LA PROF. ESTER VITACOLONNA

Dichiara che negli ultimi due anni non ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Nutrigenetica e rischio cardiometabolico nel diabete gestazionale

Ester Vitacolonna

Università “G. d’Annunzio” Chieti- Pescara

So what is Precision Medicine?

Medicina clinica individualizzata

Quel tipo di trattamento **mirato alle esigenze del singolo paziente sulla base di quelle caratteristiche genetiche, biologiche, fenotipiche o psicosociali** che **distinguono un dato paziente da un altro con simili caratteristiche**

Precision medicine as treatments targeted to the **needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient** from other patients with similar clinical presentations

DIP2017

Pathophysiological Classification

Diabete tipo 1 – E' causato da distruzione beta-cellulare, su base autoimmune o idiopatica, ed è caratterizzato da una carenza insulinica assoluta (la variante LADA, *Latent Autoimmune Diabetes in Adults*, ha decorso lento e compare nell'adulto).

Diabete tipo 2 – E' causato da un deficit parziale di secrezione insulinica, che in genere progredisce nel tempo ma non porta mai a una carenza assoluta di ormone, e che si instaura spesso su una condizione, più o meno severa, di insulino-resistenza su base multifattoriale.

Gestational diabetes mellitus (GDM). "Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes prior gestation".
GDM is diagnosed for the first time during pregnancy and generally regresses after delivery
It may recur, later, prevalently with the characteristics of Type 2 diabetes

Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic review and meta-analysis of 95,750 women

Diabetologia (2016) 59:1403–1411
DOI 10.1007/s00125-016-3927-2

Girish Rayanagoudar[1] · Amal A. Hashi[1] · Javier Zamora[1,2,3] · Khalid S. Khan[1,4] · Graham A. Hitman[1] · Shakila Thangaratinam[1,4]

Risk factor	No. of studies	No. of women with GDM	RR	I^2	*p* value
Body mass index (kg/m^2)					
>25	5	4,795	3.18 (1.96, 5.16)	77%	<0.001
>27	4	1,251	2.52 (1.69, 3.74)	23%	<0.001
>30	5	4,255	2.85 (2.21, 3.69)	45%	<0.001
Mean	14	5,350	1.95 (1.60, 2.31)	65%	<0.001
Family history	22	6,895	1.70 (1.47, 1.97)	13%	<0.001

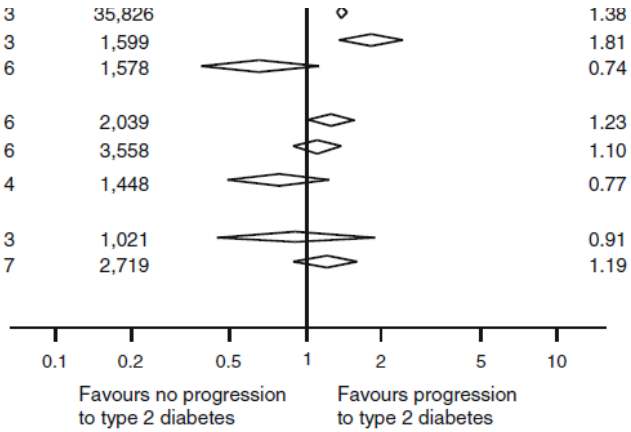
MATERNAL HEALTH

Prevention of type 2 diabetes among women with prior gestational diabetes mellitus

Moshe Hod [a], Eran Hadar [a], Luis Cabero-Roura [b,*]

International Journal of Gynecology and Obstetrics 131 (2015) S16–S18

Hypertension in pregnancy	3	35,826	1.38 (1.32, 1.45)	0%	<0.001
Preterm delivery (<37 weeks)	3	1,599	1.81 (1.35, 2.43)	0%	<0.001
Mean gestational weight gain	6	1,578	0.74 (0.44, 1.19)	69%	0.220
Parity					
Multiparous vs nulliparous	6	2,039	1.23 (1.01, 1.50)	0%	0.040
Mean	6	3,558	1.10 (0.88, 1.37)	39%	0.390
No breast feeding	4	1,448	0.77 (0.48, 1.22)	9%	0.260
Birthweight					
Macrosomia (birthweight >4 Kg)	3	1,021	0.91 (0.44, 1.86)	0%	0.790
Mean	7	2,719	1.19 (0.86, 1.58)	60%	0.270



Development of a simple tool to predict the risk of postpartum diabetes in women with gestational diabetes mellitus

M. Köhler[1,2] · A. G. Ziegler[1,2,3] · A. Beyerlein[1,2]

Acta Diabetol (2016) 53:433–437

Aims Women with gestational diabetes mellitus (GDM) have an increased risk of diabetes postpartum. We developed a score to predict the long-term risk of postpartum diabetes using clinical and anamnestic variables recorded during or shortly after delivery.

