregnancy and early in pregnancy to accelerate preventive interventions.
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