This risk score may be an important contribution to the prediction of GDM-related postpartum diabetes, allowing practitioners to easily estimate the diabetes risk in women with prior GDM to help tailor their follow-up examinations, and clinicians to identify high-risk women for targeted prevention studies

Clinical and biochemical approach to predicting post-pregnancy metabolic decompensation

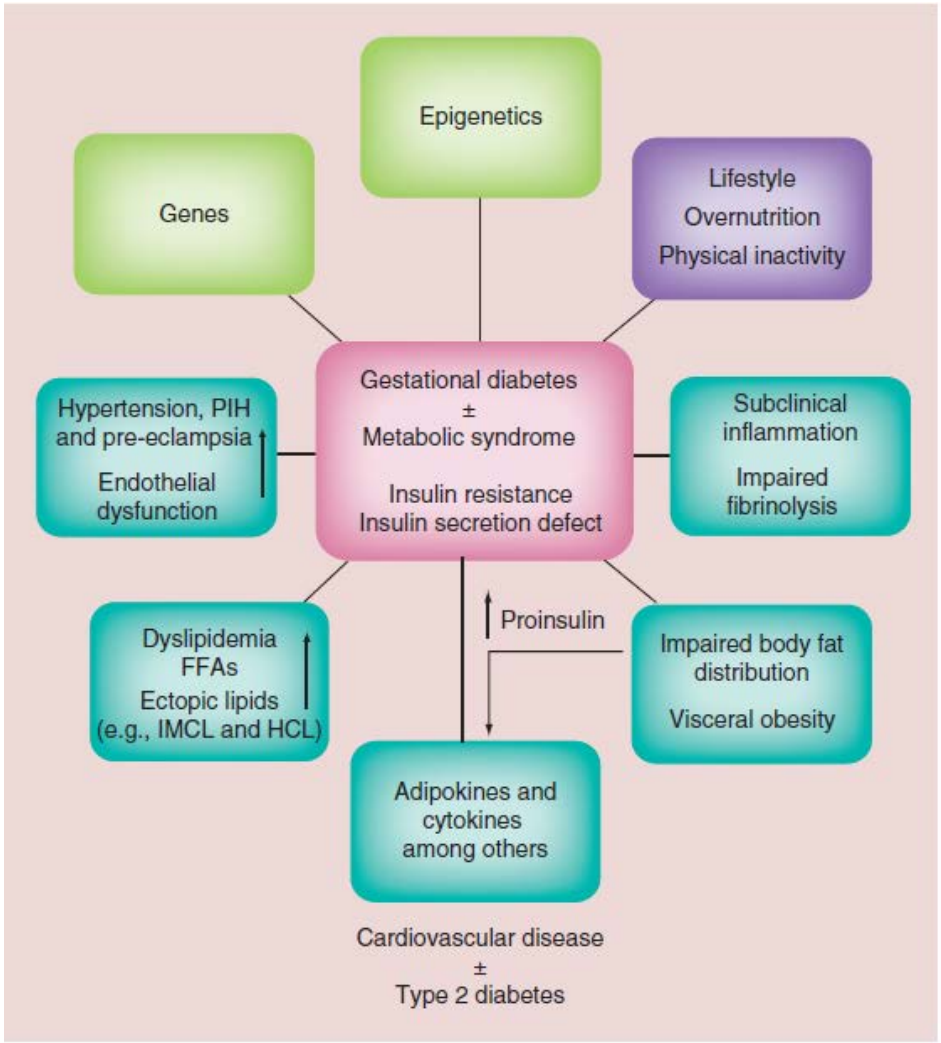
Table 1 – Predictive clinical factors according to clinical studies.

Clinical factors	References	
Prepregnancy BMI	[9–11,14,17,18]	Modifiab
Gestational week of diagnosis	[9,12,14,15]	Unmodif
Insulin therapy	[9–13]	Unmodif
Ethnicity	[11,12,15]	Unmodif
Birth weight	[13]	
Maternal age	[13,15]	Unmodif
Family history for diabetes	[15,17,18]	Unmodif
Multiparity	[15]	Unmodif
Child gender (female)	[19]	Unmodif
Breastfeeding	[36–38]	Protectiv

Table 2 – Predictive biochemical factors according to clinical studies.

Biochemical factors	References
Autoantibodies GAD IA2	[10]
FBG before pregnancy (IFG)	[17,18]
OGTT glucose AUC in pregnancy	[20,21]
OGTT FPG	[21,22]
OGTT 1 h blood glucose	[11]
OGTT 2 h blood glucose	[21,22]
A1c	[22]
Total cholesterol	[17–18]
Metabolomic pathway	[25,29,32]
Lipidomic or lipid profile	[30,31]

S. Burlina, M. G. Dalfra` , A. Lapolla
Diabetes Res Clin Pract (2018),



Relationship between GDM and subsequent cardiovascular disease: modifiable and unmodifiable risk factors.

Gestational Diabetes Mellitus Increases the Risk of Cardiovascular Disease in Women With a Family History of Type 2 Diabetes

Diabetes Care 29:2078–2083, 2006

DARCY B. CARR, MD, MS[1]
KRISTINA M. UTZSCHNEIDER, MD[2]
REBECCA L. HULL, PHD[2]
JENNY TONG, MD, MPH[2]
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SUSAN R. HECKBERT, MD, PHD[4,5]
EDWARD J. BOYKO, MD, MPH[2,6]
WILFRED Y. FUJIMOTO, MD[2]
STEVEN E. KAHN, MB, CHB[2]
THE AMERICAN DIABETES ASSOCIATION GENNID STUDY GROUP*

Table 4—*Frequency of CVD (coronary artery disease and stroke) and adjusted ORs with 95% CIs for the association between a history of GDM and CVD*

	No GDM	Prior GDM	Adjusted OR (95% CI)*	P*
CVD	81/653 (12.4)	51/329 (15.5)	1.85 (1.21–2.82)	0.005
Coronary artery disease	70/653 (10.7)	40/329 (12.2)	1.58 (1.00–2.49)	<0.05
Stroke	31/631 (4.9)	19/305 (6.2)	1.67 (0.87–3.22)	0.1

Data are *n* (number with the condition)/*N* (total number of subjects) (%).*Adjusted for age and menopausal status and clustering on the proband.

RESULTS — Women with prior GDM were younger (48.6 ± 0.7 vs. 52.4 ± 0.6 years [means ± SE]; $P < 0.001$) and less likely to be postmenopausal (48.3 vs. 57.9%; $P < 0.005$). Although both groups were obese (BMI 34.4 ± 1.2 vs. 33.7 ± 0.6 kg/m^2), women with prior GDM were more likely to have metabolic syndrome (86.6 vs. 73.5%; $P < 0.001$) and type 2 diabetes (93.4 vs. 63.3%; $P < 0.001$). Moreover, they had a higher prevalence of CVD (15.5 vs. 12.4%; adjusted odds ratio 1.85 [95% CI 1.21–2.82]; $P = 0.005$) that occurred at a younger age (45.5 ± 2.2 vs. 52.5 ± 1.9 years; $P = 0.02$) and was independent of metabolic syndrome (1.74 [1.10–2.76]; $P = 0.02$) and type 2 diabetes (1.56 [1.002–2.43]; $P < 0.05$).

Carotid Atherosclerosis Is a Stronger Predictor of Myocardial Infarction in Women Than in Men

A 6-Year Follow-Up Study of 6226 Persons: The Tromsø Study

Johnsen S.H, Mathiesen E B, and coll

Stroke. 2007;38:2873-2880.

Carotid Plaque Area and Intima-Media Thickness in Prediction of First-Ever Ischemic Stroke

A 10-Year Follow-Up of 6584 Men and Women: The Tromsø Study

Mathiesen E B, Johnsen S.H, and coll

Stroke. 2011;42:972-978

Carotid artery intima-media thickness (cIMT) is a **subclinical measure of early atherosclerosis that strongly predicts heart disease and stroke, particularly in women.**

Early Changes in Vascular Structure and Function in Women with a History of GDM

Should we consider gestational diabetes a vascular risk factor?

S. Bo[a,*], S. Valpreda[b], G. Menato[c], C. Bardelli[c], C. Botto[c], R. Gambino[a], C. Rabbia[b], M. Durazzo[a], M. Cassader[a], M. Massobrio[c], G. Pagano[a]

Atherosclerosis 194 (2007) e72–e79

cIMT is significantly higher in women with history of GDM when compared than women without, even among women without diabetes and with no components of metabolic syndrome, and irrespective of their BMI

Early Subclinical Atherosclerosis in Women With Previous Gestational Diabetes Mellitus

L. VOLPE, I. CUCCURU, C. LENCIONI, V. NAPOLI, A. GHIO, C. FOTINO, A. BERTOLOTTO, G. PENNO, L. BENZI, S. DEL PRATO,G. DI CIANNI

DIABETES CARE, VOLUME 31, NUMBER 5, MAY 2008

Considerations

- GDM can be considered an unmasking of underlying and silent risk of both diabetes and cardiovascular disease

- **"…The effect of GDM on the risk of CVD remains to be fully elucidated**: it is still not clear whether the association existing between GDM and CVD is independent of the increased risk of CVD associated with type 2 diabetes"……

Genetics of Gestational Diabetes Mellitus and Maternal Metabolism

Curr Diab Rep (2016) 16: 15
DOI 10.1007/s11892-015-0709-z

William L. Lowe Jr.[1] · Denise M. Scholtens[2] · Victoria Sandler[1,3] · M. Geoffrey Hayes[1,4]

Table 1 Candidate genes demonstrating association with GDM in meta-analyses

Gene	Chromosome	Encoded protein	Protein function
IRS1	2	Insulin receptor substrate 1	Substrate of insulin receptor tyrosine kinase; key molecule in the insulin signaling pathway
IGF2BP2	3	Insulin-like growth factor 2 mRNA-binding protein 2	Binds insulin-like growth factor-2 mRNA and may regulate protein translation; risk allele associated with decreased insulin secretion
CDKAL1	6	CDK5 regulatory subunit associated protein 1 like-1	A tRNA methylthiotransferase; non-pregnant carriers of the risk alleles have impaired oral and intravenous glucose stimulated insulin secretion
GCK	7	Glucokinase	Phosphorylates glucose in pancreatic β-cells and hepatocytes; involved in the regulation of insulin secretion
TCF7L2	10	Transcription factor 7-like 2	Transcription factor and member of the Wnt signaling pathway; risk allele associated with reduced insulin secretion
MTNR1B	11	Melatonin receptor 1B	G-protein coupled receptor that is expressed on β-cells, binds melatonin and may antagonize insulin release
KCNJ11	11	Potassium inwardly rectifying channel, subfamily J, member 11	Integral membrane protein and inward-rectifier type potassium channel which is controlled by G-proteins and associated with the sulfonylurea receptor; involved in the regulation of insulin secretion
KCNQ1	11	Potassium voltage-gated channel, KQT-like subfamily, member 1	Voltage-gated potassium channel; involved in the regulation of insulin secretion

Adapted with permission from: Lowe WL, Jr., Karban J. Genetics, genomics and metabolomics: new insights into maternal metabolism during pregnancy. Diabet Med 2014; 31:254-262) [61]

Beyond the clear similarities between the genetic architecture of metabolism in pregnant and non-pregnant populations, there are also indications that some genes may be uniquely associated with metabolic traits during pregnancy or GDM.

Interaction between rs10830963 polymorphism in *MTNR1B* and lifestyle intervention on occurrence of gestational diabetes

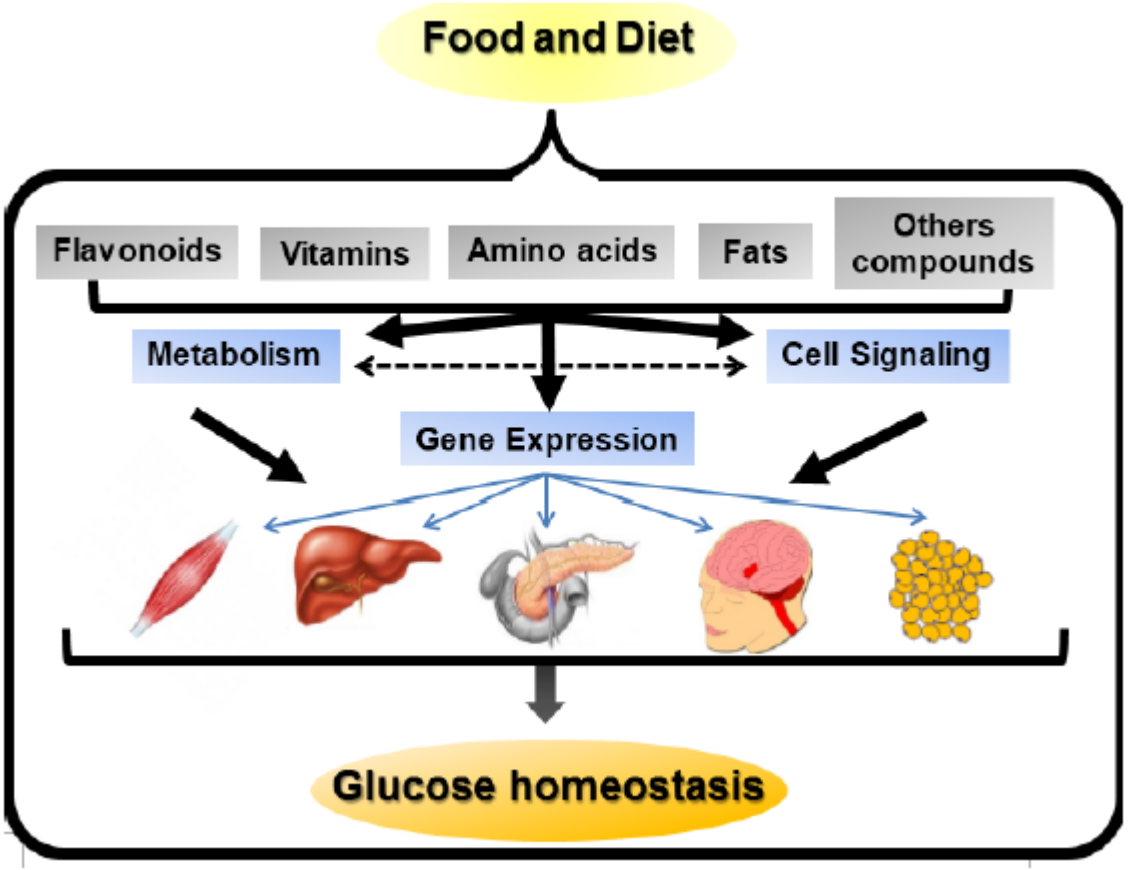
Nora E. Grotenfelt[1] · Niko S. Wasenius[1,2] · Kristiina Rönö[3] · Hannele Laivuori[3,4,5] · Beata Stach-Lempinen[6] · Marju Orho-Melander[7] · Christina-Alexandra Schulz[7] · Hannu Kautiainen[2,8] · Saila B. Koivusalo[3] · Johan G. Eriksson[1,2,9]

Diabetologia
DOI 10.1007/s00125-016-3989-1

Aims/hypothesis The aim of this study was to assess the interaction between melatonin receptor 1B gene *(MTNR1B)* rs10830963 polymorphism and lifestyle intervention during pregnancy on occurrence of gestational diabetes mellitus (GDM) in high-risk women.

In women at high risk of GDM, only those not carrying the risk allele G benefited from the lifestyle intervention. Our results indicate that certain genetic risk variants may modify the effectiveness of lifestyle interventions. This may provide important information when planning GDM prevention studies in the future.

Nutrigenetics and Nutrigenomics Insights into Diabetes Etiopathogenesis



On the one hand, the effects of nutrient-gene interaction can lead to an increase in GDM risk, as well as illness progression and complications; on the other, they can perform a protective action

.

Nutrients **2014**, *6*, 5338-5369; doi:10.3390/nu6115338

Berna G., et all

The identification of **genetic markers which could explain differences in susceptibility to GDM and cardiometabolic risk** would represent a crucial point in order to set up a strategy for the prevention, early diagnosis, and treatment of this condition.

Marica Franzago,[1,2] Federica Fraticelli,[2,3] Antonio Nicolucci,[4] Claudio Celentano,[3] Marco Liberati,[3] Liborio Stuppia,[1,2] and Ester Vitacolonna[2,3]

Molecular Analysis of a Genetic Variants Panel Related to Nutrients and Metabolism: Association with Susceptibility to Gestational Diabetes and Cardiometabolic Risk in Affected Women

Marica Franzago,[1,2] Federica Fraticelli,[2,3] Antonio Nicolucci,[4] Claudio Celentano,[3] Marco Liberati,[3] Liborio Stuppia,[1,2] and Ester Vitacolonna[2,3]

The aim of our study was **to investigate the relationship between clinical parameters in GDM and variants in genes involved with nutrients and metabolism** in 168 pregnant Caucasian women with or without GDM by High Resolution Melting (HRM) analysis.

Journal of Diabetes Research
Volume 2017, Article ID 4612623, 7 pages
https://doi.org/10.1155/2017/4612623

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An additional aim was **to identify an innovative tool for early identification and prevention of Cardio-metabolic diseases post GDM**.

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Several variants *PPARG2* rs1801282 (*C>G*); *PPARGC1A* rs8192678 (*C>T*); *TCF7L2* rs7903146 (*C>T*); *LDLR* rs2228671 (*C>T*); *MTHFR* rs1801133 (*C>T*); *APOA5* rs662799 (*T>C*); *GCKR* rs1260326 (*C>T*); *FTO* rs9939609 (*T>A*); *MC4R* rs17782313 (*T>C*) were genotyped

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Nutrigenetics in GDM

- *TCF7L2*, *PPARG2*, *PPARGC1A:* related to carbohydrate metabolism,

- *APOA5*, *GCKR:* triglycerides metabolism,
- *LDLR:* cholesterol metabolism,
- *MTHFR:* folate metabolism
- *FTO*, *MC4R:* energy metabolism

Marica Franzago,[1,2] Federica Fraticelli,[2,3] Antonio Nicolucci,[4] Claudio Celentano,[3] Marco Liberati,[3] Liborio Stuppia,[1,2] and Ester Vitacolonna[2,3]

Table 1. *Characteristics of cases and controls*

Characteristics	GDM yes (N=102)	GDM no (N=66)	P*
Age (years)[a]	34.6±5.4	31.9±5.1	<0.0001
Ethnicity[b]			
Caucasian	99.0	97.0	0.56
Other	1.0	3.0	
School education[b]			0.68
Low school	20.0	14.5	
High school	44.0	49.1	
University degree	36.0	36.4	
Employment[b]			0.11
Employed	56.9	53.6	
Unemployed	42.2	39.3	
Student	1.0	7.1	
Marital status [b]			0.24
Single	17.8	29.5	
Married	81.2	70.5	
Separated/divorced	1.0	0.0	
BMI (Kg/m^2) pre- pregnancy [a]	26.0±8.4	21.3±7.4	0.001
Systolic blood pressure (mmHg) [a]	114±14	121±14	0.10
Diastolic blood pressure (mmHg) [a]	72±14	77±15	0.03
Hypertension [b]	7.4	8.3	0.91
Smoking [b]			0.10
No	74.3	72.7	
Yes	2.0	9.1	
Ex	23.7	18.2	
Family history of DM (1st degree) [b]	33.3	17.6	0.09

** Mann Whitney U-test or Chi-square test*

[a] Data are presented as means ± SD

[b] Data are presented as percent (%)

Marica Franzago,[1,2] Federica Fraticelli,[2,3] Antonio Nicolucci,[4] Claudio Celentano,[3] Marco Liberati,[3] Liborio Stuppia,[1,2] and Ester Vitacolonna[2,3]

Molecular Analysis of a Genetic Variants Panel Related to Nutrients and Metabolism: Association with Susceptibility to Gestational Diabetes and Cardiometabolic Risk in Affected Women

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A significant correlation was observed between *TT* genotype of *TCF7L2* gene and increased risk of GDM (**OR 5.4** [95% CI 1.5–19.3]).

These results confirm previuos studies

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Transcription Factor 7-Like 2 (TCF7L2) rs7903146 Polymorphism as a Risk Factor for Gestational Diabetes Mellitus: A Meta-Analysis

Lin P-C, Lin W-T, Yeh Y-H, Wung S-F

PLOS ONE | DOI:10.1371/journal.pone.0153044 April 8, 2016

Group by Subgroup within study	Study name	Subgroup within study	Statistics for each study				
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Asian	Aris	Asian	0.434	0.017	10.764	-0.510	0.610
Asian	Cho	Asian	3.712	0.178	77.459	0.846	0.398
Asian	Shi	Asian	4.714	1.850	12.011	3.249	0.001
Asian	Thomas	Asian	1.964	0.598	6.445	1.113	0.266
Asian			3.077	1.532	6.180	3.159	0.002
Hispanic or Latino	de Melo	Hispanic or Latino	1.612	0.783	3.319	1.295	0.195
Hispanic or Latino	Huerta-Chagoya	Hispanic or Latino	1.900	0.867	4.163	1.604	0.109
Hispanic or Latino	Reyes-Lopez	Hispanic or Latino	2.209	0.596	8.193	1.185	0.236
Hispanic or Latino			1.798	1.099	2.942	2.335	0.020
White	Freathy	White	1.303	0.988	1.719	1.875	0.061
White	Klein	White	0.688	0.168	2.810	-0.522	0.602
White	Lauenborg	White	1.825	1.206	2.761	2.848	0.004
White	Pagan	White	2.105	0.374	11.856	0.844	0.399
White	Papadppoulou	White	1.904	1.373	2.641	3.857	0.000
White	Pappa	White	3.254	1.258	8.413	2.434	0.015
White	Rizk	White	1.359	0.401	4.613	0.492	0.622
White	Shaat	White	2.051	1.409	2.985	3.751	0.000
White	Vcelak	White	0.534	0.286	0.994	-1.978	0.048
White			1.561	1.334	1.826	5.552	0.000
Overall			1.628	1.407	1.885	6.529	0.000

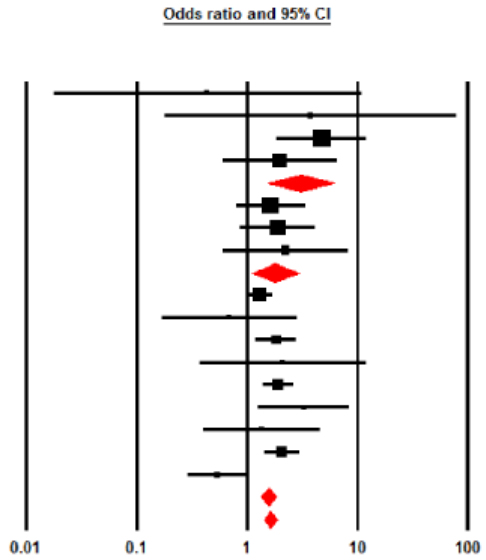

Fig 2. Forest plot of TCF7L2 rs7903146 polymorphism (TT versus CC) and GDM risk under fixed effect model in overall sample and sub-racial groups. The squares and horizontal lines correspond to the study specific odds ratios (ORs) and 95% confidence intervals (CI) respectively. The diamond represents the pooled ORs and 95% CI.

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In GDM a significant correlation was observed **between lipid parameters and genetic variations in additional genes, namely**: *PPARG2 [p=0,02], APOA5 [p=0,02], MC4R [p=0,03], LDLR [p=0,01], FTO [p= 0,02]*

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The *TCF7L2* gene

Located on chromosome 10q25.3, is an important, ubiquitously expressed transcription factor in the Wnt signaling pathway**, involved in the proliferation of pancreatic β-cells, and controlling the production of incretins such as glucagon intestinal peptide (GIP) and glucagon-like peptide 1 (GLP-1) in intestinal endocrine cells**. **Conversion from impaired glucose tolerance (IGT) to overt diabetes (Diabetes Prevention Program)**

PPARG2 rs1801282

PPARG2 rs1801282 polymorphism has been associated with impaired insulin sensitivity and was called indeed 'insulin resistance locus'

***PPARG2* Pro12Ala and *ADAMTS9* rs4607103 as "insulin resistance loci" and "insulin secretion loci" in Italian individuals. The GENFIEV study and the Verona Newly Diagnosed Type 2 Diabetes Study (VNDS) 4**

Acta Diabetol (2013) 50:401–408

M. Trombetta · S. Bonetti · M. L. Boselli · R. Miccoli · E. Trabetti · G. Malerba · P. F. Pignatti · E. Bonora · S. Del Prato · R. C. Bonadonna

- *APOA5*-1131*T*>*C* SNP **modulates the effects of macronutrient intake (total fat, carbohydrate, and protein) on BMI and obesity risk in both men and women**. It exerts an important role in the T2DM development particularly in Asian population. In fact, the presence of at least one *C* allele implicated less weight on a high fat diet than the presence of homozygosity for the *T* allele

APOA5-1131*T*>*C* variant

Strong association of the *APOA5*-1131T>C gene variant and early-onset acute myocardial infarction

Atherosclerosis 214 (2011) 397–403

Raffaele De Caterina[a,*,1], Philippa J. Talmud[b,1], Piera Angelica Merlini[c], Luisa Foco[d], Roberta Pastorino[d], David Altshuler[e,f,g], Francesco Mauri[c], Flora Peyvandi[h], Daniela Lina[i], Sekar Kathiresan[j,k], Luisa Bernardinelli[d], Diego Ardissino[i], on behalf of the Gruppo Italiano Aterosclerosi Trombosi e Biologia Vascolare

An Italian study based on 1,864 patients <45 years old suggested that this polymorphism may affect the risk of early- onset MI, with an odds ratio of 1.44 (CI: 1.23-1.69) per *C* allele

MC4R and *FTO*

Are associated with severe obesity and metabolic impairment in Caucasians. In the DPS, in men with Impaired Glucose Tolerance the *AA* genotype of rs9939609 in *FTO* was associated of 2.09-fold risk of CVD in men

Association of the *FTO* gene variant (rs9939609) with cardiovascular disease in men with abnormal glucose metabolism – The Finnish Diabetes Prevention Study

Lappalainen T. and coll DPP

Nutrition, Metabolism & Cardiovascular Diseases (2011) 21, 691–698

LDLR rs2228671 polymorphism

LDLR rs2228671 polymorphism and 3rd trimester LDL-cholesterol levels, it is interesting to note that **a recent meta-analysis has established rs2228671 as a protective factor of CHD in Europeans**

Meta-Analysis of Low Density Lipoprotein Receptor (*LDLR*) rs2228671 Polymorphism and Coronary Heart Disease

Huadan Ye and coll

BioMed Research International
Volume 2014, Article ID 564940, 6 pages

Molecular Analysis of a Genetic Variants Panel Related to Nutrients and Metabolism: Association with Susceptibility to Gestational Diabetes and Cardiometabolic Risk in Affected Women

Marica Franzago,[1,2] Federica Fraticelli,[2,3] Antonio Nicolucci,[4] Claudio Celentano,[3] Marco Liberati,[3] Liborio Stuppia,[1,2] and Ester Vitacolonna[2,3]

- Our findings support and confirm the association between *TCF7L2* rs7903146 variant with an increased GDM risk
- Our results about the investigated genetic variants provide important information about cardiometabolic risk in GDM and help to plan future prevention studies.

Journal of Diabetes Research
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Nutrigenetic variants and cardio-metabolic risk in women with or without gestational diabetes

Nine gene variants associated with nutrients and metabolism were genotyped **in 104 GDM cases and 124 controls** using High Resolution Melting (HRM) analysis.

Results: The **genetic variant rs7903146 (C > T) in TCF7L2** gene showed a **strong Association with GDM risk (OR: 2.56; 95% CI: [1.24–5.29]).** Moreover, a significant correlation was observed **between lipid parameters and polymorphisms in other genes, namely PPARG2 [p = 0,03], APOA5 [p = 0,02], MC4R [p = 0,03], LDLR [p = 0,04] and FTO [p = 0,03]**. In addition, **rs17782313 variant, mapped close to MC4R gene, was associated to BMI in pre-pregnancy [p = 0,02] and at the end of pregnancy [p = 0,03] in GDM group**.

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Supplementary table 2b. 3rd Trimester TC, HDL-C, LDL-C and TG levels of GDM patients according to genotypes (data are mean±SD).

	TC mg/dl	P*	HDL-C mg/dl	P*	LDL-C mg/dl	P*	TG mg/dl	P*
TCF7L2 rs7903146								
CC	265±55	0,56	68±14	0,77	134±66	0,44	226±83	0,41
CT	268±50		74±24		137±59		244±73	
TT	253±43		71±17		120±57		230±61	
PPARG2 rs1801282								
CC	268±49	**0,03***	71±18	0,53	137±60	**0,03***	241±73	0,08
CG	244±48		73±20		112±60		208±71	
GG	/		/		/		/	
PPARGC1A rs8192678								
CC	255±52	0,47	68±18	0,57	133±56	0,34	219±54	0,65
CT	265±52		73±20		124±69		240±80	
TT	270±37		71±15		150±35		246±84	
APOA5 rs662799								
TT	259±52	0,33	74±17	0,06	132±55	0,4	223±68	0,14
CT	271±47		69±21		134±68		240±72	
CC	243±42		61±8		101±60		302±102	
MC4R rs17782313								
TT	262±52	0,41	73±17	**0,03***	134±58	0,63	227±71	0,42
CT	259±46		66±22		124±64		252±82	
CC	287±43		76±15		140±76		217±27	
LDLR rs2228671								
CC	270±50	0,19	73±21	0,26	145±53	**0,04***	235±77	0,65
CT	248±46		66±13		106±68		235±66	
TT	226±0		85±0		106±0		176±0	

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Supplementary table 3b. 3rd Trimester TC, HDL-C, LDL-C and TG levels of GDM patients according to carrier/no carrier (data are mean±SD)

	TC mg/dl	P*	HDL-C mg/dl	P*	LDL-C mg/dl	P*	TG mg/dl	P*
TCF7L2 rs7903146								
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CT-TT	262±47		73±21		130±58		238±68	
PPARG2 rs1801282								
CC	268±49	**0,03***	71±18	0,53	137±60	**0,03***	241±73	0,08
CG-GG	244±48		73±20		112±60		208±71	
PPARGC1A rs8192678								
CC	255±52	0,32	68±18	0,29	133±56	0,99	219±54	0,36
CT-TT	266±49		73±19		130±63		241±80	
APOA5 rs662799								
TT	259±52	0,5	74±17	**0,03***	132±55	0,8	223±68	0,13
CT-CC	267±20		68±20		129±68		248±78	
MC4R rs17782313								
TT	262±52	0,78	73±18	0,05	134±58	0,88	227±71	0,28
CT-CC	264±46		68±22		127±65		246±76	
LDLR rs2228671								
CC	270±50	0,08	73±21	0,29	145±53	**0,01***	235±77	0,97
CT-TT	247±45		67±13		106±67		232±65	
GCKR rs1260326								
CC	257±54	0,55	69±24	0,18	138±56	0,65	221±50	0,5
CT-TT	265±48		72±17		129±63		239±80	
FTO rs9939609								
TT	258±51	0,46	74±17	0,16	109±69	**0,03***	234±68	0,92
AT-AA	264±49		70±19		141±55		234±76	

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CT-TT	266±49		73±19		130±63		241±80	
APOA5 rs662799								
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CT-CC	267±20		68±20		129±68		248±78	
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GCKR rs1260326								
CC	257±54	0,55	69±24	0,18	138±56	0,65	221±50	0,5
CT-TT	265±48		72±17		129±63		239±80	
FTO rs9939609								
TT	258±51	0,46	74±17	0,16	109±69	**0,03***	234±68	0,92
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Supplementary table 4a. GDM and controls pre-pregnancy BMI in according to genotypes (data are mean±SD).

	Pre-pregnancy BMI			
	GDM (N=104)	P*	No GDM (N= 124)	P*
TCF7L2 rs7903146				
CC	26,6±7,5	0,42	23,5±5,6	0,71
CT	27,5±6,0		22,7±3,28	
TT	27,7±6,6		21,7±2,6	
PPARG2 rs1801282				
CC	27,2±6,4	0,88	23,1±4,6	0,67
CG	27,4±7,6		22,5±4,3	
GG	/		/	
PPARGC1A rs8192678				
CC	27,3±5,8	0,62	23,2±4,3	**0,02***
CT	26,8±6,7		22,3±4,9	
TT	28,6±8,3		24,1±3,6	
APOA5 rs662799				
TT	27,6±7,6	0,87	23,2±4,7	0,42
CT	26,9±5,3		22,5±4,3	
CC	26,0±6,4		23,1±0,6	
MC4R rs17782313				
TT	25,9±5,7	0,06	23,2±4,5	0,43
CT	29,8±7,9		22,7±4,6	
CC	28,4±6,6		20,3±0,5	
LDLR rs2228671				
CC	27,0±6,7	0,57	22,4±4,2	**0,04***
CT	27,8±6,8		24,3±5,0	
TT	22,4±0,0			

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Conclusions (1)

The early identification of subjects who could benefit from preventive strategies is a priority for public health. The diagnosis of GDM increasingly represents an extraordinary opportunity to alter the natural course of a disease: it is important to have reliable predictive tools

Conclusions (2)

GDM represents an important opportunity in the era of “Precision Medicine” and “Precision Nutrition.”

Further studies are required to examine whether **incorporation of our panel genes into an algorithm including genetic, clinic, and metabolic variables** will help further improve the identification of women with GDM at early risk of diabetes and CVD

Conclusions (3)

Our studies provides **potential newer markers** and could improve the identification of women with GDM at early risk of diabetes and CVD to plan individualized preventive interventions.